PROTOCOL: SHP465-112

TITLE:	A Phase 1 Open-label Study of the Safety, Tolerability, and Pharmacokinetics of *d*- and *l*-Amphetamine after Multiple Daily Doses of SHP465 6.25 mg Administered in Children Aged 4 to 5 years with Attention-Deficit/Hyperactivity Disorder
DRUG:	SHP465
IND:	66,329
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Shire Development LLC 300 Shire Way, Lexington, MA 02421 US
PRINCIPAL/ COORDINATING INVESTIGATOR:	TBD
PROTOCOL HISTORY:	Original Protocol: 15 Sep 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted] MD, PhD, MPH	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP465-112.

Title: A Phase 1 Open-label Study of the Safety, Tolerability, and Pharmacokinetics of *d*- and *l*-Amphetamine after Multiple Daily Doses of SHP465 6.25 mg Administered in Children Aged 4 to 5 years with Attention-Deficit/Hyperactivity Disorder

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

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

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

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

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

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

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Nonserious AEs Required by the Protocol Form within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization/Shire Medical Monitor by fax or e-mail using the details below.

Shire Pharmacovigilance SAE Fax Number:

[redacted]

or

[redacted]

For protocol- or safety-related issues, the investigator must contact the Shire Medical Monitor:

[redacted], MD, PhD, MPH

Telephone: [redacted] (business hours 9:00 AM to 5:00 PM Eastern Standard Time)
E-mail: [redacted]
Mobile: [redacted] (24-hour coverage)

ADDITIONAL CONTACT INFORMATION

In case of any other issues, including non-safety-related issues or if the medical monitor is unable to be reached, the investigator must contact the Shire Study Manager:

[redacted]

Telephone: [redacted] (business hours)
[redacted] (24-hour coverage)

If unavailable, please contact:

[redacted]

Telephone: [redacted] (business hours)
[redacted] (24-hour coverage)

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 (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, refer to Section 8.

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

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

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (US)
[redacted]

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ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ADHD-RS-5	Attention-Deficit/Hyperactivity Disorder Rating Scale-5
AE	adverse event
$AUC_{0-\infty}$	area under the curve extrapolated to infinity
AUC_{last}	area under the curve from the time of dosing to the last measurable concentration
AUC_{0-t}	area under the curve from time 0 to the last time point of sample collection
AUC_{0-5}	area under the curve from time 0 predose to 5 hours postdose
AUC_{5-t}	area under the curve from time 5 hours to the last time point of sample collection
AUC_{tau}	area under the concentration curve over the dosing interval (24 hours), at steady state
BMI	body mass index
CGI-S	Clinical Global Impressions – Severity of Illness
CL/F	total body clearance for extravascular administration
C_{max}	maximum concentration occurring at t_{max}
CSHQ	Children's Sleep Habits Questionnaire
C_{trough}	trough plasma concentration (the predose concentrations collected at steady state)
CRA	clinical research associate
CRC	clinical research center
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	data monitoring committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EC	ethics committee
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator's brochure
ICH	International Council for Harmonisation
IRB	institutional review board
LAR	legally authorized representative
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
PK	pharmacokinetic(s)
PSQ	Post Sleep Questionnaire
SAE	serious adverse event
SAP	statistical analysis plan
T3	tri-iodothyronine
T4	thyroxine

$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
t_{max}	time of maximum observed concentration sampled during a dosing interval
US	United States
VF/ss	apparent volume of distribution at steady state
V_z/F	volume of distribution associated with the terminal slope following extravascular administration
λ_z	the first order rate constant associated with the terminal phase of elimination

STUDY SYNOPSIS

Protocol number: SHP465-112	**Drug:** SHP465, mixed salts of a single-entity amphetamine
Title of the study: A Phase 1 Open-label Study of the Safety, Tolerability, and Pharmacokinetics of *d*- and *l*-Amphetamine after Multiple Daily Doses of SHP465 6.25 mg Administered in Children Aged 4 to 5 years with Attention-Deficit/Hyperactivity Disorder	
Number of subjects (total and for each treatment arm): Approximately 24 subjects are expected to be enrolled to ensure that 10 subjects will complete the rich pharmacokinetic (PK) sampling portion of the study and an additional 10 subjects will complete the sparse PK sampling portion of the study. Enrollment will be stratified by gender to ensure that at least 2 of the 10 subjects in the rich PK sampling portion of the study and at least 3 of the 10 subjects in the sparse PK sampling portion of the study expected to complete the study are females.	
Investigators: Multicenter study	
Sites and Regions: Approximately 10 sites in the United States will participate in this study	
Study period (planned): 2017-2018	**Clinical phase:** 1

Objectives:

Primary: To evaluate the pharmacokinetics (PK), safety, and tolerability of SHP465 in children aged 4 to 5 years with attention-deficit/hyperactivity disorder (ADHD) after SHP465 multiple daily doses of 6.25 mg.

Rationale:

The proposed clinical study is being conducted to provide information on SHP465 PK, safety, and tolerability after 4 weeks of SHP465 administration at a daily dose of 6.25 mg in preschool children aged 4 to 5 years with ADHD.

Investigational product, dose, and mode of administration:

- There will be one SHP465 dose level of 6.25 mg used in this study.
- SHP465 6.25 mg will be given once daily for 28 days (±1 day) at 8:00 AM (±1 hour).
- Investigational product will be taken by either swallowing the capsule whole or sprinkling the capsule content onto 1 tablespoon of applesauce and ingesting the entire mixture immediately without chewing.

Methodology:

The study will be a Phase 1, open-label, multiple-dose, PK, safety, and tolerability study in children aged 4 to 5 years diagnosed with ADHD. Enrollment will be stratified by gender to ensure that at least 2 of the 10 subjects expected to complete the rich PK sampling portion of the study and at least 3 of the 10 subjects expected to complete the sparse PK sampling portion of the study are females. Subjects for the rich PK sampling portion of the study will be enrolled first. Once the required number of subjects is achieved, enrollment in the sparse PK sampling group will begin.

Screening Period (Includes Washout Period)

Subjects will be assessed for eligibility during the screening period. The duration of the screening period will be a maximum of 32 days. If subjects are currently taking ADHD medication, they are required to discontinue their current ADHD medication at least 7 days prior to the first dose of investigational product on Day 1 of Week 1 (washout period).

Following the screening visit, eligible subjects will return to the clinical research center (CRC) on Day 1 of Week 1 to reconfirm eligibility criteria and enter into the treatment phase.

If more than 32 days have elapsed since the screening evaluations were completed, then the following evaluations must be repeated at baseline (prior to the first dose of investigational product on Day 1 of Week 1): vital signs, clinical laboratory evaluations, blood pressure, electrocardiograms (ECGs), weight, and height. The physical examination will be abbreviated with a review of the following body systems: general appearance, respiratory, and cardiovascular.

Treatment Period

The subject will receive SHP465 6.25 mg as a daily dose for 28 days (±1 day).

PK Sample Collection

Subjects should be adequately hydrated before blood draws. Caffeinated drinks should be avoided. Details on fasting and hydration are provided in Section 6.2.2.

Rich PK Sample Scheme (9 Samples/Subject) Collection

Predose PK samples will be collected on Day 1 of Week 1, and serial blood samples for PK analysis will be drawn prior to dosing on Day 7 of Week 4 (within 60 minutes prior to dosing) and up to 48 hours after administration of the investigational product.

On Day 7 of Week 4, subset of subjects in the rich PK sampling portion will be required to remain at the CRC through 8 hours postdose. Following completion of the 8-hour PK sample collection, per investigator's discretion, subjects will have the option to remain at or leave the CRC. If they leave the CRC, subjects will either return to the CRC on Days 7, 8, and 9 of Week 4 for the 12-hour, 16-hour, 24-hour, and 48-hour postdose blood sample collections or, if the option is available at their clinical site, a qualified person may visit the subject for the 12-hour, 16-hour, and 24-hour postdose blood sample collections, but they must return to the clinic for the 48-hour blood sample collection.

Sparse PK Sample Scheme (4 Samples/Subject) Collection

Predose PK samples will be collected on Day 1 of Weeks 1 to 3 and on Day 8 of Week 4 (24 hours after dosing on Day 7 of Week 4) for subjects in the sparse PK sampling subset.

The end-of-study assessments will be performed at the last clinic visit: on Day 9 of Week 4 (approximately 48 hours after the last dose of investigational product) for subjects in the rich PK sampling portion and on Day 8 of Week 4 (approximately 24 hours after the last dose of investigational product) for subjects in the sparse PK sampling portion of the study.

Follow-up

At the last clinic visit, subjects and their parent/legally authorized representative (LAR) will be offered to rollover into the SHP465-308 study. If subjects agree and their parent/LAR signs the informed consent form, this will end their participation in the SHP465-112 study. If they do not want to participate in the SHP465-308 study, follow-up contact (study visit/telephone call) will be conducted. For those subjects with ongoing adverse events (AEs), a mandatory in-person follow-up visit at the CRC will occur 7 days (±2 days) following the subject's last dose of investigational product to collect information on any ongoing or new AEs, serious AEs (SAEs), or concomitant medications, as appropriate.

At the investigator's discretion, for those subjects with no ongoing AEs at the time of the last scheduled assessment, a telephone call initiated by the CRC staff or in-person follow-up visit at the CRC will occur 7 days (±2 days) following the subject's last dose of investigational product to collect information on any new AEs, SAEs, or concomitant medications, as appropriate.

Inclusion and exclusion criteria:

Inclusion Criteria

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

1. Subject is a male or female aged 4 years to 5 years inclusive at the time of consent.
2. Subject and parent/LAR are willing and able to fully comply with all of the testing and requirements defined in the protocol. Specifically, the parent/LAR must be available at approximately 8:00 AM (±1 hour) to administer the dose of investigational product at the time points specified in the protocol.
3. Subject's parent/LAR must sign the informed consent form, and there must be documentation of assent (if applicable) by the subject in accordance with the International Council for Harmonisation Good Clinical Practice Guideline E6 (2016) and any updates, and applicable regulations, before starting any study-related procedures.

4. Subject satisfies the following ADHD criteria during the screening period:
    - Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for a primary diagnosis of ADHD (any subtype) based on a detailed psychiatric evaluation using the Mini International Neuropsychiatric Interview for Children and Adolescents
    - Has an ADHD Rating Scale-5 Child, Home Version Total Score of ≥28 for boys and ≥24 for girls
    - Has a Clinical Global Impressions – Severity of Illness score ≥4.
5. Subject functions at an age-appropriate level intellectually, as determined by the investigator.
6. Subject has undergone an adequate course of nonpharmacological treatment **OR** the subject has a severe enough condition to consider enrollment without undergoing prior nonpharmacological treatment, based on the investigator's judgment **OR** has never taken ADHD medication **OR** has taken ADHD medication with unacceptable efficacy and/or tolerability.
7. Subject has the ability to take investigational product by either swallowing the capsule whole or sprinkling the capsule contents in applesauce and ingesting the entire mixture immediately without chewing.
8. Subject has lived with the same parent/LAR for at least 6 months.

Exclusion Criteria

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

1. Prior enrollment or participation in the study.
2. Subject has a documented allergy, hypersensitivity, or intolerance to amphetamine or to any excipients in the investigational product.
3. Subject cannot swallow a pill and/or applesauce, or has an allergy to applesauce.
4. Subject is currently taking or has taken ADHD medication with acceptable efficacy and tolerability.
5. Subject has taken ADHD medication within 7 days prior to the administration of investigational product.
6. Subject has used any medication (including over-the-counter, herbal, or homeopathic preparations) within 30 days prior to the administration of investigational product or 5-half-lives, whichever is longer, with the exception of the following:
    - Thyroid medication
    - Intermittent use of nonsteroidal anti-inflammatory drugs or acetaminophen for minor aches and pains
    - As needed use of a beta-agonists inhaler for mild asthma or exercise induced bronchospasm
    - Over-the-counter nonsedating antihistamines such as fexofenadine (ALLEGRA®, Sanofi), loratadine (CLARITIN®, Schering-Plough), or cetirizine hydrochloride (ZYRTEC®, McNeil-PPC) for allergies.
    - Subject has continuously used oral corticosteroids ≥7 days in 3 months prior to investigational product dosing. If continuous use was <7 days, 1 month of washout prior to dosing of investigational product is required.
7. Within 30 days prior to the administration of investigational product:
    - Subject has used an investigational product.
        - If the elimination half-life of the previous study's investigational product was less than 6 days, then the last dose of the previous investigational product should be 30 days prior to the first dose of SHP465.
        - If the elimination half-life of the previous study's investigational product was greater than 6 days, then the last dose of the previous investigational product should be 5 half-lives prior to the dose of SHP465.
8. Subject has glaucoma.

9. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.
10. Subject has a known history of symptomatic cardiovascular disease, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac conditions placing them at increased vulnerability to the sympathomimetic effects of a stimulant drug.
11. Subject has any clinically significant ECG or clinically significant laboratory abnormalities at the first screening visit based on the investigator's judgment. A single retest of laboratory parameters is allowed based on the investigator's judgment.
12. Subject has Marfan's syndrome.
13. Subject has a blood pressure ≥95th percentile for age, sex, and height at the screening visit.
14. Subject has a height ≤5th percentile for age and sex at the first screening visit.
15. Subject has a weight ≤5th percentile for age and sex at the first screening visit.
16. Subject has current abnormal thyroid function test results, defined as abnormal thyroid-stimulating hormone, thyroxine, and tri-iodothyronine at the first screening visit. Treatment with a stable dose of thyroid medication for at least 3 months is permitted.
17. Subject has a history of seizures (other than infantile febrile seizures).
18. Subject has a current, controlled (requiring medication or therapy) or uncontrolled, comorbid psychiatric disorder including but not limited to any of the following comorbid Axis I disorders and Axis II disorders:
    - Post-traumatic stress disorder or adjustment disorder
    - Bipolar disorder, psychosis/schizophrenia, or positive family history of these disorders in first- or second-degree relatives
    - Pervasive developmental disorder
    - Obsessive-compulsive disorder
    - A serious tic disorder, or a family history of Tourette disorder
    - Substance abuse or dependence disorder
    - Any other disorder that in the opinion of the investigator contraindicates SHP465 or amphetamine treatment or confounds safety assessments.
19. Subject is currently considered a suicide risk in the opinion of the investigator, has previously made a suicide attempt, or has a prior history of or is currently demonstrating active suicidal ideation.
20. Subject has a history of physical, sexual, or emotional abuse.
21. Subject has a primary sleep disorder (eg, sleep apnea, narcolepsy).
22. Subject has a history or is currently diagnosed with an eating disorder.
23. Subject has a clinically important abnormality on the urine drug and alcohol screen (excluding the subject's current ADHD stimulant, if applicable) at the first screening visit.
24. Subject lives with anyone who currently abuses stimulants or cocaine, based on the investigator's judgment.
25. 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.
26. Subject has any additional condition(s) such as any significant illness or unstable medical condition that, in the investigator's opinion, would prohibit the subject from completing the study and /or could lead to difficulty complying with the protocol.

Maximum duration of subject involvement in the study:

- Each subject's maximum duration of participation is expected to be approximately 9 weeks. The study will be completed in approximately 12 months.
- Screening period:
  - A maximum of 32 days before the first dose of investigational product
  - If applicable, this includes a washout period that is to start 7 days before the first dose of investigational product.
  - Treatment Period: Total duration for the treatment period is approximately 30 days for subjects in the rich PK sampling portion of the study and 29 days for subjects in the sparse PK sampling portion of the study.
- Follow-up contact: At the last clinic visit, subjects and their parent/LAR will be offered to rollover into the SHP465-308 study. If subjects agree and their parent/LAR signs the informed consent form, this will end their participation in the SHP465-112 study. If they do not want to participate in the SHP465-308 study, follow-up contact will be conducted approximately 1 week (7 days [±2 days]) following the last dose of investigational product.

Sample size and power calculations:

To objectively justify the sample size for PK sampling and PK sampling scheme for this study, the following precision is recommended in the Food and Drug Administration guidance, General Clinical Pharmacology: Considerations for Pediatric Studies for Drugs and Biological Products.

The sample size for traditional rich PK sampling for noncompartmental analysis is calculated to achieve 80% probability (power), to assure the 95% confidence interval of the point estimate of the geometric mean of clearance is within 60% to 140% of the estimate of the clearance. Although the range (60%, 140%) is not symmetric to 1, the lower confidence interval bound is within (60%, 140%) (1/1.4=0.714) as long as the upper bound is ≤1.4.

The available data in the following table are from Shire's completed study (SHP465-111) with an ADHD pediatrics population and show the reported apparent clearance (CL/F) and volume of distribution (V_z/F) for the *d*-amphetamine and *l*-amphetamine of SHP465 after oral administration of 12.5 mg in children aged 6 to 12 years and 25 mg in adolescents aged 13 to 17 years.

Estimates of Clearance and Volume of Distribution for *d*-Amphetamine and *l*-Amphetamine

CV (%)	SHP465 12.5 mg Children (6 to 12 years)		SHP465 25 mg Adolescents (13 to 17 years)	
	CL/F (L/h)	V_z/F (L)	CL/F (L/h)	V_z/F (L)
d-Amphetamine	25.0	28.5	23.7	18.4
l-Amphetamine	26.9	32.2	28.4	22.0

CV=coefficient of variation

Source: SHP465-111 Clinical Study Report Tables 9-1 and 9-4.

The sample size estimates use the within-subject *l*-amphetamine variability of 32.2%, since it is numerically bigger. Applying the methods from the manuscript by Wang et al., 2012, sample size estimations with related probability for corresponding coefficients of variation are provided as follows:

CV (%)	Number of Subjects Required	Probability of the Point Estimate Within the Prespecified Interval (%)
18.4	5	89
22.0	5	80
23.7	6	88
25.0	6	82
26.9	7	89
28.4	7	88
28.5	7	88
32.2	8	90

CV=coefficient of variation

Based on these data, the PK analysis will need at least 8 subjects in total to provide reliable PK parameter estimates.

Endpoints and statistical analysis:

Analysis Populations

The **screened set** will consist of all subjects who have provided informed consent.

The **enrolled set** will consist of all subjects who have been assigned a subject identification number.

The **safety set** will consist of all enrolled subjects who have taken at least 1 dose of investigational product.

The **PK set** will consist of all subjects in the safety set for whom at least 1 postdose PK blood sample was collected.

Pharmacokinetic Endpoints

Pharmacokinetic parameters will be determined from the plasma concentration-time data for *d*-amphetamine and *l*-amphetamine by noncompartmental analysis using Phoenix® WinNonlin® (Certara, Princeton, NJ) Version 6.4 or higher.

The PK parameters will include, but not be limited to:

- $AUC_{0-\infty}$ Area under the curve extrapolated to infinity
- AUC_{0-t} Area under the curve from time 0 to the last time point of sample collection
- AUC_{0-5} Area under the curve from time 0 predose to 5 hours postdose
- AUC_{5-t} Area under the curve from time 5 hours to the last time point of sample collection
- AUC_{last} Area under the curve from the time of dosing to the last measurable concentration
- AUC_{tau} Area under the concentration curve over the dosing interval (24 hours) at steady state
- CL/F Total body clearance for extravascular administration
- C_{max} Maximum concentration occurring at t_{max}
- C_{trough} Trough plasma concentration (the predose concentrations collected at steady state)
- $t_{1/2}$ Terminal half-life
- t_{max} Time of maximum observed concentration sampled during a dosing interval
- VF/ss Apparent volume of distribution at steady state
- V_z/F Volume of distribution associated with the terminal slope following extravascular administration
- λ_z The first order rate constant associated with the terminal phase of elimination

There will be no inferential statistical analysis of the PK data. Summary descriptive statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum and geometric mean) will be determined for all PK parameters. Plasma concentrations at each nominal sampling time will also be summarized using descriptive statistics.

Safety Endpoints

Safety will be assessed by treatment-emergent AEs (TEAEs), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature), 12-lead ECGs, weight, height, clinical laboratory tests (biochemistry, hematology, and urinalysis), Post Sleep Questionnaire (PSQ), and a validated sleep questionnaire (Children's Sleep Habits Questionnaire [CSHQ]).

Additionally, the Columbia-Suicide Severity Rating Scale (C-SSRS) scale will capture the safety of SHP465 related to suicidality.

The safety endpoints will be summarized with descriptive statistics for the safety set.

Baseline is defined as the last assessment prior to the first dose of investigational product. Potentially clinically important findings will also be summarized or listed. The potentially clinically important values will be defined in the statistical analysis plan.

Weight, height, BMI, vital signs, ECG, PSQ, and CSHQ will be summarized. The C-SSRS results will be summarized and a listing of the C-SSRS data will be provided for subjects with a positive response.

Adverse events will be coded using the agreed-upon version of 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 AEs 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.

STUDY SCHEDULE

Table 1: Schedule of Assessments for Rich Pharmacokinetic Sampling Portion

Assessment Day	Screening and Washout		Week 1 to 3		Week 4											Follow-up[a]
	D -32 to D -8	D -7 to D -1 Washout	D 1	D 2-7	D 1	D 2-6	D 7							D 8[b]	D 9 /ET[b]	
Treatment Week 4 Time Point (h)							**Predose[c]**	**0**	**2**	**5**	**8**	**12**	**16**	**24**	**48**	
Informed Consent & Assent	X															
Inclusion/Exclusion Criteria	X		X[d]													
Demographics	X															
Medical & Medication History (Includes Prior Medications and Procedures)[e]	X															
Physical Examination	X		X[f]		X[f]		X[g]								X[h]	
Vital Signs[i]	X		X		X		X			X					X[h]	
Weight[j]	X		X		X		X								X[h]	
Height[j]	X														X[h]	
Biochemistry, Hematology, and Urinalysis	X														X[h]	
TSH, T4, and T3	X														X[h]	
Urine Drug and Alcohol Screen	X															
12-lead ECG[i]	X		X				X			X					X[h]	
C-SSRS Baseline Version	X															
C-SSRS Since Last Visit Version			X		X		X								X[h]	
MINI-KID	X															
ADHD-RS-5 Child, Home Version	X															
Clinical Global Impressions – Severity of Illness	X															
CSHQ	X		X		X		X								X[h]	
PSQ	X		X		X		X								X[h]	
Eligibility Confirmation			X[d]													
Investigational Product Dispensed			X		X											
Investigational Product Administration			X[k]	X[l]	X[k]	X[l]		X[k,m]								

Table 1: Schedule of Assessments for Rich Pharmacokinetic Sampling Portion

Assessment Day	Screening and Washout		Week 1 to 3		Week 4											Follow-up[a]
	D -32 to D -8	D -7 to D -1 Washout	D 1	D 2-7	D 1	D 2-6	D 7							D 8[b]	D 9 /ET[b]	
Treatment Week 4 Time Point (h)							**Predose[c]**	**0**	**2**	**5**	**8**	**12**	**16**	**24**	**48**	
Pharmacokinetic Sample Collection			X[n]				X		X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X

ADHD-RS-5=Attention-Deficit/Hyperactivity Disorder Rating Scale-5; CRC=clinical research center; C-SSRS=Columbia-Suicide Severity Rating Scale; CSHQ=Children's Sleep Habits Questionnaire; D=day; ECG=electrocardiogram; ET=Early Termination; h=hours; MINI-KID=Mini International Neuropsychiatric Interview for Children and Adolescents; PSQ=Post Sleep Questionnaire; TSH=thyroid-stimulating hormone; T3=tri-iodothyronine; T4=thyroxine.

[a] Follow-up contact will be conducted approximately 1 week (7 days [±2 days]) following the last dose of investigational product.

[b] Day 8 and Day 9 may be conducted on an out-patient basis.

[c] These assessments should be performed within 2 hours prior to dose administration with the exception of the pharmacokinetic sample, which should be collected within 60 minutes prior to dosing.

[d] Inclusion/exclusion criteria and eligibility confirmation must be reviewed at the CRC on Day 1 of Week 1.

[e] Medical and medication history will include a detailed description of the subject's psychiatric diagnosis and a lifetime history of pharmacologic therapies for ADHD and other disorders.

[f] A brief physical examination will be performed prior to dosing on Day 1.

[g] A brief physical examination will be performed prior to dosing on Day 7 of Week 4.

[h] An attempt to perform these assessments and procedures will be made for any subjects who withdraw or are removed from the study.

[i] Subjects should be resting in a sitting position for at least 5 minutes prior to collecting vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature). Subjects should be resting in a supine position for at least 5 minutes prior to collecting ECGs. If an invasive procedure was conducted prior to blood pressure, ECG and respiratory rate recording, the subject should be resting for 15 minutes.
Blood pressure and pulse will be measured at each visit. Measurements of blood pressure and pulse will be performed 3 times (with at least 2 minutes in between each collection) using the provided age-appropriate cuff. The average of each set of 3 measurements will be used to determine continued participation in the study.
Temperature and respiratory rate will be collected at the screening visit and ET visit only.
Measurement of blood pressure and pulse will be performed 3 times (with at least 2 minutes in between each collection) using the provided age-appropriate cuff.

[j] Height and weight to be measured without shoes and with light clothing using a stadiometer for height and calibrated scale for weight.

[k] Dosing will be done at the CRC.

[l] Dosing will be done at the home.

[m] Subjects should fast for 2 hours prior to dose administration on Day 7 of Week 4 and for 2 hours postdose. At 2 hours postdose on Day 7, subjects will be allowed to consume a light breakfast, ie, a single serving of cereal with up to 8 ounces of skim milk. Starting at 4 hours postdose on Day 1, for lunch and dinner, subjects will receive a standardized moderate fat meal. Subjects will be allowed snacks starting after lunch.

[n] To be sampled predose on Week 1 only.
Whenever possible, the same individual should complete/rate consistently the following scales and questionnaires as appropriate: ADHD-RS-5 Child, Home Version; Clinical Global Impressions - Severity of Illness; Post Sleep Questionnaire; and Children's Sleep Habits Questionnaire.

Table 2: Schedule of Assessments for Sparse Pharmacokinetic Sampling Portion

Assessment Day	Screening and Washout		Week 1 to 3		Week 4			Follow-up[a]
	D -32 to D -8	D -7 to D -1 Washout	D 1	D 2-7	D 1	D 2-7	D 8 /ET	
Informed Consent & Assent	X							
Inclusion/Exclusion Criteria	X		X[b]					
Demographics	X							
Medical & Medication History[c]	X							
Physical Examination	X		X[d]		X[d]		X[e]	
Vital Signs[f]	X		X		X		X[e]	
Weight[g]	X		X		X		X[e]	
Height[g]	X						X[e]	
Biochemistry, Hematology, and Urinalysis	X						X[e]	
TSH, T4, and T3	X						X[e]	
Urine Drug and Alcohol Screen	X							
12-lead ECG[f]	X		X				X[e]	
C-SSRS Baseline Version	X							
C-SSRS Since Last Visit Version			X		X		X[e]	
MINI-KID	X							
ADHD-RS-5 Child, Home Version	X							
Clinical Global Impressions – Severity of Illness	X							
CSHQ	X		X		X		X[e]	
PSQ	X		X		X		X[e]	
Eligibility Confirmation			X[b]					
Investigational Product Dispensed			X		X			
Investigational Product Administration			X[h]	X[i]	X[h]	X[i]		
Pharmacokinetic Sample Collection - Predose			X				X	
Concomitant Medications	X	X	X	X	X	X	X[e]	X
Adverse Events	X	X	X	X	X	X	X[e]	X

ADHD-RS-5=Attention-Deficit/Hyperactivity Disorder Rating Scale-5; CRC=clinical research center; C-SSRS=Columbia-Suicide Severity Rating Scale; CSHQ=Children's Sleep Habits Questionnaire; D=day; ECG=electrocardiogram; ET=Early Termination; h=hours; MINI-KID=Mini International Neuropsychiatric Interview for Children and Adolescents; PSQ=Post Sleep Questionnaire; TSH=thyroid-stimulating hormone; T3=tri-iodothyronine; T4=thyroxine.

[a] Follow-up contact will be conducted approximately 1 week (7 days [±2 days]) following the last dose of investigational product.

[b] Inclusion/exclusion criteria and eligibility confirmation must be reviewed at the CRC on Day 1 of Week 1.

Table 2: Schedule of Assessments for Sparse Pharmacokinetic Sampling Portion

Assessment Day	Screening and Washout		Week 1 to 3		Week 4			Follow-up[a]
	D -32 to D -8	D -7 to D -1 Washout	D 1	D 2-7	D 1	D 2-7	D 8 /ET	

[c] Medical and medication history will include a detailed description of the subject's psychiatric diagnosis and a lifetime history of pharmacologic therapies for ADHD and other disorders.
[d] A brief physical examination will be performed prior to dosing on Day 1 of Weeks 1 to 4.
[e] An attempt to perform these assessments and procedures will be made for any subjects who withdraw or are removed from the study.
[f] Subjects should be resting in a sitting position for at least 5 minutes prior to collecting vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature). Subjects should be resting in a supine position for at least 5 minutes prior to collecting ECGs. If an invasive procedure was conducted prior to blood pressure, ECG and respiratory rate recording, the subject should be resting for 15 minutes.
Blood pressure and pulse will be measured at each visit.
Temperature and respiratory rate will be collected at the screening visit and ET visit only.
[g] Height and weight to be measured without shoes and with light clothing using a stadiometer for height and calibrated scale for weight.
[h] Dosing will be done at the CRC.
[i] Dosing will be done at the home.

1 BACKGROUND INFORMATION

SHP465 is a once daily, sustained-release, single-entity mixed amphetamine salt product for oral administration. The product was previously referred to as SPD465; however, it is now being studied under the code of SHP465. The amphetamine salt combination found in SHP465 is comprised of sulfate salts of dextroamphetamine and amphetamine, with dextroamphetamine saccharate and amphetamine aspartate monohydrate, which provide a composite enantiomer ratio of 3:1 *d*-amphetamine to *l*-amphetamine.

SHP465 capsule contains 3 types of drug-releasing beads providing immediate release, pulsatile delayed release, and delayed sustained release of the mixed amphetamine salts. The immediate release bead comprises a drug-layered sphere which releases rapidly in the stomach. The pulsatile delayed-release bead includes an additional pH sensitive polymer coating which is insoluble under gastric pH conditions but is soluble above pH 5.5, thereby releasing drug in the small intestine. The delayed sustained-release bead includes a pH sensitive polymer coating with an additional coating of a sustained-release polymer; this combination begins releasing drug once the gastrointestinal track reaches pH 7.0 or above.

Amphetamines are noncatecholamine sympathomimetic amines with central nervous system stimulant activity. The primary mechanism of action is to increase synaptic concentrations of monoamine neurotransmitters, thereby indirectly enhancing noradrenergic, dopaminergic neurotransmission in the central nervous system (Heal et al., 2013). Amphetamine increases the availability of biogenic amines (primarily dopamine and norepinephrine) in central nerve synapses through multiple actions, including stimulating neurotransmitter release into the nerve terminal and inhibiting reuptake from the synapse. These actions may be the basis of its therapeutic actions in attention-deficit/hyperactivity disorder (ADHD); however, the mode of therapeutic action in ADHD is not known.

1.1 Indication and Current Treatment Options

The exact etiology of ADHD is unknown. Extensive research has suggested that neurotransmitter deficits (Arnsten, 2001), genetics (Arnsten, 2001; Brown, 2003), environment (Kahn et al., 2003), and perinatal complications (Bhutta and Anand, 2002) may all be contributing factors. The hypothesized mechanism of action of effective medications in ADHD is to raise neurotransmitter levels (specifically norepinephrine and/or dopamine, or their precursors) at the synapse either by facilitating neurotransmitter release from the synapse or by decreasing neurotransmitter reuptake by binding or activating the postsynaptic receptor (Kratochvil et al., 2003; Wang et al., 2007).

According to the Diagnostic and Statistical Manual of Mental Disorders, ADHD has 3 subtypes: hyperactive/impulsive, inattentive, and combined, and individuals with ADHD may manifest considerably different symptomology depending on sex, disorder subtype, and the presence of comorbid disorders.

Compared with nonstimulants, stimulant medications (ie, amphetamine or methylphenidate) produce the most robust improvements in symptom expression across all age ranges (Spencer et al., 1996).

Furthermore, stimulant medications have a rapid onset of action, within 1 hour to 2 hours of dosing, compared with nonstimulants (eg, atomoxetine), which can require dosing for up to 4 weeks to 6 weeks to achieve maximal therapeutic benefit (Wilens et al., 2002).

Nonpharmacologic measures (psychological, educational, and social) can also be beneficial, and psychosocial treatments for adults with ADHD have been studied (Safren et al., 2004; Greenfield and Hechman, 2005). Comorbid psychiatric and learning disorders are common in adults with ADHD, and appropriate evaluation, diagnosis, and treatment are recommended (Weiss and Murray, 2003).

Importantly, symptoms may not only manifest throughout the day. Many patients continue to have residual symptoms lasting into the evening hours (Greenfield and Hechman, 2005). Adult patients may benefit from symptom relief into the evening hours for such activities as planning and organizing, or professional activities (eg, professional work at night), spousal/parental responsibilities, and driving. Similarly, impairments in nighttime activities are recognized in the pediatric population, which may need coverage all day and into the evening as well (eg, to do homework and to participate in family/social activities).

The impairments in psychosocial academic and occupational functioning associated with ADHD may arise from underlying chronic deficiencies in executive function (Brown, 1996). In general, the term executive function is used to describe a set of cognitive abilities that control and regulate judgments and behaviors which are necessary for goal-directed behavior; however, the specific definition of executive functioning varies and is debated. Understanding and treating executive functioning deficits is increasingly considered an unmet medical need in ADHD.

1.2 Product Background and Clinical Information

SHP465 and its prototypes have been evaluated in 1641 subjects in 16 clinical studies, of which 13 clinical studies were in adult subjects aged 18 years to 55 years and 3 clinical studies were in pediatric subjects aged 6 years to 17 years. The SHP465 clinical development program has shown that doses of 12.5 mg to 50 mg in adult subjects and 12.5 mg to 25 mg in pediatric subjects demonstrate a safety and efficacy comparable to the profile reflected in class labeling for stimulant products approved in the United States (US).

The pharmacokinetic (PK) profile of SHP465 is not affected if the capsule is consumed intact or if capsule contents are sprinkled onto a small amount of food (ie, 1 tablespoon of applesauce) and then ingested. The PK properties of SHP465 are not affected by sex or race. The PK properties between *d*-amphetamine and *l*-amphetamine are similar.

Acceptable safety and tolerability profiles observed were consistent with the types of side effects specified in stimulant class labeling in the US. Specifically, administration of SHP465 was associated with increases in blood pressure (mean increase approximately 2-4 mmHg) and heart rate (mean increase approximately 3-6 bpm), and treatment-emergent adverse events (TEAEs) of insomnia, decreased appetite, decreased weight, heart rate increased, and anxiety, as well as psychiatric events (eg, mania, suicidality).

Always refer to the latest version of the SHP465 investigator's brochure (IB) for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics (PK), efficacy, and safety of SHP465.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

The proposed clinical study is being conducted to provide information on SHP465 PK, safety, and tolerability after 4 weeks of SHP465 administration at a daily dose of 6.25 mg in preschool children aged 4 to 5 years with ADHD.

2.2 Study Objectives

2.2.1 Primary Objective

To evaluate the PK, safety, and tolerability of SHP465 in children aged 4 to 5 years with ADHD after SHP465 multiple daily doses of 6.25 mg.

3 STUDY DESIGN

3.1 Study Design

The study will be a Phase 1, open-label, multiple-dose, PK, safety, and tolerability study in children aged 4 to 5 years diagnosed with ADHD. Enrollment will be stratified by gender to ensure that at least 2 of the 10 subjects expected to complete the rich PK sampling portion of the study and at least 3 of the 10 subjects expected to complete the sparse PK sampling portion of the study are females. Subjects for the rich PK sampling portion of the study will be enrolled first. Once the required number of subject is achieved, enrollment in the sparse PK sampling group will begin.

Subjects will be assessed for eligibility during the screening period. The duration of the screening period will be a maximum of 32 days. If subjects are currently taking ADHD medication, they are required to discontinue their current ADHD medication at least 7 days prior to the first dose of investigational product on Day 1 of Week 1 (washout period).

Following the screening visit, eligible subjects will return to the clinical research center (CRC) on Day 1 of Week 1 to reconfirm eligibility criteria and enter into the treatment phase.

If more than 32 days have elapsed since the screening evaluations were completed, then the following evaluations must be repeated at baseline (prior to the first dose of investigational product on Day 1 of Week 1): vital signs, clinical laboratory evaluations, blood pressure, electrocardiograms (ECGs), weight, and height. The physical examination will be abbreviated with a review of the following body systems: general appearance, respiratory, and cardiovascular.

The PK of *d*-amphetamine and *l*-amphetamine will be evaluated in this study, according to the schedule in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset).

Rich PK Sample Scheme (9 Samples/Subject) Collection

Predose PK samples will be collected on Day 1 of Week 1, and serial blood samples for PK analysis will be drawn prior to dosing on Day 7 of Week 4 (within 60 minutes prior to dosing) and up to 48 hours after administration of the investigational product.

On Day 7 of Week 4, subset of subjects in the rich PK sampling portion will be required to remain at the CRC through 8 hours postdose. Following completion of the 8-hour PK sample collection, per investigator's discretion, subjects will have the option to remain at or leave the CRC. If they leave the CRC, subjects will either return to the CRC on Days 7, 8, and 9 of Week 4 for the 12-hour, 16-hour, 24-hour, and 48-hour postdose blood sample collections or, if the option is available at their clinical site, a qualified person may visit the subject for the 12-hour, 16-hour, and 24-hour postdose blood sample collections, but they must return to the clinic for the 48-hour blood sample collection.

Sparse PK Sample Scheme (4 Samples/Subject) Collection

Predose PK samples will be collected on Day 1 of Weeks 1 to 3 and on Day 8 of Week 4 (24 hours after dosing on Day 7 of Week 4) for subjects in the sparse PK sampling subset.

3.2 Duration and Study Completion Definition

Each subject's maximum duration of participation is expected to be approximately 9 weeks. The study will be completed in approximately 12 months.

- Screening period:
  - A maximum of 32 days before the first dose of investigational product
  - If applicable, this includes a washout period that is to start 7 days before the first dose of investigational product.
- Treatment Period: Total duration for the treatment period is approximately 30 days for subjects in the rich PK sampling portion of the study and 29 days for subjects in the sparse PK sampling portion of the study.
- Follow-up contact: At the last clinic visit, subjects and their parent/legally authorized representative (LAR) will be offered to rollover into the SHP465-308 study. If subjects agree and their parent/LAR signs the informed consent form, this will end their participation in the SHP465-112 study. If they do not want to participate in the SHP465-308 study, follow-up contact will be conducted approximately 1 week (7 days [±2 days]) following the last dose of investigational product.

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

The study will be conducted in approximately 10 sites in the US.

4 STUDY POPULATION

Each subject and parent/LAR must participate in the informed consent/assent process, and the parent/LAR must 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 following criteria (including test results):

1. Subject is a male or female aged 4 years to 5 years inclusive at the time of consent.
2. Subject and parent/LAR are willing and able to fully comply with all of the testing and requirements defined in the protocol. Specifically, the parent/LAR must be available at approximately 8:00 AM (±1 hour) to administer the dose of investigational product at the time points specified in the protocol.
3. Subject's parent/LAR must sign the informed consent form, and there must be documentation of assent (if applicable) by the subject in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (CGP) Guideline E6 (2016) and any updates, and applicable regulations, before starting any study-related procedures.
4. Subject satisfies the following ADHD criteria during the screening period:
   - Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for a primary diagnosis of ADHD (any subtype) based on a detailed psychiatric evaluation using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)
   - Has an ADHD Rating Scale-5 (ADHD-RS-5) Child, Home Version Total Score of ≥28 for boys and ≥24 for girls
   - Has a Clinical Global Impressions-Severity of Illness (CGI-S) score ≥4.
5. Subject functions at an age-appropriate level intellectually, as determined by the investigator.
6. Subject has undergone an adequate course of nonpharmacological treatment **OR** the subject has a severe enough condition to consider enrollment without undergoing prior nonpharmacological treatment, based on the investigator's judgment **OR** has never taken ADHD medication **OR** has taken ADHD medication with unacceptable efficacy and/or tolerability.
7. Subject has the ability to take investigational product by either swallowing the capsule whole or sprinkling the capsule contents in applesauce and ingesting the entire mixture immediately without chewing.
8. Subject has lived with the same parent/LAR for at least 6 months.

4.2 Exclusion Criteria

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

1. Prior enrollment or participation in the study.
2. Subject has a documented allergy, hypersensitivity, or intolerance to amphetamine or to any excipients in the investigational product.
3. Subject cannot swallow a pill and/or applesauce, or has an allergy to applesauce.
4. Subject is currently taking or has taken ADHD medication with acceptable efficacy and tolerability.
5. Subject has taken ADHD medication within 7 days prior to the administration of investigational product.
6. Subject has used any medication (including over-the-counter, herbal, or homeopathic preparations) within 30 days prior to the administration of investigational product or 5 half-lives, whichever is longer, with the exception of the following:
   - Thyroid medication
   - Intermittent use of nonsteroidal anti-inflammatory drugs or acetaminophen for minor aches and pains
   - As needed use of a beta-agonists inhaler for mild asthma or exercise induced bronchospasm
   - Over-the-counter nonsedating antihistamines such as fexofenadine (ALLEGRA®, Sanofi), loratadine (CLARITIN®, Schering-Plough), or cetirizine hydrochloride (ZYRTEC®, McNeil-PPC) for allergies.
   - Subject has continuously used oral corticosteroids ≥7 days in 3 months prior to investigational product dosing. If continuous use was <7 days, 1 month of washout prior to dosing of investigational product is required.
7. Within 30 days prior to the administration of investigational product:
   - Subject has used an investigational product.
     - If the elimination half-life of the previous study's investigational product was less than 6 days, then the last dose of the previous investigational product should be 30 days prior to the first dose of SHP465.
     - If the elimination half-life of the previous study's investigational product was greater than 6 days, then the last dose of the previous investigational product should be 5 half-lives prior to the dose of SHP465.
8. Subject has glaucoma.
9. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.

10. Subject has a known history of symptomatic cardiovascular disease, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac conditions placing them at increased vulnerability to the sympathomimetic effects of a stimulant drug.
11. Subject has any clinically significant ECG or clinically significant laboratory abnormalities at the first screening visit based on the investigator's judgment. A single retest of laboratory parameters is allowed based on the investigator's judgment.
12. Subject has Marfan's syndrome.
13. Subject has a blood pressure ≥95th percentile for age, sex, and height at the screening visit (Appendix 2.3 and Appendix 2.5).
14. Subject has a height ≤5th percentile for age and sex at the first screening visit (Appendix 2.2 and Appendix 2.4).
15. Subject has a weight ≤5th percentile for age and sex at the first screening visit.
16. Subject has current abnormal thyroid function test results, defined as abnormal thyroid-stimulating hormone, thyroxine (T4), and tri-iodothyronine (T3) at the first screening visit. Treatment with a stable dose of thyroid medication for at least 3 months is permitted.
17. Subject has a history of seizures (other than infantile febrile seizures).
18. Subject has a current, controlled (requiring medication or therapy) or uncontrolled, comorbid psychiatric disorder including but not limited to any of the following comorbid Axis I disorders and Axis II disorders:
    - Post-traumatic stress disorder or adjustment disorder
    - Bipolar illness, psychosis/schizophrenia, or positive family history of these disorders in first- or second-degree relatives
    - Pervasive developmental disorder
    - Obsessive-compulsive disorder
    - A serious tic disorder, or a family history of Tourette disorder
    - Substance abuse or dependence disorder
    - Any other disorder that, in the opinion of the investigator, contraindicates SHP465 or amphetamine treatment or confounds efficacy or safety assessments.
19. Subject is currently considered a suicide risk in the opinion of the investigator, has previously made a suicide attempt, or has a prior history of or is currently demonstrating active suicidal ideation.
20. Subject has a history of physical, sexual, or emotional abuse.
21. Subject has a primary sleep disorder (eg, sleep apnea, narcolepsy).
22. Subject has a history or is currently diagnosed with an eating disorder.

23. Subject has a clinically important abnormality on the urine drug and alcohol screen (excluding the subject's current ADHD stimulant, if applicable) at the first screening visit.
24. Subject lives with anyone who currently abuses stimulants or cocaine, based on the investigator's judgment.
25. 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.
26. Subject has any additional condition(s) such as any significant illness or unstable medical condition that, in the investigator's opinion, would prohibit the subject from completing the study and /or could lead to difficulty complying with the protocol.

4.3 Reproductive Potential

Contraception is not applicable as no female subjects in this study are of childbearing potential. All female subjects in this study are premenarchal, less than age 9 years, and Tanner Stage 1.

4.4 Discontinuation of Subjects

A subject may withdraw from the study, or the parent/LAR may withdraw the subject 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 (eg, 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 early withdrawal evaluations listed in Table 1 and Table 2 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 also be recorded in the source document.

Subjects who discontinue may be replaced at the discretion of the investigator and sponsor to ensure at least 10 completers in each of the PK sampling portions of the study (of which at least 2 subjects in the rich PK sample subset and at least 3 subjects in the rich PK sample subset should be female).

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 SHP465 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 of Health Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (NIH, 2004).

Increases in blood pressure (both systolic and diastolic) from the 50th to the 95th percentile (representative of a change of 2 standard deviations) range from 17 mmHg to 20 mmHg for both boys and girls in this age range. Based on this range, an increase of >15 mmHg from the baseline visit (predose on Day 1) was selected for this protocol.

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

- Elevations in average (of 3 readings) sitting systolic blood pressure defined as an increase of >15 mmHg from the baseline visit (predose on Day 1) 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 the baseline visit (predose on Day 1) 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 who meets any criterion with the medical monitor, and a joint decision between the investigator and the medical monitor will be made regarding continued participation in 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 business 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 value <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 Report's "Resting Pulse Rate Reference Data for Children, Adolescents, and Adults: United States, 1999-2008" (Ostchega et al., 2011).

An elevation in the average (of 3 readings) sitting pulse, defined as >126 bpm, equivalent to the 99th percentile for this age range, requires 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 will be made regarding continued participation in 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 business day, the subject may be discontinued from the study.

At the unscheduled visit, the investigator will notify the medical monitor of the results, 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 based 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 case report form (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 (AE)
- Protocol violation
- Withdrawal by subject or parent/LAR
- Lost to follow-up
- Blood pressure and/or pulse criteria for discontinuation 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 any subject or parent/LAR in the event that any subject is lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5 PRIOR AND CONCOMITANT TREATMENT

All nonstudy treatment (including but not limited to herbal treatments, vitamins, and nonpharmacological treatment such as behavioral treatment) received within 30 days prior to the screening visit (Day -1) (or PK equivalent of 5 half-lives, whichever is longer) and through the final study contact (including the protocol-defined follow-up period) must be recorded in the source document.

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins, nonpharmacological treatment, such as behavioral treatment) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the date of the administration of investigational product. Prior treatment information must be recorded in the source document.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the administration of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded in the source document.

5.2.1 Permitted Treatment

Subjects should refrain from taking any medications (excluding those medications that are permitted) during the course of the study. Any medication which is considered necessary for the subject's safety and well-being may be given at the discretion of the investigator. The administration of all medications (including investigational products) must be listed in the source documents.

Medications permitted during the study are listed as follows:

- Stable (ie, for at least 3 months prior to the screening visit) dose of thyroid medication
- Stable (ie, for at least 1 month prior to the screening visit) dose of bronchodilator inhalers (however, oral beta-agonists and oral corticosteroids are prohibited)
- Any medications that do not affect blood pressure, heart rate, or the central nervous system, and which are considered necessary for the subject's welfare, may be administered at the discretion of the investigator
- Nonsedating antihistamines such as fexofenadine (eg, ALLEGRA, Sanofi), loratadine (eg, CLARITIN, Schering-Plough), and cetirizine hydrochloride (eg, ZYRTEC, McNeil PPC)
- Over-the-counter nonstimulant cold remedies
- A topical numbing agent may be used to assist in the drawing of blood.

5.2.2 Prohibited Treatment

Table 3 details the washout period for common prior treatments that are excluded medications for this study.

Table 3: Common Excluded Treatments and Associated Washout Period Relative to Baseline Visit

Treatment	Minimum Number of Days Before Baseline Visit		
	7	14	30
Psychostimulants, amphetamines, and amphetamine-like agents	X		
Antihypertensives[a]	X		
Methylxanthines (theophylline and aminophylline)	X		
Antihistamines (centrally and peripherally active)		X	
Herbal preparations (including melatonin)		X	
Sedatives, anxiolytics, antipsychotics[a]			X
Monoamine oxidase inhibitors (MAOIs)[a]			X
Antidepressants[a]			X
Clonidine and guanfacine			X
Selective noradrenaline reuptake inhibitors and noradrenaline reuptake inhibitors[a]			X
Cytochrome P450 2D6 inhibitors (eg, paroxetine, fluoxetine, quinidine, ritonavir)			X
Alkalinizing agents (eg, sodium bicarbonate, acetazolamide, some thiazides)			X
Acidifying agents (eg, guanethidine, reserpine, glutamic acid hydrochloride, ascorbic acid, ammonium chloride, sodium acid phosphate, methenamine salts)			X

[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. Baseline visit is considered as predose on Day 1.

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is SHP465, which will be provided in 6.25 mg capsule form. The product was previously referred to as SPD465 and is registered with the Drug Enforcement Agency as SPD465; however, it is now being studied under the code of SHP465. The drug will be labeled with SHP465 (SPD465). Additional information is provided in the current SHP465 IB.

6.1.1 Blinding the Treatment Assignment

Not applicable.

6.2 Administration of Investigational Product

6.2.1 Allocation of Subjects to Treatment

This is an open-label, single-sequence, 1-period, multiple-dose, PK, safety, and tolerability study.

Subject numbers are assigned to all subjects as they consent/assent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. This will be a 4-digit number starting at 0001.

A 4-digit subject number, starting at 1001, will be allocated immediately prior to dosing after eligibility has been determined. If a subject number is allocated incorrectly, the study monitor must be notified as soon as the error is discovered. Once a subject number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. For enrolled subjects, the subject number will be the identifying number used throughout the CRF.

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

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

6.2.2 Dosing

There will be one SHP465 dose level of 6.25 mg used in this study.

On Day 1 of each week (Weeks 1-4), all subjects will report to the CRC approximately 2 hours prior to the time of dosing for predose evaluations. The dose will be administered daily as a single dose for 28 days (±1 day) at 8:00 AM (±1 hour). Doses on Day 1 of each week (Weeks 1-4) will be administered in the CRC. The parent/LAR will be dispensed a bottle containing the remaining doses for that week. The same parent/LAR should be available daily to dispense the dose of investigational product for the study duration.

For all subjects, investigational product will be taken by either swallowing the capsule whole or sprinkling the capsule contents onto 1 tablespoon of applesauce. The sprinkled applesauce should be consumed immediately; it should not be stored. Subjects should take the applesauce with sprinkled beads in its entirety without chewing. A single capsule cannot be split. The empty gelatinous capsule should be discarded.

On Day 7 of Week 4, subjects in the rich PK sampling subset will report to the CRC for dosing approximately 2 hours prior to dose administration. Subjects should fast for 2 hours prior to dose administration and for 2 hours postdose, and the site should record the timing and composition of the last meal consumed by the subject. Subjects in the rich PK sampling portion will be required to remain at the CRC through 8 hours postdose. At 2 hours postdose, subjects will be allowed to consume a light breakfast, eg, a single serving of cereal with up to 8 ounces of skim milk. Subjects should be well hydrated while at the CRC for PK draws. Water or other clear liquids should be given ad libitum. Caffeinated beverages should not be consumed for 2 hours prior to dosing and until 12 hours after the postdose PK sample is obtained.

6.2.3 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 following:

- 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,” and “Keep out of reach of children,”
- sponsor's name and address

Any additional labeling requirements for participating countries and/or controlled substances will also be included on the label.

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

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

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

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

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

SHP465 capsules are packaged in 9-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 (ie, certified minimum/maximum thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

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

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

6.4 Drug Accountability

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

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

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer 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 administered medication will be documented in the source documents and/or other investigational product record.

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 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 contract research organization [CRO]). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken, and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (ie, interactive response technology) 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

Compliance must be assessed by observation of dosing by the investigator or designee when the subject is being dosed in the CRC. In addition, the CRC personnel should perform a hand-and-mouth check of the subject to assure the investigational product has been ingested. The investigator/nominated person will record details on the drug accountability form(s) and/or source documents. In addition, details of the dosing time (time, date, dose level) will be captured.

The parent/LAR will also be provided with a diary with customized questions to record the times when the investigational product was given to the child.

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

Subjects who have taken 80% to 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:

For whole capsules:

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

For capsule contents sprinkled in applesauce:

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

To ensure that the maximum amount of capsule contents has been taken when sprinkled onto applesauce, the total amount of applesauce used is limited to 1 tablespoon.

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 for the rich PK sample subset and Table 2 for the sparse PK sample subset) details all procedures to be completed at each visit and should serve as the primary section of the protocol regarding visit-specific study procedures.

The following “priority order” will be in effect at the screening visit:

- Medical and medication history and physical examination
- Vital signs and ECG
- PK blood sampling
- Clinical laboratory tests

- Clinician-completed rating scales and assessments conducted by the site, ie, ADHD-RS-5, Child, Home Version; CGI-S; MINI-KID; Post Sleep Questionnaire (PSQ); and the Columbia-Suicide Severity Rating Scale (C-SSRS) must be completed by the same rater whenever possible.

At all other visits, which require more than one procedure or assessment, the following priority order will be in effect:

- Spontaneous or solicited AE reporting
- Vital signs and ECG
- PK blood sampling
- Clinical laboratory tests
- Physical examination

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

NOTE: Blood sampling for PK evaluation must be performed at the precise protocol-scheduled time. Actual sampling time(s) must be accurately recorded in the source document.

7.1.1 Screening and Washout Period

Subjects will be screened within 32 days prior to initiation of dosing of the investigational product. During the screening period, the eligibility of subjects will be assessed. All screening assessments and procedures are to be performed by the principal investigator or a qualified designee. A complete list of screening procedures to be performed is provided in Table 1 for the rich PK sample subset and Table 2 for the sparse PK sample subset.

The principal investigator or his/her designee must obtain written informed consent and assent from the subject's parent/LAR prior to any study-related procedures conducted during the screening period. There must also be documentation of assent (if required by the institutional review board [IRB]), indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions, prior to the performance of any study-related procedures.

If subjects are currently taking ADHD medication, they are to discontinue their current ADHD medication at least 7 days prior to the first dose of investigational product (please refer to Section 4.2 for additional information).

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

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

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

7.1.2 Treatment Period

The study will consist of 1 treatment period:

- The subject will receive a single 6.25-mg dose of SHP465 once daily for 28 days (±1 day) at 8:00 AM (±1 hour)

The assessments and procedures performed during the study are outlined in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset).

Rich PK Sample Collection Subset

Predose PK samples will be collected on Day 1 of Week 1, and serial blood samples for PK analysis will be drawn prior to dosing on Day 7 of Week 4 (within 60 minutes prior to dosing) and up to 48 hours after administration of the investigational product.

On Day 7 of Week 4, subset of subjects in the rich PK sampling portion will be required to remain at the CRC through 8 hours postdose. Following completion of the 8-hour PK sample collection, per investigator's discretion, subjects will have the option to remain at or leave the CRC. If they leave the CRC, subjects will either return to the CRC on Days 7, 8, and 9 of Week 4 for the 12-hour, 16-hour, 24-hour, and 48-hour postdose blood sample collections or, if the option is available at their clinical site, a qualified person may visit the subject for the 12-hour, 16-hour, and 24-hour postdose blood sample collections, but they must return to the clinic for the 48-hour blood sample collection.

Sparse PK Sample Collection Subset

Predose PK samples will be collected on Day 1 of Weeks 1 to 3 and on Day 8 of Week 4 for subjects in the sparse PK sampling subset.

The end-of-study assessments will be performed at the last clinic visit: on Day 9 of Week 4 (approximately 48 hours after the last dose of investigational product) for subjects in the rich PK sampling portion and on Day 8 of Week 4 (approximately 24 hours after the last dose of investigational product) for subjects in the sparse PK sampling portion of the study.

7.1.3 Follow-up Period

At the last clinic visit, subjects and their parent/LAR will be offered to rollover into the SHP465-308 study. If subjects agree and their parent/LAR signs the informed consent form, this will end their participation in the SHP465-112 study. If they do not want to participate in the SHP465-308 study, follow-up contact will be conducted.

For those subjects with ongoing AEs, a mandatory in-person follow-up visit at the CRC will occur 7 days (±2 days) following the subject's last dose of investigational product to collect information on any ongoing or new AEs, serious AEs (SAEs), or concomitant medications, as appropriate.

At the investigator's discretion, for those subjects with no ongoing AEs at the time of the last scheduled assessment, a telephone call initiated by the CRC staff or in-person follow-up visit at the CRC will occur 7 days (±2 days) following the subject's dose of investigational product to collect information on any new AEs, SAEs, or concomitant medications, as appropriate. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (Section 8.1).

7.1.4 Additional Care of Subjects after the Study

Subjects who have completed the study at Day 9 of Week 4 (rich PK sample subset) or at Day 8 of Week 4 (sparse PK sample subset) may be evaluated for eligibility to enter a long-term safety study of SHP465.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics such as age, gender, weight, and height will be collected according to Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset).

Clinician-completed rating scales and assessments conducted by the site, ie, ADHD-RS-5 Child, Home Version; MINI-KID; CGI-S; and C-SSRS must be completed by the same rater whenever possible. The parent/LAR-completed Children's Sleep Habits Questionnaire (CSHQ) and the PSQ must be completed by the same individual whenever possible.

7.2.1.1 Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)

The MINI-KID is a structured clinical diagnostic interview designed to assess the presence of psychiatric disorders in children and adolescents in a way that is comprehensive and concise. It follows the structure and format of the adult version of the interview and is organized in diagnostic sections or modules. Using branching tree logic, the instrument asks 2 to 4 screening questions for each disorder. The standard MINI-KID Version 7.0.2 for DSM-5 assesses the 30 most common and clinically relevant disorders or disorder subtypes in pediatric mental health. With this version, the child and parent are interviewed together. Additional symptom questions within each disorder section are asked only if the screen questions are positively endorsed. The MINI-KID is the structured psychiatric interview of choice for psychiatric evaluation and outcome tracking in clinical psychopharmacology trials and epidemiological studies. In a validation study (Sheehan et al., 2010), the MINI-KID generated reliable and valid psychiatric diagnoses for children and adolescents and does so in one-third of the time as the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version.

The MINI-KID should be completed by an individual who has experience in the evaluation of pediatric patients with ADHD and the scale, and may include physicians, or licensed psychologists/clinicians. All individuals performing this assessment must be preapproved by the sponsor or designee.

7.2.1.2 Clinical Global Impressions

The Clinical Global Impressions Scale which measures severity of illness (CGI-S) will be performed at the time points described in Table 1. The CGI-S (Guy, 1976) permits a global evaluation of the subject's severity and improvement over time. The CGI-S has been used extensively in clinical studies of ADHD (Michelson et al., 2001; Weiss et al., 2005; Wilens et al., 2001).

The investigator will perform the CGI-S to rate the severity of a subject's condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects) at the baseline visit.

The CGI-S will be completed by a clinician trained and experienced in the evaluation of preschool children with ADHD.

The title, version, and date of the CGI-S used in this study are included in Appendix 3.

7.2.1.3 The ADHD-Rating Scale-5

The ADHD-RS-5 Child, Home Version (DuPaul et al., 2016) is completed by the clinician and will be administered at baseline.

The ADHD-Rating Scale was developed to measure the behaviors of children with ADHD and is commonly used in clinical studies of ADHD (Buitelaar et al., 2007; Döpfner et al., 2006; Kratochvil et al., 2001; Michelson et al., 2001; Spencer et al., 2001). The ADHD-RS-5 consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-5 criteria. Each item is scored on a 4-point scale ranging from 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0 to 54. The 18 items may be grouped into 2 subscales: hyperactivity/impulsivity (9 items) and inattentiveness (9 items).

The ADHD-RS-5 should be completed by a clinician experienced in the evaluation of children with ADHD. Since the ADHD-RS-5 is an important measure for guidance in dosing decisions, the ADHD-RS-5 must be performed by an individual who is experienced with the scale. All individuals performing this assessment must be pre-approved by the sponsor or designee.

The title, version, and date of the ADHD-RS-5 used in this study are included in Appendix 3.

7.2.2 Safety

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

Actual safety assessment times will be monitored and recorded. The sponsor's expectation is that the investigator will ensure that every effort is made to perform all assessments at the precise protocol-scheduled time. Any safety assessment that deviates from the scheduled assessment time set forth in the protocol by more than ±30 minutes will be considered a protocol deviation.

7.2.2.1 Medical and Medication History

A complete medical and medication history, as well as demographic information, will be performed at the screening visit/time points described in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset) by a qualified licensed physician, physician's assistant, or a nurse practitioner. The medical history will be reviewed and recorded, including:

- Date of birth
- Sex
- Race and ethnicity
- Recent ingestion of medication (30 days prior to entering the screening period)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases

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

7.2.2.2 Physical Examination (Including Height and Weight)

A complete physical examination will be performed at the time points described in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset) by a qualified licensed physician, physician's assistant, or nurse practitioner.

The physical examination will include a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose, and throat
- Spine/neck/thyroid
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen (including liver and kidneys)

Abnormalities identified at the screening visit will be documented in the source documents. Changes after the screening visit will be captured as AEs as deemed appropriate by the investigator.

Height and weight will be measured at the time points described in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset).

A calibrated stadiometer must be used for all height measurements. Height should be measured in centimeters or inches without shoes with the subject standing on a flat surface and with the chin parallel to the floor. The body should be straight but not rigid. The subject's height should be recorded as accurately as possible and should be recorded to the nearest centimeter or nearest inch.

The same calibrated scale must be used for all weight measurements. Weight should be measured in kilograms or pounds without shoes and with light clothing and recorded as accurately as possible and should be recorded to the nearest 0.1 kg or nearest 0.1 lb. Weight and height measuring apparatus should be calibrated/tested prior to study initiation.

7.2.2.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain whether AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). This information should be collected before the completion of assessments at all study visits. In addition, any symptoms and signs/conditions reported during assessments and deemed to be clinically significant by the investigator will be assessed as AEs. Adverse events are collected from the time informed consent is signed. (Please refer to Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.2.4 Vital Signs

Vital signs, including systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature, will be measured at the times specified in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset). Subjects should be resting in a sitting position for at least 5 minutes prior to collecting vital signs, legs should be uncrossed, and the back and arm should be supported. Measurements of sitting systolic and diastolic blood pressure and pulse will be performed 3 times at each time point, with approximately 2 minutes between each measurement; both individual measurements and the averaged reading should be recorded in the source document.

Blood pressure will be determined by the provided age-appropriate cuff (the same equipment and the same arm should be used throughout the study). A blood pressure cuff appropriate for the subject's arm length and girth should be used for all blood pressure measurements. The cuff should be approximately two-thirds the length/width of the subject's arm (from elbow to shoulder). All blood pressure measurements should be performed by the same study center personnel (if possible) throughout the study.

Pulse rate should be counted for 1 minute.

Any deviations from baseline in vital signs which are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

Respiratory Rate

The subject should be in a comfortable position. The observer should hold the extremity of the subject as a distraction for the subject (ie, pretending he/she is taking the subject's radial pulse) and count the respiration for 1 minute.

Body Temperature

An electronic/chemical dot thermometer in the axilla or an infrared tympanic thermometer should be used for measuring the temperature. The thermometer should be left in position for sufficient time to gain an accurate reading, according to the manufacturer's instructions. The same method of obtaining temperature should be used throughout the study in a given subject.

7.2.2.5 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 is/are clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Clinical laboratory assessments will be performed at the time points indicated in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset) and include the following:

Biochemistry

Blood samples (2 mL) for serum biochemistry will be collected into a serum separator tube at the time points described in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset). The following parameters will be assessed:

Sodium
Potassium
Glucose
Blood urea nitrogen
Creatinine
Calcium
Chloride
Thyroid-stimulating hormone
Thyroxine (T4 total)
Tri-iodothyronine (T3)
Phosphorus
Total protein
Total CO_2 (bicarbonate)
Albumin
Aspartate transaminase
Alanine transaminase
Gamma glutamyl transferase
Alkaline phosphatase
Total bilirubin
Uric acid

Hematology

Blood samples (1 mL) for hematology will be collected into a K_2EDTA plastic tube at the time points described in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset). The following parameters will be assessed:

Hemoglobin	Total neutrophils (absolute and relative)
Hematocrit	Eosinophils (absolute and relative)
Red blood cells	Monocytes (absolute and relative)
Platelet count	Basophils (absolute and relative)
White blood cell count; total and differential percentage	Lymphocytes (absolute and relative)

Urinalysis

A urine sample for urinalysis will be collected at the time points described in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset). The following parameters will be assessed:

pH	Blood	Nitrites
Glucose	Ketones	Leukocyte esterase
Protein	Bilirubin	Specific gravity

Microscopic examination will be conducted if protein and/or blood is/are detected during urinalysis. At a minimum the microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

7.2.2.6 Drug and Alcohol Screen

A urine screen for drugs of abuse and alcohol will be performed at the time point shown in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset). Additional drug and alcohol screens may be performed at the investigator's discretion.

Urine samples are to be tested for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiate metabolite, and phencyclidine.

Results of urine drug and alcohol screens will be reviewed and verified by the study monitor, but will not be collected in the CRF database.

Any positive result for drugs of abuse or alcohol at the first screening visit (with the exception of the subject's current stimulant therapy) will exclude the subject from further participation in the study.

7.2.2.7 Electrocardiogram

Twelve-lead ECGs will be performed at the times specified in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset). All ECGs will be performed after 5 minutes of rest using equipment approved by the central ECG laboratory and will be sent to the central ECG provider according to the instructions in the ECG manual provided by the ECG laboratory.

Additionally, ECGs will be performed in triplicate (with a 2 to 5 minute gap between traces) at screening. The subject should be asked to remove all clothing that covers the locations of lead placement. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in approximately the same positions each time in order to achieve precise ECG recordings. A single recording, including a 10 second rhythm strip, will be obtained for all assessments after the baseline. The time and date of each ECG obtained will be recorded on the CRF. A trace ECG recording will be printed and placed in the site's study file for every ECG taken.

The initial interpretation of the ECG, normal or abnormal and clinical significance, will be performed by the Investigator immediately after collection to ensure the safety of each subject. An ECG tracing will then be evaluated by a pediatric 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, confirms 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 source document 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.

7.2.2.8 Columbia-Suicide Severity Rating Scale

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

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

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

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

- The "baseline" version will be administered at the screening visit.
- The "since last visit" version will be completed at all study visits after the screening visit.

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 Appendix 3.

7.2.2.9 Children's Sleep Habits Questionnaire

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 waking's, parasomnias, sleep disordered breathing, and daytime sleepiness. The CSHQ will be conducted at each visit to the site starting with the baseline visit (predose on Day 1 of Week 1) and will be completed by the subject's parent/LAR.

7.2.2.10 Post Sleep Questionnaire

The PSQ is a 7-item questionnaire typically used to assess sleep quality with pharmacologic treatment. The questionnaire collects data on average time to sleep, sleep latency, frequency of interrupted sleep, duration of interrupted sleep, total sleep time, and sleep quality over the last week. The PSQ will be completed by the parent/LAR with the subject and the responses will be reviewed by the clinician during the study visit. The PSQ will be completed and will be conducted at each visit to the site starting with the baseline visit (predose on Day 1 of Week 1). The title, version, and date of the PSQ version used in this study are included in Appendix 3.

7.2.2.11 Suitability of the Subject to Remain in the Study

At each visit (except for early termination) starting with the baseline visit, the investigator will assess the subject's ability to continue in the study. The investigator or a medically qualified designee will review all available safety information (including sleep behavior, weight, and body mass index) and will evaluate for the presence of insomnia or decreased appetite potentially leading to weight loss. In cases where the subject has clinically significant decrease in appetite or insomnia, the investigator should intervene as necessary based on clinical judgment (eg, diet, behavioral interventions, sleep hygiene) and consider discontinuation of treatment if necessary. In any cases where a subject has clinically significant and persistent sleep difficulties (eg, the CSHQ score of ≥41 for 2 consecutive weeks since the beginning of treatment) or has had ≥7% weight loss, the investigator must discuss the case with the medical monitor and assess whether it's in the best interest for the subject to remain in the study. The evaluation and decision should also be clearly documented in the subject's source notes.

As part of the assessment of the subject's suitability to remain in the study the investigator should also assess the subject's current potential for suicide, suicidal ideation, self-harm, or harm to others, as well as psychiatric disorders. The investigator should make this assessment by conducting a clinical interview with the subject and by reviewing of all other relevant sources available, including results of the C-SSRS.

Any subject who has 1 or more positive responses must undergo further evaluation to ensure that they are not in any way at risk. As part of this assessment, if appropriate, the investigator should discuss risk factors for suicide with the subject. Where a subject has suffered an accidental injury, the investigator should ensure that this was a true accidental injury, rather than an episode of self-harming or a suicide attempt.

The investigator should pay particular attention to:

- Any 'yes' response to Items 2, 3, 4, or 5 on the C-SSRS or any suicidal behavior

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

7.2.3 Pharmacokinetic Procedures

The name and address of the bioanalytical laboratory for this study will be maintained in the investigator's files at each site and in the Trial Master File at the CRO.

Actual PK blood sample collection times versus time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort is made to collect all PK blood samples at the precise protocol-scheduled time. Pharmacokinetic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples drawn within 4 hours postdose or by more than ±15 minutes for samples drawn beyond 4 hours postdose. Samples drawn outside these parameters will be considered a protocol deviation. On Days 8 and 9 when subjects return to the CRC or for subjects who choose to remain in the CRC for the 24-hour and 48-hour postdose collection of PK samples, all efforts should be made to meet the ±15 minute window; however, it will not be considered a protocol deviation unless the sample is collected more than ±60 minutes postdose for those collection times.

7.2.3.1 Blood Sample Collection and Handling Procedures

Blood samples will be collected at the time specified in Table 1 (rich PK sample subset) and Table 2 (sparse PK sample subset) to measure plasma concentrations of *d*-amphetamine and *l*-amphetamine. Potential metabolites may also be determined as appropriate.

Blood samples (2 mL) for PK analysis will be drawn by straight sticks or in-dwelling catheters into appropriately labelled K_2EDTA Vacutainer® blood collection tubes (BD Vacutainer K_2EDTA 2 mL tube, catalog number BD 367841, lavender top or equivalent) until the vacuum is exhausted and blood ceases to flow. Please refer to the Laboratory Manual for additional details.

The actual time that the sample was obtained will be recorded in the source document. In instances where more than 1 blood collection tube is used, the time of the initial blood draw will be recorded for all tubes collected at that time point in the source document.

All plasma samples will be stored nominally at or below -20°C, and the freezer temperature will be controlled, monitored, and recorded during the storage period until the samples are shipped to the PPD Central Laboratory.

All plasma samples will be stored nominally at or below -20°C, and the freezer temperature will be controlled, monitored, and recorded during the storage period at PPD Central Laboratory until the samples are shipped to QPS, LLC.

7.2.3.2 Shipment of Plasma Pharmacokinetic Samples

The Laboratory Manual should be followed to transfer PK plasma samples from the site to the PPD Central Laboratory and from PPD Central Laboratory to the bioanalytical laboratory (QPS, LLC).

Shipment of Pharmacokinetic Samples from PPD to Bioanalytical CRO

All PK samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that they remain frozen for at least 72 hours to allow for delays in shipment.

All PK samples, along with the corresponding documentation, will be shipped frozen on dry ice to QPS, LLC. Primary and back-up samples should be shipped separately.

Sample Coordination Group

QPS, LLC
3 Innovation Way, Suite 240
Newark, Delaware 19711
Telephone: [redacted]
Fax: [redacted]
E-mail: [redacted]

Pharmacokinetic samples will be stored nominally at -70°C at QPS, LLC prior to and after sample analysis until their disposal is authorized by Shire.

Shipping instructions will be provided separately to the CRCs and the PPD Central Laboratory.

7.2.3.3 Plasma Drug Assay Methodology

Plasma sample analysis will be performed according to QPS, LLC's Standard Operating Procedures.

Plasma concentrations of *d*-amphetamine and *l*-amphetamine will be measured using the most current validated bioanalytical method. In addition, selected plasma samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). Raw data will be stored in the archive at QPS, LLC.

7.2.4 Volume of Blood to be Drawn from Each Subject

The volume of blood to be drawn from each subject is provided in Table 4 for the rich PK sample subset and Table 5 for the sparse PK sample subset.

Table 4: Volume of Blood to be Drawn from Each Subject (Rich Pharmacokinetic Sample Subset)

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples[a]		2 or 3	9	18 - 27
Safety	Biochemistry	2	2	4
	Hematology	1	2	2
Total (mL)				24 - 33

[a] If a catheter is used, the first mL is to be discarded; the next 2 mL are to be collected into the appropriate tube for the pharmacokinetic sample. A total of 3 mL of blood drawn has been used in determination of sample volume.

Table 5: Volume of Blood to be Drawn from Each Subject (Sparse Pharmacokinetic Sample Subset)

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples		2	4	8
Safety	Biochemistry	2	2	4
	Hematology	1	2	2
Total (mL)				14

During this study, it is expected that approximately 24 mL to 33 mL of blood will be drawn from subjects in the rich PK sample subset and 14 mL of blood will be drawn from subjects in the sparse PK sample subset, regardless of sex. It is expected that a maximum of approximately 18 mL will be drawn in any 24-hour period; the 18 mL corresponds to Day 7 of Week 4, where there will be 6 PK draws from predose to 16 hours postdose × 3 mL per draw if a catheter is used.

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 24 mL to 33 mL of blood will be drawn from subjects in the rich PK sample subset and 14 mL of blood will be drawn from subjects in the sparse PK sample subset. 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, and 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 symptom, unfavorable and unintended sign (including an abnormal laboratory finding), or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guideline E2A [1994]).

All AEs are collected from the time the informed consent form 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 and signs should be recorded. If a diagnosis has not been made, then each symptom and sign should be listed individually. All AEs should be captured in the source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured.

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 pretreatment 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 the dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded in the source document).

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 an 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 in the source documents. 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 that were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

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

8.1.6 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (defined as follows) 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 following categories 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 nonmedical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- **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 as follows:
    - 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/LAR/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

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

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Pharmacovigilance and Risk Management 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 (Section 8.1.6) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Nonserious AEs Required by the Protocol 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 Global Pharmacovigilance and Risk Management Department. A copy of the Shire Clinical Study Serious Adverse Event and Nonserious AEs Required by the Protocol 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 that are the result of elective or previously scheduled surgery for pre-existing conditions and 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 an 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 Global Pharmacovigilance and Risk Management 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 Global Pharmacovigilance and Risk Management Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, or withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

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 SHP465 program.

The investigator is responsible for notifying the local IRB, local ethics committee (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 source documents. 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 enrolled, it is expected that site personnel will complete the entries in the source documents 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 Statistical Analysis Process

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

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the PK, pharmacodynamic, 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).

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

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

9.4.1 Data Monitoring Committee

An external independent data monitoring committee (DMC) will be set up for the following studies: SHP465-112, SHP465-308, and SHP465-309. The DMC will review the data pertaining to safety, tolerability, and benefit/harm of the study therapy. Confidentiality of the unblinded DMC analyses is a critical concern and to address this, an unblinded independent reporting team will be identified within a CRO. The independent reporting team will have no involvement in the conduct of the study. Further details regarding the DMC can be found in the DMC charter.

9.5 Sample Size Calculation and Power Considerations

To objectively justify the sample size for PK sampling and PK sampling scheme for this study, the following precision is recommended in the Food and Drug Administration (FDA) guidance, General Clinical Pharmacology: Considerations for Pediatric Studies for Drugs and Biological Products (DHHS, 2014).

The sample size for traditional rich PK sampling for noncompartmental analysis is calculated to achieve 80% probability (power), to assure the 95% confidence interval of the point estimate of the geometric mean of clearance is within 60% to 140% of the estimate of the clearance. Although the range (60%, 140%) is not symmetric to 1, the lower confidence interval bound is within (60%, 140%) (1/1.4=0.714), as long as the upper bound is ≤1.4.

The available data in Table 6 are from Shire's completed study (SHP465-111) with an ADHD pediatric population and shows the reported apparent clearance (CL/F) and volume of distribution (V_z/F) for the *d*-amphetamine and *l*-amphetamine of SHP465 after oral administration of 12.5 mg in children aged 6 to 12 years and 25 mg in adolescents aged 13 to 17 years.

Table 6: Estimates of Clearance and Volume of Distribution for *d*-Amphetamine and *l*-Amphetamine

CV (%)	SHP465 12.5 mg Children (6 to 12 years)		SHP465 25 mg Adolescents (13 to 17 years)	
	CL/F (L/h)	V_z/F (L)	CL/F (L/h)	V_z/F (L)
d-Amphetamine	25.0	28.5	23.7	18.4
l-Amphetamine	26.9	32.2	28.4	22.0

CV=coefficient of variation

Source: SHP465-111 Clinical Study Report Table 9-1 and Table 9-4.

The sample size estimates uses the within-subject *l*-amphetamine variability of 32.2%, since it is numerically bigger. Applying the methods from the manuscript by Wang et al.,(2012), sample size estimations with related probability for corresponding coefficients of variation are provided as follows:

CV (%)	Number of Subjects Required	Probability of the Point Estimate Within the Prespecified Interval (%)
18.4	5	89
22.0	5	80
23.7	6	88
25.0	6	82
26.9	6	89
28.4	7	88
28.5	7	88
32.2	8	90

CV=coefficient of variation.

Based on these data, the PK analysis will need at least 8 subjects in total to provide reliable PK parameter estimates.

9.6 Study Population

The **screened set** will consist of all subjects who have provided consent.

The **enrolled set** will consist of all subjects who have been assigned a subject identification number.

The **safety set** will consist of all enrolled subjects who have taken at least 1 dose of investigational product.

The **PK set** will consist of all subjects in the safety set for whom at least 1 postdose PK blood sample was collected.

9.7 Pharmacokinetic Analyses

9.7.1 Pharmacokinetic Analysis

All the PK analyses will be performed using the PK set.

Pharmacokinetic parameters will be determined from the plasma concentration-time data for *d*-amphetamine and *l*-amphetamine by noncompartmental analysis using Phoenix® WinNonlin® (Certara, Princeton, NJ) Version 6.4 or higher.

The PK parameters will include, but not be limited to:

- $AUC_{0-\infty}$ Area under the curve extrapolated to infinity
- AUC_{0-t} Area under the curve from time 0 to the last time point of sample collection
- AUC_{0-5} Area under the curve from time 0 predose to 5 hours postdose
- AUC_{5-t} Area under the curve from time 5 hours to the last time point of sample collection
- AUC_{last} Area under the curve from the time of dosing to the last measurable concentration
- AUC_{tau} Area under the concentration curve over the dosing interval (24 hours) at steady state
- CL/F Total body clearance for extravascular administration
- C_{max} Maximum concentration occurring at t_{max}
- C_{trough} Trough plasma concentration (the predose concentrations collected at steady state)
- $t_{1/2}$ Terminal half-life
- t_{max} Time of maximum observed concentration sampled during a dosing interval
- VF/ss Apparent volume of distribution at steady state
- V_z/F Volume of distribution associated with the terminal slope following extravascular administration
- λ_z The first order rate constant associated with the terminal phase of elimination

9.7.1.1 Statistical Analysis of Pharmacokinetic Parameters

There will be no inferential statistical analysis of the PK data. Summary descriptive statistics (number of observations, mean, standard deviation, coefficient of variation, median, maximum, minimum and geometric mean) will be determined for all PK parameters. Plasma concentrations at each nominal sampling time will also be summarized using descriptive statistics.

9.8 Safety Analyses

Safety will be assessed by TEAEs, vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature), 12-lead ECGs, weight, height, clinical laboratory tests (biochemistry, hematology, and urinalysis), PSQ, and a validated sleep questionnaire (CSHQ).

Additionally, the C-SSRS will capture the safety of SHP465 related to suicidality.

The safety endpoints will be summarized with descriptive statistics for the safety set.

Relevant safety endpoints as well as their changes from baseline will be summarized. Baseline is defined as the last assessment prior to the first dose of investigational product. Potentially clinically important findings will also be summarized or listed. The potentially clinically important values will be defined in the SAP.

Weight, height, BMI, vital signs, ECG, PSQ, and CSHQ will be summarized. The C-SSRS results will be summarized and a listing of the C-SSRS data will be provided for subjects with a positive response.

Adverse events will be coded using the agreed-upon version of the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs are defined as AEs that started or deteriorated on or after the date of the first dose of investigational product, and no later than 3 days following the first dose of investigational product. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, and by preferred term. Treatment-emergent AEs 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.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

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

10.1 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) and any updates, and 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 source documents 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 nonpediatric studies as per guidance.

10.1.4 Study Suspension, Termination, and Completion

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

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

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

A co-ordinating 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 co-ordinating principal investigator, in compliance with ICH Guideline 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 co-ordinating principal investigator, according to national provisions, and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

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

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

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

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

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject's diary, 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 IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc).

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

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

10.2.3.3 Audit/Inspection

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

10.2.3.4 Financial Disclosure

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

It is the responsibility of the investigator to obtain written informed consent and assent from all study subjects and their parent/LAR 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 parent/LAR, 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 (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's parent/LAR, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

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

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

10.3.2 Institutional Review Board or Ethics Committee

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

Responsibility for co-ordinating with IRBs/ECs is defined in the clinical trial agreement.

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

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

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

10.4 Privacy and Confidentiality

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

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

After subjects have consented/assented to take part in the study, the sponsor and/or its representative 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 SHP465; national or local regulatory authorities; and the IRB/EC which gave approval for the study to proceed. The sponsor and/or its representative 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 (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials 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 (eg, Good Publication Practices 2) when forming a publication steering committee. The purpose of the publication steering committee is to act as a noncommercial 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 following paragraph, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

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

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors 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	15 Sep 2017	Global

APPENDIX 2 DIAGNOSTIC CRITERIA/DISEASE CLASSIFICATION

APPENDIX 2.1 DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, FIFTH EDITION CRITERIA

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. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several impairments from the symptoms are present in 2 or more settings (eg, at school [or work] and at home).

D. There is 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:

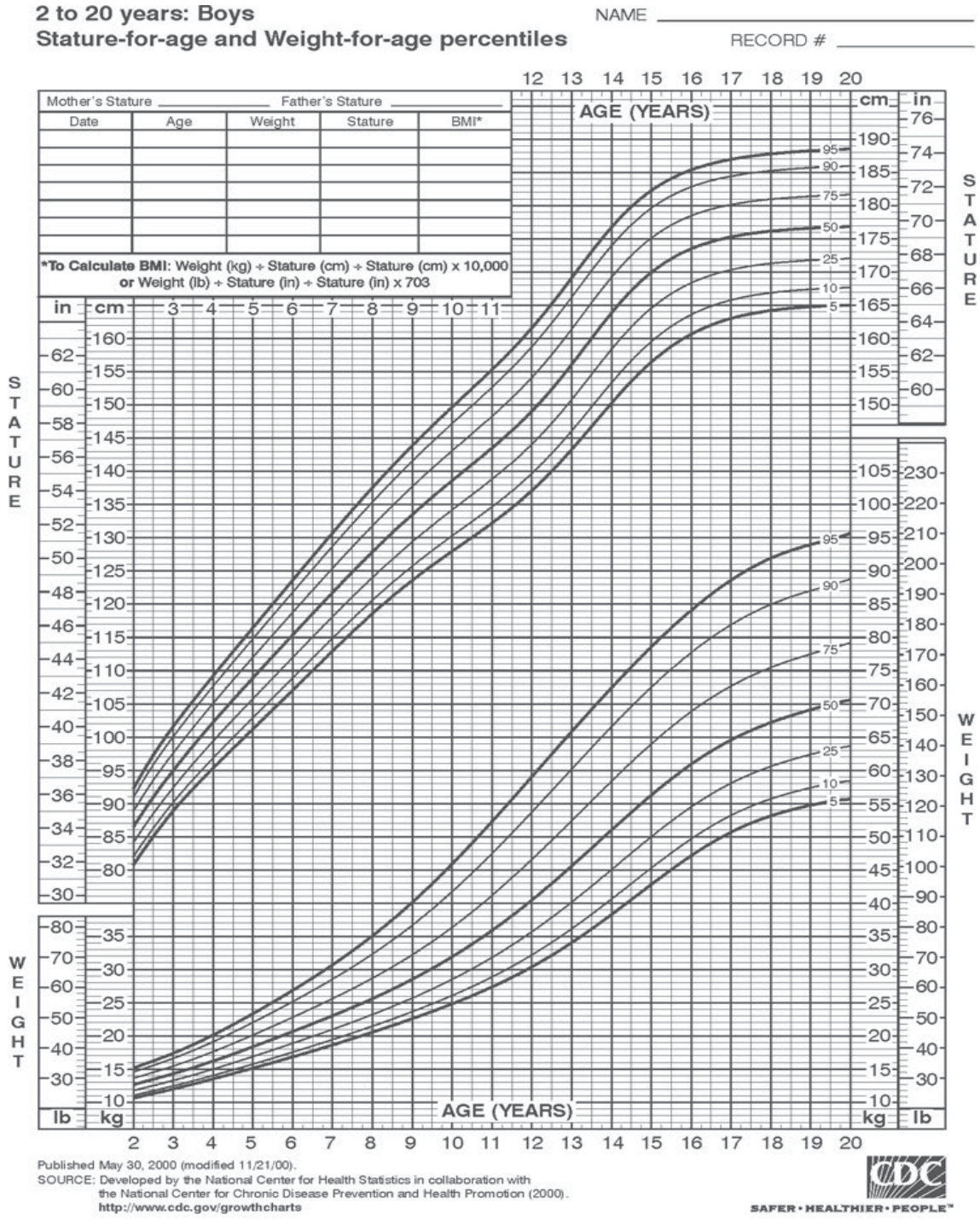
314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria A1 and A2 are met for the past 6 months

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, Fifth Edition. Copyright 2013 American Psychiatric Association.

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



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

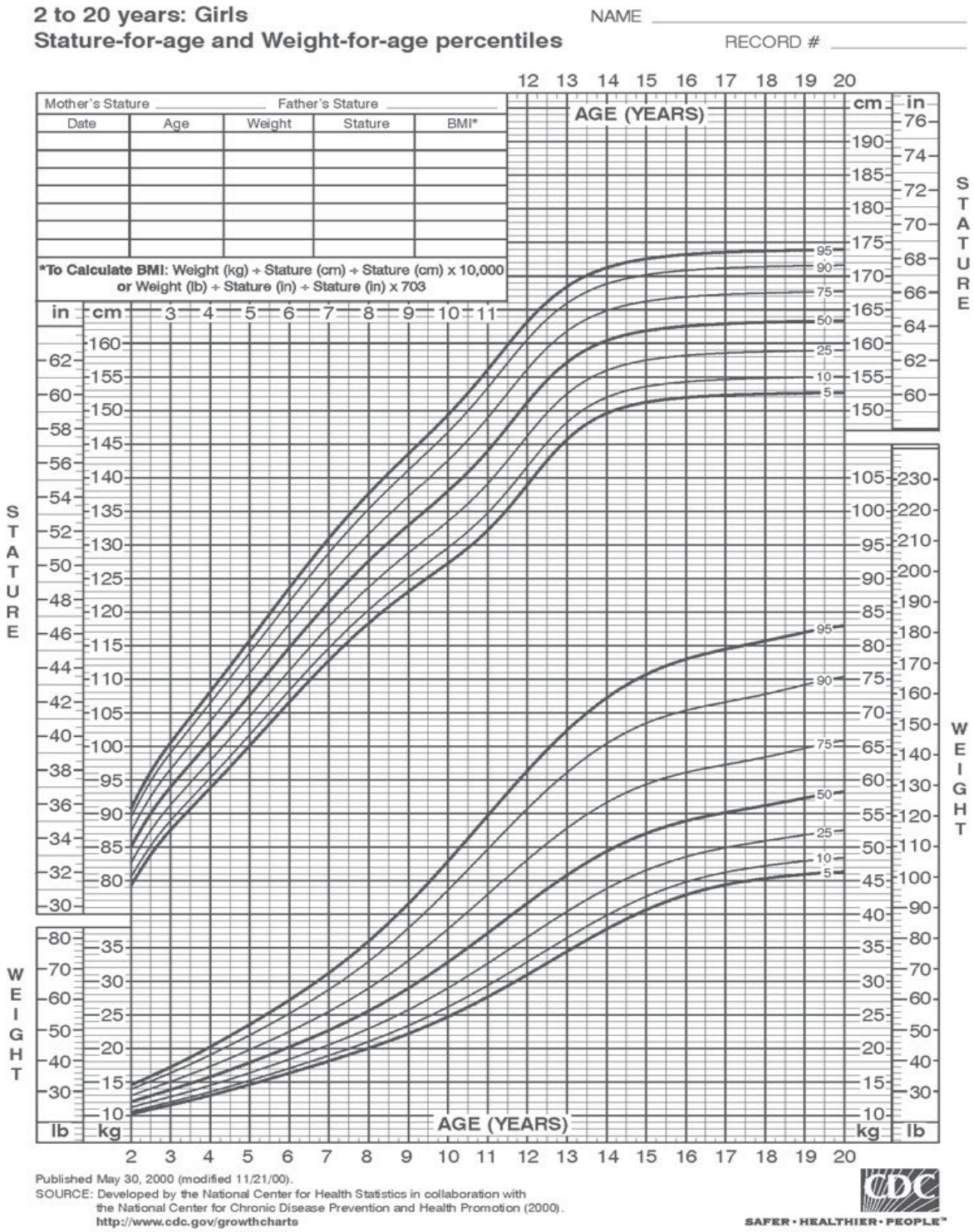
To determine the eligibility of a male subject for entry in the study (based on the study inclusion criteria), first determine the percentile of height for the subject based on their age (as a whole number based on the subject's last birthday; Appendix 2.2). For subjects who fall between the 2 height percentiles, use the lower of the 2 percentiles. Once the subject's age and height percentile for age are determined, use the following table to determine eligibility.

All blood pressure values listed as follows are 95th percentile for age and height percentile. The subject's systolic and diastolic blood pressure readings at the screening visit and the baseline visit (predose on Day 1) must not exceed the following corresponding table value 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 2.4 GIRLS' STATURE-FOR-AGE AND WEIGHT-FOR-AGE PERCENTILES



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

To determine the eligibility of a female subject for entry in the study (based on the study inclusion criteria), first determine the percentile of height for the subject based on their age (as a whole number based on the subject's last birthday; Appendix 2.4). 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 following table to determine eligibility.

All blood pressure values listed as follows are 95th percentile for age and height percentile. The subject's systolic and diastolic blood pressure readings at the screening visit and the baseline visit (predose on Day 1) must not exceed the following corresponding table value 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-RS-5	N/A	2016
CGI-I and CGI-S	N/A	1976
C-SSRS	Baseline Since Last Visit	Baseline 23 Jun 2010 Since Last Visit 23 Jun 2010
CSHQ	N/A	2009
MINI-KID	7.0.2	08 Aug 2016
PSQ	N/A	N/A

ADHD-RS-5=Attention-Deficit/Hyperactivity Disorder Rating Scale-5; CGI-I=Clinical Global Impressions - Improvement; CGI-S=Clinical Global Impressions – Severity of Illness; CSHQ=Children's Sleep Habits Questionnaire; C-SSRS=Columbia-Suicide Severity Rating Scale; MINI-KID=Mini International Neuropsychiatric Interview for Children and Adolescents; N/A=not applicable; PSQ=Post Sleep Questionnaire.

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