CLINICAL STUDY PROTOCOL

NCT Number: NCT03325881

Study Title: A Phase 3, Randomized, Double-blind, Multicenter, Placebo-controlled, Fixed-Dose, Efficacy, and Safety Study of SHP465 in Children Aged 6-12 Years with Attention-Deficit/Hyperactivity Disorder (ADHD)

Study Number: SHP465-309

Protocol Version: Protocol

Protocol Version Date: 07 September 2017

PROTOCOL: SHP465-309

TITLE:	A Phase 3, Randomized, Double-blind, Multicenter, Placebo-controlled, Fixed-Dose, Efficacy, and Safety Study of SHP465 in Children Aged 6-12 Years with Attention-Deficit/Hyperactivity Disorder (ADHD)
DRUG:	SHP465, mixed salts of a single-entity amphetamine
IND:	66,329
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Shire Development LLC 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	TBD
PROTOCOL HISTORY:	Original, 07 September 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: PPD	**Date:** PPD PPD
PPD , MD, PhD PPD	

Investigator's Acknowledgement
I have read this protocol for Shire Study SHP465-309.

Title: A Phase 3, Randomized, Double-blind, Multicenter, Placebo-controlled, Fixed-Dose, Efficacy, and Safety Study of SHP465 in Children Aged 6-12 Years with Attention-Deficit Hyperactivity Disorder (ADHD)

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

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

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

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

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

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

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

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

E-mail address: ePIP.ppdi.com (electronic query submission site)

For protocol- or safety-related issues during normal business hours 8AM-5PM eastern standard time, the investigator must contact the PPD medical monitor:

PPD, MD

Phone: PPD

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

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

Phone: PPD

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Origin of Product Quality Complaint	E-mail Address
North and South America	PPD

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Shire, Lexington, MA (USA)

PPD or PPD

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ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ADHD-RS-5	Attention-deficit/Hyperactivity Disorder Rating Scale-5
AE	adverse event
BMI	body mass index
CGI-I	Clinical Global Impressions – Global Improvement
CGI-S	Clinical Global Impressions – Severity of Illness
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CSHQ	Children's Sleep Habits Questionnaire
DSM-IV-TR®	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision®
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	ethics committee
ECG	electrocardiogram
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
β-HCG	human chorionic gonadotropin beta
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator's brochure
ICH	International Conference on Harmonisation
IR	immediate release
IRB	Institutional Review Board
IWRS	interactive web response system
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
MPH	methylphenidate

PSQ	Post Sleep Questionnaire
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
US	United States

STUDY SYNOPSIS

Protocol number: SHP465-309	**Drug: SHP465, mixed salts of a single-entity amphetamine**
Title of the study: A Phase 3, Randomized, Double-blind, Multicenter, Placebo-controlled, Fixed-Dose, Efficacy, and Safety Study of SHP465 in Children Aged 6-12 Years with Attention-Deficit/Hyperactivity Disorder (ADHD)	
Number of subjects (total and for each treatment arm): Approximately 60 subjects will be enrolled into the study. Approximately 52 subjects are expected to complete the safety and efficacy evaluation: approximately 50% of subjects will be aged 6-8 years and approximately 50% of subjects will be aged 9-12 years. Approximately 25% of all subjects will be female.	
Investigator(s): Multicenter	
Site(s) and Region(s): Approximately 45 sites in the United States (US).	
Study period (planned): 2017 to 2018	**Clinical phase:** 3
Objectives: **Primary:** To evaluate the efficacy of SHP465 at 6.25 mg compared to placebo as a daily morning dose in children 6-12 years of age (inclusive at the time of consent) diagnosed with ADHD. The primary measure of efficacy will be the clinician-administered ADHD-Rating Scale 5 Child, Home version (ADHD-RS-5) Total score. **Key Secondary:** To assess the efficacy of SHP465 at 6.25 mg compared to placebo using a global clinical measure of improvement, the Clinical Global Impression of Improvement (CGI-I) scale. **Secondary:** To evaluate safety and tolerability of SHP465 at 6.25 mg based on the occurrence of treatment-emergent adverse events (TEAEs), evaluation of vital signs (systolic and diastolic blood pressure and pulse), weight, height, body mass index (BMI); clinical laboratory and electrocardiogram (ECG) results; sleep assessment (Post Sleep Questionnaire [PSQ] and Children's Sleep Habits Questionnaire [CSHQ]); and responses to the Columbia-Suicide Severity Rating Scale (C-SSRS).	
Rationale: The purpose of this study is to evaluate the efficacy and safety of SHP465 at 6.25 mg in the treatment of ADHD in children aged 6-12 years. Results from the completed SHP465-305 study in this age group have demonstrated SHP465 to be well tolerated and efficacious in reducing ADHD symptom severity. This study will provide additional data to inform clinicians about the efficacy and safety of SHP465 at lower dose levels in the pediatric ADHD population.	
Investigational product, dose, and mode of administration: • SHP465 will be provided in 6.25 mg capsules. • Placebo will be provided as capsules identical to SHP465. The parent/legally authorized representative (LAR) will be instructed to dispense 1 capsule to the subject daily throughout the study at 7:00 AM (±2 hours). SHP465 6.25 mg will be administered in 1 of the following ways: • Swallow SHP465 capsules whole, or • Open capsule and sprinkle the entire contents on 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.

Methodology:

This study is a Phase 3 randomized, multicenter, double-blind, placebo-controlled, fixed-dose efficacy and safety study in children aged 6-12 years (inclusive at the time of consent,) diagnosed with ADHD. Children with ADHD will be randomized in a 1:1 ratio between SHP465 6.25 mg and placebo arms for a 4-week treatment. SHP465 dose of 6.25 mg or placebo will be administered to subjects for the entire treatment period.

The study will have 3 periods: (1) screening and washout: (2) treatment period; and (3) safety follow-up. The duration of the evaluation period will be 4 weeks.

Subjects will be required to visit the site up to 6 times over a 10-week period.

The investigator or designee must obtain written informed consent from the subject's parent/LAR and documentation of assent (if applicable) by the subject before any protocol-related procedure is performed. Procedures performed at each visit for all subjects are defined in the Study Schedule, Table 1.

Inclusion and exclusion criteria:

Inclusion Criteria:

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

Subject is male or female and must be 6-12 years, inclusive, at the time of consent.

1. Subject's parent or legally authorized representative (LAR) must provide signature of informed consent, and there must be documentation of assent (as applicable) by the subject in accordance with the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 (1996) and any updates and applicable regulations, before completing any study-related procedures.
2. Subject and parent/LAR are willing and able to comply with all of the testing and requirements defined in the protocol, including oversight of morning dosing. Specifically, the parent/LAR must be available at approximately 7:00 AM (±2 hours) to dispense the dose of investigational product for the duration of the study.
3. Subject must meet 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).
4. Subject who is a female and of child-bearing potential must not have a positive serum beta human chorionic gonadotropin pregnancy test at the screening visit (Visit 1) and must have a negative urine pregnancy test at the baseline visit (Visit 2) and agree to comply with any applicable contraceptive requirements of the protocol.
5. Subject has an ADHD-RS-5 Child, Home Version Total Score of ≥28 at baseline (Visit 2).
6. Subject has a Clinical Global Impression – Severity of Illness (CGI-S) score ≥4 at baseline (Visit 2).
7. Subject functions as an age-appropriate level intellectually, as determined by the investigator.
8. Subject is currently not on ADHD therapy, or is not completely satisfied with any aspect of their current ADHD therapy.
9. Subject has lived with the same parent or LAR for at least 6 months.

Exclusion Criteria:

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

1. Subject is required or anticipated to take medications that have central nervous system effects or affect performance, such as sedating antihistamines, decongestant sympathomimetics, or monoamine oxidase inhibitors. Stable use of bronchodilator inhalers is not exclusionary.
2. Subject has a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition that might confound the results of safety assessments conducted in the study or that might increase risk to the subject. Similarly, the subject will be excluded if he or she has any additional condition(s) that, in the investigator's opinion, would prohibit the subject from completing the study or would not be in the best interest of the subject. The additional condition(s) would include any significant illness or unstable medical condition that could lead to difficulty complying with the protocol. Mild, stable asthma is not exclusionary.
3. Subject has a documented allergy, hypersensitivity, or intolerance to amphetamine or to any excipients in the investigational product.
4. Subject has failed to fully respond, based on investigator judgment, to an adequate course of amphetamine therapy.
5. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.
6. Subject has a blood pressure measurement $\geq 95^{th}$ percentile for age, sex, and height at screening (Visit 1) and/or baseline (Visit 2).
7. Subject has a height $\leq$5th percentile for age and sex at screening (Visit 1) or baseline (Visit 2).
8. Subject has a weight $\leq$5th percentile for age and sex at screening (Visit 1) or baseline (Visit 2).
9. 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.
10. Subject has a history of seizures (other than infantile febrile seizures).
11. Subject is taking any medication that is excluded per the protocol.
12. Subject had any clinically significant ECG or clinical laboratory abnormalities at the screening (Visit 1) or baseline visit (Visit 2).
13. Subject has current abnormal thyroid function, defined as abnormal thyroid-stimulating hormone and thyroxine at the screening or baseline visit. Treatment with a stable dose of thyroid medication for at least 3 months is permitted.
14. 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 family history of these disorder
    - Pervasive developmental disorder
    - Obsessive-compulsive disorder
    - Serious tic disorder, or a family history of Tourette disorder
    - Any other disorder that in the opinion of the investigator contraindicates SHP465 or amphetamine treatment or confounds efficacy or safety assessments
15. Subject has a primary sleep disorder (eg, sleep apnea, narcolepsy).
16. Subject has a history or is currently diagnosed with an eating disorder.

17. 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 currently demonstrating suicidal ideation.
18. Subject has a history of physical, sexual, or emotional abuse.
19. Subject has initiated behavioral therapy within 1 month of baseline (Visit 2). Subject may not initiate behavioral therapy during the study.
20. Subject has a clinically important abnormality on the urine drug and alcohol screen (excluding the subject's current ADHD stimulant, if applicable) at screening (Visit 1) or baseline (Visit 2).
21. Subject is female and is pregnant or lactating.
22. Subject cannot swallow a pill and/or applesauce or has an allergy to applesauce.

Maximum duration of subject involvement in the study:

The estimated duration of the study is up to 10 weeks

Planned duration of screening/washout period: up to 32 days

Planned duration of treatment period: 4 weeks

- Planned duration of safety follow-up period: 1 week

Endpoints and statistical analysis:

Analysis Sets

- Screened Set: all subjects who have provided an informed consent.
- Randomized Set: all subjects in the screened set for whom a randomization number has been assigned.
- Safety Set: all subjects in the randomized set who have taken at least 1 dose of investigational product.
- Full Analysis Set (FAS)**:** all subjects in the safety set who have at least 1 post-dose ADHD-RS-5 Total Score.

Efficacy Analyses

The FAS will be used to report the efficacy data.

The primary efficacy endpoint is defined as the change from baseline for the ADHD-RS-5 Total Score at Visit 6 (Week 4), where baseline is defined as the last ADHD-RS-5 Total Score assessment prior to the first dose of double blind investigational product, usually at Visit 2. The primary and key secondary analyses will be conducted based on the entire age group in the FAS.

The primary efficacy analysis will be conducted for the change from baseline in the ADHD-RS-5 Total Scores, including all assessments from Visit 3 (Week 1) up to Visit 6 (Week 4), using the linear mixed-effects model for repeated measures (MMRM) with treatment group, visit, age group and the interaction of treatment group with visit as factors, baseline ADHD-RS-5 Total Score as a covariate, and the interaction of the baseline ADHD-RS-5 Total Score with visit adjusted in the model. The primary contrast of interest will be at Visit 6 (Week 4) for SHP465 6.25 mg compared with placebo at the 2-tailed significance level of 0.05.

The null and alternative hypotheses of the primary efficacy analysis will be the following:

- Null hypothesis: There is no difference in primary endpoint mean change from baseline at Visit 6 (week 4) in ADHD-RS-5 total scores between SHP465 6.25 mg and placebo.
- Alternative hypothesis: There is a difference in primary endpoint mean change from baseline at Visit 6 (week 4) in ADHD-RS-5 total scores between SHP465 6.25 mg and placebo.

As the primary efficacy analysis (MMRM) relies on the assumption that the missing data mechanism follows the MAR (missing-at-random) scenario, appropriate sensitivity analyses to examine the effect of data that are missing not at random and robustness on the results of the primary analysis will be conducted.

One sensitivity analysis model assumes that a subject on SHP465 6.25 mg treatment with missing data follows the distribution of the placebo responses, i.e., the means and the intra-subject correlations based on the placebo responses will apply. Another sensitivity analysis model will be performed under the assumption that subjects who drop out perform worse than MAR by a penalty. The details of the sensitivity analysis methods will be specified in the Statistical Analysis Plan (SAP).

The key secondary efficacy endpoint, CGI-I will be analyzed using the same analysis method (MMRM) as for the primary efficacy endpoint. The baseline CGI-S score will be used as the covariate. The primary contrast of interest will be at Visit 6 (Week 4) for SHP465 6.25 mg compared with placebo at the 2-tailed significant level of 0.05. Appropriate sensitivity analyses to explore the effect of data that are missing not at random on the results of the key secondary efficacy analysis will be specified in the SAP.

In order to protect the study-wide Type I error at the 2-sided 0.05 level for testing across the primary and the key secondary hypotheses, the Fixed-Sequence Test procedure will be applied. The hypotheses will be tested in order of the primary (ADHD-RS-5 Total Score) and then the key secondary (CGI-I), if significant for the primary, each at the 2-sided 0.05 significance level. Both tests in the sequence are based on the MMRM.

The key secondary efficacy measurement will also be analyzed using the proportion of subjects with an "improved" CGI-I measurement at Visit 6/ET (Week 4/ET). In this approach, the CGI-I categories will be dichotomized into 2 categories, "very much improved" and "much improved" classified as "improved" and all other assessed categories grouped together as "not improved". If missing data exist at the Visit 6 (Week 4) visit, the visit will be imputed by carrying forward the last post baseline observation value. The secondary efficacy analysis for the dichotomized CGI-I will be conducted to compare SHP465 6.25 mg and placebo on the FAS for the "improved" rate using a Cochran-Mantel-Haenszel test stratified by age group and CGI-S value at baseline.

Treatment effect of SHP465 6.25 mg on primary and key secondary efficacy measures will be estimated using a similar model as the primary efficacy endpoint for each age group (6-8 years vs. 9-12 years), sex, race (white and nonwhite), and ethnicity subgroup.

Safety Analyses

Safety data will be analyzed for the safety set. Safety endpoints include the occurrence of TEAEs, systolic and diastolic blood pressure, pulse, and weight, height, BMI, ECG results, clinical laboratory test results, PSQ, CSHQ, and C-SSRS Exposure to investigational product will be summarized.

Adverse events will be coded using the agreed upon version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergent AEs will be summarized. The number and percent of subjects with TEAEs will be calculated for each system organ class, by preferred term, and by treatment. The severity of the TEAEs, the relationship to the investigational product, TEAEs causing study discontinuation, and serious AEs will also be presented.

Vital signs (systolic and diastolic blood pressure, and pulse), weight, height, BMI, and ECG results including potentially clinically important results will be summarized by treatment and visit.

Clinical laboratory test results will be descriptively presented by treatment group for each visit. Shifts of clinical laboratory abnormality from baseline to Visit 6/ET will be presented. Number and percent of subjects with potentially clinically important laboratory values will be presented by treatment group.

The PSQ and CSHQ results will be summarized by treatment and visit.

The C-SSRS results will be summarized and listings of the C-SSRS data will be provided for subjects with a positive response.

The safety data on TEAEs will also be descriptively summarized by treatment within each age group (6-8 years vs. 9-12 years), sex, race, and ethnicity subgroups.

Sample Size Calculation and Power Considerations

Approximately 60 subjects will be randomized in a 1:1 ratio to SHP465 6.25 mg and placebo to achieve 52 completers for the study (26 in each treatment group) and 85% power for the primary efficacy analysis at the 2-sided 0.05 significance level.

The sample size planned is estimated based on the primary comparison between SHP465 6.25 mg and placebo on the primary efficacy endpoint change from baseline in ADHD-RS-5 total score at Visit 6 (Week 4). Assumptions for the calculation include the true mean difference of 11.9 with the common standard deviation (SD) of 14 for an effect size of 0.85, and a dropout rate of 15%.

The effect size of 0.85 is low compared with that observed in recently completed study (SHP465-305) of children and adolescents aged 6-17 years with ADHD treated with SHP465. The SHP465-305 study yielded an effect size of 0.93 in children aged 6-12 years (N=101 subjects).

Planned Interim Analysis

A blinded interim analysis at the late stage of the trial (when approximately 75% of all randomized subjects have either completed or discontinued from the study) will be performed to reassess the sample size in case of an underestimated variability postulated at the design stage.

Using the cumulative real data, a blinded, pooled analysis of both treatment groups for estimating variability will be conducted on the change from baseline in ADHD-RS-5 total score at Visit 6 (Week 4). If the re-estimated pooled standard deviation is larger than the 14 postulated at the design stage, the final total number of subjects to be enrolled will be calculated using the re-estimated pooled standard deviation together with the assumed treatment difference of 11.9 (Friede et al, 2006). If the re-estimated pooled standard deviation is smaller than 14, the sample size will not be adjusted.

STUDY SCHEDULE(S)

Table 1: Schedule of Assessments

	Screening/Washout[a]		Baseline	Treatment Period				Follow-up
Visit Number[b]	**1**	**Phone call**	**2**	**3**	**4**	**5**	**6/ET[c]**	**Phone call**
Study Week	**-5 to -1**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**
Study Day[b]	**–32 to –3**	**-7**	**0**	**7**	**14**	**21**	**28**	**35**
Informed consent/assent	✓							
Inclusion/exclusion criteria	✓	✓[d]	✓[d]					
Subject demography	✓							
MINI-Kid	✓							
Medical history[e] includes prior medications and procedures	✓							
Randomization			✓					
ADHD-RS-5[f]			✓	✓	✓	✓	✓	
CGI-S[f]			✓					
CGI-I[f]				✓	✓	✓	✓	
PSQ[f]			✓	✓	✓	✓	✓	
Urine drug screen	✓		✓[g]					
Serum pregnancy test[k]	✓		✓[g]					
Urine pregnancy test[k]			✓				✓	
Physical examination	✓		✓[g]					
Height[h]	✓		✓	✓	✓	✓	✓	
Weight[h]	✓		✓	✓	✓	✓	✓	
Vital signs[i, j]	✓		✓	✓	✓	✓	✓	
Clinical laboratory test	✓		✓[g]				✓	
Electrocardiogram (12-lead)[i]	✓[i]		✓[g, i]		✓		✓	

Table 1: Schedule of Assessments

	Screening/Washout[a]		Baseline	Treatment Period				Follow-up
Visit Number[b]	**1**	**Phone call**	**2**	**3**	**4**	**5**	**6/ET[c]**	**Phone call**
Study Week	**-5 to -1**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**
Study Day[b]	**–32 to –3**	**-7**	**0**	**7**	**14**	**21**	**28**	**35**
C-SSRS baseline version	✓							
C-SSRS since last visit version			✓	✓	✓	✓	✓	
PSQ[f]			✓	✓	✓	✓	✓	
CSHQ[f]			✓	✓	✓	✓	✓	
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓
Subject check to remain in study[f]			✓	✓	✓	✓		
IWRS	✓		✓	✓	✓	✓	✓	
Study drug dispensed			✓	✓	✓	✓		
Study drug capsules returned				✓	✓	✓	✓	

ADHD-RS-5=Attention-deficit/Hyperactivity disorder-Rating Scale 5 Child, Home Version; BMI=body mass index; CGI=Clinician's Global Impression; C-SSRS=Columbia-Suicide Severity Rating Scale; ET=early termination; IWRS=interactive web response system; MINI=Mini International Neuropsychiatric Interview (MINI) Kid version for Children and Adolescents; PSQ=Post Sleep Questionnaire

[a] Following successful screening, a site representative will contact the subject's parent/LAR to instruct the subject on discontinuing any prohibited medication for the washout period.

[b] Visit windows are with respect to baseline (Visit 2) and ±2 days during the treatment period and +2 days for the safety follow-up phone call.

[c] Subjects who terminate early will undergo the evaluations listed for Visit 6.

[d] Inclusion/exclusion criteria will be reviewed during the washout phone call and at baseline (Visit 2).

[e] Medical history will include all lifetime psychiatric and nonpsychiatric medications and procedures.

[f] Whenever possible, the same individual should complete/rate consistently the following scales and questionnaires as appropriate: ADHD-RS, CGI-S/I, and subject check to remain in the study; and the same caregiver/LAR for PSQ and CSHQ. Include assessment of decreased appetite.

[g] If >32 days have elapsed since the screening evaluation was completed at Visit 2, then the following evaluations must be repeated at baseline (Visit 2): vital signs, serum pregnancy test, urine drug screen, clinical laboratory evaluations, and ECGs in triplicate. The physical exam will be abbreviated with a review of the following body systems: general appearance, respiratory, and cardiovascular.

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

Table 1: Schedule of Assessments

	Screening/Washout[a]		Baseline	Treatment Period				Follow-up
Visit Number[b]	1	Phone call	2	3	4	5	6/ET[c]	Phone call
Study Week	-5 to -1	-1	0	1	2	3	4	5
Study Day[b]	–32 to –3	-7	0	7	14	21	28	35

[i] Vital signs include oral or tympanic temperature, pulse, sitting blood pressure, and respiration rate. The subject will have been seated for a minimum of 3 minutes before blood pressure, pulse and respiration rate measurements are taken. Measurement of blood pressure and pulse will be collected 3 times (with approximately 2 minutes in between each collection). The average of each set of 3 measurements will be used to determine continued participation in the study.

[j] Blood pressure and pulse rate will be measured at each study visit. Temperature and sitting respiration rate will be measured at screening (Visit 1) and/or baseline (Visit 2) only.

[k] For females of child-bearing potential only.

[l] Electrocardiograms will be recorded in triplicate with approximately 3 minutes in between each collection at screening only and at baseline only if >32 days have elapsed since the screening evaluation was completed at Visit 1.

1 BACKGROUND INFORMATION

SHP465 extended-release capsules contain mixed salts of a single-entity amphetamine, a CNS stimulant. The product was previously referred to as SPD465 however it is now being studied under the code of SHP465. SHP465 contains equal amounts (by weight) of 4 salts: dextroamphetamine sulfate and amphetamine sulfate, dextroamphetamine saccharate and amphetamine aspartate monohydrate. This results in a 3:1 mixture of dextro- to levo- amphetamine base equivalent.

SHP465 capsules are for oral administration. They contain 3 types of drug-releasing beads, an immediate release and 2 different types of delayed release (DR) beads. The first DR bead releases amphetamine at pH 5.5 and the other DR bead releases amphetamine at pH 7.0.

Amphetamines are noncatecholamine sympathomimetic amines with central nervous system stimulant activity. Amphetamine increases the availability of biogenic amines (primarily dopamine and norepinephrine) in central nerve terminals 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 ADHD; however, the mode of therapeutic action in ADHD is not known.

Additional information can be found in the current Investigator's Brochure (IB) for SHP465.

1.1 Indication and Current Treatment Options

Attention-deficit/hyperactivity disorder is a psychiatric disorder characterized by developmentally inappropriate degrees of inattentiveness, impulsivity, and hyperactivity. Although ADHD is the most common neurodevelopmental disorder of childhood (Rowland et al. 2002) and it has been extensively studied in young children, ADHD occurs in all age groups (Brown 2000).

Prevalence estimates of ADHD in school-age children have ranged from 2-18% in community samples (Rowland et al. 2002; Centers for Disease Control and Prevention 2005). The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision® estimates that the disorder is prevalent in 3-7% of school-age children (American Psychiatric Association 2000). An analysis of data from the National Survey of Children's Health performed by the Centers for Disease Control and Prevention (2005) estimates that 7.8% of children aged 4-17 years have been diagnosed with the disorder in the US as of 2003.

Although ADHD was initially believed to be predominantly a childhood disorder, the advent of consensus diagnostic criteria for ADHD along with more rigorous prospective research has documented the persistence of this disorder into adolescence in up to 70% and into adulthood in up to 66% of childhood cases (Mannuzza et al. 1998; Barkley 1998; Zametkin and Ernst 1999). Despite the prevalence of ADHD in all age groups, the majority of studies have been done in children and adults.

A review of available literature indicates that psychostimulants are efficacious in treating adolescents as well as the treatment for younger children with ADHD (Biederman et al. 1996; Findling et al. 2001).

The 3 main symptoms of ADHD are inattention, hyperactivity, and impulsivity. Symptoms of inattention include difficulty paying attention, making careless mistakes, difficulty organizing tasks, not finishing tasks, not listening, and being forgetful and easily distracted. Symptoms of hyperactivity and impulsivity include fidgeting, running, or moving about when expected to be still, difficulty playing quietly, talking excessively, and interrupting others. Many people have symptoms like these occasionally, but patients with ADHD have these symptoms more often and to a greater extent than others their age. These symptoms must appear before age 7 years, be present for more than 6 months, and must be adversely affecting social, occupational, or school functioning for the diagnosis of ADHD to be made.

The presumed pathophysiology of ADHD is an abnormality in central dopaminergic and noradrenergic tone (Biederman and Spencer 1999). This presumption is based on the discovery that effective pharmacotherapies in children and adults have an impact on these 2 neurotransmitters (Wilens and Spencer 2000; Faraone and Biederman 1998).

Stimulants, including amphetamine and methylphenidate products are currently the most prescribed medications for the treatment of ADHD. Other nonstimulant classes of medications are also approved for the treatment of ADHD including a norepinephrine reuptake inhibitor, STRATTERA® (atomoxetine hydrochloride) and alpha-2-agonists, INTUNIV® (guanfacine hydrochloride) and KAPVAY® (clonidine hydrochloride). However, comprehensive reviews of clinical studies investigating the pharmacotherapy of ADHD clearly demonstrate that stimulant medications (ie, methylphenidate and amphetamine) produce the most robust improvements in symptom expression across age ranges as compared with nonstimulant therapies (Faraone et al. 2006).

1.2 Product Background and Clinical Information

1.2.1 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 to 55 years and 3 clinical studies were in pediatric subjects aged 6 to 17 years. The SHP465 clinical development program has shown that doses of 12.5 to 50 mg in adult subjects and 6.25 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- and l-amphetamine are similar.

Acceptable safety and tolerability profiles observed were consistent with the types of side effect 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 IB for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, PK, efficacy, and safety of SHP465.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

The purpose of this study is to evaluate the efficacy and safety of SHP465 at 6.25 mg in the treatment of ADHD in children aged 6-12 years. Results from the completed SHP465-305 study in this age group have demonstrated SHP465 to be well tolerated and efficacious in reducing ADHD symptom severity. This study will provide additional data to inform clinicians about the efficacy and safety of SHP465 at lower dose levels in the pediatric ADHD population.

2.2 Study Objectives

2.2.1 Primary Objectives

To evaluate the efficacy of SHP465 at 6.25 mg compared to placebo as a daily morning dose in children 6-12 years of age (inclusive at the time of consent) diagnosed with ADHD. The primary measure of efficacy will be the clinician-administered ADHD-Rating Scale 5 Child, Home version (ADHD-RS-5) Total score.

2.2.2 Secondary Objectives

Key Secondary:

- To assess the efficacy of SHP465 at 6.25 mg compared to placebo using a global clinical measure of improvement, the Clinical Global Impression of Improvement (CGI-I) scale.

Secondary:

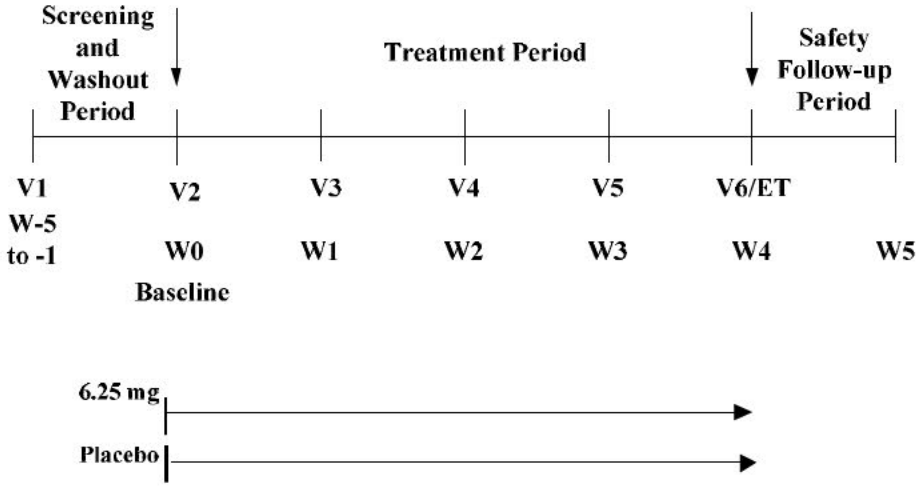
- To evaluate safety and tolerability based on the occurrence of treatment-emergent adverse events (TEAEs), evaluation of vital signs (systolic and diastolic blood pressure and pulse), weight, height, body mass index (BMI); clinical laboratory and electrocardiogram (ECG) results; sleep assessments (Post Sleep Questionnaire **[**PSQ**]** and Children's Sleep Habits Questionnaire [CSHQ]); and responses to the Columbia-Suicide Severity Rating Scale (C-SSRS).

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This study is a Phase 3, randomized, multicenter, double-blind, placebo-controlled, fixed-dose study in which children aged 6-12 years (inclusive at the time of consent) diagnosed with ADHD will be randomized in a 1:1 ratio at baseline (Visit 2) to SHP465 6.25 mg or placebo for a 4-week treatment period. SHP465 6.25 mg or placebo will be administered to subjects for the entire treatment period (see Figure 1 for the study design flow chart).

Figure 1: Study Design Flow Chart



Approximately 60 subjects will be enrolled into the study. Approximately 52 subjects are expected to complete the efficacy and safety evaluation: approximately 50% of subjects will be aged 6-8 years and approximately 50% of subjects will be aged 9-12 years. Approximately 25% of all subjects will be female, consistent with the literature-defined gender distribution in ADHD clinic samples (Szatmari et al. 1989; Wallis et al. 2008; Thapar 2003).

Subjects enrolled in this study will be randomly assigned to either SHP465 6.25 mg or placebo at the baseline visit (Visit 2). The study will consist of 3 periods: (1) screening and washout period, (2) treatment period, and (3) safety follow-up period.

Efficacy evaluations will consist of the ADHD-RS-5 and CGI-I. Safety assessments will consist of TEAEs, vital signs, weight, and BMI, clinical laboratory test and ECG results, and responses to PSQ, CSHQ, and C-SSRS.

3.2 Duration and Study Completion Definition

The subject's duration of participation is expected to be approximately 6-10 weeks. The study will be completed in approximately 7 months.

- Planned duration of screening/washout period: up to 32 days
- Planned duration of treatment period: 4 weeks
- Planned duration of safety follow-up: 1 week

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 45 sites in the US.

4 STUDY POPULATION

Each subject and parent/LAR must participate in the informed consent process and provide written informed consent and/or assent (as applicable) before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

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

1. Subject is male or female aged 6-12 years inclusive at the time of consent.
2. Subject's parent or LAR must provide signature of informed consent, and there must be documentation of assent (as applicable) by the subject in accordance with the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 (1996) and any updates and applicable regulations, before completing any study-related procedures.
3. Subject and parent/LAR are willing and able to comply with all of the testing and requirements defined in the protocol, including oversight of morning dosing. Specifically, the parent/LAR must be available at approximately 7:00 AM (±2 hours) to dispense the dose of investigational product for the duration of the study.
4. Subject must meet Diagnostic and Statistical Manual of Mental Disorders, 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 version for Children and Adolescents (MINI-KID).
5. Subject who is a female and of child-bearing potential must not have a positive serum beta human chorionic gonadotropin pregnancy test at the screening visit (Visit 1) and must have a negative urine pregnancy test at the baseline visit (Visit 2) and agree to comply with any applicable contraceptive requirements of the protocol.
6. Subject has an ADHD-RS-5 Child, Home Version Total Score of ≥28 at baseline (Visit 2).
7. Subject has a Clinical Global Impression – Severity of Illness (CGI-S) score ≥4 at baseline (Visit 2).
8. Subject functions as an age-appropriate level intellectually, as determined by the investigator.
9. Subject is currently not on ADHD therapy, or is not completely satisfied with their current ADHD therapy.
10. 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. Subject is required or anticipated to take medications that have central nervous system effects or affect performance, such as sedating antihistamines, decongestant sympathomimetics, or monoamine oxidase inhibitors. Stable use of bronchodilator inhalers is not exclusionary.
2. Subject has a concurrent chronic or acute illness (such as severe allergic rhinitis or an infectious process requiring antibiotics), disability, or other condition that might confound the results of safety assessments conducted in the study or that might increase risk to the subject. Similarly, the subject will be excluded if he or she has any additional condition(s) that, in the investigator's opinion, would prohibit the subject from completing the study or would not be in the best interest of the subject. The additional condition(s) would include any significant illness or unstable medical condition that could lead to difficulty complying with the protocol. Mild, stable asthma is not exclusionary.
3. Subject has a documented allergy, hypersensitivity, or intolerance to amphetamine or to any excipients in the investigational product.
4. Subject has failed to fully respond, based on investigator judgment, to an adequate course of amphetamine therapy.
5. Subject has a known family history of sudden cardiac death or ventricular arrhythmia.
6. Subject has a blood pressure measurement ≥95th percentile for age, sex, and height at screening (Visit 1) and/or baseline (Visit 2).
7. Subject has a height ≤5th percentile for age and sex at screening (Visit 1) or baseline (Visit 2).
8. Subject has a weight ≤5th percentile for age and sex at screening (Visit 1) or baseline (Visit 2).
9. 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.
10. Subject has a history of seizures (other than infantile febrile seizures).
11. Subject is taking any medication that is excluded per the protocol.
12. Subject had any clinically significant ECG or clinical laboratory abnormalities at the screening Visit 1) or baseline visit (Visit 2).
13. Subject has current abnormal thyroid function, defined as abnormal thyroid-stimulating hormone and thyroxine at the screening or baseline visit. Treatment with a stable dose of thyroid medication for at least 3 months is permitted.

14. 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 family history of these disorder
    - Pervasive developmental disorder
    - Obsessive-compulsive disorder
    - Serious tic disorder, or a family history of Tourette disorder
    - Any other disorder that in the opinion of the investigator contraindicates SHP465 or amphetamine treatment or confounds efficacy or safety assessments
15. Subject has a primary sleep disorder (eg, sleep apnea, narcolepsy).
16. Subject has a history or is currently diagnosed with an eating disorder.
17. 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 currently demonstrating suicidal ideation.
18. Subject has a history of physical, sexual, or emotional abuse.
19. Subject has initiated behavioral therapy within 1 month of baseline (Visit 2). Subject may not initiate behavioral therapy during the study.
20. Subject has a clinically important abnormality on the urine drug and alcohol screen (excluding the subject's current ADHD stimulant, if applicable) at screening (Visit 1) or baseline (Visit 2).
21. Subject is female and is pregnant or lactating.
22. Subject cannot swallow a pill and/or applesauce or has an allergy to applesauce.

4.3 Reproductive Potential

4.3.1 Female Contraception

Sexually active females of child-bearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used they should be administered according to the package insert. Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.

Female children and adolescent subjects should be either:

- Premenarchal and either Tanner Stage 1 or less than age 9 years, or
- Females of child-bearing potential with a negative serum β-HCG pregnancy test at the screening visit (Visit 1) and a negative urine pregnancy test at the baseline visit (Visit 2) prior to randomization**.** Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the screening visit (Visit 1), plus condoms. Note: if subject becomes sexually active during the study, they should use 1 of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.3.2 Male Contraception

Male subjects must agree to either abstain from sexual activity or to use condoms.

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

Subjects who discontinue will not be replaced.

4.4.1 Management of Blood Pressure and Pulse During the Study

To ensure that potential blood pressure and pulse increases associated with the use of SHP465 in this population are carefully monitored and appropriately managed, all subjects must be further evaluated if they meet any of the criteria defined below.

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).

Prior to obtaining vital signs (blood pressure and pulse) the subjects should be at rest for at least 3 minutes.

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

- Elevations in the average (of 3 readings) sitting systolic blood pressure defined as an increase of >15 mmHg from the baseline visit (Visit 2) OR a value >95th percentile for age, sex, and height.
- Elevations in average (of 3 readings) sitting diastolic blood pressure defined as an increase of >15 mmHg from the baseline visit (Visit 2) OR an average (of 3 readings) sitting diastolic blood pressure value >95th percentile for age, sex, and height.

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

4.4.1.2 Pulse

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

Any subject that has a resting, sitting pulse rate >116 bpm (based on the average of 3 readings) and or is symptomatic requires further assessment. In this case an unscheduled visit needs to be conducted within 1 business day. At the unscheduled visit, if the subject's pulse rate remains >116 bpm (based on the average of 3 readings) or if the subject is symptomatic then the subject's investigator will discuss the findings with the medical monitor. In careful consideration of the subject's pulse value, magnitude of increase from the baseline, and symptoms, a joint decision between the investigator and the medical monitor will be made regarding continued participation in the study. If a visit cannot be scheduled the next day, the subject may be discontinued from the study.

Any subject with a pulse rate equal or lower than the number for age defined above 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 source documents. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source documents and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol violation
- Withdrawal by subject or parent/LAR
- Lost to follow-up
- Lack of efficacy
- Blood pressure and/or pulse criteria met
- Other (must be specified).

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

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

5 PRIOR AND CONCOMITANT TREATMENT

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

In addition, the subject's lifetime psychoactive medication history and the subject's lifetime nonpharmacological interventions (behavioral therapy) for ADHD will be documented at the screening visit (Visit 1). The type of nonpharmacological intervention for ADHD and dates of occurrences should be recorded.

Psychoactive medications other than the investigational products are not allowed in the study.

Table 2 details the washout period for common prior treatments and highlights excluded medications.

5.1 Prior Treatment

Prior treatment includes all treatment including but not limited to herbal treatments, vitamins, nonpharmacological treatment such as psychotherapy as appropriate received within 30 days prior to the screening visit (Visit 1) or pharmacokinetics equivalent of 5 half-lives, whichever is longer of the date of first dose of investigational product. Prior treatment information must be recorded on the subject's source documents.

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

5.2 Concomitant Treatment

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

5.2.1 Permitted Treatment

Medications permitted during the study are listed below:

- Stable (ie, for at least 3 months prior to the screening visit [Visit 1]) dose of thyroid medication is permitted
- Stable (ie, for at least 1 month prior to the screening visit [Visit 1]) dose of bronchodilator inhalers (however, oral beta-agonists and chronic use of 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 (ALLEGRA®, Sanofi), loratadine (CLARITIN®, Schering-Plough), and cetirizine hydrochloride (ZYRTEC®, McNeil-PPC)
- Over-the-counter nonstimulant cold remedies
- Hormonal contraceptives for female subjects used for at least 30 days prior to the baseline visit (Visit 2) and at least 30 days following the end of the subject's participation in the study
- Continued participation in behavioral therapy, provided the subject has been receiving the therapy for at least 1 month at the time of the baseline visit (Visit 2)

5.2.2 Prohibited Treatment

Shown in Table 2 are excluded medications for this study. Subjects can only be instructed to discontinue a medication for this study after informed consent has been obtained.

Table 2: Common Excluded Treatments and Associated Washout Period Relative to Baseline Visit (Visit 2)

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

[a] These medications may signal that an exclusionary diagnosis is present. The medical monitor should be consulted before instructing a subject to discontinue 1 of these medications for this study.

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

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

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

6.1.1 Blinding the Treatment Assignment

The actual treatment given to individual subjects is determined by a randomization schedule. A randomization schedule will be prepared to assign eligible subjects to 1 of 2 treatment groups with an allocation ratio of 1:1 (SHP465 6.25 mg or placebo). The associated treatment assignments giving details of individual subject treatment are automatically defined by the IWRS. At each visit, subjects will be supplied bottles of investigational product that have been individually allocated by IWRS, and instructed to take 1 capsule every morning. All investigational product (SHP465 6.25 mg or placebo) will appear identical, in order to protect the study blind.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

An IWRS will be employed in this study to manage the tracking and confirmation of shipment, supply, inventory, ordering, expiration, site-assignments, subject randomization, returns, and emergency unblinding of the investigational product.

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

6.2.2 Allocation of Subjects to Treatment

This is a double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule. Subjects will be randomly assigned in a 1:1 ratio to SHP465 6.25 mg or placebo. Randomization will be stratified to ensure approximately 50% of subjects in each age group (6-8 years and 9-12 years), and to facilitate balance of treatment allocation within each age group.

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

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

Individual subject treatment is automatically assigned by the interactive response technology.

Investigational product packaging identification numbers, separate from randomization numbers/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.

6.2.3 Dosing

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

The investigational product may be administered in 1 of the following ways:

- Swallow the capsule whole, or
- Open capsule and sprinkle the entire contents over a spoonful of applesauce. The sprinkled applesauce should be consumed immediately; it should not be stored. Subjects should take the sprinkled applesauce in its entirety without chewing. The dose of a single capsule should not be divided. The empty capsule shells should be discarded.

6.2.4 Unblinding the Treatment Assignment

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

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded on the IWRS and the source documents. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. Any code-breaks that occur must be reported to the CRO and sponsor. Code-break access will be provided to the investigator/designated person at the site and by the CRO medical monitor for the study.

For blinded studies, there will be a provision for unblinding to ensure adequate treatment of the subject in the case of an emergency.

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.

A computer-generated label is applied to the investigational product. All investigational product is labeled with a minimum of the protocol number, pack 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 statement 'CAUTION: New Drug - Limited by Federal (or United States) Law to Investigational Use', and 'Keep out of reach of children', and the sponsor's name and address. Any additional labeling requirements for participating countries and/or controlled substances will also be included on the label.

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

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

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

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

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

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 initials on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

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

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

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

6.4 Drug Accountability

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

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form. The investigator or designee will be required to have a valid DEA Form 223 certificate of registration for 2N Controlled Substances for the duration of the study, and be able to order and distribute 2N Controlled Substances via a valid DEA Form 222.

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

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

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

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

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.

7 STUDY PROCEDURES

7.1 Study Schedule

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

Clinician completed rating scales and assessments conducted by the site, ie, ADHD-RS-5, CGI-S, CGI-I, and C-SSRS should be completed by the same rater with input from the same parent/LAR whenever possible. The parent/LAR completed CSHQ should be completed whenever possible.

Throughout the treatment period of the study, visits should be scheduled as outlined (±2 days) with reference to the baseline visit (Visit 2). The safety follow-up call should be scheduled 7 days post last dose with a +2 day visit window.

Additional unscheduled visits and/or assessments may occur as needed for safety (eg, unscheduled visits for blood pressure and/or pulse measurements).

7.1.1 Screening and Washout Period

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

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

Screening procedures may take place across multiple days to allow enough time to complete all procedures and confirm initial subject eligibility. Screening procedures and dates should be well documented in the source documents. The date of the screening visit (Visit 1) is the date the parent/LAR has signed informed consent for this study. Subjects requiring washout must have an abbreviated physical examination, clinical laboratory tests, and 12-lead ECG repeated if >32 days have elapsed since the safety measurements at the screening visit (Visit 1) were collected.

7.1.1.1 Screening Visit (Visit 1)

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

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

- Eligibility will be established per inclusion and exclusion criteria, including documentation of any prior nonpharmacological treatment, specified Mini International Neuropsychiatric Interview for Children and Adolescents (MINI KID), and C-SSRS criteria. Areas of impairment will be recorded for all subjects for assessing the severity of the subject's condition.
- All adverse events (AEs) occurring after signature of informed consent must be recorded in the source documents and CRF.
- Three ECGs will be taken, with approximately 3 minutes in between each one, to ensure appropriate baseline intervals are established. The investigator will perform the initial interpretation of the ECG immediately after collection to ensure the safety of each subject. The ECG tracing will be sent to the central reader for analysis. Upon review of the report from the central reader, the investigator will re-evaluate the clinical significance of the ECG in light of other safety data for the subject. If abnormal and significant results are observed following assessment by the central reader, the investigator, in consultation with the appointed CRO Medical Monitor, will confirm the subject's eligibility to participate in this study.
- Blood pressure and pulse will be collected 3 times (with approximately 2 minutes in between each collection) using the age-appropriate cuff during the visit.
- The "baseline" version of the C-SSRS should be completed.
- Record historical/concomitant medications as follows:
  - All lifetime psychoactive medications and lifetime nonpharmacological interventions (behavioral therapy) for ADHD
  - Other medications used during the 30 days prior to the screening visit (Visit 1)

A screen failure is a subject who has given informed consent and failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria and has not been randomized or administered investigational product. For screen failure subjects, the investigator or assigned site staff designee will access the IWRS to record the subject as a screen failure.

Subjects cannot be rescreened once they have been designated as a screen failure.

7.1.1.2 Washout Telephone Call

The washout period should be initiated after clinical laboratory test results and 12-lead ECG results have been received and reviewed by the investigator. Eligible subjects will be contacted by a member of the site staff and provided with instructions on discontinuing any protocol-prohibited medications.

During washout, a subject's current prohibited medications (if applicable) will be discontinued for a period of a minimum of 5 times the half-life of the medication. Washout periods for prohibited medications are defined in Table 2.

As part of the washout telephone call, site personnel should perform the following procedures.

- Schedule the baseline visit (Visit 2).
- Review the inclusion/exclusion criteria.
- Ask about any concomitant medications that the subject is taking. If new concomitant medications that require washout are noted, instructions for appropriate washout should be provided.
- Provide instructions on discontinuing any medication requiring washout.
- Determine if any AEs have occurred since the screening visit (Visit 1).

If a medication washout is not necessary, the washout telephone call will include all the above procedures except providing instructions on discontinuing any current medications and must occur prior to the baseline visit.

7.1.1.3 Baseline Visit (Visit 2)

Once the screening central clinical laboratory tests and 12-lead ECG results have been obtained, in addition to repeat assessments (if required), and the subject has completed the required washout period (if applicable), the subject will return to the site for the baseline visit (Visit 2).

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

Table 1 outlines all procedures to be conducted during the baseline visit (Visit 2) with further clarification provided below:

- For subjects with >32 days since the safety measurements at the screening visit (Visit 1) were collected, an abbreviated physical examination, 12-lead ECG in triplicate, serum pregnancy test, urine drug screen, and all clinical laboratory tests must be repeated, and the results reviewed by the investigator prior to the subject being enrolled.
- Blood pressure and pulse will be collected 3 times (with approximately 2 minutes in between each collection) using the age-appropriate cuff during the visit.
- If >32 days since the screening visit, 3 ECGs will be taken, with approximately 3 minutes in between each one, to ensure appropriate baseline intervals are established. The investigator will perform the initial interpretation of the ECG immediately after collection to ensure the safety of each subject and to determine eligibility. The ECG tracing will be sent to the central reader for analysis. Upon review of the report from the central reader, the investigator will re-evaluate the clinical significance of the ECG in light of other safety data for the subject. If abnormal and significant results are observed following assessment by the central reader, the investigator, in consultation with the appointed CRO Medical Monitor, will confirm the subject's continued participation in this study.

- The C-SSRS "since last visit" version should be completed.
- For eligible subjects, the investigator or assigned site staff designee will access the IWRS to enroll the subject and obtain an investigational product bottle number to dispense to the subject. Subjects will be dispensed a 9-count bottle of investigational product to cover them until their next regularly scheduled visit. Subjects will be instructed to take 1 capsule each day. Dosing will begin the morning following the baseline visit (Visit 2).

7.1.2 Treatment Period

7.1.2.1 Treatment Period (Visits 3-5)

During the 4 weeks of treatment, visits will be scheduled every 7 days (±2 days) to assess safety and efficacy based on TEAEs, efficacy, and the dosing guidelines in Section 6.2.3.

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

- Table 1 outlines all procedures to be conducted during Visits 3 to 5 and should serve as the primary point of reference regarding study procedures. Further clarification for these visits is outlined as follows: Subjects will be dispensed a 9-count bottle of investigational product to cover them until their next regularly scheduled visit. Subjects will be instructed to take 1 capsule each day. Dosing will begin the morning after each visit.
- Blood pressure and pulse will be collected 3 times (with at least 2 minutes in between each collection) during the visit. The average of each set of 3 measurements will be used to determine continued participation in the study (see Section 4.4.1).
- Scales should be completed by the same rater with input from the same parent/LAR whenever possible.
- The C-SSRS "Since Last Visit" Version of the Pediatric/Cognitively Impaired Version should be completed during the last treatment visit.

7.1.2.2 End of Study/Early Termination Visit (Visit 6/ET)

All enrolled subjects who complete the study or discontinue early will complete Visit 6/ET.

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

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

- Unused investigational product and empty containers will be collected to calculate medication compliance.
- Blood pressure and pulse will be collected 3 times (with approximately 2 minutes in between each collection) using the age-appropriate cuff during the visit. The average of each set of 3 measurements will be used to determine continued participation in the study (see Section 4.4.1).

- Scales should be completed by the same rater with input from the same parent/LAR whenever possible.

7.1.3 Safety Follow-up Period

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

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

7.1.4 Additional Care of Subjects After the Study

Subjects who have completed the study at Visit 6 may be evaluated for eligibility to enter a long-term safety study of SHP465.

The subject's primary care physician will be responsible for determining the appropriate and available treatment options upon study completion for subjects who did not enroll into the long-term safety study of SHP465. However, to maintain the integrity of the study, subjects will not be unblinded to treatment assignment at the end of their participation in the study.

7.2 Study Evaluations and Procedures

The individual indicated in each scale description will perform all assessments listed below. Assessments are to be performed according to the schedule shown in Table 1.

Care must be taken by the site personnel or the investigator to fully explain the scale prior to completion.

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

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics such as age, sex, weight, and height will be collected throughout the study according to Table 1.

7.2.2 Screening Assessments

7.2.2.1 Mini International Neuropsychiatric Interview for Children and Adolescents

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.

Additional symptom questions within each disorder section are asked only if the screen questions are positively endorsed. The MINI 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 a third of the time as the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version. The MINI-KID Standard Version 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. 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.

7.2.3 Efficacy

7.2.3.1 Attention-deficit/Hyperactivity Rating Scale

The ADHD-RS-5 Child, Home Version (DuPaul et al. 2016), the primary efficacy measure, is completed by the clinician and will be administered at baseline (Visit 2) and each subsequent visit up to and including Visit 6/ET to capture the ADHD symptoms within each study period.

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 0-54. 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.

7.2.3.2 Clinical Global Impression

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

The investigator will perform the CGI-S to rate the severity of a subject's condition on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill subjects) at the baseline visit (Visit 2). Additionally at the baseline visit, the investigator should establish 3 target areas of improvement with the subject and the subject's parent/LAR.
To generate the targets, an open-ended question such as "If this program of treatment works for

your child, what things do you hope he/she will be doing better?" should be asked. Ratings will be completed with respect to ADHD symptoms.

At each visit from Visit 3 up to and including Visit 6/ET, the investigator will assess the subject's improvement relative to the 3 target areas of improvement recorded at the baseline visit (Visit 2), on the CGI-I, a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

The CGI-S and CGI-I should be completed by a clinician experienced in the evaluation of children with ADHD. Since the CGI-I is an important measure for guidance in dosing decisions, the CGI-I must be performed by a principal investigator or sub-investigator who is medically/clinically responsible for the subject and 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 CGI-S and the CGI-I used in this study are included in Appendix 3.

7.2.4 Safety

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

7.2.4.1 Medical and Medication History

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

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

7.2.4.2 Physical Examination

A full physical examination will be performed at the screening visit (Visit 1) and Visit 6/ET. Additionally, an abbreviated physical examination is required at the baseline visit (Visit 2) if more than 32 days have elapsed since the physical examination completed as part of the screening visit (Visit 1) was performed. The physical examination will be performed by a qualified, licensed individual per local requirements (eg, physician, physician assistant, or nurse practitioner).

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

- General appearance
- Skin
- Head, Eyes, Ears, Nose, and Throat

- Spine/Neck/Thyroid
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Musculoskeletal
- Neurological

If an abbreviated physical examination is required at the baseline visit (Visit 2), a review of the body systems will include the following:

- General Appearance
- Respiratory
- Cardiovascular

Abnormalities identified at the screening visit (Visit 1) will be documented in the subject's source documents. Changes after the screening visit (Visit 1) will be captured as AEs, as determined by the investigator.

7.2.4.3 Adverse Event Collection

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

7.2.4.4 Vital Signs (Including Height and Weight)

Measurements of oral or tympanic temperature and sitting respiratory rate will be performed at the screening visit (Visit 1) and/or baseline (Visit 2) only.

Measurements of sitting systolic and diastolic blood pressure and pulse will be performed at each visit to the site. Blood pressure, pulse, and respiratory rate will be determined after subjects have remained seated for a minimum of 3 minutes.

Blood pressure will be determined by an age-appropriate cuff (the same unit and 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 age-appropriate cuff should be approximately two-thirds the length/width of the subject's arm (from elbow to shoulder). All blood pressure measurements should be taken using the same arm and be performed by the same site personnel (if possible) throughout the study.
The age-appropriate cuff will obtain 3 measurements with approximately 2 minutes in between each collection for blood pressure and pulse and report the average of the 3 measurements for

each parameter. The 3 individual measurements, time collected, and averaged reading should be recorded in the source.

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

Weight will be captured at each visit to the site. The same calibrated scale should be used for all weight measurements. Weight should be measured in pounds or kilograms without shoes and with light clothing and should be recorded to the nearest 0.1 pound or 0.1 kilogram.

Any clinically significant deviations from screening (Visit 1) vital signs which are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

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

Clinical laboratory assessments will be performed at the screening visit (Visit 1) and Visit 6/ET. Additionally, clinical laboratory tests are required to be repeated prior to the baseline visit (Visit 2) with results reviewed before enrolling the subject in the study if more than 32 days have elapsed since the clinical laboratory assessments completed as part of the screening visit (Visit 1) were performed.

The following clinical laboratory assessments will be performed:

Biochemistry and Endocrinology

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

Total Cholesterol	Calcium
Aspartate Aminotransferase	Urate
Phosphorus	Blood Urea Nitrogen
Alanine Aminotransferase	Total Bilirubin

Sodium	Creatinine
Alkaline Phosphatase	Glucose
Potassium	Albumin
Gamma Glutamyl Transferase	Protein
Thyrotropin	Lactate Dehydrogenase
Thyroxine, Free	

Hematology

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

Hemoglobin	Neutrophils
Hematocrit	Lymphocytes
Red Blood Cells	Monocytes
Platelets	Eosinophils
White Blood Cell count – total and differential	Basophils
Mean Corpuscular Hemoglobin	Neutrophils Band Form
Mean Corpuscular Hemoglobin Concentration	Mean Corpuscular Volume

Urinalysis

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

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

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

7.2.4.6 Urine Drug Screen

A urine drug and alcohol screen will be conducted at the screening visit (Visit 1). As a reminder, a urine drug screen should be repeated prior to the baseline visit (Visit 2) if more than 32 days have elapsed since the screening visit (Visit 1).

Urine samples (~10 mL) will be collected for this testing and will be evaluated at the central laboratory. The following drugs/drug classes will be tested:

Urine Drug Screen

Cocaine	Cannabinoids
Phencyclidine	*d*-amphetamine
Benzodiazepines class	Barbiturates class
Opiates class	Propoxyphene
Methaqualone	Methadone
Methamphetamine	

The urine drug screen must be negative at the screening visit (Visit 1) for the subject to be eligible to enroll in the study.

If the subject has a positive urine drug screen at the screening visit (Visit 1) that the investigator is able to attribute to a medication that has been prescribed to the subject, the urine drug screen must be repeated prior to the baseline visit (Visit 2) and must be negative so the investigator can verify that the disallowed medication which caused a positive result at the screening visit (Visit 1) has been discontinued prior to the baseline visit (Visit 2).

7.2.4.7 Pregnancy Test

A serum β-HCG pregnancy test is performed on all females of child-bearing potential at the screening visit (Visit 1). Additionally, the serum pregnancy test must be repeated at the baseline visit (Visit 2) if greater than 32 days have elapsed since the screening visit (Visit 1). The results must be reviewed by the investigator before the subject can be randomized.

A urine pregnancy test is performed on all females of child-bearing potential at the baseline visit (Visit 2), and at the final visit (Visit 6/ET), or if pregnancy is suspected, or on withdrawal of the subject from the study.

7.2.4.8 Electrocardiogram

A 12-lead ECG will be performed at the screening visit (Visit 1), Visit 4, and Visit 6/ET. At screening, 3 ECGs taken approximately 3 minutes apart will be collected; if >32 days have passed since screening, these ECGS will be collected in triplicate at Visit (Visit 2) to ensure appropriate baseline intervals are established. Additional ECGs may be performed during the study at the investigator's discretion.

All ECGs will be performed after 3 minutes of rest using the central ECG provider's equipment and will be sent to the central ECG provider electronically.

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

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

All ECGs transmitted to the central ECG reader will be analyzed. If the central ECG reader receives multiple ECGs, the first readable ECGs will be analyzed as the scheduled ECG. Every ECG transmitted to the central ECG reader will have corresponding 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.

7.2.4.9 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 wakings, parasomnias, sleep disordered breathing, and daytime sleepiness. The CSHQ will be conducted at each visit to the site starting with the baseline visit (Visit 2) and will be completed by the subject's parent/LAR.

7.2.4.10 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 at Baseline (Visit 2), and each visit through Visit 6/ET. The title, version, and date of the PSQ version used in this study are included in Appendix 3.

7.2.4.11 Columbia-Suicide Severity Rating Scale

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

The C-SSRS contains 2 required items pertaining to suicidal ideation, 4 required items pertaining to suicidal behavior, and 1 required item pertaining to nonsuicidal self-injurious behavior. There are 8 additional suicidal ideation items and 2 additional suicidal behavior items which are completed in cases of positive responses for other items, as well as 2 items for completed suicide and suicide behavior present during the interview. Thus, there is a maximum of 19 items to be completed.

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

Two versions of the C-SSRS are used in this study:

- The "baseline" version will be administered at the screening visit (Visit 1) and will be completed for all subjects.
- The "since last visit" version will be completed for all subjects at all study visits after the screening visit (Visit 1).

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.

7.2.4.12 Suitability of the Subject to Remain in the Study

At each visit (except for Visit 6/ET) starting with the baseline visit (Visit 2), 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 BMI) and will evaluate for the presence of insomnia or decreased appetite potentially leading to weight loss. In cases where the subject has clinically significant decreases 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.

7.2.5 Others

No clinical pharmacology, pharmacodynamic, pharmacogenomics, or health-related quality of life assessments will be performed.

7.2.6 Volume of Blood to be Drawn From Each Subject

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

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Safety[a]	Biochemistry and Choriogonadotropin Beta (β-HCG)[b]	3	2	6
	Hematology [a]	2	2	4
Total mL				10

β-HCG= beta human chorionic gonadotropin

[a] Biochemistry and hematology clinical laboratory tests will be repeated at baseline if 32 days or longer have elapsed since the screening visit (Visit 1).

[b]β-HCG testing for females of childbearing potential only.

During this study, it is expected that approximately 10 mL of blood will be drawn from all subjects, regardless of sex.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 10 mL. 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. If a catheter is used, the first 1 mL of blood from each sampling will be discarded.

8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

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

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

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

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

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of 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 first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

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

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

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

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Outcome Categorization

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

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

8.1.4 Symptoms of the Disease Under Study

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

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the 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 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.3.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Pharmacovigilance Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report 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. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Trial Serious Adverse Event Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Trial Serious Adverse Event Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

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

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a 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 an investigational product exceeding a prespecified total daily dose of 1 capsule of the product.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

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

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

The dispensing, administration, and/or use of the unassigned treatment is/are always reportable as a medication error.

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 SHP465 investigator's brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Pharmacovigilance Department and the CRO/Shire Medical Monitor within 24 hours of the first awareness of the event.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

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

8.2.3 Serious Adverse Event Definition

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

- Results in death.
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

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

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

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

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

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

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

In addition the clinical CRO is 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 EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

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

9.2 Clinical Data Management

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

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

9.3 Data Handling Considerations

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

9.4 Statistical Analysis Process

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

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

The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513).

9.5 Data Monitoring Committee

An external independent Data Monitoring Committee (DMC) was set up to review the data pertaining to safety and tolerability of the study therapy for the duration of this program, which includes studies SHP465-112, SHP465-308, and SHP465-309. The DMC will review the data pertaining to safety and tolerability 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, which will be available before the administration of investigational product.

9.6 Planned Interim Analysis

A blinded interim analysis at the late stage of the trial (when approximately 75% of all randomized subjects have either completed or discontinued from the study) will be performed to reassess the sample size in case of an underestimated variability postulated at the design stage.

Using the cumulative real data, a blinded, pooled analysis of both treatment groups for estimating variability will be conducted. If the re-estimated pooled standard deviation is larger than the 14 postulated at the design stage, the final total number of subjects to be enrolled will be calculated using the re-estimated pooled standard deviation together with the assumed treatment difference of 11.9 (Friede and Kieser 2006). If the re-estimated pooled standard deviation is smaller than 14, the sample size will not be adjusted.

9.7 Sample Size Calculation and Power Considerations

The sample size planned at study initiation was estimated for the primary comparison of SHP465 at 6.25 mg with placebo by using nQuery Advisor 7.0.

Approximately 60 subjects will be randomized in a 1:1 ratio to SHP465 at 6.25 mg and placebo to achieve 52 completers for the study (26 in each treatment group) and 85% power for the primary efficacy analysis at the 2-sided 0.05 significance level. The sample size planned is estimated based on the primary comparison between SHP465 at 6.25 mg and placebo on the primary efficacy endpoint, change from baseline in ADHD-RS-5 total score at Visit 6 (Week 4). Assumptions for the calculation include the true mean difference of 11.9 with the common standard deviation (SD) of 14 for the primary efficacy endpoint, for an effect size of 0.85, and a dropout rate of 15%.

The effect size of 0.85 is low compared with that observed in recently completed study (SHP465-305) of children and adolescents aged 6-17 years with ADHD treated with SHP465. The SHP465-305 study yielded an effect size of 0.93 in children aged 6-12 years (101 subjects).

9.8 Study Population

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

The **randomized set** will consist of all subjects in the screened set for whom a randomization number has been assigned.

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

The **full analysis set** (FAS) will consist of all subjects in the safety set who have at least 1 post-dose ADHD-RS-5 Total Score.

9.9 Efficacy Analyses

All efficacy analyses will be performed using the FAS. All statistical tests will be 2-sided hypothesis tests. Also, all confidence intervals will be 2 sided with 95% coverage, unless stated otherwise. The primary and key secondary analyses will be conducted based on the entire age group in the FAS.

Handling of missing data rules will be described in the SAP.

9.9.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the change from baseline of the ADHD-RS-5 Total Score at Visit 6 (Week 4). The baseline ADHD-RS-5 Total Score is the last value obtained prior to taking the first dose of investigational product, usually at Visit 2.

The primary efficacy analysis will be conducted over the FAS for the change from baseline in the ADHD-RS-5 Total Scores, including all assessments from Visit 3 (Week 1) up to Visit 6 (Week 4). The primary efficacy endpoint will be analyzed by using the linear mixed-effects model for repeated measures (MMRM) with treatment group, visit, age group (6-8 years vs. 9-12 years), and the interaction of treatment group with visit as factors, baseline ADHD-RS-5 Total Score as a covariate, and the interaction of baseline ADHD-RS-5 Total Score with visit adjusted in the model. The primary contrast of interest will be at Visit 6 (Week 4) for SHP465 6.25 mg compared with placebo at the 2-tailed significance level of 0.05.

The null and alternative hypotheses of the primary efficacy analysis will be the following:

- Null hypothesis: There is no difference in primary endpoint mean change from baseline at Visit 6 (Week 4) in ADHD-RS-5 total scores between SHP465 6.25 mg and placebo
- Alternative hypothesis: There is a difference in primary endpoint mean change from baseline at Visit 6 (Week 4) in ADHD-RS-5 total scores between SHP465 6.25 mg and placebo.

As the primary efficacy analysis (MMRM) relies on the assumption that the missing data mechanism follows the MAR (missing-at-random) scenario, sensitivity analyses to examine the effect of data that are missing not at random and the robustness on the results of the primary analysis will be conducted. One sensitivity analysis model assumes that a subject on SHP465 6.25 mg treatment with missing data follows the distribution of the placebo responses, ie, the means and the intrasubject correlations based on the placebo responses will apply. Another sensitivity analysis model assumes that subjects who drop out perform worse than MAR by a penalty. The details of the sensitivity analysis methods will be specified in the SAP.

The observed and change from baseline ADHD-RS-5 Total Score will be summarized at each applicable visit using the number of subjects, mean, standard deviation, median, minimum, and maximum values.

9.9.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoint, CGI-I, will be analyzed using the same analysis method (MMRM) as for the primary efficacy endpoint. The baseline CGI-S score will be used as the covariate. The primary contrast of interest will be at Visit 6 (Week 4) for SHP465 6.25 mg compared with placebo at the 2-tailed significance level of 0.05. Appropriate sensitivity analyses to explore the effect of data that are missing not at random on the results of the key secondary efficacy analysis will be specified in the SAP.

The CGI-I will be summarized at each applicable visit using the number of subjects, mean, standard deviation, median, minimum, and maximum values.

The key secondary efficacy measurement will also be analyzed using the proportion of subjects with an “improved” CGI-I measurement at Visit 6/ET (Week 4/ET). The CGI-I categories will be dichotomized into 2 categories, “very much improved” and “much improved” classified as “improved” and all other assessed categories grouped together as “not improved”. If missing data exist at the Visit 6 (Week 4) visit, the visit will be imputed by carrying forward the last post baseline observation value. The secondary efficacy analysis for the dichotomized CGI-I will be conducted to compare SHP465 6.25 mg and placebo on the FAS for the “improved” rate using a Cochran-Mantel-Haenszel test stratified by age group and CGI-S value at baseline.

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

In order to protect the study-wide Type I error at the 2-sided 0.05 level for testing across the primary and the key secondary hypotheses, the Fixed-Sequence Test procedure will be applied. The hypotheses will be tested in order of the primary (ADHD-RS-5 Total Score) and then the key secondary (CGI-I), if significant for the primary, each at the 2-sided 0.05 significance level. Both tests in the sequence are based on the MMRM.

9.9.3 Exploratory Efficacy Endpoints

Each ADHD-RS-5 subscale will be analyzed using a similar model as the primary efficacy endpoint and summarized descriptively at each visit by treatment group.

Treatment effect of SHP465 6.25 mg on primary and key secondary measures will be estimated using a similar model as the primary efficacy endpoint for each age group (6-8 years vs. 9-12 years), sex, race (white and nonwhite), and ethnicity subgroup.

The primary and key secondary data will be descriptively summarized by treatment within each sex, race (white and nonwhite), and ethnicity subgroup.

9.10 Safety Analyses

The safety data will be analyzed on the safety set. Safety endpoints include the occurrence of TEAEs, vital signs (systolic and diastolic blood pressure, pulse), BMI and weight, ECG results, clinical laboratory test results, and responses to CSHQ and C-SSRS.

Exposure to investigational product will be summarized.

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

The number of events, incidence, and percentage of TEAEs will be calculated overall, by SOC, by preferred term, and by treatment group. Treatment-emergent adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Vital signs (systolic and diastolic blood pressure, and pulse), weight, height, and BMI including potentially clinically important vital signs will be summarized by treatment and visit using the appropriate descriptive statistics.

The ECG results including potentially clinically important results will be summarized by treatment and visit.

Clinical laboratory test results will be descriptively presented by treatment group for each visit. Shifts of clinical laboratory abnormality from baseline to Visit 6/ET will be presented. Number and percent of subjects with potentially clinically important laboratory values will be presented by treatment group.

The PSQ results will be summarized by treatment and visit. Continuous variables, e.g., time to go to sleep and time spent awake, will be summarized using number of observations, mean and standard deviation, median, and minimum and maximum values. Categorical values, e.g., quality of sleep, will be summarized using number of observations and percentages. Detailed analyses of the PSQ will be described in the SAP.

The CSHQ results will be summarized by treatment and visit using appropriate descriptive statistics. Detailed analyses of the CSHQ will be described in the SAP.

The C-SSRS results will be summarized and listings of the C-SSRS data will be provided for subjects with a positive response.

As the exploratory safety endpoint, the safety data on TEAEs will also be descriptively summarized by treatment within each age group (6-8 years vs. 9-12 years), sex, race (white and nonwhite), and ethnicity subgroup.

A listing of the C-SSRS data will be provided for subjects with a positive response. A listing of clinical laboratory data will be presented for all subjects.

As the exploratory safety endpoints, the safety data on TEAEs, vital signs, ECGs, clinical laboratory test results, PSQ and CSHQ will also be descriptively summarized by treatment within each age group.

10 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

The name and address of each third party vendor (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 EU Directive 2001/20/EC (2001), as well as all applicable national and local laws and regulations.

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

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

10.1.2 Public Posting of Study Information

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

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

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for 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, EU Directive 2001/20/EC (2001), and applicable regulatory requirements and guidelines.

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

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

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

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC (2001) as amended by Directive 2003/63/EC (2003) and ICH Guidance E3 (1996).

10.2.2 Protocol Adherence and Investigator Agreement

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

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

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

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

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

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

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

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

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

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

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc). These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

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

10.2.3.3 Audit/Inspection

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

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

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

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

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent, where applicable from all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject and/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 where applicable which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

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

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

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

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

The investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor, the investigator or for multicenter studies the coordinating principal investigator. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

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

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

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP465; national or local regulatory authorities; and the IRB(s) /EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (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, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a 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 paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

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

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors 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, Version 1.0	07 September 2017	Global

APPENDIX 2 DIAGNOSTIC CRITERIA/DISEASE CLASSIFICATION

APPENDIX 2.1 DSM-5 CRITERIA FOR ATTENTION DEFICIT/HYPERACTIVITY DISORDER

A. Either (1) or (2):

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

Inattention

a) often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities

b) often has difficulty sustaining attention in tasks or play activities

c) often does not seem to listen when spoken to directly

d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)

e) often has difficulty organizing tasks and activities

f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)

g) often loses things necessary for tasks or activities (eg, toys, school assignments, pencils, books, or tools)

h) is often easily distracted by extraneous stimuli

i) is often forgetful in daily activities

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

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat

(b) often leaves seat in classroom or in other situations in which remaining seated is expected

(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)

(d) often has difficulty playing or engaging in leisure activities quietly

(e) is often “on the go” or often acts as if “driven by a motor”

(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed

(h) often has difficulty awaiting turn

(i) often interrupts or intrudes on others (eg, butts into conversations or games)

B. 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:

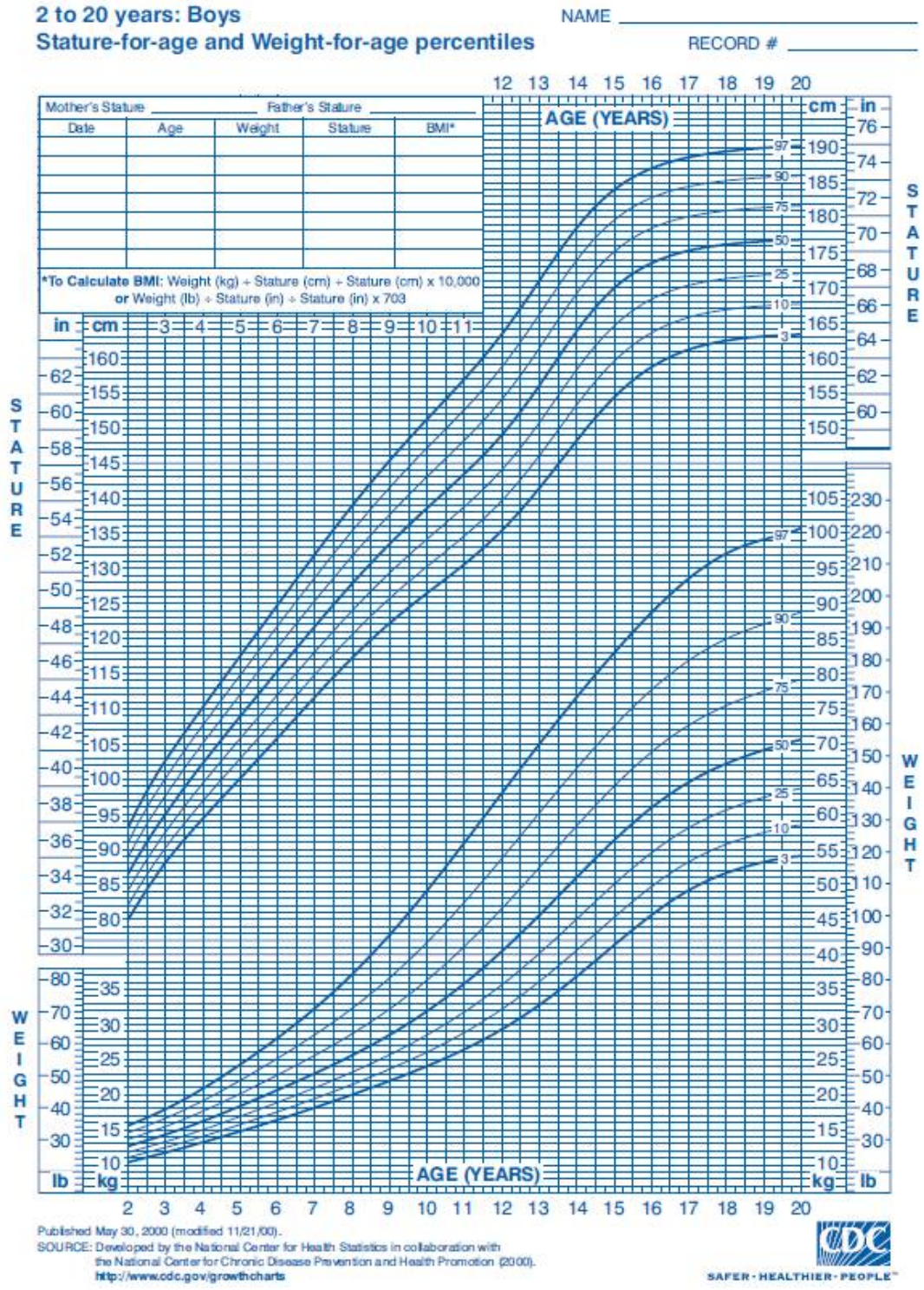
314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type:
if both Criteria A1 and A2 are met for the past 6 months

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 FOR BOYS BY AGE AND HEIGHT PERCENTILE

Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

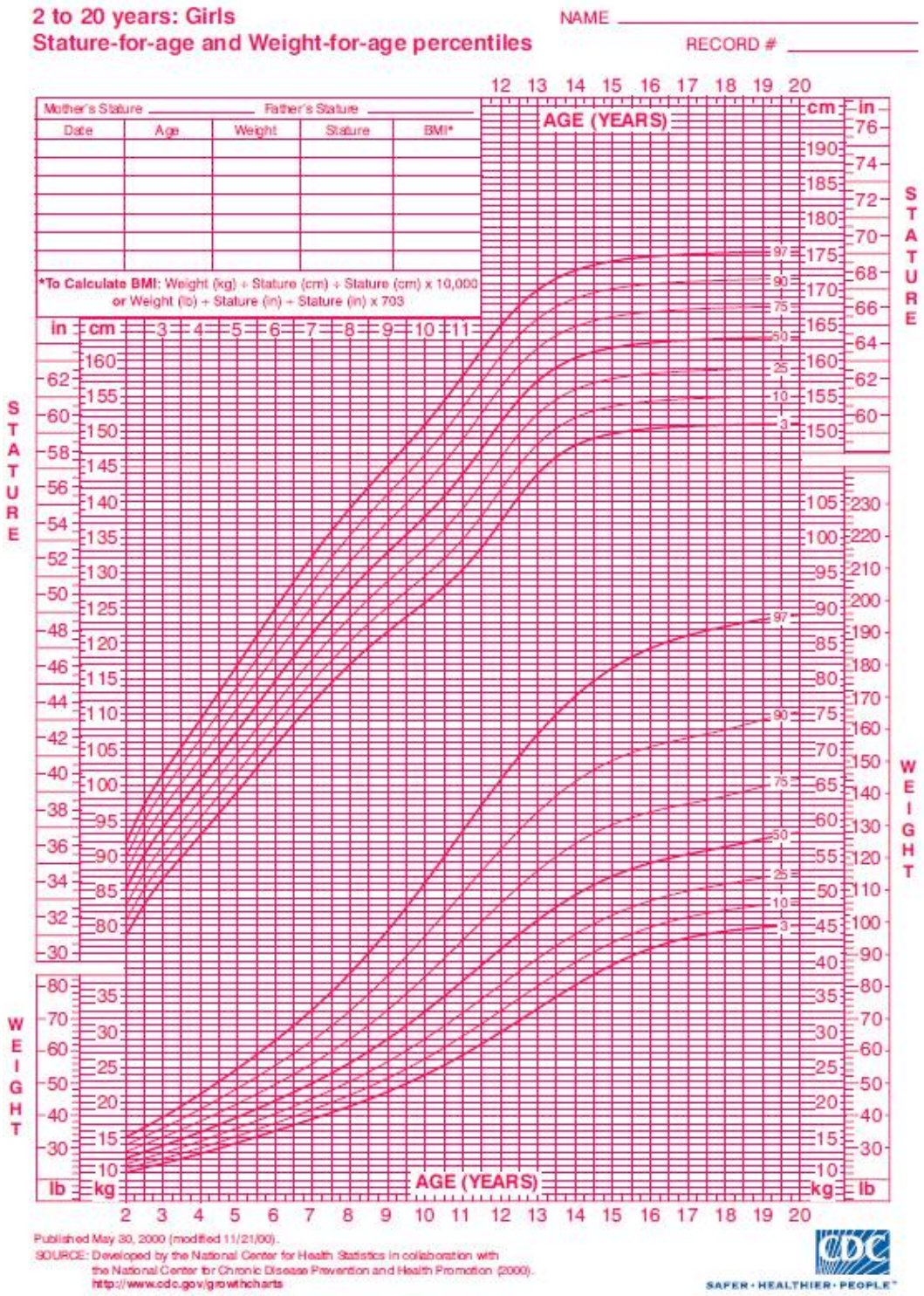
* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for boys with height percentiles given in Table 3 (i.e., the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

Source: National Heart Lung and Blood Institute; May 2004
http://www nhlbi nih.gov/guidelines/hypertension/child_tbl htm

Note: To determine the eligibility of a male subject for entry in the study (based on the study inclusion criteria), first determine the percentile of height for the subject based on their age (as a whole number based on the subject's last birthday; see the Boys' Stature-for-age and Weight-for age Percentiles). For subjects who fall between 2 height percentiles, use the lower of the 2 percentiles. Once the subject's age and height percentile for age are determined, use the table above to determine eligibility. The subject's systolic and diastolic blood pressure readings at the screening visit (Visit 1) and the baseline visit (Visit 2) must not exceed the corresponding table value (90^{th} blood pressure percentile) for their age and height percentile.

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

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

For research purposes, the standard deviations in Appendix Table B–1 allow one to compute BP Z-scores and percentiles for girls with height percentiles given in Table 4 (i.e., the 5th,10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z-scores given by (5% = -1.645; 10% = -1.28; 25% = -0.68; 50% = 0; 75% = 0.68; 90% = 1.28%; 95% = 1.645) and then computed according to the methodology in steps 2–4 described in Appendix B. For children with height percentiles other than these, follow steps 1–4 as described in Appendix B.

Source: National Heart Lung and Blood Institute; May 2004
http://www nhlbi nih.gov/guidelines/hypertension/child_tbl htm

Note: To determine the eligibility of a female subject for entry in the study (based on study inclusion criteria), first determine the percentile of height for the subject based on their age (as a whole number based on the subject's last birthday; see the Girls' Stature-for-age and Weight Percentiles). For subjects who fall between 2 height percentiles, use the lower of the 2 percentiles. Once the subject's age and height percentile for age are determined, use the table above to determine eligibility. The subject's systolic and diastolic blood pressure readings at the screening visit (Visit 1) and the baseline visit (Visit 2) must not exceed the corresponding table value (90^{th} blood pressure percentile) for their age and height percentile.

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 Child, Home Version	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 above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above and a new master file containing the revised scale/assessment will be provided to the site.