STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP465-308
Protocol Title:	A Phase 3, Open-label, Multicenter, 12-Month Safety and Tolerability Study of SHP465 in Children Aged 4 to 12 Years Diagnosed with Attention-deficit/Hyperactivity Disorder
Drug:	SHP465
Sponsor:	Shire Development LLC 300 Shire Way, Lexington, MA 02421
Version No. and Date	Version 2.0, 14 February 2019

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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	Clinical Global Impressions
CGI-I	Clinical Global Impressions – Improvement
CGI-S	Clinical Global Impressions – Severity of Illness
CRF	case report form
CRO	contract research organization
CSHQ	Children's Sleep Habits Questionnaire
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	data monitoring committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EC	Ethics Committee
ECG	electrocardiogram
ET	early termination
FAS	full analysis set
FoTA	Final on-Treatment Assessment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IWRS	interactive web response system
LAR	legally authorized representative
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
PSQ	Post Sleep Questionnaire
PK	pharmacokinetic(s)
RBC	red blood cells
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
US	United States
WBC	white blood cells
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of safety and efficacy data as described in the SHP465-308 study protocol Amendment version 2.0 dated 18 May 2018, the protocol administrative change #1 dated 17 Oct 2017, the protocol administrative change #2 dated 27 Nov 2017, the protocol administrative change #3 dated 22 Mar 2018, and the protocol administrative change #4 dated 21 Sep 2018. Specifications for tables, figures, and listings are contained in a separate document.

Final results of the SHP465-309 study have confirmed that the dose of 6.25 mg was safe and well-tolerated but was not efficacious in the treatment of ADHD in children 6-12 years old. Shire decided to terminate the ongoing open-label SHP465-308 study on 14 Dec 2018. All data collected will be used in the analyses and the analysis results will be reported.

2. STUDY DESIGN

2.1 General Study Design

Study SHP465-308 is a Phase 3, open-label, multicenter, 12-month safety and tolerability study of SHP465 in children (aged 4-12 years, inclusive, at the time of consent was obtained in the antecedent study [SHP465-112 or SHP465-309] or at the time of consent into this study if directly enrolled) with ADHD.

Approximately 80 subjects will be enrolled into this study. Subjects enrolled in this study will be divided into 2 groups based on participation in antecedent studies as follows:

- Subjects in Group A are those who have been rolled over from antecedent studies (SHP465-112 or SHP465-309). These subjects do not need additional screening and washout procedures.
- Subjects in Group B will be directly enrolled subjects who will be required to undergo full screening and washout procedures before first dose.

Antecedent study SHP465-112 is a Phase 1 study in subjects aged 4-5 years who were administered 6.25 mg SHP465. Antecedent study SHP465-309 is a Phase 3 study in subjects aged 6-12 years who were randomized to either 6.25 mg SHP465 or placebo.

For subjects in Group A, the baseline defined in the antecedent study, SHP465-112 or SHP465-309, will serve as the baseline visit (Visit 2) for analyses of this study. For subjects in Group B, a screening visit will precede a washout period. Data will be summarized using the following layouts:

- For full analysis, data will be summarized using the following 5 columns:
  - Antecedent Study:
    - Group A 112 SHP465 6.25mg
    - Group A 309 Placebo
    - Group A 309 SHP465 6.25mg
  - Direct Enrollment: Group B SHP465 6.25mg
  - Total
- For full analysis by-age group summaries, data will be summarized using the following 3 columns:
  - Group A Antecedent Study
  - Group B Direct Enrollment
  - Total

For all subjects in Group A and Group B, SHP465 will be administered as a daily morning dose of 6.25 mg in the treatment of ADHD.

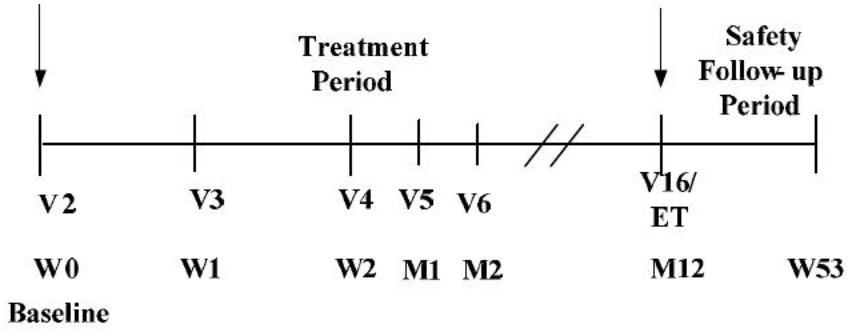
The study periods are as outlined below and presented in Figure 1 and Figure 2:

- **Group A**:
  - Treatment period (12 months)
  - Safety follow-up (7 days)
- **Group B**:
  - Screening and washout period (up to 32 days)
  - Treatment period (12 months)
  - Safety follow-up (7 days)

The duration of treatment and evaluation for subjects in both groups will be 12 months. For safety and efficacy assessments, subjects in Group A will be required to visit the site up to 15 times and subjects in Group B will be required to visit the site up to 16 times.

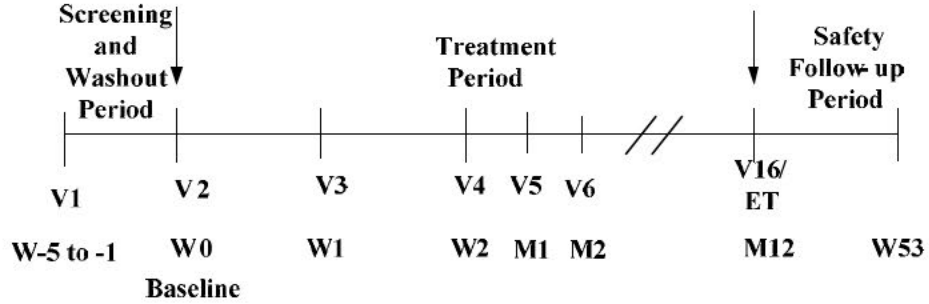
This study will be conducted at approximately 50 sites in the United States (US).

Figure 1: Study Design Flow Chart for Group A



ET=early termination; M=month; V=visit; W=week

Figure 2: Study Design Flow Chart for Group B



ET=early termination; M=month; V=visit; W=week

2.2 Randomization

No randomization will be conducted for this study.

2.3 Blinding

This is an open-label study. No blinding is needed.

2.4 Schedule of Assessments

Table 1 and Table 2 below present a schedule of study assessments.

Table 1 Schedule of Assessments for Group A

Period	**Baseline**	**Treatment Period**														**1-Week Safety Follow-up**
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ ET**[b]	**Telephone Call**
Assessment Week/Month	**0**	**W1**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**W53**
Assessment Day	**0**	**7**	**14**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**	**367**
Informed consent/assent																
Inclusion/exclusion criteria[c]	✓															
Subject demographics	✓															
Medical and medication history [d]	✓															
Physical examination	✓														✓	
Vital signs[e, f]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Height[g]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Weight[g]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Clinical laboratory tests[h]	✓								✓						✓	
Electrocardiogram (12-lead)[i]	✓		✓		✓		✓		✓		✓		✓		✓	
Serum pregnancy test[l]	✓															
Urine pregnancy test[l]				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
ADHD-RS-5[k]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CGI-I[j]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
PSQ[j]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CSHQ[j]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
C-SSRS since last visit version[k]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Suitability of subject to remain in study[j]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

Table 1 Schedule of Assessments for Group A

Period	Baseline	Treatment Period														1-Week Safety Follow-up
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16/ ET[b]	Telephone Call
Assessment Week/Month	0	W1	W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	W53
Assessment Day	0	7	14	30	60	90	120	150	180	210	240	270	300	330	360	367
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Access IWRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigational product dispensed	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Investigational product returned		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigational product compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

ADHD-RS-5 =Attention-deficit/Hyperactivity Disorder-Rating Scale 5, Child, Home Version; BMI=body mass index; CGI-I=Clinician's Global Impressions − Improvement; CGI--S=Clinician's Global Impressions – Severity of Illness; CSHQ=Children's Sleep Habits Questionnaire; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; IWRS=interactive web response system; M=month; MINI-KID=Mini International Neuropsychiatric Interview for Children and Adolescents; PSQ=Post Sleep Questionnaire; W=week.

[a] Visit windows are with respect to baseline (Visit 2): ±2 days for Visit 3-4 and ±5 days for Visit 5-16 during treatment period, and +2 days for the safety follow up telephone call.

[b] Subjects who terminate early will undergo the evaluations listed for Visit 16.

[c] Inclusion/exclusion criteria will be reviewed at baseline (Visit 2).

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

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

[f] Blood pressure and pulse rate will be measured at each study visit. Temperature and respiratory rate will be measured at baseline (Visit 2).

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

[h] Clinical laboratory evaluations will include hematology, biochemistry, endocrinology, and urinalysis.

[i] Electrocardiograms will be recorded in triplicate with at least 3 minutes in between each collection at baseline only.

[j] Whenever possible, the same individual should complete/rate consistently the following scales and questionnaires as appropriate: ADHD-RS-5, CGI-I, and subject check to remain in the study; PSQ, and CSHQ. Include assessment of decreased appetite.

[k] C-SSRS Pediatric/Cognitively impaired "Since Last Visit" version is completed for all visits. The scale will be compared with the C-SSRS Pediatric/Cognitively impaired

Table 1 Schedule of Assessments for Group A

Period	Baseline	Treatment Period														1-Week Safety Follow-up
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16/ ET[b]	Telephone Call
Assessment Week/Month	0	W1	W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	W53
Assessment Day	0	7	14	30	60	90	120	150	180	210	240	270	300	330	360	367

"Baseline" from the antecedent study.

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

Table 2 Schedule of Assessments for Group B

Period	Screening/ Washout[a]		Baseline	Treatment Period														1-Week Safety Follow-up
Visit Number[b]	**1**	**Phone call**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ ET**[c]	**Telephone Call**
Assessment Week/Month	**-5 to -1**		**0**	**W1**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**W53**
Assessment Day[b]	**–32 to –3**		**0**	**7**	**14**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**	**367**
Informed consent/assent	✓																	
Inclusion/exclusion criteria[d]	✓	✓	✓															
Subject demographics	✓																	
MINI-KID	✓																	
Medical and medication history includes prior medications and procedures[e]	✓																	
Urine drug screen	✓		✓[g]															
Serum pregnancy test[i]	✓		✓[g]															
Urine pregnancy test[i]			✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
ADHD-RS-5[f]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CGI-S[f]			✓															
CGI-I[f]				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination	✓		✓[g]														✓	
Height[h]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Weight[h]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs[j, k]	✓		✓[g]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Table 2 Schedule of Assessments for Group B

Period	Screening/ Washout[a]		Baseline	Treatment Period														1-Week Safety Follow-up
Visit Number[b]	**1**	**Phone call**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ ET**[c]	**Telephone Call**
Assessment Week/Month	**-5 to -1**		**0**	**W1**	**W2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**W53**
Assessment Day[b]	**–32 to –3**		**0**	**7**	**14**	**30**	**60**	**90**	**120**	**150**	**180**	**210**	**240**	**270**	**300**	**330**	**360**	**367**
Clinical laboratory tests[l]	✓		✓[g]								✓						✓	
Electrocardiogram (12-lead)[m]	✓[m]		✓[g, m]		✓		✓		✓		✓		✓		✓		✓	
C-SSRS baseline version[f]	✓																	
C-SSRS since last visit version[f]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
PSQ[f]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CSHQ[f]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Suitability of subject to remain in study[f]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
IWRS	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Study drug dispensed			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Study drug capsules returned				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Table 2 Schedule of Assessments for Group B

Period	Screening/ Washout[a]		Baseline	Treatment Period														1-Week Safety Follow-up
Visit Number[b]	1	Phone call	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16/ ET[c]	Telephone Call
Assessment Week/Month	-5 to -1		0	W1	W2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	W53
Assessment Day[b]	–32 to –3		0	7	14	30	60	90	120	150	180	210	240	270	300	330	360	367

ADHD-RS-5 =Attention-deficit/Hyperactivity Disorder-Rating Scale 5, Child, Home Version; BMI=body mass index; CGI-I=Clinician's Global Impressions − Improvement; CGI--S=Clinician's Global Impressions – Severity of Illness; CSHQ=Children's Sleep Habits Questionnaire; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; IWRS=interactive web response system; M=month; MINI-KID=Mini International Neuropsychiatric Interview for Children and Adolescents; PSQ=Post Sleep Questionnaire; W=week.

[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): ±2 days for Visit 3-4 and ±5 days for Visit 5-16 during treatment period, and +2 days for the safety follow-up telephone call.

[c] Subjects who terminate early will undergo the evaluations listed for Visit 16.

[d] Inclusion/exclusion criteria will be reviewed during the washout telephone 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-5, CGI-S/I, and subject check to remain in the study; PSQ and CSHQ. Include assessment of decreased appetite.

[g] If >32 days have elapsed since the screening evaluation was completed at Visit 1, then the following evaluations must be repeated at baseline (Visit 2): vital signs, clinical laboratory evaluations, and ECGs in triplicate. The physical examination 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 stadiometer for height and calibrated scale for weight

[i] For females of child-bearing potential only

[j] Vital signs include oral or tympanic temperature, pulse, sitting blood pressure, and respiratory rate. The subject will have been seated for a minimum of 3 minutes before blood pressure, pulse, and respiratory rate measurements are taken. Measurement of blood pressure and pulse will be collected 3 times (with at least 2 minutes in between each collection) using the age-appropriate cuff.

[k] Blood pressure and pulse rate will be measured at each study visit. Temperature and respiratory rate will be measured at screening (Visit 1) only.

[l] Clinical laboratory evaluations will include hematology, biochemistry, endocrinology, and urinalysis.

[m] ECGs will be recorded in triplicate with at least 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.

2.5 Determination of Sample Size

Approximately 80 subjects will be enrolled into this study to ensure 60 subjects complete at least 6 months of study treatment. Subjects will enroll into this study from antecedent studies, SHP465-112 or SHP465-309 as well as de novo subjects who will be enrolled directly. The sample size was established to provide long-term safety data in children aged 4 to 12 years and will include at least 40 subjects aged 4-5 years at the time of informed consent in the antecedent study or this study, if directly enrolled. The sample size for this study is not based on statistical considerations.

2.6 Multiplicity Adjustments for Type I Error Control

Efficacy and safety data will be summarized descriptively for this study. No formal statistical tests will be done and multiplicity adjustment is not needed.

3. OBJECTIVES

3.1 Primary Objective

The primary objective is to evaluate the long-term safety and tolerability of SHP465 at 6.25mg administered as a daily morning dose in children aged 4-12 years (inclusive at the time of consent) diagnosed with Attention-deficit/Hyperactivity Disorder (ADHD).

The evaluation of safety and tolerability will be based on the occurrence of treatment-emergent adverse events (TEAEs), 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).

3.2 Secondary Objectives

The secondary objectives are:

- To describe the long-term efficacy of SHP465 using the clinician administered ADHD Rating Scale 5 (ADHD-RS-5) Child, Home Version.
- To describe the long-term efficacy of SHP465 using the Clinical Global Impressions–Improvement (CGI-I) scale.

4. SUBJECT POPULATION SETS

The following subject sets are applicable to this study:

4.1 Screened Set

The Screened Set will consist of all subjects who have provided informed consent.

4.2 Enrolled Set

The Enrolled Set will consist of all subjects who been assigned a subject identification number and enrolled at the Baseline Visit (Visit 2).

4.3 Safety Set

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

4.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the Safety Set who have completed at least 1 post-dose efficacy assessment using ADHD-RS-5 Total Score.

5. SUBJECT DISPOSITION

A listing of all screen failures (ie, subjects who were screened but not enrolled) will be presented along with reasons for the failing the screening assessments and details of any reported adverse events (AEs).

All disposition data will be summarized for the Safety Set by treatment group in the antecedent studies (SHP465 or Placebo), current treatment (SHP465) for each enrollment type (rolled-over or directly enrolled), and current treatment (SHP465) for overall.

The number of subjects included in each analysis set (ie, Screened, Enrolled, Safety, and Full Analysis) will be summarized.

The number and percentage of subjects who completed and discontinued during the treatment period will be presented. The reasons for discontinuation from the treatment period, as recorded on the Study Completion page of the electronic case report form (eCRF), will be summarized (number and percentage). A subject who completes the final assessments and procedures specified at the final scheduled visit at the end of the treatment period (i.e., Visit 16) will have completed the study.

In addition, the number and percentage of subjects who completed the study visits will be presented.

Any subject who discontinued during the treatment period will be listed by discontinuation reason for the Safety Set.

Follow-up information, new (post-treatment) AEs and new (post-treatment) medication, will be listed for the Safety Set.

6. PROTOCOL DEVIATIONS

Protocol deviations and violations will be recorded by the site separately from the clinical database. The CRO/Shire will classify the protocol deviations and violations per the agreed protocol violation and deviation management plan. The Shire study team will review the protocol deviations and their classification throughout the study and before database lock.

Decisions of the review will include:

- Accuracy of protocol deviations and violations categorization.
- For any criteria for protocol deviations that can be completely implemented by a computer program, the detailed algorithm will be agreed upon. Details of such algorithms will be included in the derived dataset specifications and finalized before database lock.

Confirmed protocol violations and protocol deviations will be documented in the Protocol Violation/Deviation tracker tool for the study. Protocol deviations/violations will be summarized by category and site for each treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall for the Safety Set. Protocol deviations/violations will be listed for the Safety Set.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented for the Safety Set and FAS by treatment group of the antecedent studies (SHP465 or Placebo), current treatment of SHP465 for each enrollment type (rolled over or direct enrollment), and current treatment of SHP465 for overall.

The following demographic characteristics will be summarized in the following order in the tables: age, age group (4-5 years, 6-12 years), sex, ethnicity, race, weight, height, and body mass index (BMI). In addition, other baseline characteristics such as years since diagnosis of ADHD, baseline ADHD-RS-5 Child, Home Version total score for children aged 4-5 years and for children aged 6-12 years, and baseline Clinical Global Impressions-Severity (CGI-S) will be summarized. Baseline is defined as the last assessment before the first administration of the investigational product for Group B and as the non-missing assessment for the last visit of the antecedent study for Group A.

Age, weight, height, BMI, years since diagnosis of ADHD, ADHD-RS-5 Child, Home Version total score for children aged 4-5 years and for children aged 6-12 years will be summarized as continuous variables using number of subjects, mean and SD, median, and minimum and maximum values. Sex, ethnicity, race, and baseline CGI-S will be summarized as categorical variables using number of subjects and percentages for each category. For Group A, all summarized values will be taken from the baseline value from antecedent studies, while for Group B, summarized values will be taken from the Screening Visit (Visit 1), except for baseline ADHD-RS-5 Child, Home version Total Score and baseline CGI-S, which will be taken from the Baseline Visit (Visit 2). In addition, baseline weight and baseline height will be summarized in both conventional and international system of units.

Age will be calculated as the difference between date of birth (DOB) and earliest date of informed consent (DINFC) (i.e., consent date from antecedent studies for Group A and consent date from SHP465-308 for Group B), truncated to months, using the following:

- Age = floor((intck('month',DOB,DINFC) - (day(DINFC) < day(DOB))) / 12)

BMI will be calculated using one of the following:

- Weight in pounds * 703 / (Height in inches)^2
- Weight in kilograms / (Height in meters)^2

Number of years since diagnosis of ADHD will be based on the date of the earliest informed consent (i.e., consent date from antecedent studies for Group A and consent date from SHP465-308 for Group B). Demographics and baseline characteristics will be listed for the Safety Set.

7.2 Medical History

Medical history will be collected at the Screening visit from antecedent studies for subjects in Group A and at the Screening Visit (Visit 1) for subjects in Group B. Medical history will be listed for the Safety Set.

The psychiatric diagnosis will be established using the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) Version 7.0.2 for DSM-5 Disorder at the Screening visit (Visit 1) for subjects in Group B only and will be listed for the Safety Set.

ADHD non-medication treatment history, behavioral therapy history, collected at the Screening Visit of antecedent studies for subjects in Group A and at the Screening Visit (Visit 1) for subjects in Group B, will be listed for the Safety Set.

For ADHD medication history collected at Screening Visits, version WHODRUG March 2017 of the World Health Organization (WHO) drug dictionary will be used to classify ADHD medications by preferred term. ADHD medication history will be summarized separately by the number and percentage of subjects receiving each medication within each preferred term by treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall for the Safety Set. ADHD medication history will be listed for the Safety Set.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational Product

Exposure to the investigational product (SHP465) will be summarized for the Safety Set by treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall. The following statistics will be calculated by visit for the investigational product:

- Days of dosing: number of days on which dose information was available and non-zero
- Total dose (mg) for SHP465: total number of capsules taken × dose level
- Average daily dose (mg/day) for SHP465: the total dose / total days of dosing
- Cumulative dose (mg) for SHP465: sum of total dose since start of treatment

The following statistics will be calculated for the investigational product for the whole treatment period:

- Total days of dosing = sum of the number of days dosed for each visit during that period
- Duration of exposure in weeks = the total number of days dosed / 7 days per week
- Total dose (mg) for SHP465 = total number of capsules taken × dose level
- Average daily dose (mg/day) for SHP465 = the total dose / total number of days of dosed

An appropriate statistical summary will be applied to each of the above statistical quantities.

Subjects will be categorized in 4 week increments by overall duration of exposure in days and will be presented by subject counts and percentages.

In addition, person-time (overall total exposure in days) will be derived for SHP465. It is calculated as the total number of days in which SHP465 was taken for each subject (total days of dosing for the Treatment period), and then sum over all subjects for the Treatment period.

All dosing information, for example, total dose, average daily dose and cumulative dose, will be listed.

If a bottle has missing start and end dates then the subject's dose information from this bottle will be treated as missing. In particular, for the subjects who are lost in the follow up after the Baseline Visit (Visit 2), it will not be assumed that any of the investigational product has been ingested unless there is a post-baseline safety assessment. The days, from which there are no records showing that subjects have taken investigational product, will be excluded from the calculation of exposure. Subjects that do not return the investigational product but return to the site for the following visit will have the dose return information entered into the database on the scheduled visit.

8.2 Measurement of Treatment Compliance

Investigational product dosing compliance during the whole treatment period, are defined as the total number of capsules actually taken by a subject during that period divided by the total number of capsules expected to be taken during the same period multiplied by 100. The total number of

capsules actually taken is calculated by the total number of capsules dispensed minus the number of capsules returned. If a bottle is not returned, the number of capsules returned for that bottle will be imputed to zero, unless it is the last visit during study. If a subject is early terminated from the study without returning any bottles or providing number of capsules returned on any bottles that are dispensed at the visit before early termination, the number of capsules taken from these bottles will be treated as missing. The number of capsules expected to be taken is calculated as the number of days the subject was in the particular period multiplied by the number of capsules to be taken per day during that period.

Summary statistics for investigational product compliance will be presented by treatment group of the antecedent studies, current treatment (SHP465), and overall for and the whole treatment period for the Safety Set. The investigational product treatment compliance will be categorized as <80%, 80-120%, or >120% for and the whole treatment period. The category 80-120% is considered compliant for analysis purpose. The categorical data will be presented for the Safety Set.

Calculated compliance data for each subject will be listed.

9. PRIOR AND CONCOMITANT MEDICATION

Version WHODRUG March 2017 of the WHO drug dictionary will be used to classify prior and concomitant medications by preferred term.

Prior medication is defined as any medication taken prior to the date of first dose of investigational product in this study.

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of investigational product and continuing after the first dose of investigational product or with a start date between the dates of the first dose and last dose of investigational product, inclusive.

Any medication with a start date after the date of the last dose of investigational product (post-treatment) will not be considered a concomitant medication

Both prior and concomitant medication usage will be summarized separately by the number and percentage of subjects receiving each medication within each preferred term by treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall for the Safety Set. Medications can be counted both as prior and concomitant medication. Multiple medication usage by a subject in the same category will be counted only once for the purpose of the summaries.

All prior, concomitant and post-treatment medications will be listed for the Safety Set.

10. EFFICACY ANALYSES

All efficacy analyses will be performed using the FAS. Efficacy data will be summarized descriptively and no formal statistical tests will be performed. Only post-baseline assessments from Visit 3 (Week 1) up to Visit 16 (Month 12) that were collected on or 2 days after the last dose of investigational product will be analyzed. Summarization will be by treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall.

10.1 Primary Efficacy Endpoint and Analysis

No primary efficacy endpoint is defined for this study.

10.2 Key Secondary Efficacy Endpoint(s) and Analysis

10.2.1 ADHD-RS-5 Child, Home Version

To assess long-term efficacy, ADHD-RS-5 Child, Home version will be administered to children aged 4-5 years and 6-12 years. Baseline ADHD-RS-5 total score is defined as the last valid assessment prior to taking the first dose of investigational product for Group B and as the baseline value from the antecedent study for Group A. The observed and change from baseline in ADHD-RS-5 total score will be summarized at each applicable visit using the number of subjects, mean, SD, median, minimum, maximum values, and 95% confidence interval. A corresponding line graph of mean change from baseline and associated 95% CI in ADHD-RS-5 total score by visit and treatment group of the antecedent studies and current treatment (SHP465) for each enrollment type will be presented.

The items in the ADHD-RS-5 will also be grouped into 2 subscales: hyperactivity/ impulsivity (9 items for hyperactivity/impulsivity) and inattentiveness (9 items for inattentiveness). Each subscale will be summarized descriptively at each applicable visit. A corresponding line graph of mean change from baseline and associated 95% CI in the ADHD-RS-5 subscale scores by visit and treatment group of the antecedent studies and current treatment (SHP465) for each enrollment type will be presented.

Summaries will be repeated by age group (4-5 years and 6-12 years), sex, race (white and non-white), and ethnicity sub-group.

ADHD-RS-5 scores, including individual, subscale, and total scores, will be listed for FAS.

10.2.2 CGI-I scores

The CGI-S scores will be collected at Baseline Visit (Visit 2) for subjects in Group B and at the Screening Visit (study SHP465-112) or the Baseline Visit (study SHP465-309) for subjects in Group A and summarized descriptively. The CGI-I will be summarized descriptively at each applicable visit using the number of subjects, mean, SD, median, minimum, and maximum values.

The CGI-I categories will also be dichotomized into 2 categories: "improved" and "not improved". The category of "improved" will include CGI-I scores of 1 ("very much improved")

and 2 ("much improved)". The category "not improved" will include all CGI-I scores >2. Missing CGI-I scores will not be imputed. The observed and dichotomized CGI-I values will be summarized at each applicable visit, using number of subjects and percentages, as well.

Summaries will be repeated by age group (4-5 years and 6-12 years), sex, race (white and non-white), and ethnicity subgroups.

A corresponding bar chart showing the percentage of subjects improved by visit and treatment group of the antecedent studies and current treatment (SHP465) for each enrollment type will be presented. CGI-I values and CGI-S values will be listed for FAS and CGI-S will be also listed for the Safety Set.

10.3 Exploratory Efficacy Endpoint(s) and Analysis

No exploratory efficacy endpoint is defined for this study.

11. SAFETY ANALYSES

Safety data will be analyzed for the Safety Set by treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall. Safety endpoints include the occurrence of TEAEs, vital signs (systolic and diastolic blood pressure, and pulse), height, weight, body mass index (BMI); clinical laboratory and ECG results, C-SSRS, and sleep questionnaires (PSQ and CSHQ). For each safety endpoint, the last value collected before the first dose of investigational product in this study will be used as baseline for all analyses of that safety endpoint. Except for adverse event data, only post-baseline assessments from Visit 2 (Week 0) up to Visit 16 (Month 12) that were collected on or 2 days after the last dose of investigational product will be analyzed. A Final on-Treatment Assessment (FoTA) will be defined as the last valid assessment obtained after Baseline and whilst on investigational product (on or before 2 days after the last dose date).

11.1 Adverse Events

Adverse events will be coded using Version 18.0 of Medical Dictionary for Regulatory Activities (MedDRA).

An AE (classified by preferred term) that occurs during the treatment period will be considered a TEAE if it has a start date on or after the first dose of investigational product or if it has a start date before the date of the first dose of investigational product, but increases in severity 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. If more than 1 AE with the same preferred term is reported before the date of the first dose of investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the treatment period under the preferred term.

An overall summary of the number of subjects with TEAEs will be presented, including the number and percentage of subjects with any TEAEs, serious TEAEs, TEAEs related to investigational product, TEAEs leading to drug withdrawal, TEAEs by maximum severity, and serious TEAEs Leading to death.

The number and percentage of subjects reporting TEAEs will be tabulated by system organ class (SOC) and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and relationship to investigational product. If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product.

The incidence of common (≥ 2% of subjects in any treatment group of the antecedent studies, rollover or direct enroll group, or overall population) will be summarized by preferred term, sorted in decreasing frequency in the overall population. The incidence of TEAEs, serious TEAEs, and TEAEs leading to withdrawal will be summarized by SOC and preferred term, sorted in decreasing frequency in the overall population.

For the Safety Set, listings will be presented for all AEs, TEAEs related to investigational product, TEAEs leading to drug withdrawal, and serious TEAEs.

11.1.1 Adverse Events of Special Interest

Adverse events of special interest will include psychiatric events of interest (categorized as psychosis/mania, suicidal, aggression and other events) listed in Table 3. Adverse event terms of special interest will be searched across the TEAE data and summarized with the total exposure (in subject-days).

Table 3 Psychiatric Events

Category	Preferred Term/Verbatim term
Signs and/or symptoms of psychosis/mania	Hallucination *(any type, including visual, auditory, tactile, mixed, etc.)*
	Delusion (*any type including somatic, persecutory, grandeur, reference)*
	Schizophrenia *(any type)*
	Psychotic disorder
	Transient psychosis
	Acute psychosis
	Paranoia
	Childhood psychosis
	Schizophreniform disorder
	Schizoaffective disorder
	Catatonia
	Mania
	Hypomania
Suicidal ideation and behavior	Depression suicidal
	Gun shot wound
	Intentional self-injury
	Non-accidental overdose
	Overdose
	Self injurious behavior
	Self injurious ideation
	Self-mutilation
	Suicidal ideation
	Suicidal attempt
	Completed suicide
Aggression and violent behavior	Aggression
	Anger
	Hostility
	Homicidal ideation
	Sexual offense
	Murder
	Imprisonment

Table 3 Psychiatric Events

Category	Preferred Term/Verbatim term
Miscellaneous psychiatric events (include events with serious outcome only)	Abnormal behavior
	Agitation
	Amnesia
	Confusional state
	Depressed mood
	Depression
	Disorientation
	Emotional disorder
	Emotional distress
	Feeling abnormal
	Memory impairment
	Mood altered
	Mood swings
	Personality change
	Thinking abnormal
	Anxiety
	Fearfulness
	Phobia
	Panic attack
	Sleep disturbance
	Tics
	Obsessive or compulsive behavior
	Trichotillomania

A separate listing will be provided for psychiatric AEs of special interest.

Adverse events of clinical interest include insomnia (including AEs with preferred terms of 'INSOMNIA', 'INITIAL INSOMNIA','MIDDLE INSOMNIA' and 'TERMINAL INSOMNIA'), weight decrease and decreased appetite. The preferred terms for these 3 AEs will be reviewed prior to database lock to determine which will be used to identify them.

For each of these 3 AEs (insomnia, weight decrease and decreased appetite), the following information will be presented:

- Number and percentage of subjects reporting the TEAE
- Number of TEAEs
- Summary of onset day of first TEAE: The onset day of first TEAE is calculated as (onset date of first TEAE-date of first dose) + 1 for subjects who experienced the TEAE
- Summary of duration of TEAE while on study drug: The duration of each event is the number of days from the onset of the TEAE, while on study drug during SHP465 6.25mg, until the earlier of the end date of the TEAE or the date of last dosing + 3 days.

If the date of the last dose is missing, then the date of the last day on study will be used. TEAEs that either overlap in time, or are adjacent in time will be merged into one TEAE only for the purposes of calculating duration of event. If a subject has multiple TEAEs that are not overlapping or adjacent in time, then the durations will be averaged for that subject. Summary statistics are then based on the averaged subject durations. The calculated duration includes only the duration of TEAEs.

- Number and percentage of mild, moderate, and severe TEAEs: Overlapping TEAEs with different preferred terms are counted as multiple TEAEs.
- Summary of the number of TEAEs per subject: Overlapping TEAEs with different preferred terms are counted as multiple TEAEs.
- Number and percentage of TEAEs that:
- Resolved while on study drug
- Ongoing
- Dose interrupted
- Dose withdrawn
- TEAEs leading to discontinuation
- Number of subjects who discontinued investigational product due to the event
- Also, for each of these 3 AEs (insomnia, weight decrease and decreased appetite), the following information will be presented by actual dose and month:
- Number of subjects in the study
- Number and percentage of subjects with the TEAE
- Number of TEAEs
- Number and percentage of subjects who discontinued due to the TEAE
- Number and percentage of mild, moderate and severe TEAEs. If a subject has more than one TEAE in the same week, then the worst severity is counted.

Month 1 will include TEAEs reported to have started from Visit 2 (Baseline) through Visit 5 (Month 1); Month 2 will include TEAEs reported to have started after Visit 5 (Month 1) through Visit 6 (Month 2), etc.

In addition, for each subject, all occurrences of each of these 3 AEs will be listed separately by treatment group of the antecedent studies, subject number, start date and stop date. The information presented will include: subject, sex, age, race, ethnicity, preferred term/adverse event, start date, stop date, onset day, study visit, last dose date, duration/imputed duration of TEAE (days), SAE, severity, effect on dosing and treatment on AE.

11.2 Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in SI units) and changes from Baseline to Visit 16/ET as well as shift tables from Baseline to Visit 16/ET for quantitative variables will be presented by treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall for the following clinical laboratory variables:

Biochemistry and Endocrinology

Total cholesterol	Calcium
Aspartate aminotransferase	Urate
Phosphorus	Blood urea nitrogen
Alanine aminotransferase	Total bilirubin
Sodium	Creatinine
Alkaline phosphatase	Glucose
Potassium	Albumin
Gamma-glutamyl transferase	Total protein
Thyroid-stimulating hormone	Lactate dehydrogenase
Thyroxine, Free	

Hematology

Hemoglobin	Neutrophils
Hematocrit	Lymphocytes
Red blood cells	Monocytes
Platelet count	Eosinophils
White blood cell count – total and differential	Basophils
Mean corpuscular hemoglobin	Neutrophils Band Forms
Mean corpuscular hemoglobin concentration	Mean corpuscular volume

Urinalysis

Glucose	pH
Specific gravity	Urobilinogen
Blood	Color
Ketones	Leukocyte esterase
Protein	Nitrite
Bilirubin	

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

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria. The PCI criteria are listed in Table 4 for subjects aged 4-5 years and Table 5 for subjects aged 6-12 years. The number and percentage of subjects with post-baseline PCI values will be tabulated. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 post-baseline PCI value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, baseline, and post-baseline values.

Table 4 Criteria for Potentially Clinically Important Laboratory Tests for Subjects Aged 4-5 Years

Parameter	SI Unit	Lower Limit	Higher Limit
Biochemistry			
Albumin	g/L	< 30g/L	-
Aspartate transaminase (AST)	-	-	>3 x ULN
Alanine transaminase (ALT)	-	-	> 3 x ULN
Alkaline phosphatase			>2.5 x ULN
Blood urea nitrogen	mmol/L	-	> 10.7mmol/L or > 2.5 x ULN
Calcium	mmol/L	< 2	> 2.9
Total cholesterol	mmol/L	-	> 7.8
Creatinine	µmol/L	-	> 176.8 µmol/L or > 1.5 x ULN
Gamma glutamyl transferase	-	-	≥ 2.5 x ULN
Glucose	mmol/L	< 3.1	> 8.9
Lactate dehydrogenase	-	-	> 3 x ULN
Phosphorus, inorganic	mmol/L	< 0.8	> 2.3
Potassium	mmol/L	< 3.0	> 5.5
Thyroid stimulating hormone	-	< LLN	> 2 x ULN
Sodium	mmol/L	< 130	> 150
Urate	µmol/L	-	> 594.8
Bilirubin, total	µmol/L	-	> 34.2
Total protein	g/L	< 50	> 90
Hematology			
Neutrophils Band Form	-	-	> $0.27x10^3$/µL or > 5%
Basophils	-	-	> 10%
Hemoglobin	g/L	< 90	> 160
Hematocrit	%	< 30%	> 50%
Platelet count	10^9/L	< 75	> 600

Table 4 Criteria for Potentially Clinically Important Laboratory Tests for Subjects Aged 4-5 Years

Parameter	SI Unit	Lower Limit	Higher Limit
Red blood cells	10^{12}/L	< 2.5	> 7.5
White blood cell count	10^{9}/L	< 3	> 16.0
Neutrophils	109/L	< 1x10^{9}/L or < 30%	> 6.2 109/L or > 70%
Eosinophils	109/L OR %	-	0.5 x 109/L or > 10%
Lymphocytes	%	< 10%	> 70%
Monocytes	%	-	> 20%
Urinalysis			
Glucose	-	-	Positive Value (excluding trace)
Protein	-	-	Positive Value (excluding trace)
Blood	-	-	Positive Value (excluding trace)
Ketones	-	-	Positive Value (excluding trace)
Bilirubin	-	-	Positive Value (excluding trace)
Leukocyte Esterase			Positive Value (excluding trace)
Nitrite			Positive Value (excluding trace)

LLN: Lower limit of normal value provided by the laboratory

ULN: Upper limit of normal value provided by the laboratory

Age is calculated from the informed consent date from antecedent studies for Group A and from the informed consent date from SHP465-308 for Group B.

Table 5 Criteria for Potentially Clinically Important Laboratory Tests for Subjects Aged 6-12 Years

Parameter	PCI Criteria
Biochemistry	
Cholesterol-H	>300mg/dl** (>7.8mmol/L)
Glucose, serum	<55mg/dl or >160mg/dl (<3.1mmol/L or >8.9mmol/L)
Bilirubin, total	>1.5 x ULN
Transaminase, SGOT, AST	>3 x ULN
Transaminase, SGPT, ALT	>3 x ULN
Gamma Glutamyl Transpeptidase (GGT)	>3 x ULN
Alkaline phosphatase	>2.5 x ULN
Lactate dehydrogenase (LDH)	>3 x ULN*
Sodium	<130mEq/L (grade 3) or >150mEq/L (mmol/L)
Potassium, serum/plasma	<3mEq/L (grade 3) or >5.5mEq/L (mmol/L)
Calcium	<8mg/dl or >11.5mg/dl (<2mmol/L or >2.9mmol/L)
Phosphorus, inorganic	<2.5mg/dl or >7.0mg/dl** (<0.8mmol/L or >2.3mmol/L)
Urate	>10mg/dl (>0.6mmol/L or >594.8µmol/L)
Thyroid Stimulating Hormone (TSH) ~	< 0.35 µIU/ml or > 6 µIU/mL (0.35mIU/L or >6mIU/L)
Blood Urea nitrogen (BUN)	>2.5 x ULN* (or alternatively >30mg/dl**, >10.7mmol/L)
Creatinine, serum	>1.5 x ULN (or alternatively >2mg/dl**, >176.8µmol/L)
Albumin	<3g/dl (<30g/L)
Total protein, plasma or serum	<5g/dl* or >9g/dl* (<50g/L or >90g/L)
Hematology	
Hemoglobin (He.)	<10g/dl (<100g/L)
Hematocrit	<32% or >45% (<0.32 or >0.45 Fraction of 1)
Blood Cells (RBC)	male: <2.5 x10_6/µL; female: <2.0 x10_6/µL (male: <2.5 x 10^12/L; female: <2.0 x 10^12/L)
Mean Corpuscular Hemoglobin (MCH)~	< 27pg or > 32pg
Mean Corpuscular Volume (MCV)~	< 70fL or > 110fL
Mean Corpuscular He. Concentration (MCHC)~	< 28g/dL or > 41g/dL (<280g/L or >410g/L)
Platelet count	<75 x 10_9/L or >500 x 10_9/L

Table 5 Criteria for Potentially Clinically Important Laboratory Tests for Subjects Aged 6-12 Years

Parameter	PCI Criteria
Biochemistry	
White Blood Cell Count (WBC)	<3 x 10^9/L or >16 x 10^9/L
Neutrophils Band Form	> 5%
Neutrophils	< 15%
Eosinophils	> 10%
Basophils	> 15%
Lymphocytes	> 80%
Monocytes	> 40%
ANC (%neutrophils x WBC count)	<1.3x10e9/L
Urinalysis	
Glucose	Positive Value (excluding trace)
Blood	Positive Value (excluding trace)
Ketones	Positive Value (excluding trace)
Protein	Positive Value (excluding trace)
Bilirubin	Positive Value (excluding trace)
Leukocyte Esterase	Positive Value (excluding trace)
Nitrite	Positive Value (excluding trace)

*The NCI has not specified a value, Shire physicians have agreed on lab values provided.

** Values taken from the Reviewer Guidance, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review, Table 7.1.7.3.2.1 pp 70-72. US DHHS FDA CDER, February 2005.

~These values were taken from Clinical Laboratory Diagnostics, ed. L. Thomas, MD, Frankfurt, Germany, 1998.

ULN: Upper limit of normal value provided by the laboratory

Age is calculated from the informed consent date from antecedent studies for Group A and from the informed consent date from SHP465-308 for Group B.

All laboratory data will be listed for the Safety Set.

11.3 Vital Signs (Including Height and Weight)

The averaged values of the 3 measurements collected for blood pressure and pulse at each visit will be used for all summaries and determination of PCIs. Summaries for vital signs will be presented by treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall.

Descriptive statistics for vital signs (sitting systolic and diastolic blood pressure, pulse and weight) and their changes from baseline at each post-baseline visit and FoTA will be presented in a summary table. These summaries will also include BMI. BMI will be automatically

calculated using the height and weight collected at each visit. In the case of multiple assessments at post-baseline visits, the first readable value at the visit will be used in the summary tables.

Additionally, figures with the mean change from baseline ±SD of the vital signs values (sitting systolic and diastolic blood pressure, and pulse) will be presented by visit for each treatment group of the antecedent studies and current treatment (SHP465) for each enrollment type.

Height, weight and BMI will also be converted to percentile values based on the subject's age and sex at each visit and summarized categorically (<5th, 5th to <95th, and ≥95th) at each visit and at the FoTA. Post-baseline shifts in height, weight and BMI percentile category (<5th, 5th to <95th, and ≥95th) from baseline will be summarized at each visit and at the FoTA. In addition, z-scores for weight and BMI will be based on the subject's age at each visit and will be summarized categorically (<-2, ≥-2 to <-1, ≥-1 to <1, ≥1 to <2, and ≥2) at each visit and at the FoTA. Percentiles and z-scores will be derived using the CDC growth charts (Kuczmarski et al. 2002). A SAS program for the 2000 CDC Growth Charts will be used to derive the percentiles and z-scores (www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm).

Vital sign values will be considered PCI if they meet the criteria listed in Table 6 for Age 4-5 or if they meet the criteria in Table 7 for Age 6-12. The number and percentage of subjects with PCI post-baseline values will be summarized. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline vital sign value. A supportive listing of subjects with post-baseline PCI values will be provided including the treatment group of the antecedent studies, subject number, site, baseline, and post-baseline PCI values. A listing of all AEs for subjects with post-baseline PCI vital sign values will also be provided.

Table 6 Criteria for Potentially Clinically Significant Vital Sign Findings in Subjects Aged 4-5 Years

Vital Sign Parameter	Flag	Criteria[a]	
		Observed Value	Change from Baseline
Sitting Systolic blood pressure (mmHg)	High	≥120	Increase of >10
	Low	<75	Decrease of >10
Sitting Diastolic blood pressure (mmHg)	High	≥85	Increase of >10
	Low	<40	Decrease of >10
Pulse rate (beats per minute)	High	≥130	Increase of >15
	Low	≤55	Decrease of >15
Weight (kg)	High	-	Increase of ≥7%
	Low	-	Decrease of ≥7%
Temperature (deg. C)	High	>39	-
	Low	<35	-
BMI (kg/m^2)	High	>95th percentile for age and sex	-
	Low	<5th percentile for age and sex	-

[a] A post-baseline value is considered a PCI finding if its meets either the criteria for observed value or the criteria for the change from baseline.

Age is calculated from the informed consent date from antecedent studies for Group A and from the informed consent date from SHP465-308 for Group B.

Table 7 Criteria for Potentially Clinically Significant Vital Sign Findings for Subjects Aged 6-12 Years

Vital Sign Parameter	PCI Criteria
Weight Loss (kg)	≥7% of weight (determined at baseline)
Systolic BP (mmHg), seated, 6 – 12 years~	>120* >120* on 2 or more consecutive visits >10 increase from baseline >10 increase from baseline on 2 or more consecutive visits >120* and increase >10 from baseline >120* and increase >10 from baseline on 2 or more consecutive visits
Diastolic BP (mmHg), seated, 6 – 12 years~	>80* >80* on 2 or more consecutive visits >10 increase from baseline >10 increase from baseline on 2 or more consecutive visits

Table 7 Criteria for Potentially Clinically Significant Vital Sign Findings for Subjects Aged 6-12 Years

Vital Sign Parameter	PCI Criteria
	>80* and increase >10 from baseline >80* and increase >10 from baseline on 2 or more consecutive visits
Pulse (beats/minute)	<=50* <=50* and decrease >15 from baseline >=100* >=100* on 2 or more consecutive visits >=100* and increase >15 from baseline >=100* and increase >15 from baseline on 2 or more consecutive visits
Temperature (tympanic)	>38.0°C (100.4°F)
Temperature (oral)	>37.5°C (99.5°F)
Respiratory Rate (breaths per minute)	<10 or >24

~Given the pharmacological effect of the drugs used in ADHD and based on experience gained in previous ADHD trials, the focus is on rise of blood pressure only.

*The NCI has not specified a value, Shire physicians have agreed on values provided.

Age is calculated from the informed consent date from antecedent studies for Group A and from the informed consent date from SHP465-308 for Group B.

Pulse rate (beats per minute) will be considered abnormal if a value is lower than the 1st percentile or higher than the 99th percentile cut-off values listed in Table 8.

Table 8 Normal Range of Pulse Rate (beats/min)

Age	1st Percentile	99th Percentile
	Males	
4-5 years	69	120
6-8 years	59	114
9-11 years	56	110
12 years	52	108
	Females	
4-5 years	70	132
6-8 years	61	117
9-11 years	58	113
12 years	54	110

Source: National health statistics report: Resting Pulse Rate Reference Data for Children, Adolescents, and Adults: United States, 1999–2008

https://www.cdc.gov/nchs/data/nhsr/nhsr041.pdf

The number and percentage of subjects with abnormal pulse rate values for at least 1 post-baseline assessment will be tabulated by treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall for the lower than the 1st percentile

and higher than the 99th percentile cut-off values, respectively, for male and female separately. The denominator will be the number of subjects in the Safety Set (per gender) with at least 1 post-baseline pulse measurement. The numerator is the total number of subjects with at least 1 abnormal pulse record. A supportive listing of subjects with abnormal pulse rate values will be provided.

In addition, following the US Department of Health and Human Services standards, blood pressure values higher than the 95th percentile determined by sex, age, and height percentiles will be considered abnormal. The cut-off values are presented in Table 9 If a height percentile falls between the listed percentiles, as a conservative approach the lower end of the percentiles will be used to identify the corresponding 95th percentile of blood pressures. If a height percentile is less than 5th percentile, the 5th percentile will be used to identify the corresponding 95th percentile of blood pressures.

Table 9 95th Percentile Cut-off Values of Blood Pressure Norms by Sex, Age, and Height Percentiles

	Systolic Blood Pressure (mmHg)								Diastolic Blood Pressure (mmHg)						
Age (y)	Percentile of Height								Percentile of Height						
	Boys														
	5%	10%	25%	50%	75%	90%	95%		5%	10%	25%	50%	75%	90%	95%
4	106	107	109	111	112	114	115		66	67	68	69	70	71	71
5	108	109	110	112	114	115	116		69	70	71	72	73	74	74
6	109	110	112	114	115	117	117		72	72	73	74	75	76	76
7	110	111	113	115	117	118	119		74	74	75	76	77	78	78
8	111	112	114	116	118	119	120		75	76	77	78	79	79	80
9	113	114	116	118	119	121	121		76	77	78	79	80	81	81
10	115	116	117	119	121	122	123		77	78	79	80	81	81	82
11	117	118	119	121	123	124	125		78	78	79	80	81	82	82
12	119	120	122	123	125	127	127		78	79	80	81	82	82	83
	Girls														
4	105	106	107	108	110	111	112		68	68	69	70	71	71	72
5	107	107	108	110	111	112	113		70	71	71	72	73	73	74
6	108	109	110	111	113	114	115		72	72	73	74	74	75	76
7	110	111	112	113	115	116	116		73	74	74	75	76	76	77
8	112	112	114	115	116	118	118		75	75	75	76	77	78	78
9	114	114	115	117	118	119	120		76	76	76	77	78	79	79
10	116	116	117	119	120	121	122		77	77	77	78	79	80	80
11	118	118	119	121	122	123	124		78	78	78	79	80	81	81
12	119	120	121	123	124	125	126		79	79	79	80	81	82	82

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

The number and percentage of subjects with any post-baseline blood pressure values higher than the 95th percentile (exclusive) will be tabulated by gender and treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall. The denominator will be the number of subjects in the Safety Set (per gender) with at least 1 post-Baseline blood pressure measurement. The numerator will be the total number of subjects with at least 1 blood pressure value higher than the 95th percentile. A supportive listing of all subjects with abnormal blood pressure values will be provided.

All vital signs data will be listed for the safety Set.

11.4 Electrocardiogram (ECG)

Electrocardiogram (ECG) data will be summarized by treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall. ECG results and change from baseline will be summarized at each visit and at the FoTA. If there are multiple assessments for the interpretation at any visit, the worst interpretation will be used in the summary tables. For the interval parameters at post- baseline visits, the first readable result will be used if there are multiple assessments.

For the ECG interval parameters, baseline is defined as the average of all valid ECG measurements as the last assessment obtained prior to the first dose of the investigational product. For the ECG interpretation, baseline will be the ECG with the worst interpretation obtained at the baseline Visit (Visit 2), providing this is prior to the first dose of the investigational product.

PCI criteria will be applied to all ECG data at each visit including any repeat/unscheduled assessments and presented by visit. PCI criteria are defined in Table 10 for Age 4-5 years or if they meet the criteria in Table 11 for Age 6-12 years.

Table 10 Criteria for Potentially Clinically Important ECG Values for Age 4-5 Years

ECG Parameter	Unit	Observed Value		Change from Baseline	
		Lower Limit	Higher Limit	Lower Limit	Higher Limit
ECG Result	-	-	Abnormal (core lab) and Clinically significant from investigator	-	-
Heart Rate	Beats/minute	<55	>130	Decrease >15	Increase >15
PR Interval	msec	-	≥200	-	-
QT Interval	msec	-	≥440	-	≥30 and <60 ≥60
QTcF Interval	msec	-	≥440 and <480 ≥480 and <500 ≥500	-	≥30 and <60 ≥60
QTcB Interval	msec	-	≥440 and <480 ≥480 and <500 ≥500	-	≥30 and <60 ≥60
QRS Interval	msec	-	≥90	-	-
Rhythm	-	-	Any rhythm other than sinus rhythm*	-	-

Age is calculated from the informed consent date from antecedent studies for Group A and from the informed consent date from SHP465-308 for Group B.

Table 11 Criteria for Potentially Clinically Important ECG Values for Age 6-12 Years

ECG Parameter	Outlier Criteria
ECG result	Shift from a normal baseline to an abnormal finding or from an abnormal baseline to a new abnormal finding
Heart rate	≤50 beats/minute* or ≥100 beats/minute*
PR interval (increase)	≥200 msec*
QRS interval	≥120 msec*
QTcF/QTcB	≥450 msec* and <480 msec* ≥480 msec* and <500 msec* ≥ 500msec*
QT/QTc from Baseline	≥30 msec* and <60 msec* ≥60 msec*

*The NCI has not specified a value, Shire physicians have agreed on values provided.

ECG=electrocardiogram; QTcB=Bazett's corrected QT interval; QTcF=Fridericia's corrected QT interval

Age is calculated from the informed consent date from antecedent studies for Group A and from the informed consent date from SHP465-308 for Group B.

The number and percentage of subjects with post-baseline PCI values will be tabulated. The percentages for the observed value criteria will be calculated relative to the number of subjects with at least 1 post-baseline assessment available per parameter and visit. The percentages for the change from baseline criteria will be calculated relative to the number of subjects with available baseline and at least 1 post-baseline assessment per parameter and visit. The numerator is the total number of subjects with at least 1 PCI post-baseline ECG value.

Additionally, a summary table showing the number and percentage of subjects with the Central Reader's assessment of the ECG result as normal, abnormal or unable to evaluate, and the investigator's assessment of abnormal ECG results as not clinically significant or clinically significant at each visit and at the FoTA will be produced. A shift table showing the change in evaluation from baseline to the FoTA will also be produced.

Listings of ECG data including the central reader's assessment and investigator's interpretation by individual subject will be produced. Separate listings will be produced for subjects with ECG results meeting the PCI criteria. Data from unscheduled visits will be listed, but not summarized.

11.5 Other Safety Variables

Other safety data will be summarized by treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall using the Safety Set.

11.5.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS 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 two required items pertaining to suicidal ideation, four required items pertaining to suicidal behavior, and one required item pertaining to non-suicidal self-injurious behavior. There are eight additional suicidal ideation items and two additional suicidal behavior items which are completed in cases of positive responses for other items, as well as two items for suicide and suicide behavior present during the interview. Most items are rated on a dichotomous scale (yes or no) or 3- or 5-point Likert scale. In addition, the total number of attempts (including interrupted and aborted attempts) is recorded. In the event of a positive categorical response the interviewer can provide text or narrative that further describes the thought or behavior.

Two versions of C-SSRS, the "Baseline" version and the "Since Last Visit" version, will be used in this study. For subjects in Group A, the "Since Last Visit" version will be completed at all study visits. The scale will be compared with the "Baseline" version from the antecedent study. For subjects in Group B, the "Baseline" version will be administered at the Screening Visit (Visit 1) and the "Since Last Visit" version will be completed for all subjects at all study visits after the Screening Visit (Visit 1).

Positive results from the C-SSRS data will be descriptively summarized for overall during the study and by visit.

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

11.5.2 Post Sleep Questionnaire (PSQ)

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 conducted at each visit to the site starting with the baseline visit (Visit 2) and will be completed by the subject's parent/LAR.

The PSQ results will be summarized by visit. Continuous variables, for example, time to go to sleep and time spent awake, will be summarized using number of subjects, mean and standard deviation, median, and minimum and maximum values. Categorical values, for example, quality of sleep, will be summarized using number of subjects and percentages for each category.

11.5.3 Children's Sleep Habit Questionnaire (CSHQ)

The Child's Sleep Habits Questionnaire (CHSQ) consists of 33 items for scoring and several extra items intended to provide administrators with other potentially useful information about respondents. Each scored question except for Watching TV and Riding in car is rated on a 3-point scale:

- occurring "usually" (i.e., 5–7 times within the past week): score = 3
- occurring "sometimes" (i.e., 2–4 times within the past week): score = 2
- occurring "rarely" (i.e., never or 1 time within the past week): score = 1

The following six questions should be reversed in scoring for calculation of subscale score and total sleep disturbance score so that higher score reflects more disturbed sleep behavior: "Goes to bed at same time", "Falls asleep in own bed", "Falls asleep in 20 minutes", "Sleeps the right amount", "Sleeps same amount each day", "Wakes by himself". These six questions are rated on 3-point scale depending on the frequency of occurring:

- "usually" (5– times within the past week): score = 1
- "sometimes" (2– times within the past week): score = 2
- "rarely" (never or 1 time within the past week): score = 3

Questions of Watching TV and Riding in car is rated on a 3-point scale (more than 1 occurrences can apply for each question, highest score contributes as the question score):

- occurring "not sleepy": score = 0
- occurring "very sleepy": score = 1
- occurring "falls asleep": score = 2

The instrument evaluates the child's sleep based on behavior within 8 different subscales:

1. Bedtime resistance (sum of the responses for Goes to bed at same time, Falls asleep in own bed, Falls asleep in other's bed, Needs parent in room to sleep, Struggles at bedtime and Afraid of sleeping alone)
2. Sleep-onset delay (Falls asleep in 20 minutes item)
3. Sleep duration (sum of the responses for Sleeps too little, Sleeps the right amount and Sleeps same amount each day)
4. Sleep anxiety (sum of the responses for Needs parent in room to sleep, Afraid of sleeping in the dark, Afraid of sleeping alone and Trouble sleeping away)
5. Night wakings (sum of the responses for Moves to other's bed in night, Awakes once during night and Awakes more than once)
6. Parasomnias (sum of the responses for Wets the bed at night, Talks during sleep, Restless and moves a lot, Sleepwalks, Grinds teeth during sleep, Awakens screaming, sweating and Alarmed by scary dream)
7. Sleep-disordered breathing (sum of the responses for Snores loudly, Stops breathing and Snorts and gasps)
8. Daytime sleepiness (sum of the responses for Wakes by himself, Wakes up in negative mood, Others wake child, Hard time getting out of bed, Takes long time to be alert, Seems tired, Watching TV and Riding in car)

Total sleep disturbance score is sum of the 8 subscale scores minus Needs parent in room to sleep and Afraid of sleeping alone (as Needs parent in room to sleep and Afraid of sleeping alone are included in two subscales (1 and 4) and need to be included once). Missing data will not be imputed.

Total sleep disturbance score, each subscale and each individual item will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum) at each visit (and Visit 6/ET) by treatment group of the antecedent studies, current treatment (SHP465) for each enrollment type, and overall . All CSHQ data will be listed for the Safety Set.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable.

13. OTHER ANALYSES

No other analyses are planned for this study.

14. INTERIM ANALYSIS

After no fewer than 50 subjects have completed 6 months of study treatment and approximately 20 subjects have completed 12 months of study treatment, the database will be archived and all available safety and efficacy data will be analyzed for regulatory reporting reasons. Additional analyses will be performed as required for regulatory purposes, such as subsequent safety updates if required and development of the final clinical study report.

Due to the early termination of the study, the interim analysis above will not be performed. All collected data will be included in the final analyses and reported.

15. DATA MONITORING/REVIEW COMMITTEE

A data monitoring committee (DMC) will be involved in the management of this study. The purpose of the DMC is to monitor safety and tolerability of the investigational product and to protect the interests of subjects in the study and of those still to be entered. The data provided to the DMC will not be considered 'clean' until the database is locked.

The analyses for DMC will be a subset of the analyses specified in this SAP. Further details regarding the DMC can be found in the DMC charter, which will be available before the administration of investigational product.

16. COMPUTER METHODS

Statistical analyses will be performed using Version 9.3 (or newer) of SAS® on a suitably qualified environment.

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Not applicable.

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, SD, minimum, and maximum. Unless specified otherwise, summary statistics will be presented to 1 more significant digit than the raw data. The minimum and maximum values will be presented to the same number of decimal places as the raw data; the mean and median will be presented to 1 more decimal place than the raw data; and the SD and standard error will be presented to 2 more decimal places than the raw data.

Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. Percentages will be presented to 1 decimal place.

P-values will generally be presented to 4 decimal places; values less than 0.001 will be presented as <0.001.

18.2 Derived Efficacy Endpoints

The ADHD-RS-5 Child, Home Version total score will be calculated as the sum of the individual items from the ADHD-RS-5 Child, Home Version. The ADHD-RS/ADHD-RS-5 Child, Home Version consists of 18 items designed to reflect current symptomatology of ADHD based on Diagnostic and Statistical Manual of Mental Disorders Five Edition (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. As noted in Section 10.2, the items in the ADHD-RS-5 Child, Home Version will also be grouped into 2 subscales: hyperactivity/impulsivity (9 items for hyperactivity/impulsivity) and inattentiveness (9 items for inattentiveness), with subscale scores ranging from 0-27.

A missing individual item in the ADHD-RS-5 Child, Home Version is imputed as follows (DuPaul et al.1998): if only 1 single item is missing in a given subscale, the mean score for all other items in the subscale for the specific visit is imputed as the score rounded up to the nearest integer for the missing score. The total score is computed as the sum of the imputed subscale scores. If more than 1 item is missing in a subscale then the subscale score and total score would be missing.

18.3 Association of Early Termination Assessments to Scheduled Visits

For purposes of reporting early termination assessments during the study, each early termination visit will be assigned the next nominal visit number after the last completed visit. This rule applies to both efficacy variables (e g , ADHD-RS-5 - Child, Home Version total score) and safety variables (e g , vital signs) except for the lab data, which will be analyzed and/or summarized by visit.

18.4 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline.

If a subject has repeated assessments at any post-baseline visit, the first recorded assessment will be assigned to the visit for generating descriptive statistics. For vital signs (sitting systolic and diastolic blood pressure, and pulse), this will be the average of the 3 measurements from the first recorded assessment.

If final on-treatment safety assessments are repeated or unscheduled, the last post-baseline assessment will be used as the final on-treatment assessment for generating descriptive statistics. For vital signs (sitting systolic and diastolic blood pressure, and pulse), this will be the average of the 3 measurements from the last post-baseline assessment.

However, all post-baseline assessments will be used for PCI value determination and all assessments will be presented in the data listings.

All repeat and unscheduled visits will be listed.

18.5 Missing Dispensed or Returned Date or Number of Capsules of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of investigational product exposure.

18.6 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

18.6.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then 31 December will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

18.6.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day

- If either the year is before the year of the date of the last dos of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

18.7 Missing Date Information for Adverse Events

For AEs, incomplete (i.e., partially missing) start dates will be imputed and will follow the same rules as in Section 18.6.1. Incomplete stop dates will not be imputed.

18.8 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

18.9 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

18.10 Character Values of Clinical Laboratory Variables

The actual values of clinical laboratory variables as reported in the database will be presented in data listings. No coded values (e.g., when a character string is reported for a numerical variable) are necessary.

19. REFERENCES

DuPaul GJ, Power TJ, Anastopoulos AD, Reid R, 1998. *ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation*, New York, NY: Guilford Press.

Kuczmarski RJ, Ogden CL, Guo SS, et al., 2002. 2000 CDC growth charts for the United States: Methods and development. National Center for Health Statistics, Vital Health Stat 11(246).

20. TABLE OF CONTENTS FOR FIGURES, TABLES, AND LISTINGS

Table of contents for figures, tables and listings will be provided in a separate document with the table, figure and listing templates.