STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP465-112
Protocol Title:	A Phase 1 Open-label Study of the Safety, Tolerability, and Pharmacokinetics of *d*- and *l*-Amphetamine after Multiple Daily Doses of SHP465 6.25 mg Administered in Children Aged 4 to 5 years with Attention Deficit/Hyperactivity Disorder
Drug:	SHP465
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ABBREVIATIONS

ADHD	attention-deficit/hyperactivity disorder
ADHD-RS-5	ADHD Rating Scale Version 5
AE	adverse event
AUC	area under the concentration-time curve
AUC_{last}	area under the concentration-time curve from the time of dosing to the last measurable concentration
AUC_{0-t}	area under the concentration-time curve from the time 0 to the last time point of sample collection
AUC_{0-5}	area under the concentration-time curve from time 0 to 5 hours postdose
AUC_{5-12}	area under the concentration-time curve from 5 hours to 12 hours postdose
AUC_{12-16}	area under the concentration-time curve from 12 hours to 16 hours postdose
AUC_{16-24}	area under the concentration-time curve from 16 hours to 24 hours postdose
AUC_{5-t}	area under the concentration-time curve from 5 hours postdose to the last time point of sample collection
$AUC_{tau,ss}$	area under the concentration-time curve over the dosing interval (24 hours), at steady-state
BLQ	below the limit of quantitation
BMI	body mass index
C12	the observed concentration at 12 hours after dose administration
C16	the observed concentration at 16 hours after dose administration
C24	the observed concentration at 24 hours after dose administration
CDC	Centers for Disease Control and Prevention
CGI-S	Clinical Global Impression - Severity of Illness
CI	confidence interval
CL/F	total body clearance for extravascular administration divided by the fraction of dose absorbed
C_{max}	maximum concentration occurring at t_{max}
CRC	clinical research center
CSHQ	Children's Sleep Habits Questionnaire
C-SSRS	Columbia-Suicide Severity Rating Scale
$C_{trough,ss}$	trough plasma analyte concentration (the predose concentrations collected at steady-state)
CV	coefficient of variation
DINFC	date of informed consent

DMC	data monitoring committee
DOB	date of birth
eCRF	electronic case report form
ECG	Electrocardiogram
ET	early termination
FoTA	final on-treatment assessment
IP	investigational product
LAR	legally authorized representative
LLOQ	lower limit of quantitation
MINI-Kid	Mini International Neuropsychiatric Interview for Children and Adolescents
MedDRA	Medical Dictionary for Regulatory Activities
n	number of subjects
NQ	not quantitative
PCI	potentially clinically important
PK	pharmacokinetic(s)
PSQ	Post Sleep Questionnaire
PT	preferred term
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
$t_{½}$	terminal half-life
t_{max}	time of maximum observed concentration sampled during a dosing interval
V/F_{ss}	apparent volume of distribution at steady-state
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan provides a technical and detailed elaboration of the statistical analyses of pharmacokinetic (PK), safety, and tolerability data as described in the final study protocol SHP465-112 version 1.0 dated 15 Sep 2017 and the protocol administrative change #1 dated 31 Oct 2017. Specifications for tables, figures, and listings are contained in a separate document.

2. STUDY DESIGN

2.1 General Study Design

The study will be a Phase 1, open-label, multiple-dose, PK, safety, and tolerability study in children aged 4 to 5 years diagnosed with attention-deficit/ hyperactivity disorder (ADHD). Enrollment will be stratified by sex to ensure that at least 2 of the 10 subjects expected to complete the rich PK sampling portion of the study and at least 3 of the 10 subjects expected to complete the sparse PK sampling portion of the study are females.

Following the screening visit, eligible subjects will return to the clinical research center (CRC) on Day 1 of Week 1 to reconfirm eligibility criteria and enter into the treatment phase. Total duration for the treatment period is approximately 30 days for subjects in the rich PK sampling portion of the study and 29 days for subjects in the sparse PK sampling portion of the study. In the study, single 6.25 mg dose of SHP465 will be administered daily for 28 days (±1 day) at 8:00 AM (±1 hour).

Rich PK Sample Scheme (9 Samples/Subject) Collection

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

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

Sparse PK Sample Scheme (4 Samples/Subject) Collection

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

2.2 Randomization

Not applicable.

2.3 Blinding

This is an open-label study so blinding is not applicable.

2.4 Schedule of Assessments

Table 1: Schedule of Assessments for Rich Pharmacokinetic Sampling Portion

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

Table 1: Schedule of Assessments for Rich Pharmacokinetic Sampling Portion

Assessment Day	Screening and Washout		Week 1 to 3		Week 4										Follow-up[a]
	D -32 to D -8	D -7 to D -1 Washout	D 1	D 2-7	D 1	D 2-6	D 7							D 8[b]	D 9 /ET[b]	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X

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

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

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

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

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

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

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

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

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

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

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

[k] Dosing will be done at the CRC.

[l] Dosing will be done at the home.

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

[n] To be sampled predose on Week 1 only.

Whenever possible, the same individual should complete/rate consistently the following scales and questionnaires as appropriate: ADHD-RS-5 Child, Home Version; Clinical Global Impressions - Severity of Illness; Post Sleep Questionnaire; and Children's Sleep Habits Questionnaire.

Table 2: Schedule of Assessments for Sparse Pharmacokinetic Sampling Portion

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

Table 2: Schedule of Assessments for Sparse Pharmacokinetic Sampling Portion

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

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

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

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

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

[d] A brief physical examination will be performed prior to dosing on Day 1 of Weeks 1 to 4.

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

[f] Subjects should be resting in a sitting position for at least 5 minutes prior to collecting vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature). Subjects should be resting in a supine position for at least 5 minutes prior to collecting ECGs. If an invasive procedure was conducted prior to blood pressure, ECG and respiratory rate recording, the subject should be resting for 15 minutes.
Blood pressure and pulse will be measured at each visit.
Temperature and respiratory rate will be collected at the screening visit and ET visit only.

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

[h] Dosing will be done at the CRC.

i Dosing will be done at the home

2.5 Determination of Sample Size

To objectively justify the sample size for PK sampling and PK sampling scheme for this study, the precision below (in accordance with FDA guidance) is used.

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

The data presented in Table 3 are from Shire's completed study (SHP465-111) in pediatric subjects with ADHD and show that the reported apparent clearance (CL/F) and volume of distribution (Vz/F) for the d-amphetamine and l-amphetamine of SHP465 after oral administration of SHP465 12.5 mg in children aged 6 to 12 years and 25 mg in adolescents aged 13 to 17 years.

Table 3: Estimates of Clearance and Volume of Distribution for *d*-Amphetamine and *l*-Amphetamine

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

CL/F=body clearance; CV=coefficient of variation; Vz/F=volume of distribution
Source: SHP465-111 Clinical Study Report (06 May 2016) Tables 9-1 and 9-4.

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

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

CV=coefficient of variation

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

Approximately 24 subjects are expected to be enrolled to ensure that 10 subjects will complete the rich PK sampling portion of the study and an additional 10 subjects will complete the sparse PK sampling portion of the study. Enrollment will be stratified by sex to ensure that at least 2 of the 10 subjects in the rich PK sampling portion of the study and at least 3 of the 10 subjects in the sparse PK sampling portion of the study expected to complete the study are females.

3. OBJECTIVES

3.1 Primary Objective

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

4. STUDY POPULATION SETS

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 have been assigned a subject identification number and enrolled at baseline (predose on Day 1) visit.

4.3 Safety Set

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

4.4 Pharmacokinetic Set

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

5. SUBJECT DISPOSITION

The number of subjects included in each subject set (i.e. enrolled, safety and PK) will be summarized.

The number and percentage of subjects who completed and discontinued the study will be presented for the enrolled set. Reasons for discontinuation as recorded on the termination page of the electronic case report form (eCRF) will be summarized (number and percentage) for the enrolled set. All enrolled subjects who discontinued from the study will be listed and the reason for discontinuation will be provided. The subjects who completed the study will be those who completed the final scheduled visit on Day 9 of Week 4 for the rich PK sample subset or on Day 8 of Week 4 for the sparse PK sample subset.

Subject disposition and study analysis sets will be listed for the enrolled set.

6. PROTOCOL DEVIATIONS

All 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 study deviation tools. The Shire study team will review the protocol deviations and their classification throughout the study and before the 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 the database lock.

Confirmed protocol violations and protocol deviations will be documented in the Protocol Violation/Deviation tracker for the study. Protocol deviations/violations will be summarized by category and site, for the safety set. Protocol deviations/violations will be listed for the enrolled set.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1 Demographic and other Baseline Characteristics

Descriptive summaries of demographic and other baseline characteristics will be presented for the safety set and PK set.

The following demographic characteristics will be summarized in the following order in the tables: age, sex, ethnicity, race, weight, height, and body mass index (BMI). In addition, other baseline characteristics such as years since diagnosis of ADHD, ADHD Subtype, baseline ADHD-RS-5 (Child, Home Version) total score, and baseline Clinical Global Impressions - Severity of Illness (CGI-S) score will be summarized.

The ADHD-RS-5, which measures the behavior of children, is an 18-item questionnaire that requires the respondent to rate the frequency of occurrence of ADHD symptoms as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Each item is scored on a 4-point scale ranging from 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0 to 54. The ADHD-RS-5 total score will be calculated as the sum of the individual items from the ADHD-RS-5.

The CGI-S is performed 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).

Continuous variables, such as age, weight, height, BMI, years since diagnosis of ADHD, and baseline ADHD-RS-5 total score will be summarized using descriptive statistics including number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables such as sex, ethnicity, race, ADHD Subtype, and baseline CGI-S score will be summarized by reporting the number and percentage of subjects in each category. All summarized values will be taken from the Screening Visit or Predose assessments (for baseline weight and BMI).

Age will be calculated as the difference between date of birth (DOB) and date of informed consent (DINFC), truncated to years, using the following formula:

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

For PK analyses age will also be calculated without truncation as the difference between DOB and DINFC.

Height and weight will be summarized in international system of units.

Height and weight at predose assessment will be used to calculate BMI using the formula below:

BMI = Weight in kilograms / (Height in meters)^2

Number of years since diagnosis of ADHD will be based on DINFC.

Demographics and baseline characteristics will be listed for the safety set.

7.2 Medical History

At the Screening Visit demographic information, a complete medical and medication history will be collected including recent ingestion of medication (30 days prior to entering the screening period) and history of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases.

Medical history will be listed for the safety set.

The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) version 7.0.2 collected at the Screening Visit will be listed for the safety set.

ADHD non-medication treatment history, behavioral therapy history, collected at the Screening Visit (Visit 1) will be listed for the safety set.

For ADHD medication history collected at the Screening Visit (Visit 1), version September 1, 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 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

A listing will be created by subject number and will show the date and time of dose administration and investigational product accountability for the safety set.

Exposure to SHP465 6.25 mg will be summarized for the safety set.

For the investigational product SHP465 all dosing information (total dose, average daily dose and cumulative dose) will be listed and the following statistics will be calculated by study visit:

- Days of dosing: number of days on which dose information was available and non-zero
- Total dose (mg): total number of capsules taken × dose level (6.25 mg)
- Average daily dose (mg/day): the total dose / total days of dosing
- Cumulative dose (mg): sum of total dose since start of treatment
- Duration of exposure in weeks: the total days of dosing / 7

A statistical summary will be applied to present for each of the above statistical quantities.

Subjects will be categorized in 1 week increments by their overall duration of exposure in days and will be presented using subject counts and percentages.

In addition, person-time (overall total exposure in days) will be derived for SHP465 6.25mg. It is calculated as total number of days in which SHP465 6.25mg was taken for each subject (total days of dosing for the treatment period), and then sum over all subjects for the treatment period.

If a subject is lost to follow up without returning the leftover of investigational product and without providing subsequent safety information, then the subject's dose information will be treated as missing. In particular, for subjects who are lost in the follow up after the Baseline Visit (predose on Day 1), it will not be assumed that any of the investigational product has been ingested unless there is a post-baseline safety assessment. Subjects who 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

Treatment compliance will be calculated as follows:

For whole capsules:

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

For capsule contents sprinkled in applesauce:

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

Where,

- if the subject completed the treatment period: capsules prescribed per protocol = 28;
- if the subject discontinued early in the treatment period, capsules prescribed per protocol = date of treatment discontinuation – date of first dose +1.

Descriptive statistics for investigational product compliance will be presented for the safety set. Individual subject treatment compliance will be listed by category. The investigation product treatment compliance will be categorized as <80%, 80-120%, or >120%. The category 80-120% will be considered compliant for analysis purpose.

9. PRIOR AND CONCOMITANT MEDICATIONS/TREATMENTS

The WHO Drug Dictionary version September 1, 2017 will be used to classify prior and concomitant medications by preferred drug name.

Prior medication or treatment is defined as any medication (including but not limited to herbal treatments, vitamins, nonpharmacological treatment, such as behavioral treatment) received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) prior to the date of the administration of investigational product.

Concomitant medication or treatment is defined as any medication or treatment 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 for the safety set. Medications can be counted both as prior and concomitant medication. For the purpose of summaries multiple medication usage by a subject in the same category will be counted only once.

All prior, concomitant and post-treatment medications/treatments will be listed for the safety set.

10. EFFICACY ANALYSES

Not applicable.

11. SAFETY ANALYSES

The safety analysis will be performed using the safety set. Safety endpoints include the occurrence of treatment-emergent AEs (TEAEs), vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature), weight, height, electrocardiogram (ECG) results, the Columbia-Suicide Severity Rating Scale (C-SSRS), clinical laboratory tests (biochemistry, hematology, and urinalysis), the parent/ legally authorized representative (LAR)-completed Children's Sleep Habits Questionnaire (CSHQ) and the Post Sleep Questionnaire (PSQ).

For each safety endpoint, unless otherwise specified, the last value collected before the first dose of the administration of investigational product will be used as baseline for all analyses of that safety endpoint.

Except for AE data, only baseline assessments from baseline visit (predose on Day 1 of Week 1) and post-baseline assessment up to the final scheduled visit (Day 9 of Week 4 for rich PK sample subset or Day 8 of Week 4 for sparse PK sample subset) that were collected on or before 2 days after the last dose of the 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 20.1 of the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent AEs are defined as AEs that started or deteriorated on or after the date of the first dose of investigational product, and no later than 3 days following the 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 the 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 discontinuation from the study, and TEAEs leading to death.

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

For subjects on SHP465 the incidence of all TEAEs will be summarized by preferred term, and sorted by decreasing frequency. Serious TEAEs, TEAEs related to investigational product, and TEAEs leading to discontinuation from the study will be summarized by SOC and PT for the safety set. Listings will be presented for all AEs, serious TEAEs, TEAEs related to investigational product, and TEAEs leading to discontinuation from the study.

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 miscellaneous psychiatric events) listed in Table 4. Adverse event terms of special interest will be searched across the TEAE data and summarized with the total exposure (in subject-days).

Table 4: 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
	Gunshot 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
Miscellaneous psychiatric events (include events with serious outcome only)	Abnormal behavior
	Agitation
	Amnesia
	Confusional state
	Depressed mood
	Depression
	Disorientation
	Emotional disorder

Table 4: Psychiatric Events

Category	Preferred Term/Verbatim term
	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 AEs of special interest.

Adverse events of particular interest include insomnia (including AEs with preferred terms of 'INSOMNIA', 'INITIAL INSOMNIA', 'MIDDLE INSOMNIA', and 'TERMINAL INSOMNIA'), weight decrease and decreased appetite.

For each of these 3 AEs, 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 SHP465 6.25 mg, until the earlier of the end date of the TEAE or the date of last dosing + 3 days (if the date of last dosing is missing, the date of 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, the durations will be averaged for that subject. Summary statistics are then based on the averaged subject durations. The calculated duration only includes 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 (and other action categories related to dose)
    - TEAEs leading to discontinuation
    - Number of subjects who discontinued investigational product due to the event

Also, for each of these 3 AEs, the following information will be presented by week:

- 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.

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

11.2 Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline to Week 4/ET as well as shift tables from baseline to Week 4/ET for quantitative variables will be presented for the following clinical laboratory variables.

Hematology Hemoglobin, hematocrit, red blood cells, platelet count, white blood cell count – total and differential, total neutrophils (absolute and relative), eosinophils (absolute and relative), monocytes (absolute and relative), basophils (absolute and relative), and lymphocytes (absolute and relative).

Biochemistry Sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, chloride, thyroid-stimulating hormone, thyroxine, tri-iodothyronine, phosphorus, total protein, total CO_2 (bicarbonate), albumin, aspartate transaminase, alanine transaminase, gamma glutamyl transferase, alkaline phosphatase, total bilirubin, and uric acid.

Urinalysis pH, glucose, protein, blood, ketones, bilirubin, nitrites, leukocyte esterase, and specific gravity.

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

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 5. 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 5: Criteria for Potentially Clinically Important Laboratory Tests

Parameter	SI Unit	Lower Limit	Higher Limit
Biochemistry			
Albumin	g/L	< 30g/L	-
Alkaline phosphatase			≥ 2.5 x ULN
Aspartate transaminase	-	-	≥ 3 x ULN
Alanine transaminase	-	-	≥ 3 x ULN
Blood urea nitrogen	mmol/L	-	> 10.71 mmol/L or > 2.5 x ULN
Calcium, total	mmol/L	2	2.88
Creatinine	µmol/L	-	> 176.80 µmol/L or > 1.5 x ULN
Gamma glutamyl transferase	-	-	≥ 2.5 x ULN
Glucose	mmol/L	< 3.05	> 8.88
Phosphorus, inorganic	mmol/L	< 0.81	2.26
Potassium	mmol/L	< 3.0	> 5.5
Thyroid stimulating hormone	-	< LLN	> 2 x ULN
Sodium	mmol/L	< 130	> 150
Uric acid	µmol/L	-	> 594.85
Bilirubin, total	µmol/L	-	> 34.21
Protein. total	g/L	< 50	> 90
Hematology			
Basophils	-	-	> 10%
Hemoglobin	g/L	90	160
Hematocrit	%	< 30%	> 50%
Platelet count	10^9/L	75	600
Red blood cells	X 10^{12}/L	2.5	7.5
White blood cell count	X 10^9/L	< 3.0	> 16.0
Neutrophils	X 10^9/L OR %	< 1x10^9/L OR < 30%	> 6.2 x 10^9/L OR > 70 %
Eosinophils	10^9/L OR %	NA	0.5 x 10^9/L OR > 10%
Lymphocytes	%	< 10%	> 70%
Monocytes	%	-	> 20%
URINALYSIS			
Glucose	-	-	Positive Value (excluding trace)
Protein	-	-	Positive Value (excluding trace)
Blood	-	-	Positive Value (excluding trace)

Table 5: Criteria for Potentially Clinically Important Laboratory Tests

Parameter	SI Unit	Lower Limit	Higher Limit
Ketones	-	-	Positive Value (excluding trace)
Bilirubin	-	-	Positive Value (excluding trace)
Leukocyte esterase	-	-	Positive Value (excluding trace)
Nitrites	-	-	Positive Value (excluding trace)

LLN: Lower limit of normal value provided by the laboratory
ULN: Upper limit of normal value provided by the laboratory

All clinical laboratory data will be listed for the safety set.

11.3 Vital Signs (Including Height and Weight)

Descriptive statistics for vital signs (e.g. systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and their changes from baseline at each post-baseline assessment time point and at FoTA will be presented.

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 time point 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 time point and at the FoTA. In addition, z-scores for height, weight, and BMI will be based on the subject's age at each time point 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).

Vital sign values will be considered PCI if they meet both the observed value criteria and the change from baseline criteria listed in Table 6. The number and percentage of subjects with PCI post-baseline values will be tabulated. 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 subject number, baseline, and post-baseline PCI values.

The averaged values of the 3 measurements for sitting systolic, diastolic blood pressure and pulse at each time point will be used for all summaries and determination of PCIs.

Table 6: Criteria for Potentially Clinically Significant Vital Signs

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 as a PCI value if its meets either the criteria for observed value or the criteria for change from baseline.

Measurements of oral or tympanic temperature, sitting respiratory rate will be performed at the screening visit and ET visit only.

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 7.

Table 7: Normal Range of Pulse Rate (beats/min)

	1st Percentile	99th Percentile
Males, 4-5 years	69	120
Females, 4-5 years	70	132

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 for the lower than the 1st percentile and higher than the 99th percentile cut-off values, respectively, for males and females separately. The denominator will be the number of subjects in the safety set (per sex) 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 8.

Table 8: 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
	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

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 sex. The denominator will be the number of subjects in the safety set (per sex) 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)

Descriptive statistics for ECG variables (eg, heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) and their changes from baseline at each assessment time point will be presented. QTc interval will be calculated using both Bazett ($QTcB=QT/(RR)^{1/2}$) and Fridericia ($QTcF=QT/(RR)^{1/3}$) corrections; and if RR is not available, it will be replaced with 60/heart rate in the correction formula. Electrocardiogram interpretation will be summarized by assessment time point for all scheduled assessments. A shift table from baseline to each assessment time point for qualitative ECG results will be presented.

For the ECG interval parameters, baseline is defined as the average of the triplicate ECG measurements obtained at the baseline visit (predose on Day 1) prior to the administration of the investigational product. For the ECG interpretation, baseline will be the ECG with the worst interpretation obtained at the baseline visit (predose on Day 1), providing this is prior to the administration of the investigational product. The ECG interpretation of normal will be considered better than abnormal, and not clinically significant abnormal will be considered better than clinically significant abnormal.

Electrocardiogram variable values will be considered PCI if they meet or exceed the upper limit values listed in Table 9. 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 non-PCI baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline ECG value. A listing of all subjects with post-baseline PCI value will be provided including the subject number, baseline, and post-baseline PCI values.

Table 9: Criteria for Potentially Clinically Important ECG Values

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 **ECG evaluation –abnormal rhythm** • Complete Heart Block • Tachycardia • Bradycardia • Wandering Atrial Pacemaker • Ectopic Atrial Rhythm • Atrial Fibrillation • Atrial Flutter • Multifocal Atrial Tachycardia • Supraventricular Tachycardia • Atrial Bigeminy • Ventricular Bigeminy • Atrial Couplets • Ventricular Couplets • Ventricular Tachycardia • Torsade des Pointes • Ventricular Fibrillation • Junctional Rhythm • Idioventricular Rhythm • Escape Beat • Atrial Pacemaker	-	-

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 time point and at the FoTA will be produced. A shift table showing the change in evaluation from baseline to the FoTA by treatment group will also be produced.

All ECG data will be listed for the safety set. Listings of ECG data including the central reader's assessment and investigator's interpretation by individual subject will also be produced.

11.5 Other Safety Variables

11.5.1 Columbia-Suicide Severity Rating Scale

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

The C-SSRS contains 2 required items pertaining to suicidal ideation, 4 required items pertaining to suicidal behavior, and 1 required item pertaining to non-suicidal self-injurious behavior. In situations where there is a positive response to the screening questions, there are 8 additional suicidal ideation items and 2 additional suicidal behavior items which are completed. There are also 2 items for suicide and suicide behavior present during the interview. Thus, there is a maximum of 19 items to be completed. 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 the C-SSRS will be used in this study as follows:

- The Pediatric/Cognitively Impaired - Lifetime Recent-Clinical version will be administered at the screening visit.
- The Pediatric/Cognitively Impaired -Since Last Visit - Clinical version will be completed at all study visits after the screening visit.

The number and percentage of subjects with positive responses for each suicidal ideation item, intensity of ideation item, suicidal behavior item, actual attempts item will be presented for overall and at each time point. Descriptive statistics for number of attempts of suicidal behavior will also be summarized.

Listings of the C-SSRS data will be provided for subjects with a positive response for the safety set.

11.5.2 Post Sleep Questionnaire

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

Items with continuous responses, such as length of time to fall sleep per night, number of times woke up per night, length of time awake per night, length of time sleeping per night will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum). Items with categorical responses such as woke up during the night, number of times woke up per night, overall quality of sleep during the past week, typical week, reason the past week was not typical, overall quality of sleep during the past school week will be summarized by reporting the number and percentage of subjects in each category.

All PSQ data will be listed for the safety set.

11.5.3 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. Each scored question except for Watching TV and Riding in car are rated on a 3-point scale depending on the frequency of occurring:

- "usually" (5–7 times within the past week): score = 3
- "sometimes" (2–4 times within the past week): score = 2
- "rarely" (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" (5–7 times within the past week): score = 1
- "sometimes" (2–4 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):

- "not sleepy": score = 0
- "very sleepy": score = 1

- "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)
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)

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

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).

Total sleep disturbance score, each subscale score and each individual item will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum) at each time point. All CSHQ data will be listed for the safety set.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

12.1 Pharmacokinetic Methods

All summaries and analyses of the PK data will be based on the PK set.

12.1.1 Concentration Data

During this study blood samples for the determination of plasma *d*- and *l*-amphetamine concentrations will be drawn from each subject. For subjects enrolled onto the Rich PK sample portion blood samples will be collected on Day 1 of Week 1 at predose, and on Day 7 of Week 4 at predose, and at 2, 5, 8, 12, 16, 24, and 48 hours after administration of the investigational product. For subjects enrolled onto the Sparse PK sample portion blood samples will be collected on Day 1 of Weeks 1 to 3, and on Day 8 of Week 4 at predose only. Plasma *d*- and *l*-amphetamine concentrations will be measured using the most current validated bioanalytical method.

Individual plasma *d*- and *l*-amphetamine concentrations will be listed by subject, week, day, and time based on the PK set and summarized by time based on the PK set with the following descriptive statistics: n, arithmetic mean, SD, coefficient of variation (CV%), median, minimum, maximum, and geometric mean. The individual and mean plasma *d*- and *l*-amphetamine concentration versus time profiles will be presented in figures on both linear and semi-logarithmic concentration scales for the Rich PK sampling portion. Mean (±SD) plasma *d*- and *l*-amphetamine concentration versus time profiles will be presented using nominal time and individual plasma *d*- and *l*-amphetamine concentration versus time profiles will be presented using actual time based on the PK set. Individual and mean (±SD) plasma *d*- and *l*-amphetamine trough concentrations versus day will be presented in figures on linear concentration scale.

12.1.2 Handling BLQ Values

The following conventions will be used for reporting plasma analyte concentrations that are below the lower limit of quantitation (LLOQ) (reported as not quantitative [NQ]):

- Plasma samples with analyte concentrations that are below the limit of quantitation (BLQ) are reported as zero on the data listings.
- Plasma samples with analyte concentrations that are BLQ will be treated as zero in the calculation of summary statistics (eg, mean, SD, etc.) for the plasma analyte concentrations at individual time points.
- If analyte concentrations is BLQ in all plasma samples, mean plasma analyte concentrations will be reported as zero, and no descriptive statistics will be reported.
- If the calculated mean (± SD) plasma analyte concentration is less than the LLOQ, the value will be reported as calculated. The mean values derived using these conventions will be used to create the mean plasma analyte concentration versus time plots.

12.1.3 Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by non-compartmental analysis using Phoenix® WinNonlin® from the plasma *d*- and *l*-amphetamine concentration-time data in subjects from the Rich PK sampling portion only. All calculations will be based on actual sampling times.

For calculation of area under the concentration-time curve (AUC), BLQ values are set equal to zero in the PK dataset loaded into WinNonlin. For concentration greater than the LLOQ at the first time point WinNonlin uses the zero values, but for all later time points WinNonlin excludes the zero values from the AUC calculation.

The following primary PK parameters will be reported:

C_{max}	Maximum concentration occurring at t_{max}
$C_{trough,ss}$	Plasma analyte trough concentration (the predose concentrations collected at steady-state)
t_{max}	Time of maximum observed plasma analyte concentration sampled during a dosing interval
AUC_{0-t}	Area under the concentration-time curve from the time 0 to the last time point of sample collection
AUC_{0-5}	AUC from time 0 to 5 hours postdose
AUC_{5-t}	AUC from 5 hours postdose to the last-point of sample collection
AUC_{last}	AUC from the time of dosing to the last measurable concentration
$AUC_{tau,ss}$	AUC over the dosing interval (24 hours) at steady-state
λ_z	First order rate constant associated with the terminal phase of elimination
$t_{½}$	Terminal half-life
CL/F	Total body clearance for extravascular administration
V/F_{ss}	Apparent volume of distribution at steady-state calculated as: $V/F_{ss} = Dose/ (AUC_{tau,ss} \cdot \lambda_z)$

AUC-Area under the concentration time curve

The following secondary PK parameters will also be reported:

C12	The observed plasma analyte concentration at 12 hours after dose administration
C16	The observed plasma analyte concentration at 16 hours after dose administration
C24	The observed plasma analyte concentration at 24 hours after dose administration
AUC_{5-12}	Area under the concentration-time curve from 5 hours to 12 hours postdose
AUC_{12-16}	Area under the concentration-time curve from 12 hours to 16 hours postdose
AUC_{16-24}	Area under the concentration-time curve from 16 hours to 24 hours postdose

12.2 Summary of Pharmacokinetic Parameters

PK parameters will be summarized based on the PK set. The PK parameters of *d*- and *l*-amphetamine will be summarized with descriptive statistics (n, arithmetic mean, SD, CV%, median, minimum, maximum, and geometric mean. Individual PK parameters versus age will be presented in figures on both linear and semi-logarithmic PK parameter scales for $AUC_{0\text{-}t}$, $AUC_{tau,ss}$, C_{max}, CL/F, and V/F_{ss}.

12.3 Pharmacodynamic Methods (if applicable)

Not applicable.

12.4 Statistical Analysis of Pharmacodynamic Data (if applicable)

Not applicable.

12.5 Analyses of Pharmacokinetic/Pharmacodynamic Relationships (If applicable)

Not applicable.

12.6 Pharmacokinetic References

Not applicable.

13. OTHER ANALYSES

No other analyses are planned for this study.

14. INTERIM ANALYSIS

No interim analysis is planned for this study.

15. DATA MONITORING/REVIEW COMMITTEE

An external independent data monitoring committee (DMC) will be set up for the following studies: SHP465-112, SHP465-308, and SHP465-309. The DMC will review the data pertaining to safety, tolerability, and benefit/harm of the study therapy. Confidentiality of the unblinded DMC analyses is a critical concern and to address this, an unblinded independent reporting team will be identified within a contract research organization. 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.

16. COMPUTER METHODS

Statistical analyses will be performed using Version 9.3 or higher of SAS® (SAS Institute, Cary, NC 27513) on a suitably qualified environment. Pharmacokinetic parameters will be determined using a validated version of Phoenix™ WinNonlin® Version 6.4 or higher.

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

The PK parameters $AUC_{0-\infty}$ and V_z/F for *d*- and *l*-amphetamine have been omitted from the PK analysis, given that only steady-state PK concentrations will be available. These parameters are not appropriate for calculation and interpretation in multiple dosing scenarios. There are no other changes from the PK analysis methods stated in the protocol.

Protocol section 9.8 (Safety Analyses) states: Treatment-emergent AEs are defined as AEs that started or deteriorated on or after the date of the first dose of investigational product, and no later than 3 days following the **first** dose of investigational product. Since this is a multiple-dose study and the dose will be administered daily as a single dose for 28 days, the definition of TEAE in the protocol will exclude the AEs started or deteriorated on or after the fourth dose, which will not be appropriate for safety analysis. The following definition for TEAEs is used in the Statistical Analysis Plan: Treatment-emergent AEs are defined as AEs that started or deteriorated on or after the date of the first dose of investigational product, and no later than 3 days following the **last** dose of investigational product.

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, 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 will be presented to 2 more decimal places than the raw data.

Body mass index, averaged laboratory results e.g. diastolic/systolic blood pressure and pulse (when taken in triplicate), and derived questionnaire scores will be rounded to 1 decimal place for reporting.

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 as whole numbers.

18.2 Derived Efficacy Endpoints

Not applicable.

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 all 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 or unscheduled 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. For the ECG interval parameters, this will be the average of the triplicate ECG measurements obtained at the baseline visit (predose on Day 1) 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 (predose on Day 1), providing this is prior to the first dose of the investigational product.

If a subject has repeated assessments at any post-baseline assessment time point, the first recorded assessment will be assigned to the assessment time point for generating descriptive statistics. For vital signs (sitting systolic blood pressure, diastolic blood pressure, and pulse), this will be the average of the 3 measurements from the first recorded assessment. For the ECG interpretation, if there are multiple assessments at any assessment time point, the worst interpretation will be used for generating descriptive statistics.

If end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study 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, including unscheduled and repeated assessments, will be presented in the data listings.

18.5 Missing Date 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 this date from the investigator. If after all efforts the date of the last dose of IP is still missing, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

18.6 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (ie, 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 IP, then the day and month of the date of the first dose of IP 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 IP, then December 31 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 IP, 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 IP, then the day of the date of the first dose of IP will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of IP or if both years are the

same but the month is before the month of the date of the first dose of IP, 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 IP or if both years are the same but the month is after the month of the date of the first dose of IP, 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 IP, then the day and month of the date of the last dose of IP 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 IP, 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 IP, 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 IP, then the day of the date of the last dose of IP will be assigned to the missing day.
- If either the year is before the year of the date of the last dose of IP or if both years are the same but the month is before the month of the date of the last dose of IP, 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 IP or if both years are the same but the month is after the month of the date of the last dose of IP, 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 IP, 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 IP, 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 Investigation Product for Adverse Events

If the relationship to IP is missing for an AE starting on or after the date of the first dose of IP, a causality of "Related" will be assigned. The imputed values for relationship to the IP 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

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