U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 022-063
Supplement #:	O-1 (SN0022 SN0023)
Drug Name:	Mydayis (mixed salts of a single-entity amphetamine product) Sustained-Release Capsules
Indication(s):	Attention-deficit/Hyperactivity Disorder (ADHD)
Applicant:	Shire
Date(s):	Letter date: Dec 20, 2016
	PDUFA due date: Jun 20, 2017
Review Priority:	Priority (resubmission)
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Yang Wang, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph. D., Team Leader
	H.M. James Hung, Ph.D., Division Director
Medical Division:	Division of Psychiatry Products
Clinical Team:	Nancy Clark Dickinson, M.D., Clinical Reviewer
	Javier Muniz, M.D., Clinical Team Leader
Project Manager:	Latrice Wilson, Pharm.D.

Keywords:

Link to keywords:

http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

The efficacy results from two Phase 3 studies (SHP465-305 and SHP465-306) supported Sponsor's claim that SHP465 is efficacious as a long-acting stimulant at dose levels of 12.5 mg and 37.5 mg in adults and at a dose range between 12.5 and 25 mg in pediatrics (based on body weight) for the treatment of ADHD.

2. INTRODUCTION

2.1 Overview

The original NDA for SHP465 (NDA 22-063) was submitted under the trade name (b) (4) on July 21, 2006. An Approvable Letter was issued to Shire on May 18, 2007, tentatively approving the dosage strengths of 12.5 and 25 mg for the treatment of ADHD in adults in addition to specifying 2 post-marketing commitments. References are made to FDA's April 25, 2014 Written Responses Only (WRO) and June 17, 2015 meeting minutes in which FDA classified this complete response to the May 18, 2007 Approvable Letter as a 505(b)(1) Class 2 Resubmission.

The SHP465 clinical development program consists of a total of 16 clinical studies, 13 of which were included in the original NDA, and 3 of which are new and included in this NDA resubmission.

The initial clinical development program for SHP465 included the following 13 clinical studies:

- 7 phase 1 PK studies conducted in healthy adult subjects,
- 4 controlled Phase 2 and 3 efficacy studies conducted in adults with ADHD (SPD465-201, SPD465-203, SPD465-301, SPD465-303),
- 1 placebo- and active-controlled Phase 2 efficacy study conducted in adolescents with ADHD (SPD465-202),
- 1 long-term (12 months), open-label Phase 3 safety study with efficacy as a secondary objective in adults with ADHD (SPD465-304).

Both pivotal phase 3 studies included in the original NDA (SPD465-301 and SPD465-303) demonstrated that adults with ADHD treated with 25, 50, or 75 mg SHP465 experienced statistically significantly reduced ADHD symptoms (as assessed by Attention-Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV)) and a global improvement (as assessed by the clinical global impression improvement scale (CGI-I)) compared with adults treated with placebo.

The NDA resubmission includes 3 additional clinical studies to support a proposed indication for SHP465 for the treatment of ADHD with dosage strengths of 12.5, 25, 37.5, and 50 mg in both adult and pediatric patients:

- SHP465-111, an open-label Phase 1 pharmacokinetics study;
- SHP465-305, a Phase 3, randomized, double-blind, multicenter, placebo-controlled, dose-optimization, safety and efficacy study of SHP465 12.5 mg to 25 mg in children and adolescents aged 6 to 17 years with ADHD, conducted as a premarketing study in pediatric patients with ADHD, as a component in the complete response to the Approvable Letter; and
- SHP465-306, Study SHP465-306 is a Phase 3, randomized, double-blind, multicenter, placebo-controlled, forced-dose titration, safety and efficacy study of SHP465 in adults aged 18 to 55 years with ADHD, conducted as a post-marketing commitment for exploration of dose response for effectiveness as requested in the Approvable Letter.

The two Phase 3 studies SHP465-305 and SHP465-306 are the main focus of this review and listed below.

Table 1: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
SHP465-305	*Phase 3*	*4 weeks*	*7 days*	*257 in FAS: 129 in Placebo and 128 in SHP465*	*Children and adolescents (aged 6-17 years) with ADHD*
SHP465-306	*Phase 3*	*4 weeks*	*7 days*	*263 in FAS: 86 in placebo, 89 in SHP465 12.5 mg, and 88 in SHP465 37.5 mg.*	*Adults (aged 18-55 years) with ADHD*

Objectives of SHP465-305:
Primary: to evaluate the efficacy of SHP465 administered as a daily morning dose compared to placebo in the treatment of children and adolescents (aged 6-17 years, inclusive) diagnosed with ADHD.
Key secondary: to assess the efficacy of SHP465 compared to placebo using a global clinical measure of improvement, the Clinical Global Impression - Global Improvement scale (CGI-I).

Objectives of SHP465-306:
Primary: to evaluate the efficacy of each SHP465 dose (12.5 and 37.5 mg) administered daily in the morning compared to placebo in the treatment of adults (18-55 years of age, inclusive) diagnosed with ADHD.
Key secondary: to evaluate the efficacy of each SHP465 dose (12.5 and 37.5 mg) compared with placebo using a global clinical measure of improvement, the Clinical Global Impression – Improvement (CGI-I).

2.2 Data Sources

The following data sources were considered in this review:
a) Applicant's study report
(\\CDSESUB1\evsprod\NDA022063\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5351-stud-rep-contr\shp465-305)
(\\CDSESUB1\evsprod\NDA022063\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5351-stud-rep-contr\shp465-306)
b) Data sets
(\\CDSESUB1\evsprod\NDA022063\0022\m5\datasets\shp465-305\analysis\adam\datasets)
(\\CDSESUB1\evsprod\NDA022063\0022\m5\datasets\shp465-306\analysis\adam\datasets)
c) Software code
(\\CDSESUB1\evsprod\NDA022063\0023\m5\datasets\shp465-305\analysis\programs)

(\\CDSESUB1\evsprod\NDA022063\0023\m5\datasets\shp465-306\analysis\programs)
d) Response to FDA information request
(\\CDSESUB1\evsprod\NDA022063\0022\m1\us)
(\\CDSESUB1\evsprod\NDA022063\0023\m1\us)

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor has complied with our requests for providing necessary datasets, definition files, and statistical programs for their analyses. This reviewer found the quality of their submissions acceptable and was able to replicate the primary results from the sponsor's Clinical Study Report (CSR).

3.2 Evaluation of Efficacy

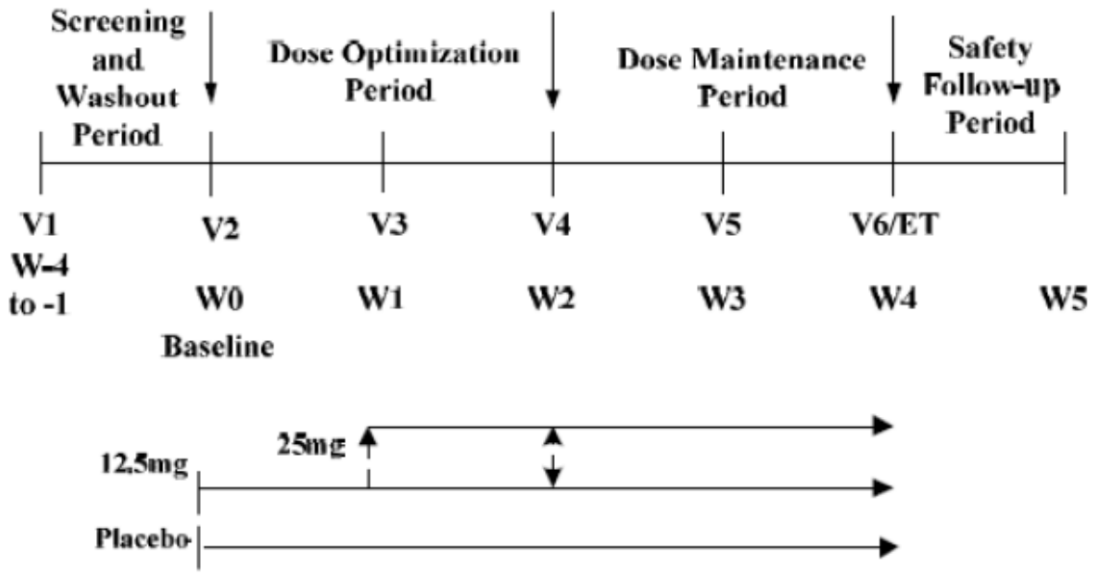
3.2.1 Study Design and Endpoints

3.2.1.1 Study SHP465-305

SHP465-305 was a randomized, multicenter (36 sites in the United States (US)), double-blind, placebo-controlled, dose-optimization study in children and adolescent subjects (6-17 years of age inclusive) with ADHD.

After the screening visit, a washout period was included to prevent any carry-over effects of residual prior medications before randomization. Subjects were stratified within each age group (6-12 years vs 13-17 years), and randomly assigned in a 1:1 ratio to SHP465 or placebo at baseline (Visit 2) and then would have 4 weeks of double-blind evaluation (2 weeks of dose-optimization and 2 weeks of dose-maintenance periods) of safety and efficacy. All enrolled subjects who completed the study or discontinued early were to complete Visit 6/early termination (ET). The follow-up period for this protocol was 7 days (+2 days) from the last dose of the investigational product.

Figure 1: Study Design Schematic of SHP465-305



Source: figure 1 on page 29 of Sponsor's CSR.

Table 2: Schedule of Assessments – SHP465-305

Visit[a]	Screening and Washout		Baseline	Dose Optimization		Dose Maintenance		Safety Follow-up
	1	Telephone Call[i]	2	3	4	5	6/ET	Telephone Call
Assessment Day	-28 to -7	-7	0	7	14	21	28/Any	35/Any
Assessment Week	-4	-1	0	1	2	3	4	5
ADHD-RS-IV[h]			X	X	X	X	X	
CGI-S[h]			X					
CGI-I[h]				X	X	X	X	

Source: table 3 on page 41-42 of Sponsor's CSR.

The primary measure of efficacy was the ADHD-RS-IV, consisting of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV-TR criteria. Each item is scored on a 4-point scale ranging from 0 (reflecting no symptoms) to 3 (reflecting severe symptoms) with total scores ranging from 0-54. The 18 items may be grouped into 2 subscales: hyperactivity/impulsivity (even-numbered items 2-18) and inattentiveness (odd-numbered items 1-17).

The primary efficacy endpoint was the change from baseline in the ADHD-RS-IV Total Score at Visit 6 (Week 4). The baseline ADHD-RS-IV Total Score was defined as the last valid ADHD-RS-IV Total Score assessment prior to taking the first dose of double-blind investigational product, usually at Visit 2 (Week 0).

The key secondary measure was CGI-I to assess the 3 target areas of improvement recorded at the baseline visit (Visit 2) by a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

The full analysis set (FAS) consisted of all subjects who signed informed consent, had been assigned a randomization number, had taken at least 1 dose of investigational product, and had at least 1 post-dose ADHD-RS-IV Total Score assessment.

3.2.1.2 Study SHP465-306

SHP465-306 was a Phase 3, randomized, multicenter (43 sites in the United States), double-blind, parallel-group, placebo-controlled, forced-dose titration study.

The study had 4 periods: screening and washout, forced-dose titration (Weeks 1 and 2), dose maintenance (Weeks 3 and 4), and safety follow-up. The duration of the double-blind evaluation period (forced-dose titration and dose maintenance periods) was 4 weeks. Subjects were randomly assigned at baseline (Visit 2) in a 1:1:1 ratio to 1 of 3 treatment groups: SHP465 12.5 mg, SHP465 37.5 mg, or placebo. Subjects received an oral dose of investigational product each morning for 4 weeks as detailed in the following table.

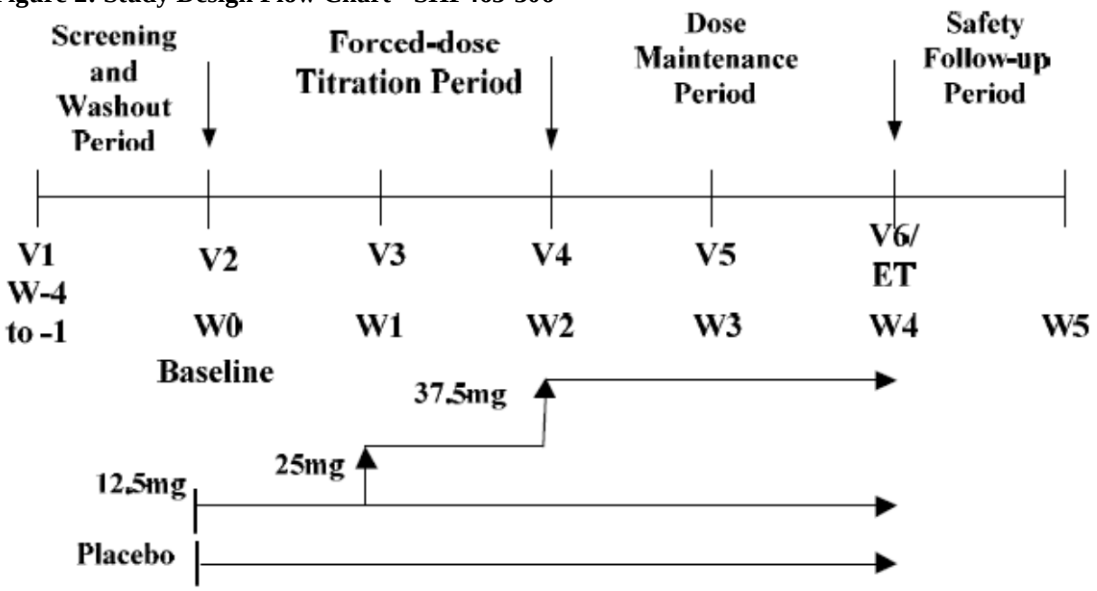
Table 3: Dosing Schedule

Treatment Group	Week 1 (Visits 2-3)	Week 2 (Visits 3-4)	Week 3 (Visits 4-5)	Week 4 (Visits 5-6)
SHP465 12.5 mg	12.5 mg	12.5 mg	12.5 mg	12.5 mg
SHP465 37.5 mg	12.5 mg	25 mg	37.5 mg	37.5 mg
Placebo	Placebo	Placebo	Placebo	Placebo

Source: table 2 on page 27 of Sponsor's CSR.

All randomly assigned subjects who completed the study or discontinued early were to complete Visit 6/early termination (ET). The follow-up period was 7 (+2) days from the last dose of the investigational product.

Figure 2: Study Design Flow Chart - SHP465-306



Source: figure 1 on page 28 of Sponsor's CSR.

Table 4: Schedule of Assessments – SHP465-306

Period	Screening and Washout		Baseline	Forced-dose Titration		Dose Maintenance		Safety Follow-up
Visit[a]	1	Telephone Call	2	3	4	5	6/ET	Telephone Call
Assessment day	-28	-7	0	7	14	21	28/Any	35/Any
Assessment week	-4	-1	0	1	2	3	4	5
Adult ADHD-RS with prompts[b]			✓	✓	✓	✓	✓	
CGI-S[b]			✓					
CGI-I[b]				✓	✓	✓	✓	

Source: table 4 on page 39-40 of Sponsor's CSR.

The primary measure of efficacy was the clinician-administered adult ADHD-RS with prompts consisting of 18 items designated to reflect current symptomatology of ADHD based on the DSM-5 criteria. Each item is scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms), with the total score for the rating scale ranging from 0 to 54. The scale is subdivided into 2 subscales of 9 symptoms each: hyperactivity/impulsivity and inattentiveness.

The primary efficacy endpoint was defined as the change from baseline of the adult ADHD-RS with prompts total score at Visit 6 (Week 4). Baseline adult ADHD-RS with prompts total score was defined as the last valid adult ADHD-RS with prompts total score assessment prior to taking the first dose of double-blind investigational product, usually at Visit 2 (Week 0).

The key secondary efficacy endpoint was the CGI-I score.

The full analysis set (FAS) consisted of all subjects who signed informed consent, had been assigned a randomization number, took at least 1 dose of investigational product, and had at least 1 post-dose baseline primary efficacy assessment (ADHD-RS with prompt total score) on treatment.

3.2.2 Statistical Methodologies

3.2.2.1 Study SHP465-305

3.2.2.1.1 Primary Analyses

The primary efficacy endpoint was analyzed by using the linear mixed-effects model for repeated measures (MMRM) with treatment group, visit, age group (6-12 years vs 13-17 years), and the interaction of treatment group with visit as factors, baseline ADHD-RS-IV Total Score as a covariate, and the interaction of baseline ADHD-RS-IV Total Score with visit adjusted in the model.

The key secondary efficacy measurement, CGI-I, was analyzed using the same analysis method (MMRM) as for the primary efficacy endpoint, including treatment group, nominal visit, age group, interaction of the treatment group with the visit as factors, baseline CGI-S as a covariate, and an adjustment for the interaction of the baseline CGI-S with the visit. The model is based on a restricted maximum likelihood (REML) method of estimation and utilizes an unstructured covariance type. The primary contrast of interest was at Visit 6 (Week 4) for SHP465 compared with placebo.

The fixed-sequence test procedure was applied to protect the study-wide Type I error at the 2-sided 0.05 for testing across the primary and the key secondary hypotheses.

3.2.2.1.2 Interim Analysis

A blinded interim analysis was planned, when approximately 75% of all randomly assigned subjects had either completed or discontinued from the study, to reassess the sample size in case of an underestimated variability postulated at the design stage.

If the re-estimated pooled standard deviation (SD) by a blinded analysis of the cumulative real data was larger than the 10.0 postulated at the design stage, the final total number of subjects to be enrolled was to be calculated using the re-estimated pooled SD together with the assumed treatment difference of 6.0. If the re-estimated pooled SD was smaller than 10.0, the sample size was not to be adjusted.

No data monitoring or review committee was planned for this study.

3.2.2.1.3 Additional Analyses

The CGI-I categories were dichotomized into 2 categories: “improved” (which included the categories of “very much improved” and “much improved”) and “not improved” (which included all other assessed categories grouped together). The key secondary efficacy measurement was analyzed using the proportion of subjects with an “improved” CGI-I measurement at Visit 6 (Week 4) using a Cochran-Mantel-Haenszel test that was stratified by age group and CGI-S value at baseline. If missing data exist at Visit 6 (Week 4), the visit was imputed by carrying forward the last post-baseline observation value.

3.2.2.1.4 Sensitivity Analyses

MMRM relies on the assumption that the missing data mechanism follows the missing at random (MAR) scenario, assuming that the probability of missing data is unrelated to the unobserved value itself, after controlling for observed data. For both the primary efficacy endpoint and the key secondary efficacy endpoint, two sensitivity analysis models that assume different missing not at random (MNAR) mechanisms were carried out to examine the robustness of the MMRM analysis results using pattern-mixture models.

Model 1 - Placebo multiple imputation based on the distribution of placebo group responses over time, assuming a subject on the active treatment with missing data follows the distribution of the placebo responses, i.e., the means and the intra-subject correlations based on the placebo responses will apply. The MNAR assumption is implemented by applying penalties to missing items in a multiple imputations process based on treatment-specific multivariate normal distribution for response. The penalty applied is a fraction of the estimated standard deviation for the primary endpoint.

Step 1: Imputations
A total of 200 sets of posterior mean and co-variance estimates are extracted from the SAS MI procedure using the available non-missing placebo data, 100 of which applied to the active treatment group and the other 100 to the placebo group. One set of imputations for all missing values will be generated based on each variation of posterior estimates. All 100 sets for imputations within a treatment group will be ordered from 1 to 100, and combined between active treatment and placebo, for a total of 100 completely imputed data sets.

Step 2: Analysis of complete data sets
The primary endpoint will be analyzed for each of the 100 complete data sets with imputed data using an ANCOVA with treatment group and age group as factors, and the baseline value as a covariate.

Step 3: Inference
The LS mean difference estimates will be averaged and the associated SEs will be summarized based on within-imputation and between-imputation variance using the SAS MIANALYZE procedure to yield a final estimate with associated 95% CI and p-value.

Model 2 – Multiple imputations with penalties applied to dropouts, assumed subjects who discontinue have worse changes than that predicted using MAR after discontinuation by a penalty. The MNAR assumption is implemented by extracting posterior mean and covariance in a multiple imputations process based on placebo patients, and applied to all SHP465 dropouts. Penalties were fractions of the SD for the primary and key secondary endpoints, and 5 different penalties were applied. SD is the estimated standard deviation for the primary endpoint (the square root of the estimated element for Visit 6 of the covariance matrix R from the primary MMRM).

Step 1a: Imputations
Based on the MAR assumption, missing data will be multiply imputed for 100 times on a treatment specific, multivariate normal distribution of the response over time using the SAS MI procedure with treatment in the BY statement.

Step 1b: Application of penalty
A fraction of the estimated standard deviation (SD) for the primary endpoint: (0*SD), (0.25*SD), (0.5*SD), etc. will be applied as a penalty to the multiply imputed values at Visit 6 (Week 4). SD is the square root of the estimated element for Visit 6 of the co-variance matrix R from the primary MMRM model.

Step 2 (analysis of complete data sets) and **Step 3 (inference)** are the same as Step 2 and Step 3, respectively, for Model 1.

3.2.2.1.5 Sample Size Determination

To detect an assumed difference of 6.0 for the change from baseline in the ADHD-RS-IV Total Score between the SHP465 treatment group and the placebo group with the assumed common SD of 10.0, 60 subjects per group were needed to provide 90% power for a 2-sided t-test with an α level of 0.05. This yielded a total of 120 subjects (60 subjects on active treatment and 60 subjects on placebo). Taking into account an expected post-randomization dropout rate of 20%, the randomization target was set at 150 subjects in total. It was estimated that approximately 25% of the enrolled subjects would be 6-12 years old. The final total number of subjects randomly assigned between the 2 groups was to be calculated in the blinded interim analysis, based on the estimate of the pooled variance.

A blinded interim analysis for sample size re-estimation was performed based on all subjects randomly assigned as of Aug 12, 2015 (the interim cohort), among which 118 subjects were in the FAS and 107 subjects completed the study. Based on the derived pooled SD of 13.66, the recalculated sample size was 110 subjects in each treatment group, or 220 subjects in total, without changing other original assumptions. Taking into account an expected post-randomization dropout rate of 20% for subjects not in the interim cohort, the overall randomization target was set at 264 subjects.

3.2.2.2 Study SHP465-306

3.2.2.2.1 Primary Analyses

The primary efficacy endpoint was analyzed by using the linear mixed-effects model for repeated measures (MMRM) with treatment group, visit, and the interaction of treatment group with visit as factors, baseline adult ADHD-RS with prompts total score as a covariate, and the interaction of baseline adult ADHD-RS with prompts total score with visit adjusted in the model.

The key secondary efficacy endpoint was analyzed using the same analysis method (MMRM) as for the primary efficacy endpoint. The baseline CGI-S score was used as the covariate. The primary contrast of interest was at Visit 6 (Week 4) for the specific SHP465 treatment group compared with placebo.

In order to protect the study-wide Type I error at the 2-sided 0.05 for testing across the primary and key secondary hypotheses, the fixed-sequence test procedure was applied in the following order based on the MMRM:

- SHP465 37.5 mg vs. placebo on change from baseline adult ADHD-RS with prompts total score at Visit 6 (Week 4)
- SHP465 12.5 mg vs. placebo on change from baseline adult ADHD-RS with prompts total score at Visit 6 (Week 4)
- SHP465 37.5 mg vs. placebo on CGI-I at Visit 6 (Week 4)

- SHP465 12.5 mg vs. placebo on CGI-I at Visit 6 (Week 4)

3.2.2.2.2 Additional Analyses

The CGI-I categories were dichotomized into 2 categories: “improved” (which included the categories of “very much improved” and “much improved”) and “not improved” (which included all other assessed categories grouped together). The key secondary efficacy measurement was analyzed using the proportion of subjects with an “improved” CGI-I measurement at Visit 6 (Week 4) using a Cochran-Mantel-Haenszel test that was stratified by age group and CGI-S value at baseline. If missing data exist at Visit 6 (Week 4), the visit was imputed by carrying forward the last post-baseline observation value.

3.2.2.2.3 Sensitivity Analyses

MMRM relies on the assumption that the missing data mechanism follows the missing at random (MAR) scenario, assuming that the probability of missing data is unrelated to the unobserved value itself, after controlling for observed data. For both the primary efficacy endpoint and the key secondary efficacy endpoint, two sensitivity analysis models that assume different missing not at random (MNAR) mechanisms were carried out to examine the robustness of the MMRM analysis results using pattern-mixture models.

Model 1 - Placebo multiple imputation based on the distribution of placebo group responses over time, assumed dropouts with missing values on the active treatment follow placebo pattern, i.e., the means and the intra-subject correlations based on the placebo responses will apply. The MNAR assumption is implemented by extracting posterior mean and covariance in a multiple imputations process based on placebo patients, and applied to all SHP465 dropouts.

Step 1: Imputations
A total of 300 sets of posterior mean and co-variance estimates are extracted from the SAS MI procedure using the available non-missing placebo data. One hundred of the posterior sets will be applied to each SHP465 treatment group respectively, the other 100 applied to the placebo group. One set of imputations for all missing values will be generated based on each variation of posterior estimates. All 100 sets for imputations within a treatment group will be ordered from 1 to 100, and combined between SHP465 treatment groups and placebo, for a total of 100 completely imputed data sets.

Step 2: Analysis of complete data sets
The primary endpoint will be analyzed for each of the 100 complete data sets with imputed data using an ANCOVA with treatment as the factor and the baseline value as a covariate.

Step 3: Inference
The LS mean difference estimates will be averaged and the associated standard errors will be summarized based on within-imputation and between-imputation variance using the SAS MIANALYZE procedure to yield a final estimate with associated 95% CI and p-value.

Model 2 - Multiple imputations with penalties applied to dropouts, assumed subjects who discontinue have worse changes than that predicted using MAR after discontinuation by a penalty. The MNAR assumption is implemented by applying penalties to missing items in a multiple imputations process based on treatment-specific multivariate normal distribution for response. The penalty applied is a fraction of the estimated standard deviation for the primary and key secondary endpoints, and 5 different penalties were applied.

Step 1a: Imputations
Missing data will be multiply imputed for 100 times based on a treatment specific, multivariate normal distribution of the response over time using the SAS MI procedure with treatment in the BY statement. This step is based on the MAR assumption.

Step 1b: Application of penalty
A penalty will then be applied to the multiply imputed values at Visit 6 (Week 4). The penalty will be a fraction of the estimated SD for the primary endpoint (the square root of the estimated element for Visit 6 of the co-variance matrix R from the primary MMRM model): (0*SD), (0.25*SD), (0.5*SD), etc.

Step 2 (analysis of complete data sets) and **Step 3 (inference)** are the same as Steps 2 and 3 respectively for Model 1.

3.2.2.2.4 Sample Size Determination

To detect an assumed difference of 7.0 for the change from baseline in the adult ADHD-RS with prompts total score between SHP465 dose group and the placebo group with the assumed common SD of 11.6 (corresponding to the effect size of 0.6), sixty subjects per group would be needed to provide 90% power for a 2-sided t-test with an α level of 0.05. Therefore, a total of 180 subjects (60 on each active dose treatment and 60 on placebo) would need to be randomly assigned. Taking into account an expected post-randomization dropout rate of 30%, the randomization target was set at 258 subjects in total.

No interim analysis was performed.

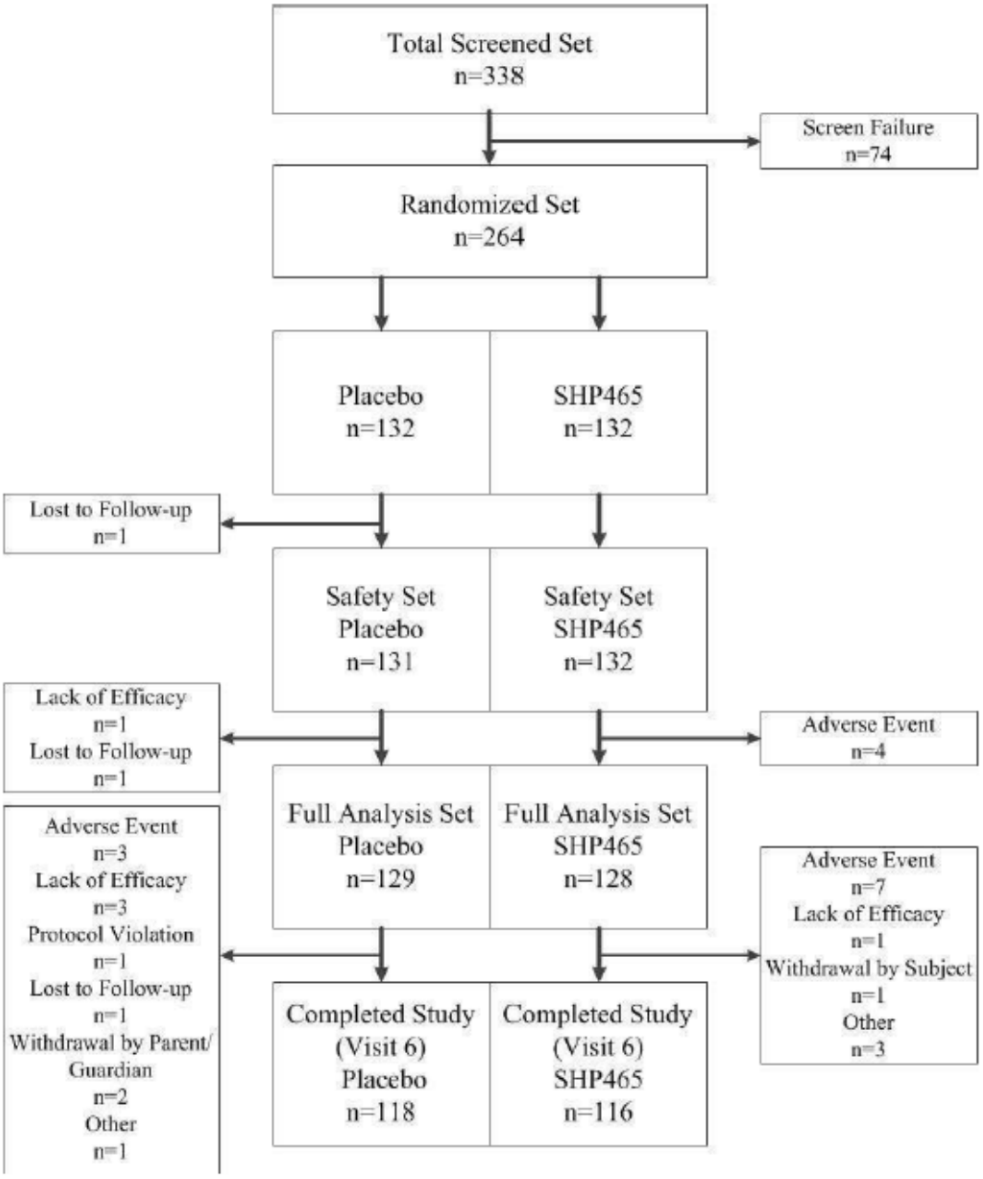
3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

3.2.3.1.1 Study SHP465-305

A total of 338 subjects were screened for this study, 264 of whom were included in the randomized set, 132 subjects randomized to the placebo treatment group and 132 subjects to the SHP465 treatment group. The full analysis set consisted of 257 subjects, 129 in the placebo treatment group and 128 in the SHP465 treatment group.

Figure 3: Subject Disposition - SHP465-305



Source: figure 2 on page 63 of Sponsor's CSR.

There were 118 subjects (90.1%) in the placebo treatment group and 116 subjects (87.9%) in the SHP465 treatment group who completed the study. The most common reasons for early termination were lack of efficacy [4 subjects (3.1%)] in the placebo treatment group and adverse event [11 subjects (8.3%)] in the SHP465 treatment group.

Table 5: Disposition by Withdrawal Reason - SHP465-305

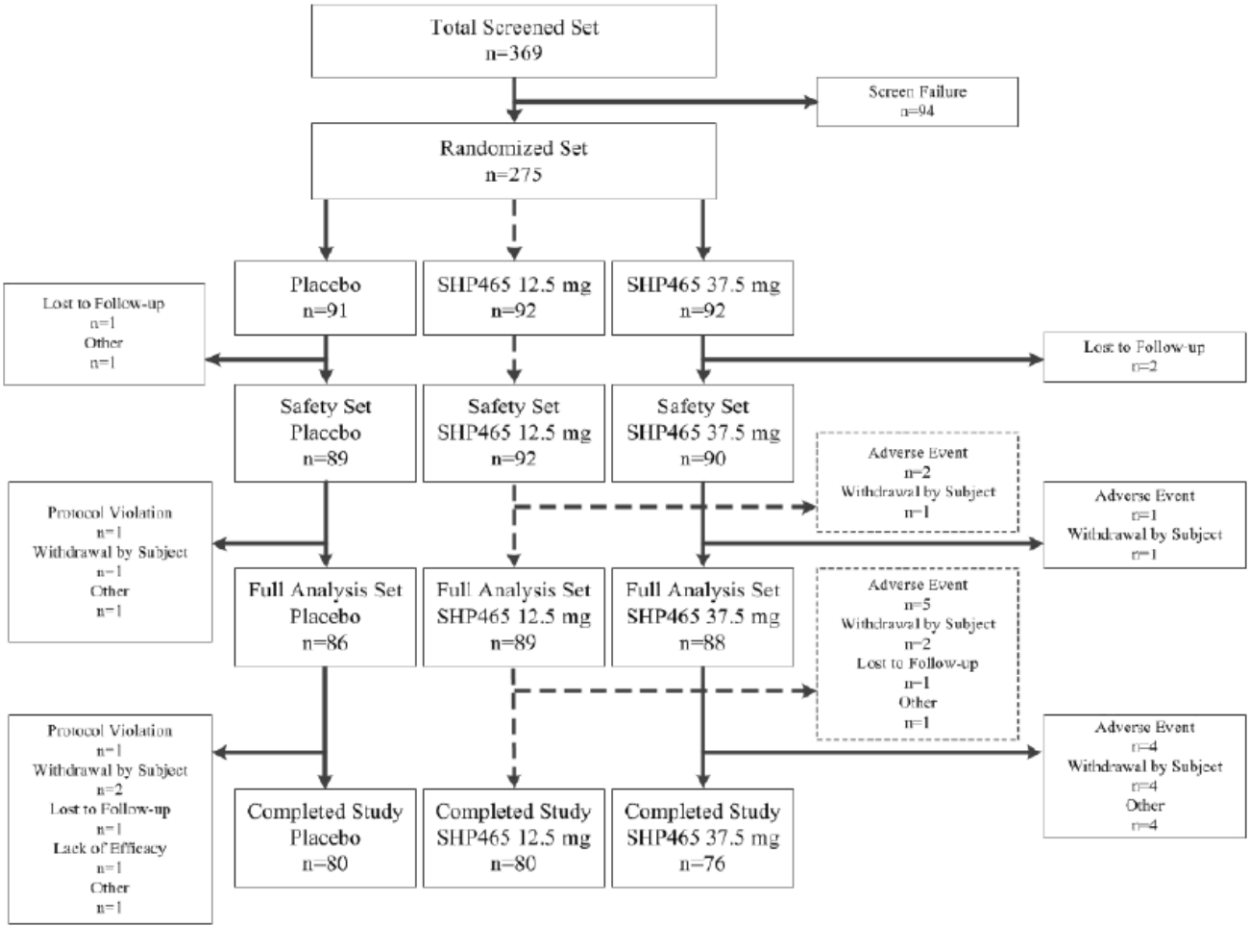
	Placebo N(%)	SHP465 N(%)	Total N(%)
Randomized Set	132	132	264
Safety Set	131 (99.2)	132 (100)	263 (99.6)
Full Analysis Set	129 (98.5)	128 (97.0)	257 (97.7)
Completed Study	118 (90.1)	116 (87.9)	234 (89.0)
Completed Follow-up	126 (96.2	132 (100)	258 (98.1)
Did not Complete Study	13 (9.9)	16 (12.1)	29 (11.0)
Primary Reason for Withdrawal			
Adverse Event	3 (2.3)	11 (8.3)	14 (5.3)
Lack of Efficacy	4 (3.1)	1 (0.8)	5 (1.9)
Lost To Follow-up	2 (1.5)	0	2 (0.8)
Protocol Violation	1 (0.8)	0	1 (0.4)
Withdrawal by Subject	0	1 (0.8)	1 (0.4)
Withdrawal by Parent/Guardian	2 (1.5)	0	2 (0.8)
Other	1 (0.8)	3 (2.3)	4 (1.5)

Source: reviewer's table by table 1.1.1 on page 156 of Sponsor's CSR.

3.2.3.1.2 Study SHP465-306

A total of 369 subjects were screened for this study, 275 of whom were included in the randomized set, 91 subjects randomized to the placebo treatment group, 92 to the SHP465 12.5 mg treatment group, and 92 to the SHP465 37.5 mg dose-titration treatment group. The full analysis set consisted of 263 subjects, 86 in the placebo treatment group, 89 in the SHP465 12.5 mg treatment group, and 88 to the SHP465 37.5 mg dose-titration treatment group.

Figure 4: Subject Disposition - SHP465-306



Source: figure 2 on page 59 of Sponsor's CSR.

There were 80 subjects (89.9%) in the placebo treatment group, 80 subjects (87.0%) in the SHP465 12.5 mg treatment group, and 76 subjects (84.4%) in the SHP465 37.5 mg treatment group who completed the study. The most common reasons for early termination were adverse events occurring in 7 subjects in the SHP465 12.5 mg treatment group and 5 subjects in the SHP465 37.5 mg treatment group.

Table 6: Disposition by Withdrawal Reason - SHP465-306

	Placebo N(%)	SHP465 12.5mg N(%)	SHP465 37.5mg N(%)	Total N(%)
Randomized Set	91	92	92	275
Safety Set	89 (97.8)	92 (100)	90 (97.8)	271 (98.5)
Full Analysis Set	86 (96.6)	89 (96.7)	88 (97.8)	263 (97.0)
Completed Study	80 (89.9)	80 (87.0)	76 (84.4)	236 (87.1)
Completed Follow-up	85 (95.5)	89 (96.7)	85 (94.4)	259 (95.6)
Did not Complete Study	9 (10.1)	12 (13.0)	14 (15.6)	35 (12.9)
Primary Reason for Withdrawal				
Adverse Event	0	7 (7.6	5 (5.6)	12 (4.4)
Protocol Violation	2 (2.2)	0	0	2 (0.7)
Withdrawal by Subject	3 (3.4)	3 (3.3)	5 (5.6)	11 (4.1)
Lost To Follow-up	1 (1.1)	1 (1.1)	0	2 (0.7)
Lack of Efficacy	1 (1.1)	0	0	1 (0.4)
Other	2 (2.2)	1 (1.1)	4 (4.4)	7 (2.6)

Source: reviewer's table based on table 1.1.1 on page 122 of Sponsor's CSR.

3.2.3.2 Demographic and Baseline Characteristics

3.2.3.2.1 Study SHP465-305

In general, subjects are comparable between placebo and SHP465 treatment groups for the demographic variables, such as age, ethnicity, and race, and baseline characteristic, such as weight, height, and body mass index (BMI).

Table 7: Demographic and Baseline Characteristics by Treatment Group - SHP465-305

Characteristic	Statistic	Placebo (N=50)	SHP465 (N=51)	Total (N=101)
Age (years)	Mean (SD)	9.1 (2.08)	9.2 (2.03)	9.2 (2.04)
	Median	9	9	9
	Min, Max	6, 12	6, 12	6, 12
Sex				
Male	n (%)	31 (62.0)	36 (70.6)	67 (66.3)
Female	n (%)	19 (38.0)	15 (29.4)	34 (33.7)
Ethnicity				
Hispanic or Latino	n (%)	8 (16.0)	8 (15.7)	16 (15.8)
Not Hispanic or Latino	n (%)	42 (84.0)	43 (84.3)	85 (84.2)
Race				
White	n (%)	29 (58.0)	29 (56.9)	58 (57.4)
Non-white	n (%)	21 (42.0)	22 (43.1)	43 (42.6)

Source: reviewer's table based on table 1.2.3 on page 169 of Sponsor's CSR.

3.2.3.2.2 Study SHP465-306

In general, subjects are comparable between placebo and SHP465 treatment groups for the demographic variables, such as age, ethnicity, and race, and baseline characteristic, such as weight, height, and body mass index (BMI).

Table 8: Demographic and Baseline Characteristics by Treatment Group - FAS - SHP465-306

Characteristic	Statistic	Placebo (N=86)	SHP465 12.5mg (N=89)	SHP465 37.5mg (N=88)	Total (N=263)
Age (years)	Mean (SD)	34.8 (10.83)	33.4 (10.32)	32.3 (9.88)	33.5 (10.36)
	Median	33	32	29	32
	Min, Max	18, 55	18, 54	18, 54	18, 55
Sex					
Male	n (%)	41 (47.7)	56 (62.9)	50 (56.8)	147 (55.9)
Female	n (%)	45 (52.3)	33 (37.1)	38 (43.2)	116 (44.1)
Ethnicity					
Hispanic or Latino	n (%)	13 (15.1)	10 (11.2)	10 (11.4)	33 (12.5)
Not Hispanic or Latino	n (%)	73 (84.9)	79 (88.8)	78 (88.6)	230 (87.5)
Race					
White	n (%)	72 (83.7)	75 (84.3)	69 (78.4)	216 (82.1)
Non-white	n (%)	14 (16.3)	14 (15.7)	19 (21.6)	47 (17.9)

Source: reviewer's table based on table 1.2.2 on page 131 of Sponsor's CSR.

3.2.4 Results and Conclusions

3.2.4.1 Study SHP465-305

3.2.4.1.1 Primary Analyses

Efficacy analyses were completed using the FAS including 129 subjects in the placebo group and 128 subjects in the SHP465 group. Among those 128 SHP465 treated subjects, 21 received SHP465 12.5 mg (9 children (6-12 years) and 12 adolescents (13-17 years)) and 107 received SHP465 25 mg (42 children and 65 adolescents).

Table 9 : Testing Hierarchy - SHP465-305

Item Tested	p-value	Section
Primary Efficacy Variable		
ADHD-RS-IV Total Score Change from Baseline at Visit 6 (Week 4)	p<0.001	Section 9.2.1
Key Secondary Variables		
CGI-I Score (LS Mean) Change from Baseline at Visit 6 (Week 4)	p<0.001	Section 9.2.2.1

Source: table 13 on page 70 of Sponsor's CSR.

The reduction from baseline in ADHD-RS-IV Total Score was statistically significantly greater in the SHP465 treatment group compared with the placebo treatment group (p<0.001). The difference in LS mean (95% CI) was -9.9 (-13.0, -6.8), favoring SHP465 treatment.

Table 10: Primary Analysis of ADHD-RS-IV Total Score at Visit 6 (Week 4) - FAS - SHP465-305

Statistic	Treatment Group	
	Placebo (N=129)	SHP465 (N=128)
Number of subjects with observations at Visit 6 (Week 4)	117	113
Mean change from baseline (SD)	-11.7 (13.37)	-21.5 (11.53)
LS mean change from baseline[a]	-10.8	-20.7
Difference of LS mean change from baseline (95% CI) SHP465 vs placebo[a]		-9.9 (-13.0, -6.8)
Effect size[b]		0.80
p-value[a]		<0.001

Note:

a. From an MMRM that includes treatment group, nominal visit, age group, interaction of the treatment group with the visit as factors, baseline ADHD-RS-IV Total Score as a covariate, and an adjustment for the interaction of the baseline ADHD-RS-IV Total Score with the visit. The model is based on an REML method of estimation and utilizes an unstructured covariance type.

b. The effect size is the difference in LS mean divided by the estimated standard deviation from the unstructured covariance matrix.

Source: table 14 on page 71 of Sponsor's CSR.

At Visit 6 (Week 4), the CGI-I score for the SHP465 treatment group was statistically significantly lower (indicating greater improvement) compared with the placebo treatment group (p<0.001). The difference in LS mean (95% CI) was -0.8 (-1.1, -0.5) favoring SHP465 treatment.

Table 11: Primary Analysis of CGI-I Scores at Visit 6 (Week 4) - FAS - SHP465-305

	Placebo (N=129)	SHP465 (N=128)
Number of subjects with observations at Visit 6 (Week 4)	117	112
Mean (SD) at Visit 6 (Week 4)	2.9 (1.20)	2.1 (1.13)
LS mean (SEM) at Visit 6 (Week 4)[a]	3.0 (0.11)	2.2 (0.11)
Difference of LS mean at Visit 6 (Week 4) (95% CI) SHP465 vs placebo[a]		-0.8 (-1.1, -0.5)
Effect size[b]		0.65
p-value[a]		<0.001

Note:

a. From an MMRM that includes treatment group, nominal visit, age group, interaction of the treatment group with the visit as factors, baseline CGI-S as a covariate, and an adjustment for the interaction of the baseline CGI-S with the visit. The model is based on an REML method of estimation and utilizes an unstructured covariance type.
b. The effect size is the difference in LS mean divided by the estimated standard deviation from the unstructured covariance matrix.

Source: table 17 on page 76 of Sponsor's CSR.

3.2.4.1.2 Interim Analysis

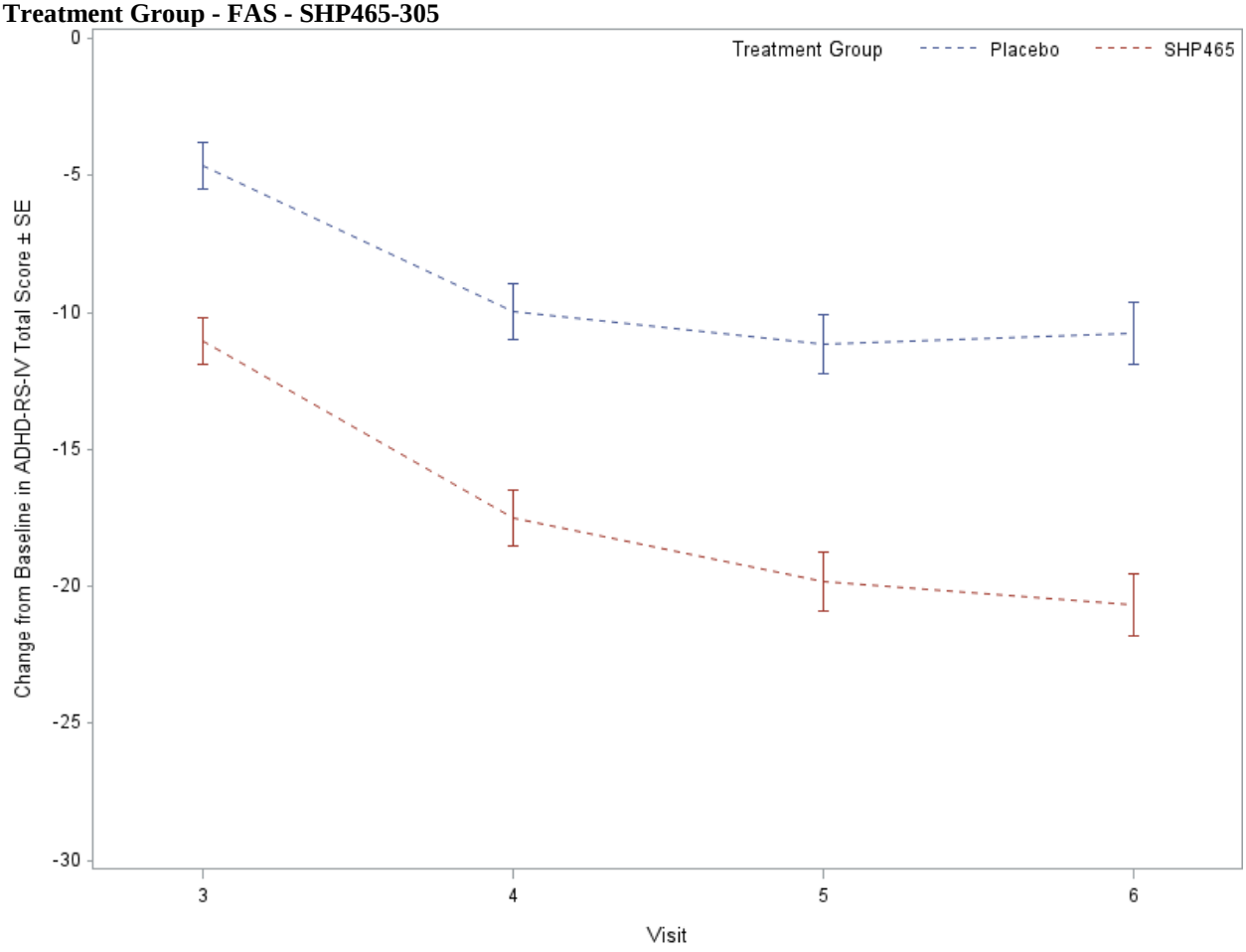
A blinded interim analysis for sample size re-estimation was performed based on all subjects randomly assigned as of Aug 12, 2015 (the interim cohort), among whom 118 subjects were in the FAS and 107 subjects completed the study.

An MMRM was fit over the FAS in the interim cohort. The model is similar to that for the primary efficacy analysis, but with explanatory variables and interactions reduced as necessary for blinded data. The pooled SD was calculated using the estimated variance for Visit 6 (Week 4) from the unstructured intra-subject covariance matrix. This led to a pooled SD of 13.66.

3.2.4.1.3 Additional Analyses

Differences in the LS mean of ADHD-RS-IV Total Score change from baseline between the SHP465 and placebo treatment groups were observed beginning at Visit 3 (Week 1) and continued throughout the entire 4-week treatment period.

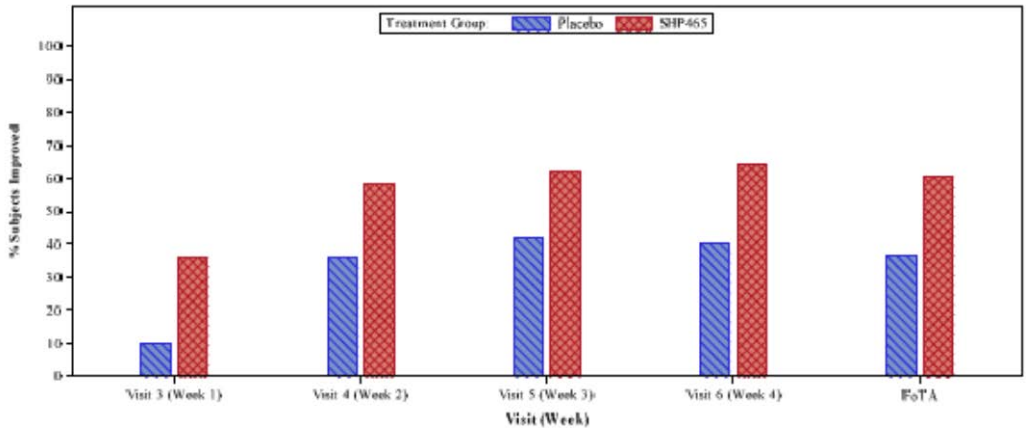
Figure 5: Least Squares Mean (±SE) of Change from Baseline in ADHD-RS-IV Total Score by Visit and Treatment Group - FAS - SHP465-305



Source: reviewer's plot.

At the final on-treatment assessment (FoTA), 129 subjects in the placebo treatment group and 128 subjects in the SHP465 treatment group had a CGI-I score to be included in the analysis. Of these, 47 subjects (36.4%) in the placebo treatment group had a CGI-I assessment of "improved" compared to 77 subjects (60.2%) in the SHP465 treatment group. This difference was statistically significant ($p<0.001$) according to a Cochran-Mantel-Haenszel test stratified by age group and CGI-S value at baseline.

Figure 6: Dichotomized CGI-I by Visit and Treatment Group - FAS - SHP465-305



Source: figure 6 on page 78 of Sponsor's CSR.

3.2.4.1.4 Sensitivity Analyses

The results of the sensitivity analysis supported the robustness of the primary analysis for the primary and the key secondary efficacy endpoints across model assumptions.

Table 12: Sesitivity Analysis Results of ADHD-RS-IV Total Score - FAS - SHP465-305

Model	Treatment Group	
Statistic	Placebo (N=129)	SHP465 (N=128)
Model 1[a]		
LS mean[b]	-10.5	-20.2
Difference in LS mean change from baseline (95% CI) SHP465 vs placebo[c]		-9.7 (-12.9, -6.5)
p-value[c]		<0.001
Model 2[c]		
No penalty (0*SD)		
LS mean[b]	-10.5	-20.6
Difference in LS mean change from baseline (95% CI) SHP465 vs placebo[d]		-10.1 (-13.2, -7.0)
p-value[d]		<0.001
.25*SD Penalty		
LS mean[b]	-10.2	-20.3
Difference in LS mean change from baseline (95% CI) SHP465 vs placebo[d]		-10.0 (-13.2, -6.9)
p-value[d]		<0.001
.50*SD Penalty		
LS mean[b]	-9.9	-19.9
Difference in LS mean change from baseline (95% CI) SHP465 vs placebo[d]		-10.0 (-13.2, -6.7)
p-value[d]		<0.001
.75*SD Penalty		
LS mean[b]	-9.6	-19.5
Difference in LS mean change from baseline (95% CI) SHP465 vs placebo[d]		-9.9 (-13.2, -6.6)
p-value[d]		<0.001
1*SD Penalty		
LS mean[b]	-9.4	-19.1
Difference in LS mean change from baseline (95% CI) SHP465 vs placebo[d]		-9.8 (-13.2, -6.4)
p-value[d]		<0.001

Note:

a. Assuming dropouts follow placebo pattern
b. From an ANCOVA model, with change from baseline in ADHD-RS-IV total score as the outcome variable, treatment group and age group as factors, and baseline ADHD-RS-IV total score as a covariate
c. Assuming subjects who discontinue have worse changes than predicted using MAR after discontinuation, SD is the estimated standard deviation for the primary endpoint (the square root of the estimated element for Visit 6 of the covariance matrix R from the primary MMRM). SD=sqrt(153.0357)=12.3708.
d. LS mean difference estimates were averaged, and the associated SEM was computed based on within-imputation and between-imputation variance to yield a final estimate with associated 95% CI and p-value. Difference in LS means is calculated as SHP465 – placebo.

Source: table 15 on page 72 of Sponsor's CSR.

Table 13: Sesitivity Analysis Results of CGI-I - FAS - SHP465-305

Model Statistic	Treatment Group Placebo (N=129)	 SHP465 (N=128)
Model 1[a]		
LS mean[b]	3.0	2.2
Difference in LS mean (95% CI) SHP465 vs placebo[c]		-0.8 (-1.1, -0.5)
p-value[c]		<0.001
Model 2[c]		
No penalty (0*SD)		
LS mean[b]	3.0	2.2
Difference in LS mean (95% CI) SHP465 vs placebo[d]		-0.8 (-1.1, -0.5)
p-value[d]		<0.001
.25*SD Penalty		
LS mean[b]	3.0	2.2
Difference in LS mean (95% CI) SHP465 vs placebo[d]		-0.8 (-1.1, -0.5)
p-value[d]		<0.001
.50*SD Penalty		
LS mean[b]	3.0	2.3
Difference in LS mean change from baseline (95% CI) SHP465 vs placebo[d]		-0.8 (-1.1, -0.4)
p-value[d]		<0.001
.75*SD Penalty		
LS mean[b]	3.1	2.3
Difference in LS mean change from baseline (95% CI) SHP465 vs placebo[d]		-0.7 (-1.1, -0.4)
p-value[d]		<0.001
1*SD Penalty		
LS mean[b]	3.1	2.3
Difference in LS mean change from baseline (95% CI) SHP465 vs placebo[d]		-0.7 (-1.1, -0.4)
p-value[d]		<0.001

Note:

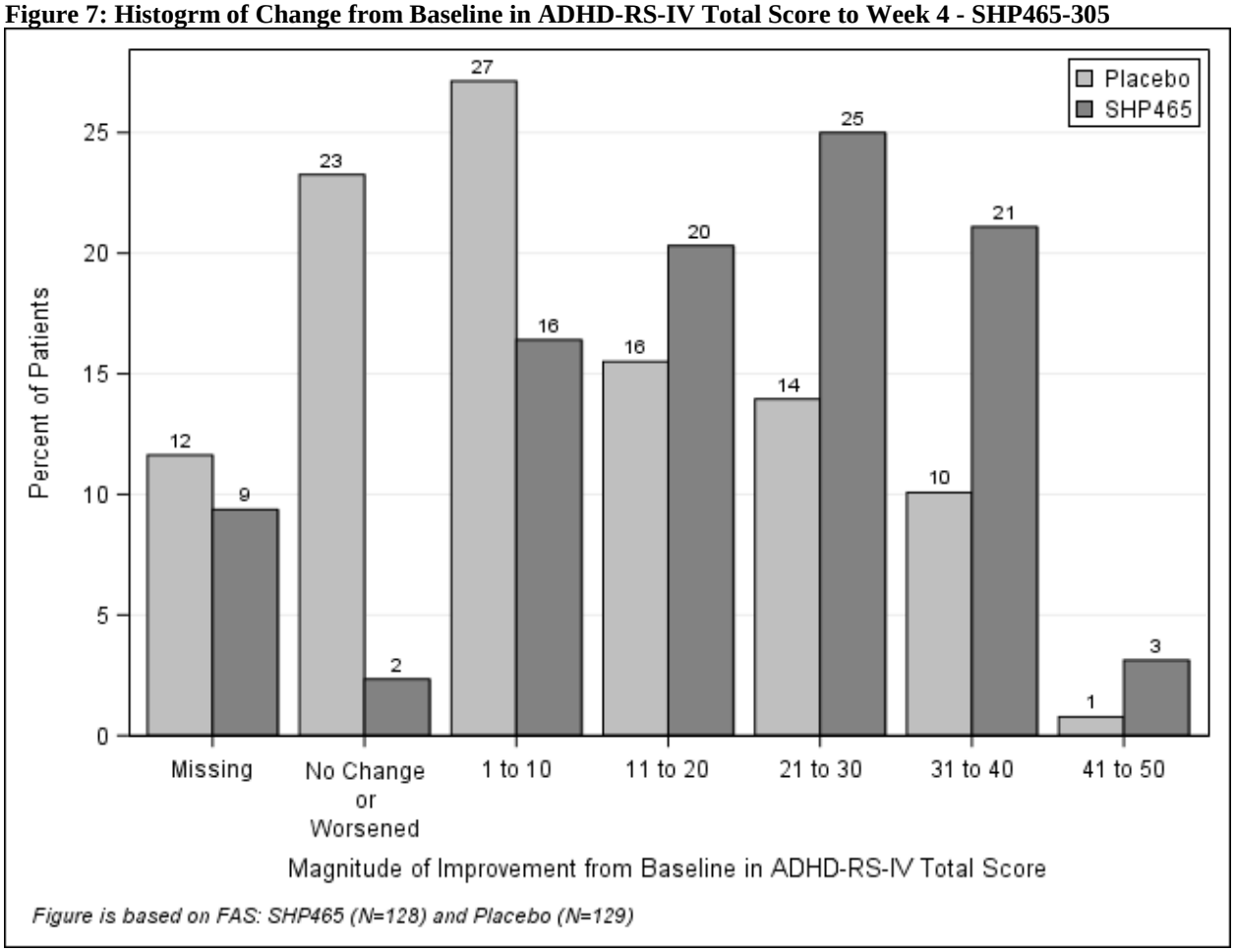
a. Assuming dropouts follow placebo pattern
b. From an ANCOVA model, with CGI-I as the outcome variable, treatment group and age group as factors, baseline CGI-S as a covariate.
c. Assuming subjects who discontinue have worse changes than predicted using MAR after discontinuation. SD=sqrt(1.3763)=1.1731.
d. LS mean difference estimates were averaged and the associated SEM was computed based on within-imputation and between-imputation variance to yield a final estimate with associated 95% CI and p-value. Difference in LS means is calculated as SHP465 – Placebo.

Source: table 18 on page 77 of Sponsor's CSR.

3.2.4.1.5 Reviewer's Analyses

In study SHP465-305, the following histogram suggests an improvement in change from baseline in ADHD-RS-IV Total score to Visit 6 (Week 4).

Figure 7: Histogrm of Change from Baseline in ADHD-RS-IV Total Score to Week 4 - SHP465-305



Source: reviewer's plot.

3.2.4.2 Study SHP465-306

3.2.4.2.1 Primary Analyses

Efficacy analyses were completed using the FAS, which included 86 subjects in the placebo group, 89 subjects in the SHP465 12.5 mg group, and 88 subjects in the SHP465 37.5 mg group.

Table 14: Testing Hierarchy - SHP465-306

Item Tested	p-value	Section
Primary Efficacy Variable		
ADHD-RS with prompts total score Change from Baseline at Visit 6 (Week 4) for 37.5 mg compared with placebo	p<0.001	Section 9.2.1
ADHD-RS with prompts total score Change from Baseline at Visit 6 (Week 4) for 12.5 mg compared with placebo	p<0.001	Section 9.2.1
Key Secondary Variables		
CGI-I Score at Visit 6 (Week 4) for 37.5 mg compared with placebo	p<0.001	Section 9.2.2.1
CGI-I Score at Visit 6 (Week 4) for 12.5 mg compared with placebo	p<0.001	Section 9.2.2.1

Source: table 12 on page 67 of Sponsor's CSR.

The reduction from baseline in ADHD-RS with prompts total score was statistically significantly greater in the SHP465 12.5 mg and the SHP465 37.5 mg treatment groups compared with the placebo treatment group (p<0.001). The difference in LS mean (95% CI) was -8.1 (-11.7, -4.4) for the SHP465 12.5 mg treatment group; the difference in LS mean (95% CI) was -13.4 (-17.1, -9.7) for the SHP465 37.5 mg treatment group.

Table 15: Primary Analysis of ADHD-RS with Prompts Total Score at Visit 6 (Week 4) - FAS - SHP465-306

Statistic	Treatment Group		
	Placebo (N=86)	SHP465 12.5 mg (N=89)	SHP465 37.5 mg (N=88)
Number of subjects with observations at Visit 6 (Week 4)	77	78	73
Mean change from baseline (SD)	-11.0 (11.47)	-18.1 (13.42)	-23.8 (11.89)
LS mean change from baseline[a]	-10.4	-18.5	-23.8
Difference of LS mean change from baseline (95% CI) SHP465 vs placebo[a]		-8.1 (-11.7, -4.4)	-13.4 (-17.1, -9.7)
Effect size[b]		0.67	1.11
p-value[a]		p<0.001	p<0.001

Note:

a. From an MMRM that includes treatment group, nominal visit, interaction of the treatment group with the visit as factors, baseline ADHD-RS with prompts total score as a covariate, and an adjustment for the interaction of the baseline ADHD-RS with prompts total Score with the visit. The model is based on an REML method of estimation and utilizes an unstructured covariance type.

b. The effect size is the difference in LS mean divided by the estimated standard deviation from the unstructured covariance matrix. Difference in LS mean is calculated as SHP465 dose – Placebo.

Source: table 14 on page 71 of Sponsor's CSR.

At Visit 6 (Week 4), the CGI-I scores for the SHP465 12.5 mg and SHP465 37.5 mg treatment groups were statistically significantly lower (indicating greater improvement) compared with the placebo treatment group (p<0.001). The difference in LS mean (95% CI) was -0.8 (-1.1, -0.4) for the SHP465 12.5 mg treatment; the difference in LS mean (95% CI) was -1.2 (-1.6, -0.9) for the SHP465 37.5 mg treatment both favoring SHP465 treatment.

Table 16: Primary Analysis of CGI-I Scores at Visit 6 (Week 4) - FAS - SHP465-306

	Placebo (N=86)	SHP465 12.5 mg (N=89)	SHP465 37.5 mg (N=88)
Number of subjects with observations at Visit 6 (Week 4)	77	78	73
Mean (SD) at Visit 6 (Week 4)	3.1 (1.05)	2.4 (1.16)	1.9 (1.10)
LS mean (SEM) at Visit 6 (Week 4)[a]	3.1 (0.12)	2.4 (0.12)	1.9 (0.13)
Difference of LS mean at Visit 6 (Week 4) (95% CI) SHP465 dose vs placebo[a]		-0.8 (-1.1, -0.4)	-1.2 (-1.6, -0.9)
Effect size[b]		0.68	1.11
p-value[a]		<0.001	<0.001

Note:

a. From an MMRM that includes treatment group, nominal visit, interaction of the treatment group with the visit as factors, baseline CGI-S as a covariate, and an adjustment for the interaction of the baseline CGI-S with the visit. The model is based on an REML method of estimation and utilizes an unstructured covariance type.

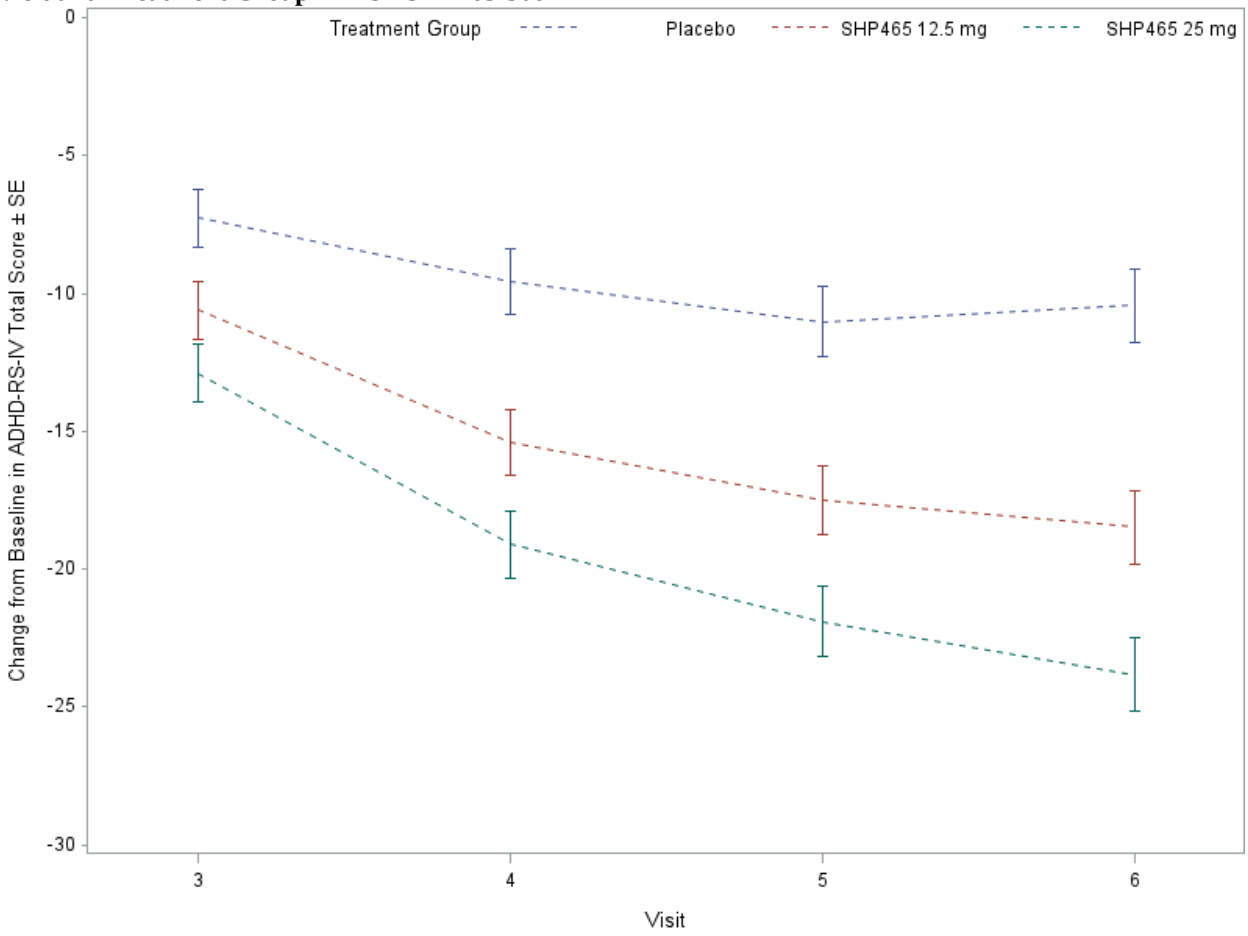
b. The effect size is the difference in LS mean divided by the estimated standard deviation from the unstructured covariance matrix. Difference in LS means is calculated as SHP465 dose – Placebo.

Source: table 16 on page 75 of Sponsor's CSR.

3.2.4.2.2 Additional Analyses

Differences in the LS mean of ADHD-RS with prompts total score change from baseline indicated subjects treated with SHP465 12.5 mg and 37.5 mg had improved responses compared with subjects who received placebo beginning at Visit 3 (Week 1) and continued throughout the entire 4-week treatment period.

Figure 8: Least Squares Mean (±SE) of Change from Baseline in ADHD-RS with Prompts Total Score by Visit and Treatment Group - FAS - SHP465-306



Source: reviewer's plot.

At the FoTA, 86 subjects in the placebo treatment group, 89 subjects in the SHP465 12.5 mg treatment group, and 88 subjects in the SHP465 37.5 mg treatment group had a CGI-I score to be included in the CGI-I categorical analysis. Of these, 26 subjects (30.2%) in the placebo treatment group had a CGI-I assessment of "improved" compared with 49 subjects (55.1%) in the SHP465 12.5 mg treatment group and 66 subjects (75.0%) in the SHP465 37.5 mg treatment group. These differences were statistically significant ($p<0.001$) for each of the SHP465 treatment groups compared with placebo according to a Cochran-Mantel-Haenszel test stratified by CGI-S value at baseline.

Table 17: Summary of CGI-I and Dichotomized CGI-I by Treatment Group - FAS - SHP465-306

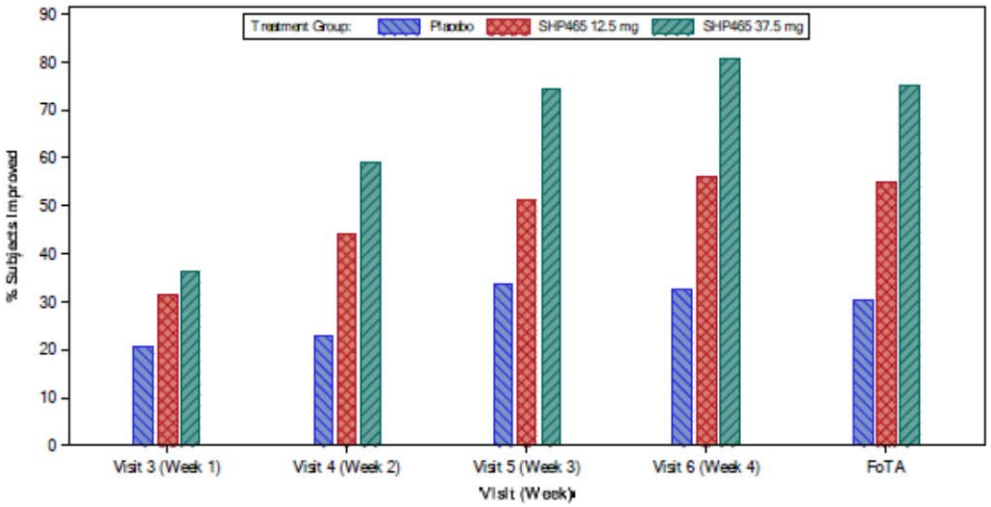
	Treatment Group		
	Placebo (N=86) n (%)	**SHP465 12.5 mg (N=89) n (%)**	**SHP465 37.5 mg (N=88) n (%)**
Final on-Treatment Assessment			
Very much improved	7 (8.1)	24 (27.0)	37 (42.0)
Much improved	19 (22.1)	25 (28.1)	29 (33.0)
Minimally improved	17 (19.8)	17 (19.1)	12 (13.6)
No change	39 (45.3)	22 (24.7)	8 (9.1)
Minimally worse	3 (3.5)	1 (1.1)	1 (1.1)
Much worse	1 (1.2)	0	1 (1.1)
Very much worse	0	0	0
Not assessed[a]	0	0	0
Missing	0	0	0
Dichotomized CGI-I at FoTa			
Improved[b]	26 (30.2)	49 (55.1)	66 (75.0)
Not Improved[c]	60 (69.8)	40 (44.9)	22 (25.0)
95% CI for Improved[d]	(20.8, 41.1)	(44.1, 65.6)	(64.6, 83.6)
p-Value[e]		<0.001	<0.001

Note:

a. 'Not assessed' is a response on the questionnaire. Subjects with no response are counted as 'missing'.
b. The 'Improved' category includes responses of 'Very Much Improved' and 'Much Improved'.
c. The 'Not improved' category includes responses of 'Minimally improved', 'No change', 'Minimally worse', 'Much worse' and 'Very much worse'.
d. 95% confidence intervals based on binomial proportion.
e. From a Cochran-Mantel-Haenszel (CMH) test stratified by baseline CGI-S value.

Source: table 18 on page 77 of Sponsor's CSR.

Figure 9: Dichotomized CGI-I by Visit and Treatment Group – FAS – SHP465-306



Source: figure 6 on page 78 of Sponsor's CSR.

3.2.4.2.3 Sensitivity Analyses

The results of the sensitivity analysis supported the robustness of the primary analysis for the primary and the key secondary efficacy endpoints across model assumptions.

Table 18: Sesitivity Analysis Results of ADHD-RS with Prompts Total Score - FAS - SHP465-306

Model Statistic	Treatment Group Placebo (N=86)	 SHP465 12.5 mg (N=89)	 SHP465 37.5 mg (N=88)
Model 1[a]			
LS mean[b]	-10.4	-18.1	-22.8
Difference in LS mean change from baseline (95% CI) SHP465 dose vs placebo[d]		-7.6 (-11.3, -4.0)	-12.4 (-16.1, -8.7)
p-value[d]		<0.001	<0.001
Model 2[c]			
No penalty (0*SD)			
LS mean[b]	-10.4	-18.6	-23.8
Difference in LS mean change from baseline (95% CI) SHP465 dose vs placebo[d]		-8.2 (-11.9, -4.5)	-13.4 (-17.1, -9.7)
p-value[d]		<0.001	<0.001
.25*SD Penalty			
LS mean[b]	-10.1	-18.2	-23.3
Difference in LS mean change from baseline (95% CI) SHP465 dose vs placebo[d]		-8.1 (-11.8, -4.4)	-13.2 (-16.9, -9.4)
p-value[d]		<0.001	<0.001
.50*SD Penalty			
LS mean[b]	-9.8	-17.8	-22.7
Difference in LS mean change from baseline (95% CI) SHP465 dose vs placebo[d]		-8.1 (-11.8, -4.3)	-13.0 (-16.8, -9.2)
p-value[d]		<0.001	<0.001
.75*SD Penalty			
LS mean[b]	-9.5	-17.5	-22.2
Difference in LS mean change from baseline (95% CI) SHP465 dose vs placebo[d]		-8.0 (-11.8, -4.2)	-12.8 (-16.6, -8.9)
p-value[d]		<0.001	<0.001
1*SD Penalty			
LS mean[b]	-9.2	-17.1	-21.7
Difference in LS mean change from baseline (95% CI) SHP465 dose vs placebo[d]		-7.9 (-11.8, -4.0)	-12.6 (-16.5, -8.6)
p-value[d]		<0.001	<0.001

Note:

a. Assuming dropouts follow placebo pattern
b. From an ANCOVA model, with change from baseline in ADHD-RS with prompts total score as the outcome variable, treatment group as a factor, and baseline ADHD-RS with prompts total score as a covariate
c. Assuming subjects who discontinue have worse changes than predicted using MAR after discontinuation, SD is the estimated standard deviation for the primary endpoint (the square root of the estimated element for Visit 6 of the covariance matrix R from the primary MMRM). SD=sqrt(144.2894)= 12.0121.

d. LS mean difference estimates were averaged, and the associated SEM was computed based on within-imputation and between-imputation variance to yield a final estimate with associated 95% CI and p-value. Difference in LS means is calculated as SHP465 dose – placebo.

Source: table 14 on page 69 of Sponsor's CSR.

Table 19: Sesitivity Analysis Results of CGI-I - FAS - SHP465-306

Model Statistic	Treatment Group Placebo (N=86)	 SHP465 12.5 mg (N=89)	 SHP465 37.5 mg (N=88)
Model 1[a]			
LS mean[b]	3.1	2.4	2.0
Difference in LS mean (95% CI) SHP465 dose vs placebo[c]		-0.7 (-1.1, -0.4)	-1.1 (-1.5, -0.8)
p-value[c]		<0.001	<0.001
Model 2[d]			
No penalty (0*SD)			
LS mean[b]	3.2	2.4	1.9
Difference in LS mean (95% CI) SHP465 dose vs placebo[c]		-0.8 (-1.1, -0.4)	-1.2 (-1.6, -0.9)
p-value[c]		<0.001	<0.001
.25*SD Penalty			
LS mean[b]	3.2	2.4	1.9
Difference in LS mean (95% CI) SHP465 dose vs placebo[c]		-0.8 (-1.1, -0.4)	-1.2 (-1.6, -0.9)
p-value[c]		<0.001	<0.001
.50*SD Penalty			
LS mean[b]	3.2	2.4	2.0
Difference in LS mean change from baseline (95% CI) SHP465 dose vs placebo[c]		-0.8 (-1.1, -0.4)	-1.2 (-1.6, -0.9)
p-value[c]		<0.001	<0.001
.75*SD Penalty			
LS mean[b]	3.2	2.5	2.0
Difference in LS mean change from baseline (95% CI) SHP465 dose vs placebo[c]		-0.8 (-1.1, -0.4)	-1.2 (-1.6, -0.8)
p-value[c]		<0.001	<0.001
1*SD Penalty			
LS mean[b]	3.3	2.5	2.1
Difference in LS mean change from baseline (95% CI) SHP465 dose vs placebo[c]		-0.7 (-1.1, -0.4)	-1.2 (-1.5, -0.8)
p-value[c]		<0.001	<0.001

Note:

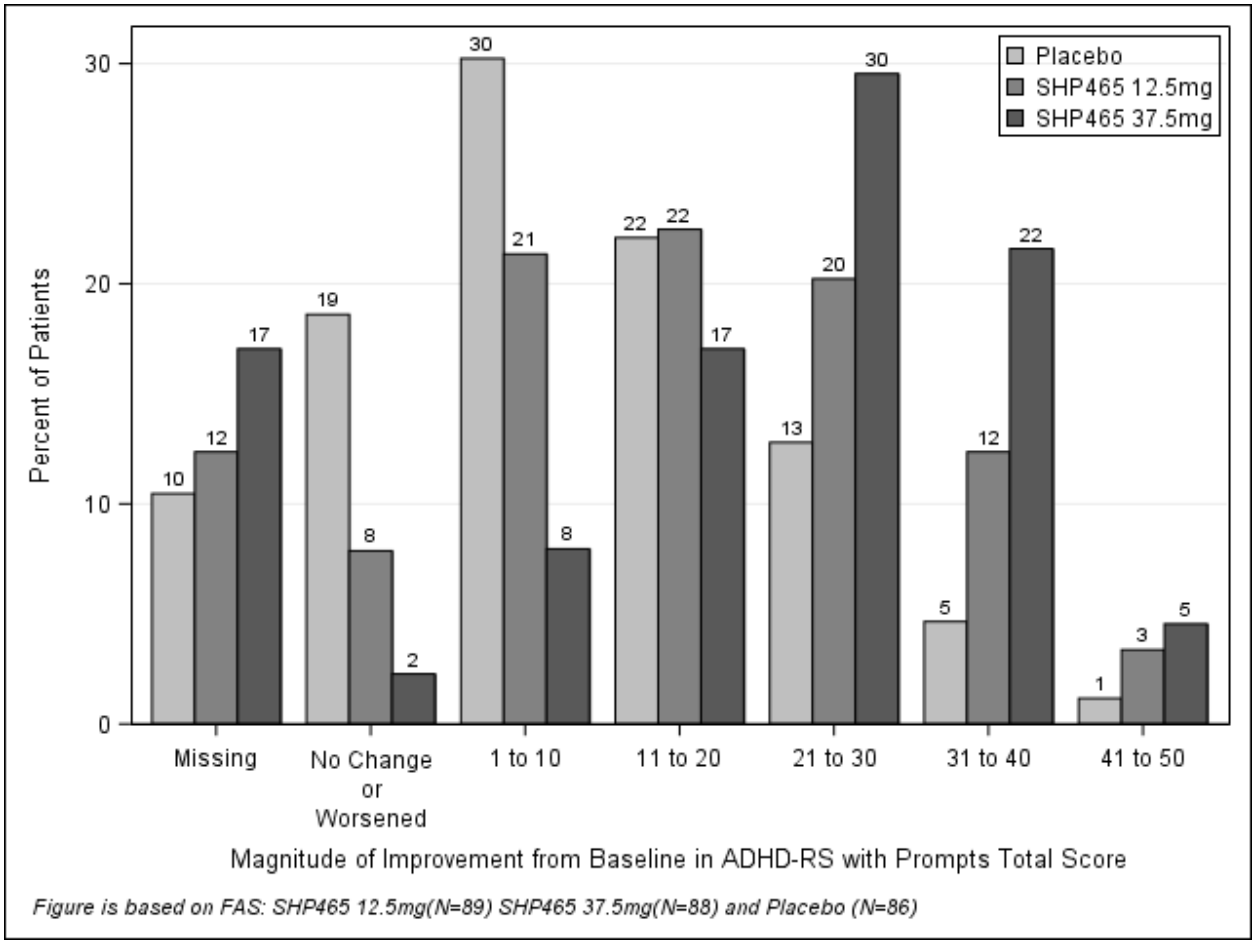
a. Assuming dropouts follow placebo pattern
b. From an ANCOVA model, with CGI-I as the outcome variable, treatment group as a factor, baseline CGI-S as a covariate.
c. LS mean difference estimates were averaged and the associated SEM was computed based on within-imputation and betweenimputation variance to yield a final estimate with associated 95% CI and p-value. Difference in LS means is calculated as SHP465 dose – Placebo.
d. Assuming subjects who discontinue have worse changes than predicted using MAR after discontinuation, SD is the estimated standard deviation for the key secondary endpoint (the square root of the estimated element for Visit 6 of the covariance matrix R from the key secondary MMRM). SD=sqrt(1.2556)=1.1205.

Source: table 17 on page 75-76 of Sponsor's CSR.

3.2.4.2.4 Reviewer's Analyses

In study SHP465-306, the following histogram suggests an improvement in change from baseline in ADHD-RS with Prompts Total score to Visit 6 (Week 4) for both SHP465 dose levels compared to placebo. In addition, SHP465 37.5mg shows greater reduction than SHP465 12.5mg in change from baseline in ADHD-RS with Prompts Total score to Visit 6 (Week 4).

Figure 10: Histogrm of Change from Baseline in ADHD-RS with Prompts Total Score to Week 4 - SHP465-306



Source: reviewer's plot.

3.3 Evaluation of Safety

Please refer to Dr. Dickinson's clinical review for details on the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Study SHP465-305

4.1.1.1 Change from Baseline by Region

All the centers in this study are in the US. Thus, no exploratory subgroup analysis is conducted by region.

4.1.1.2 Change from Baseline by Gender

Greater reductions in ADHD-RS-IV Total Scores from baseline to Visit 6 (Week 4) were observed in both males and females treated with SHP465 compared with placebo. For males, the mean ADHD-RS-IV Total Score reduction was -23.4 in the SHP465 treatment group compared with -13.9 in the placebo group. For females, the ADHD-RS-IV Total Score reduction was -18.0 in SHP465 treatment group and -8.9 in placebo group.

Table 20: Summary and Analysis of ADHD-RS with Prompts Total Score by Sex - FAS -SHP465-305

Statistic	Males		Females	
	Placebo (N=76)	SHP465 (N=83)	Placebo (N=53)	SHP465 (N=45)
Number of subjects with observations at Visit 6 (Week 4)	66	74	51	39
Mean change from baseline (SD)	-13.9 (13.73)	-23.4 (11.05)	-8.9 (12.48)	-18.0 (11.73)
LS mean change from baseline[a]	-12.5	-22.6	-8.2	-17.1
Difference of LS mean change from baseline (95% CI) SHP465 vs placebo[a]		-10.1 (-14.1, -6.1)		-8.9 (-13.9, -3.9)

Note:

a. From an MMRM that includes treatment group, nominal visit, age group, interaction of the treatment group with the visit as factors, baseline ADHD-RS-IV Total Score as a covariate, and an adjustment for the interaction of the baseline ADHD-RS-IV Total Score with the visit. The model is based on a REML method of estimation and utilizes an unstructured covariance type.

b. The effect size is the difference in LS mean divided by the estimated standard deviation from the unstructured covariance matrix.

Source: table 20 on page 80 of Sponsor's CSR.

4.1.1.3 Change from Baseline by Race

Greater reductions in ADHD-RS-IV Total Scores from baseline to Visit 6 (Week 4) were observed in both white and non-white subgroups treated with SHP465 compared with placebo. For the white group, the mean ADHD-RS-IV Total Score reduction was -20.8 in the SHP465

treatment group compared with -12.0 in the placebo group. For the non-white group, the ADHD-RS-IV Total Score reduction was -22.6 in SHP465 treatment group and -11.3 in placebo group.

Table 21: Summary and Analysis of ADHD-RS with Prompts Total Score by Race - FAS -SHP465-305

Statistic	White		Non-white	
	Placebo (N=81)	SHP465 (N=77)	Placebo (N=48)	SHP465 (N=51)
Number of subjects with observations at Visit 6 (Week 4)	74	69	43	44
Mean change from baseline (SD)	-12.0 (12.79)	-20.8 (11.68)	-11.3 (14.47)	-22.6 (11.34)
LS mean change from baseline[a]	-10.9	-20.6	-10.7	-20.9
Difference of LS mean change from baseline (95% CI) SHP465 vs placebo[a]		-9.7 (-13.6, -5.7)		-10.2 (-15.5, -4.9)

Note:

c. From an MMRM that includes treatment group, nominal visit, age group, interaction of the treatment group with the visit as factors, baseline ADHD-RS-IV Total Score as a covariate, and an adjustment for the interaction of the baseline ADHD-RS-IV Total Score with the visit. The model is based on a REML method of estimation and utilizes an unstructured covariance type.

d. The effect size is the difference in LS mean divided by the estimated standard deviation from the unstructured covariance matrix.

Source: table 21 on page 81 of Sponsor's CSR.

4.1.1.4 Change from Baseline by Age Group

Greater reductions in ADHD-RS-IV total scores from baseline to Visit 6 (Week 4) were observed in both children and adolescent age subgroups treated with SHP465 compared with placebo. For children, the mean ADHD-RS-IV Total Score reduction was -23.0 in the SHP465 treatment group compared with -10.4 in the placebo group. For adolescents, the ADHD-RS-IV Total Score reduction was -20.6 in SHP465 treatment group and -12.5 in placebo group.

Table 22: Summary and Analysis of ADHD-RS-IV Total Score by Age - FAS - SHP465-305

Statistic	Children (6-12 Years)		Adolescents (13-17 Years)	
	Placebo (N=50)	SHP465 (N=51)	Placebo (N=79)	SHP465 (N=77)
Number of subjects with observations at Visit 6 (Week 4)	44	44	73	69
Mean change from baseline (SD)	-10.4 (14.14)	-23.0 (12.33)	-12.5 (12.93)	-20.6 (10.98)
LS mean change from baseline[a]	-9.8	-21.8	-11.6	-20.3
Difference of LS mean change from baseline (95% CI) SHP465 vs placebo[a]		-12.0 (-17.3, -6.7)		-8.7 (-12.6, -4.8)

Note:

a. From an MMRM that includes treatment group, nominal visit, age group, interaction of the treatment group with the visit as factors, baseline CGI-S as a covariate, and an adjustment for the interaction of the baseline CGI-S with the visit. The model is based on an REML method of estimation and utilizes an unstructured covariance type.

b. The effect size is the difference in LS mean divided by the estimated standard deviation from the unstructured covariance matrix.

Source: table 19 on page 79 of Sponsor's CSR.

4.1.2 Study SHP465-306

4.1.2.1 Change from Baseline by Region

All the centers in this study are in the US. Thus, no exploratory subgroup analysis is conducted by region.

4.1.2.2 Change from Baseline by Gender

Greater reductions in ADHD-RS with prompts total scores from baseline to Visit 6 (Week 4) were observed in both males and females treated with SHP465 12.5 mg and SHP465 37.5 mg compared with placebo. For males, the mean ADHD-RS with prompts total score reduction was -17.5 in the SHP465 12.5 mg treatment group and -23.3 in the SHP465 37.5 mg treatment group compared with –10.2 in the placebo group. For females, the mean ADHD-RS with prompts total score reduction was –19.1 in the SHP465 12.5 mg treatment group and -24.3 in the SHP465 37.5 mg treatment group compared with –11.8 in the placebo group.

Table 23: Summary and Analysis of ADHD-RS with Prompts Total Score by Sex - FAS - SHP465-306

Statistic	Males			Females		
	Placebo (N=41)	SHP465 12.5 mg (N=56)	SHP465 37.5 mg (N=50)	Placebo (N=45)	SHP465 12.5 mg (N=33)	SHP465 37.5 mg (N=38)
Number of subjects with observations at Visit 6 (Week 4)	37	48	41	40	30	32
Mean change from baseline (SD)	-10.2 (12.49)	-17.5 (13.57)	-23.3 (11.20)	-11.8 (10.54)	-19.1 (13.34)	-24.3 (12.89)
LS mean change from baseline[a]	-9.4	-17.5	-22.7	-11.5	-19.7	-25.1
Difference of LS mean change from baseline (95% CI) SHP465 dose vs placebo[a]		-8.2 (-13.2, -3.2)	-13.4 (-18.5, -8.2)		-8.3 (-13.9, -2.7)	-13.6 (-19.1, -8.1)

Note:

a. From an MMRM that includes treatment group, nominal visit, interaction of the treatment group with the visit as factors, baseline ADHD-RS with prompts total score as a covariate, and an adjustment for the interaction of the baseline ADHD-RS with prompts total score with the visit. The model is based on a REML method of estimation and utilizes an unstructured covariance type.

b. The effect size is the difference in LS mean divided by the estimated standard deviation from the unstructured covariance matrix. Difference in LS means is calculated as SHP465 dose – Placebo.

Source: table 19 on page 79 of Sponsor's CSR.

4.1.2.3 Change from Baseline by Race

Greater reductions in ADHD-RS with prompts total score from baseline to Visit 6 (Week 4) were observed in both white and non-white subgroups treated with SHP465 compared with placebo. For the white group, the mean ADHD-RS with prompts total score reduction was -18.0 in the SHP465 12.5 mg treatment group and -22.6 in the SHP465 37.5 mg treatment group compared with -10.9 in the placebo group. For the non-white group, the ADHD-RS with prompts total score reduction was –18.5 in 12.5 mg treatment group and -27.8 in the SHP465 37.5 mg treatment group compared with -11.5 in the placebo group.

Table 24: Summary and Analysis of Change from Baseline in ADHD-RS with Prompts Total Score by Race - FAS - SHP465-306

Statistic	White			Non-white		
	Placebo (N=72)	SHP465 12.5 mg (N=75)	SHP465 37.5 mg (N=69)	Placebo (N=14)	SHP465 12.5 mg (N=14)	SHP465 37.5 mg (N=19)
Number of subjects with observations at Visit 6 (Week 4)	64	67	57	13	11	16
Mean change from baseline (SD)	-10.9 (11.45)	-18.0 (13.22)	-22.6 (12.32)	-11.5 (12.03)	-18.5 (15.25)	-27.8 (9.50)
LS mean change from baseline[a]	-10.4	-18.4	-22.7	-10.0	-19.8	-27.7
Difference of LS mean change from baseline (95% CI) SHP465 dose vs placebo[a]		-8.0 (-12.1, -3.9)	-12.3 (-16.5, -8.1)		-9.7 (-18.9, -0.6)	-17.6 (-25.7, -9.5)

Note:

a. From an MMRM that includes treatment group, nominal visit, interaction of the treatment group with the visit as factors, baseline ADHD-RS with prompts total score as a covariate, and an adjustment for the interaction of the baseline ADHDRS with prompts total score with the visit. The model is based on a REML method of estimation and utilizes an unstructured covariance type.

b. The effect size is the difference in LS mean divided by the estimated standard deviation from the unstructured covariance matrix. Difference in LS means is calculated as SHP465 dose – Placebo.

Source: table 20 on page 80 of Sponsor's CSR.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No statistical issues have been identified.

5.2 Collective Evidence

For pediatrics (aged 6-17), SHP465 is shown to be more effective than placebo, at the optimal dose level by body weight, in improving symptoms associated with ADHD, as measured by change from baseline at Visit 6 (Week 4) in the ADHD-RS-IV Total Score, and by the CGI-I score at Visit 6 (Week 4), based on study SHP465-305.

For adults (aged 18-55), SHP465 is shown to be more effective than placebo, at the dose levels of 12.5 mg and 37.5 mg, in improving symptoms associated with ADHD, as measured by change from baseline at Visit 6 (Week 4) in the ADHD-RS with prompts total score, and by the CGI-I score at Visit 6 (Week 4), based on study SHP465-306.

5.3 Conclusions and Recommendations

The statistical efficacy results provide adequate evidence to support a claim of SHP465's favorable effect at dose levels of 12.5 mg and 37.5 mg in adults and at a dose range between 12.5 and 25 mg in children and adolescents aged 6-17 for the treatment of ADHD.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YANG WANG
05/18/2017

PEILING YANG
05/18/2017

HSIEN MING J HUNG
05/18/2017