NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	022063/S-001
Priority or Standard	Standard
Submit Date(s)	3/13/19
Received Date(s)	3/13/19
PDUFA Goal Date	9/13/19
Division/Office	Division of Psychiatry/ Office of Drug Evaluation 1
Review Completion Date	8/27/19
Established/Proper Name	Mixed salts of single-entity amphetamine
Trade Name	Mydayis
Pharmacologic Class	CNS stimulant
Applicant	Shire
Dosage form	Capsule
Applicant proposed Dosing Regimen	6.25 mg once daily upon awakening
Applicant Proposed Indication(s)/Population(s)	Treatment of ADHD in pediatric patients (4 to 12 years)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Stimulant drug therapy for attention deficit hyperactivity disorder
Recommendation on Regulatory Action	Approve labeling change and grant exclusivity

Table of Contents

Reference ID: 4491482

Table of Tables

Table of Figures

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction and Regulatory Background

Mydayis (formerly SHP465 and SPD465) is a CNS stimulant (extended-release capsules of mixed salts of a single-entity amphetamine) approved on June 20, 2017, for the treatment of attention-deficit/hyperactivity disorder (ADHD) in patients ages 13 and older. The approved product labeling includes a Limitation of Use statement advising prescribers that patients 12 years of age and younger experienced higher plasma exposure than patients 13 years of age and older at the same dose. These younger patients also experienced higher rates of adverse reactions, mainly insomnia and decreased appetite.

Mydayis contains equal amounts (by weight) of four salts: dextroamphetamine sulfate, amphetamine sulfate, dextroamphetamine saccharate, and amphetamine aspartate monohydrate. This results in a 3:1 mixture of dextro- to levoamphetamine base equivalents. It is available in 12.5, 25, 37.5, and 50 mg strength capsules for oral administration. The capsules contain three types of drug releasing beads, an immediate-release and two types of delayed-release beads. Mydayis is formulated to last longer (roughly 16 hours) than Adderall XR and other mixed amphetamine salts extended-release formulations (MAS ER).

This supplemental NDA S-001 is submitted in response to a Pediatric Written Request (PWR) and PREA postmarketing requirements (which are the same trials) requiring Shire to evaluate a lower-than-approved dose of Mydayis (6.25 mg) in the following studies:

1. Study 1 (SHP465-309): Pediatric efficacy and safety study in patients ages 6 to 12 with attention deficit hyperactivity disorder [PMR# 3224-5]

2. Study 2 (SHP465-112): Pediatric safety, tolerability, and pharmacokinetic (PK) study in patients ages 4- to 5-years [PMR# 3224-1]

3. Study 3 (SHP465-308): Pediatric open-label safety study in patients age 4- to 12-years with attention deficit hyperactivity disorder [PMR# 3224-4]

The purpose of this review is to document the evaluation of effectiveness and safety of Mydayis 6.25 mg in pediatric patients in the preschool population (4 to 5 year-olds) and up to age 12 years in patients with ADHD. Refer to other archived documents for the extensive and detailed history of the review of the above protocols, including guidance meetings with Applicant, Pediatric Review Committee (PeRC) meetings, and the amended PWR. Note that the Applicant was released from PMR# 3224-4 after the Study 1 failed to demonstrate the efficacy of the 6.25-mg dose.

1.2.Conclusions on the Substantial Evidence of Effectiveness

The 4-week efficacy and safety study (SHP465-309) resulted in lack of efficacy of SHP465 6.25 mg compared to placebo in 6- to 12-year-olds. The PK study (SHP465-112) was conducted in patients 4- to 5-years-old and was intended to support extrapolation of efficacy from data in pediatric patients 6 to 12 years of age. Patients from the efficacy study (6- to 12-years) and PK study (4- to 5-years) participated in a safety extension study (SHP465-308) which was terminated early after efficacy was not demonstrated in the short-term study. The chemistry, manufacturing, and controls reviewer confirmed that the trials were conducted using SHP465 6.25 mg in accordance with the specifications.

1.3.Benefit-Risk Assessment

The Applicant studied the efficacy and safety of SHP465 (Mydayis) 6.25 mg in patients 6 to <13 years old with ADHD in a randomized, multicenter, double-blind, placebo-controlled, fixed-dose clinical trial. The chosen endpoint (ADHD-RS-5 at Week 4) is accepted by the Agency for ADHD studies in pediatric patients. The study was adequate and well-controlled. There was no statistically significant difference in the reduction from baseline in ADHD-RS-5 total score between the SHP465 group and the placebo group at Week 4 (p-value=0.451). Because stimulants are well-recognized as highly effective treatments for ADHD, the Division has no reason to expect that the results of this study represent chance findings. Therefore, no efficacy was demonstrated for this dose in this age group.

Mydayis is approved to treat ADHD in patients ≥13 years old (refer to NDA review dated June 20, 2017). Though efficacy was demonstrated in pediatric patients 6 to <13 years old, this age group experienced unacceptably high rates of adverse reactions (mainly insomnia and decreased appetite) following administration of 12.5 mg and 25 mg Mydayis. The label contains a limitation of use for the 6 to <13 year-old patients. The Applicant conducted Study SHP465-309 to determine whether the 6.25 mg dose was safe and effective in patients 6 to <13 with ADHD. Although the 6.25 mg dose caused less adverse reactions in this age group, efficacy was not demonstrated. Therefore, the 6.25 mg dose will not be included in the label and the limitation of use will remain.

2 Therapeutic Context

2.1.Analysis of Condition and Treatment Options

ADHD is a childhood-onset disease with core symptoms of inattentiveness and/or hyperactivity. Psychostimulants or central nervous system (CNS) stimulants, have been the mainstay of pharmacologic therapy for ADHD for a half-century. The approved stimulants are amphetamine, mixed salts of single-entity amphetamine, dextroamphetamine,

dexmethylphenidate, methylphenidate, and lisdexamfetamine. These stimulants are available in various extended-release dosage forms. Guanfacine, atomoxetine, and clonidine are non-stimulant treatment options.

3 Clinical Pharmacology

3.1.Executive Summary

Mydayis (SHP465) is a once-daily, triple-bead, sustained-release, single-entity mixed amphetamine salt (MAS) capsule for oral administration. The first two beads provide a double-pulsed delivery of MAS, with the first bead immediately releasing MAS and the second bead providing a delayed release of MAS. The third bead provides an additional delayed-dose of MAS. This triple-bead, sustained-release delivery is intended to extend the release of the MAS from SHP465 for symptom coverage up to 16 hours post-administration. The capsule contains a 3:1 mixture of dextro (d)-to levo (l) - amphetamine (AMP) base equivalents.

This supplemental NDA (sNDA) contains full Clinical Study Reports from two pediatric studies: SHP465-309 and SHP465-112. Study SHP465-309 is a phase 3 study evaluating the efficacy and safety of SHP465 6.25 mg in children aged 6 to 12 years with ADHD. Study SHP465-112 is a phase 1 study evaluating the safety, tolerability, and PK of d- and l-AMP after multiple daily doses of SHP465 6.25 mg in children aged 4 to 5 years old with ADHD. SHP465-112 was conducted to meet a post marketing requirement (PMR 3224-1)

- PMR 3224-1: A single-dose, open-label, randomized pharmacokinetic study of MYDAYIS (mixed salts of a single-entity amphetamine extended-release) in male and female children (4 to less than 6 years of age) with ADHD

and in accordance with a pediatric written request (PWR) (PWR Study 2) for Mydayis:

- PWR Study 2: Safety, Tolerability, and Pharmacokinetic Study to evaluate the safety, tolerability, and pharmacokinetics of amphetamine in 4 to 5 years-old patients with ADHD.

In trial SPH-465-309, SHP465 6.25 mg failed to demonstrate superiority over placebo in the primary efficacy endpoint [change from baseline to Visit 6 (Week 4) in the total score of the clinician-administered ADHD-RS-5]. Of note, the effectiveness and safety of 12.5 mg and 25 mg Mydayis have been evaluated in children 6 to 12 years old previously (refer to clinical review in DARRTS dated June 20, 2017). Though efficacy was demonstrated, pediatric patients 6 to 12 years old experienced higher rates of adverse reactions, mainly insomnia and decreased appetite following administration of 12.5 mg and 25 mg Mydayis. Therefore, use of Mydayis in 6 to 12 years old is limited per current label.

Of note, no labeling changes based on results from PK study SHP465-112 are being proposed by the Applicant at this time.

3.2.Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology reviewed the submission. It has been concluded that the reported study has fulfilled the pharmacokinetic (PK) study requirement for PMR# 3224-1 and PWR study 2.

3.3.Comprehensive Clinical Pharmacology Review

3.3.1. General Pharmacology and Pharmacokinetic Characteristics

The major PK parameters of d- and l-AMP following multiple administration of 6.25 mg Mydayis in children 4 to 5 years old with ADHD, are summarized in Table 1.

Table 1: Plasma PK Parameters (Mean±SD) of d- and l- AMP Following Once Daily Dosing of 6.25 mg Mydayis for 28 Days (rich PK group, n=11)

	d-AMP	l-AMP
C_{max} (ng/mL)	32.8±10.4	10.4±3.4
$C_{trough,ss}$ (ng/mL)	7.9±6.3	3.1±2.5
T_{max} (hr)	7.9 (5.0, 16.3)	7.9 (5.0, 16.3)
$AUC_{tau,ss}$ (hr*ng/mL)	540.9±154.9	178.9±55.1
AUC_{0-t} (hr*ng/mL)	667.9±178.1	231.5±68.9
$T_{1/2}$ (hr)	10.6±1.7	12.4±1.9
Tmax: medican (range) -Source: Table 8 of CSR		

3.3.2. Clinical Pharmacology Questions

3.3.2.1. How are the PK properties of d- and l- AMP in pediatric patients aged 4 to 5 years old compared to other age groups following administration of Mydayis?

The PK parameters of d- and l-AMP following administration of Mydayis amongst different age groups were populated in Table 2 below. It is noticed that the mean Tmax of d- and l-AMP was about 8 h in all age groups, and the mean $T_{½}$ was about 10 -11 hours and 12 to 13 hours for d- and l-AMP, respectively, across all age groups (Table 2). Following single-dose Mydayis administration, the mean dose normalized Cmax of d-AMP were about 145%, 102%, and 40%, higher in children 4 to 5 years old, compared to adults, adolescents 13 to 17 years old, and children 6 to 12 years old, respectively. Following single dose Mydayis administration, the mean dose normalized AUC of d-AMP were about 199%, 142%, and 66%, higher in children 4 to 5

years old, compared to adults, adolescents 13 to 17 years old, and children 6 to 12 years old, respectively. A similar trend was observed for l-AMP (Table 3).

Table 2: PK Parameters (Mean [SD]) of d- and l-AMP Following Mydayis Single Dose Administration in Different Age Groups

		d-AMP				l-AMP			
Population (age range; N)	Dose (mg)	Tmax (hour)	C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	T1/2 (hour)	Tmax (hour)	C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	T1/2 (hour)
Adults (19-52; 20)	37.5	8.2 (2.0)	50.3 (7.5)	1085 (196)	10.1 (1.3)	8.4 (2.1)	14.7 (2.2)	373 (73.5)	12.5 (1.7)
Adolescents (13-17; 14)	25	8.0 (6, 10)	40.6 (9.3)	893 (209)	11.4 (2.0)	8.0 (6, 10)	12.9 (3.2)	326 (92.9)	13.2 (2.9)
Children (6-12; 13)	12.5	8.0 (6, 24)	29.2 (7.3)	652 (174)	9.9 (1.9)	9.0 (6,24)	9.3 (2.4)	225 (65.3)	11.8 (2.8)
Children (4-5; 11)[$]	6.25	7.9 (5.0,16.3)	32.8 (10.4)[#]	541 (155)*	10.6 (1.7)	7.9 (5.0, 16.3)	10.4 (3.4)[#]	179 (55.1)*	12.4 (1.9)

$ data for children 4-5 years old were from multiple dose study; #Cmax,ss; *AUCtau Tmax: medican (range) -Source: Table 8 of CSR; Dr. Kofi Kumi review (DARRTS date: 6/12/2017)

Table 3: Exposure in Children 4 to 5 Years Old with ADHD Compared to Other Age Groups Following Single Dose Administration of Mydayis

% Higher	d-AMP		l-AMP	
	C_{max}/Dose (ng/mL/mg)	AUC_{inf} /Dose (hr*ng/mL/mg)	C_{max}/Dose (ng/mL/mg)	AUC_{inf} /Dose (hr*ng/mL/mg)
4-5 yrs/Adults	145	199	165	188
4-5 yrs/13-17 yrs	102	142	102	122
4-5 yrs/6-12 yrs	40	66	40	59

Note: in 4-5yrs old values for C_{max} is $C_{max,ss}$/1.6 (accumulation ratio in adult), AUC_{inf} is $AUC_{tau,ss}$
-Source: Table 8 of CSR; Dr. Kofi Kumi review (DARRTS date: 6/12/2017)

4 Sources of Clinical Data and Review Strategy

4.1. Table of Clinical Studies

The three studies submitted in support of this supplemental NDA are listed in Table 4.

Table 4: Table of SHP465 clinical trials

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	SHP465-112	Define multidose PK, safety	Phase 1, open-label, multiple dose	Capsules, 6.25 mg SHP465; QDx28 days; oral	24 subjects enrolled	children aged 4-5 years with ADHD	28 days	Completed; Full
Efficacy	SHP465-309	Efficacy, safety	Phase 3, randomized, double-blinded, placebo-controlled	Capsules, 6.25 mg SHP465; QDx28 days; oral	89 subjects randomized: 45 SHP465 44 placebo	children aged 6-12 years with ADHD	28 days	Completed; Full
Safety	SHP465-308a	Long-term safety and tolerability	Phase 3, open-label	Capsules, 6.25 mg SHP465; QDx1 year; oral	141 subjects enrolled	children aged 4-12 years with ADHD	1 year, planned	Discontinued; CSR submitted June 2019

(Source: Adapted from NDA 022063 Supplement 1 submission dated 3/13/19)

4.2.Review Strategy

The evaluation of efficacy is derived from review of Study SHP465-309, the efficacy study. The safety evaluation focuses on the efficacy study because it includes a placebo comparator to SHP465. The clinical reviewer assessed appetite and weight changes in the 4- to 12- year-old patients over time from the safety extension study (SHP465-308).

5 Statistical and Clinical Evaluation

5.1.Review of Relevant Individual Trials Used to Support Efficacy

5.1.1. SHP465-309

Trial Design

Study SHP465-309 was a 4-week, randomized, double-blind efficacy and safety study of SHP465 (6.25 mg once a day) in children 6-12 years-old with ADHD. The study was conducted in the United States at 27 clinical centers.

Study Endpoints

The primary efficacy endpoint was the change from baseline of the ADHD-RS-5 total score at Visit 6 (Week 4). The ADHD-RS-5 contains two, 9-item symptom subscales (inattention and hyperactivity-impulsivity). The 18-item total scale corresponds to the 18 items in the DSM-5 criteria, plus a 6-domain functional impairment assessment.

Statistical Analysis Plan

The SAP Version 1.0 (dated December 18, 2017) was updated and replaced with Version 2.0 (August 16, 2018). Both versions of the SAP were finalized before the database lock (August 21, 2018).

The primary efficacy endpoint was analyzed by using the linear mixed-effects model for repeated measures (MMRM) with treatment group (SHP465 and placebo), visit, age group (6 to 8 years versus 9 to 12 years), and the interaction of treatment group with visit as factors; the baseline ADHD-RS-5 total score as a covariate; and the interaction of baseline ADHD-RS-5 total score with visit adjusted in the model.

5.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant and investigators abided by Good Clinical Practices as described in 21 CFR Parts 50, 56, and 312 and the ICH GCP Guidelines.

Financial Disclosure

The financial disclosure submitted with the supplemental NDA is acceptable. Study SHP465-309 listed 27 primary investigators. Of these, two investigators disclosed that significant payments were received on or after February 2, 1999, from the Applicant of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or as honoraria. The amount of payments were not listed. The investigators were (b) (6). Both investigators signed non-bias memorandums to their respective Investigational Review Boards (IRB).

Patient Disposition

The study enrolled 88 patients (45 patients in SHP465 group and 43 patients in the placebo group), whereas, 83 patients completed the study [42 (93.3%) patients in the SHP465 group and 41 (95.3%) patients in the placebo group].

Of the 83 patients who completed the study, 39 (44.3%) completed the follow-up [20 (44.4%) patients in the SHP465 group and 19 (44.2%) patients in the placebo group]. The overall study completion rate was 94% and similar between the two treatment groups. Pre-specified sensitivity analyses (a) multiple imputation based on efficacy in placebo group and (b) multiple imputation with added penalty yielded results consistent with the primary analysis.

The reasons for withdrawal in the SHP465 group were withdrawal by patient or parent (n=2) and protocol violation (n=1); both withdrawals in the placebo group were due to lack of efficacy.

Protocol Violations/Deviations

Of the 88 patients enrolled in the study, 49 (55.7%) patients had at least one protocol deviation and 27 (30.7%) patients had at least one protocol violation. The highest percentage of protocol deviations was “other” at 28 deviations (32%) which included procedural errors of not meeting the assessment time window. The Applicant reported n = 8 (9%) in the protocol deviation “abuse, misuse, overdose, medication error” category. The deviations were not abuse-related and included non-compliance or becoming unblinded by the urine screen. The sensitivity analysis excluded potentially unblinded patients, and its results were consistent with the primary analysis and is unlikely the reason for the treatment group not reaching statistical significance.

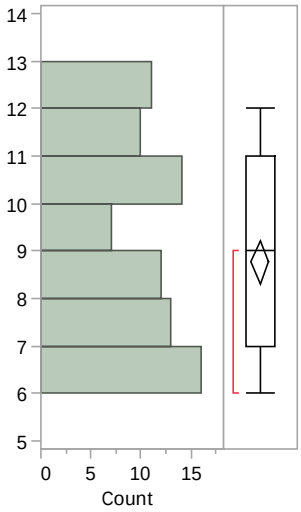
Demographic Characteristics

The sex and racial demographic distributions for the ADHD pediatric population from 27 clinical U.S.-sites reflect the population of ADHD. The population in the United States is approximately two-thirds male and of Caucasian race.

The efficacy study (SHP465-309) enrolled 88 patients 6- to 12-years-old. The age distribution was 16 patients 6-years old, 34 patients 7 to ≤ 9-years old, and 38 patients 10- to 12-years old.

Figure 1 shows the number of patients by age. The Applicant reported the age distribution subgroups as 6- to 8- years-old (n=44) and 9- to 12-years-old (n=44), which is evenly distributed. There were 64% males and 36% females. Most of the patients were Caucasian (66%) or of Hispanic ethnicity (42%). The placebo and SHP465 groups were balanced.

Figure 1: Age distribution in Study SHP465-309



(Source: Clinical reviewer created using JMP Clinical 7.0)

Efficacy Results – Primary Endpoint

The primary efficacy endpoint for the study was the ADHD Rating Scale 5 (ADHD-RS-5) total score at Week 4. The ADHD-RS-5 is available in versions for children ≤ 10 and > 10 years old. Correlating CGI-I and ADHD-RS-IV scores, estimates of clinically meaningful changes in a pediatric population are[1]:

- -17 to -50 “very much to much improved”
- -5 to -17 “minimally improved”
- 13 to -5 “no change” or “worse”

Study SHP465-309 was completed and the primary efficacy analysis demonstrated a lack of significant symptom reduction and clinical improvement from baseline in patients diagnosed with ADHD and recieving treatment with SHP465 6.25 mg compared with patients receiving placebo.

[1] Goodman D, et al. Interpreting ADHD Rating Scale scores: Linking ADHD Rating Scale scores and CGI levels in two randomized controlled trials of lisdexamfetamine dimesylate in ADHD. Primary Psychiatry 2010; 17(3):44-52.

The statistical reviewer replicated the primary efficacy results of Study SHP465-309 as presented by the Applicant in Table 7 (page 67) of the study report. The difference in LS Means of change from baseline in the ADHD-RS-5 total score to Week 4 between the 6.25 mg SHP465 dose and placebo is estimated as -1.89 (95% CI: -6.8, 3.1), indicating a numerical, but not statistically significant (p = 0.45) trend in favor of the SHP465 treated patients at two-sided alpha of 0.05.

A blinded interim analysis was performed when approximately 75% of all randomized patients had either completed or discontinued from the study to reassess the sample size in case the variability used for the sample size calculation was underestimated. The Applicant had assumed a common standard deviation (SD) of 14. The estimated pooled common standard deviation at the interim of 13.29 was less than 14 and an increase in sample size was not required per the SAP-specified rule.

Data Quality and Integrity

The raw data submitted was acceptable for the biometrics reviewer to replicate the Applicant's results.

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoint was the Clinical Global Impression – Improvement (CGI-I). The Clinical Global Impression-Improvement (CGI-I) scale is a clinician-rated, 7-point scale that is designed to assess how much the subject's illness has improved or worsened relative to a baseline state at the beginning of the intervention.

Formal statistical testing of the CGI-I score at Week 4 was not permissible due to the pre-specified sequential testing strategy and the lack of sufficient evidence in favor of SHP465 on the primary efficacy endpoint. The estimated difference in the CGI-I scores of -0.1 was small.

Dose/Dose Response

The Applicant manufactured a dose lower (6.25 mg) than the approved doses of 12.5 and 25 mg, which were evaluated in 6- to 12-year-olds in a registration trial (SHP465-305). The 6.25 mg dose lacked the efficacy and adverse events of decreased appetite and insomnia seen with the higher doses. The dose reponse is consistent with the known efficacy and adverse event profile related to MAS ER.

5.2.Review of Safety

5.2.1. Safety Review Approach

The clinical reviewer, Nancy Dickinson, PharmD, focused on the efficacy study to compare differences between treatment groups. Dr. Dickinson used the programs JMP Clinical 7.0 and JMP 13.0 to review the adverse event and demographic datasets. Then, the reviewer evaluated growth over time reported in the the abbreviated CSR of the open-label safety extension study.

5.2.2. Review of the Safety Database

Overall exposure and adequacy of the safety database:

The size of database was acceptable to generalize to the preschool ADHD population and older children. There were 140 patients exposed for an average of 6-months duration. This is a shorter duration than is recommended by the E1 ICH guideline, *Population Exposure: The Extent of Population Exposure to Assess Clinical Safety*, for a chronic use medication, but the long-term safety profile of MAS ER is well known.

The open-label safety study (SHP465-308) enrolled patients from Studies -309 and -112). There were 70 patients in each age group of 4- to 5- years and 6- to 12-years; 140 total. The mean duration of exposure was 17.1 (SD 8.5) weeks from the PK study. From the efficacy study, patients enrolled into the safety extension study there were 30.7 (SD 10.8) weeks of exposure from placebo group and 29.0 (SD 15.0) weeks from SHP465 group. An additional 26.5 (SD 15.7) weeks of exposure was in patients directly enrolled in the safety study. Based on data presented in Table 6 in the CSR (SN 0290 6/26/19), at least 60 patients were exposed to drug at least 6-months (26-weeks). The average duration was 6-months, as calculated from Table 5 in the CSR.

5.2.3. Adequacy of Applicant's Clinical Safety Assessments

The Applicant's safety assessments were acceptable and previously reviewed in the SHP465-309 protocol. The safety assessments were reporting treatment-emergent adverse events, vital signs, weight and body mass index (BMI), clinical laboratory tests, ECG, responses to Post Sleep Questionaire, Children's Sleep Habits Questionaire, and the Columbia-Suicide Severity Rating Scale. The safety data was analyzed by the Applicant by assigned-treatment within each age group (6 to 8 years vs. 9 to 12 years), sex, and race.

5.2.4. Safety Results

No deaths, serious adverse events, or AEs leading to discontinuation were reported.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent AEs (assessed by the investigator to be related to the treatment product) were reported in similar numbers in the two treatment groups. In the SHP465 group, four (8.9%) patients collectively reported a total of four AEs. The AEs were abdominal pain upper, medication error, tremor, or affect lability. In the placebo group, five (11.6%) patients collectively reported a total of eight AEs. The AEs were decreased appetite, headache, dry mouth, fatigue, or insomnia.

The AEs reported at a rate >2% are listed in Table 5. There are no clinically significant differerences between treatment groups.

Table 5: AEs report over 2% among treatment groups (Sutdy SHP465-309)

		SHP465 6.25 mg N=45		Placebo N=43		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Gastrointestinal disorders	Diarrhoea	1	2.2%	1	2.3%	2
Injury, poisoning and procedural complications	Medication error	1	2.2%	1	2.3%	2
Metabolism and nutrition disorders	Decreased appetite	1	2.2%	2	4.7%	3
Nervous system disorders	Headache	2	4.4%	3	7.0%	5

(Source: Clinical reviewer created using JMP Clinical 7.0)

Likewise, there were no differences between age-groups (6 to 8 years) and (9 to 12 years) in the number of AEs reported, nor between treatment groups.

There were two psychiatric AEs of interest. One subject in the SHP465 6.25 mg treatment group (6- to 8-years) experienced affect lability. This is a labeled AE for MAS ER. In the 9- to 12-year-old group, one female 11-year-old patient taking SHP465 6.25 mg reported suicidal ideation (SI) of "wish to be dead" (judged as mild and not related to treatment) at the Week 1 assessment. No action was taking with either AE and the patient completed the study.

Laboratory Findings

No clinically significant laboratory findings were reported and abnormal laboratory results were similar between treatment groups.

Vital Signs

No clinically significant changes from baseline or apparent differences between the treatment groups in pulse rate were reported.

In the SHP465 treatment group, both systolic (SBP) and diastolic blood pressure (DBP) were increased, which is labeled for MAS ER products. The mean SBP change from baseline was -1.0 mmHG in the placebo group and +1.8 mmHG in the SHP465 treatment group. The mean DBP change from baseline was +0.3 mmHG in the placebo group and +3.1 mmHG in the SHP465 treatment group.

Electrocardiograms (ECGs)

No clinically meaningful changes in ECG parameters between the SHP465 group and the placebo group over time were reported.

5.2.5. Analysis of Submission-Specific Safety Issues

Based on the limitation of use of SHP465]due to higher exposure levels, insomnia, and decreased appetite in the registration trials of SHP465 12.5 and 25 mg per day in pediatric

patients (6- to 12-years)], the Applicant was asked to report on these specific safety findings with a lower dose of 6.25 mg in the 6- to 12-year-olds. The results are not clinically significant.

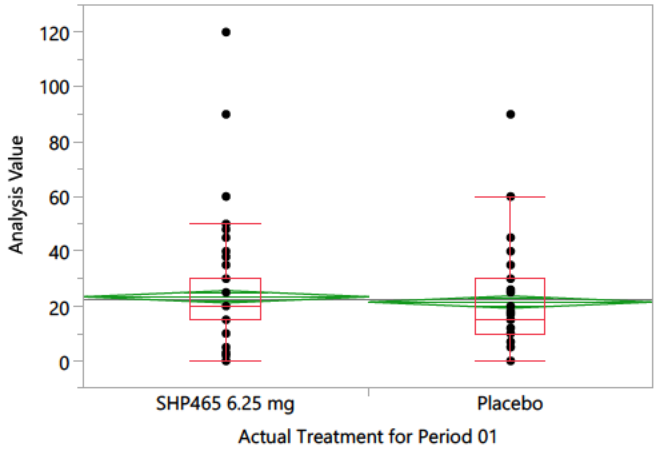
Insomnia

In Study SHP465-309, insomnia was assessed by the Post Sleep Questionnaire (PSQ) at baseline and each weekly visit, the Children's Sleep Habit Questionnaire (CSHQ), and reported as an AE, if applicable. Only one patient reported an AE of insomnia and this patient was taking placebo and in the 9- to 12-years age group.

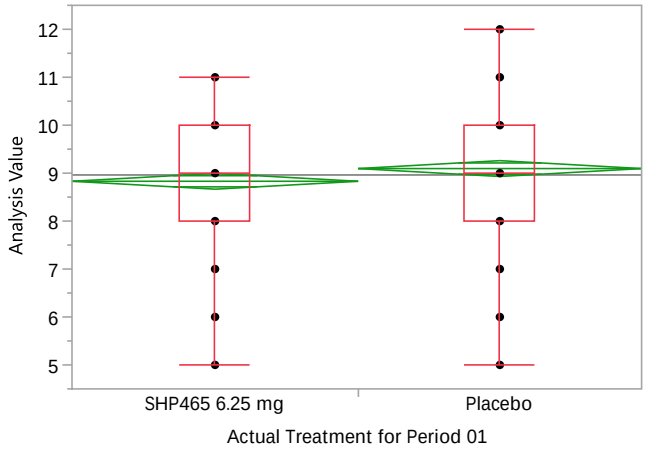
The CSHQ is a parent-reported measurement of sleep for school-age children ages 4- to 10-years. There were, generally, no differences between the SHP465 group and the placebo group at baseline and Visit 6 (Week 4) on sleep habits.

The PSQ is a 7-question patient-related outcome measure. For each question on the measurement scale, patients randomized to the SHP465 6.25 mg treatment group answered comparably to those in the placebo group. To illustrate this, Figures 2 and 3 show minutes to fall asleep and average hours asleep on school nights between treatment groups. There is one outlier in the SHP465-treatment group, but the patient did not alter the mean comparison on the histogram in Figure 2.

Figure 2: Post Sleep Questionnaire Minutes to Fall Asleep Avg School Night Results (Study SHP465-309)



How Long Sleep Per Night Avg School Nite Results



(Source: Clinical reviewer created using JMP 13.0 and JMP Clinical 7.0)

Decreased appetite

Three subjects reported decreased appetite as an AE. There was one patient in the SHP465 group and was aged 6- to 8-years. The event occurred at Week 1, was considered mild in severity, the dose was not changed, and the AE resolved. In the placebo group two patients, one in each age group (6- to 8-years or 9- to 12-years) reported decreased appetite. Both reports were early in the trial at Week 1 or Week 2. Decreased appetite AEs are common during early treatment with stimulants.

5.2.6. Safety Analyses by Demographic Subgroups

The clinical reviewer analyzed changes from baseline for height (cm) and weight (kg) up to the Week 4 clinical site visit for both age groups. Although unlikely to observe clinically-relevant changes in height over 4 weeks, Figure 3 shows that patients in the SHP465 treatment group had a slight (0.05 cm), non-clinically significant gain in height compared to the placebo group patients. Contrarily, in Figure 4, patients in the placebo group had a mean weight gain slightly (0.35 kg), but not clinically significant, over the SHP465 group.

Figure 3: Change from baseline mean height by age group (Study SHP465-309)

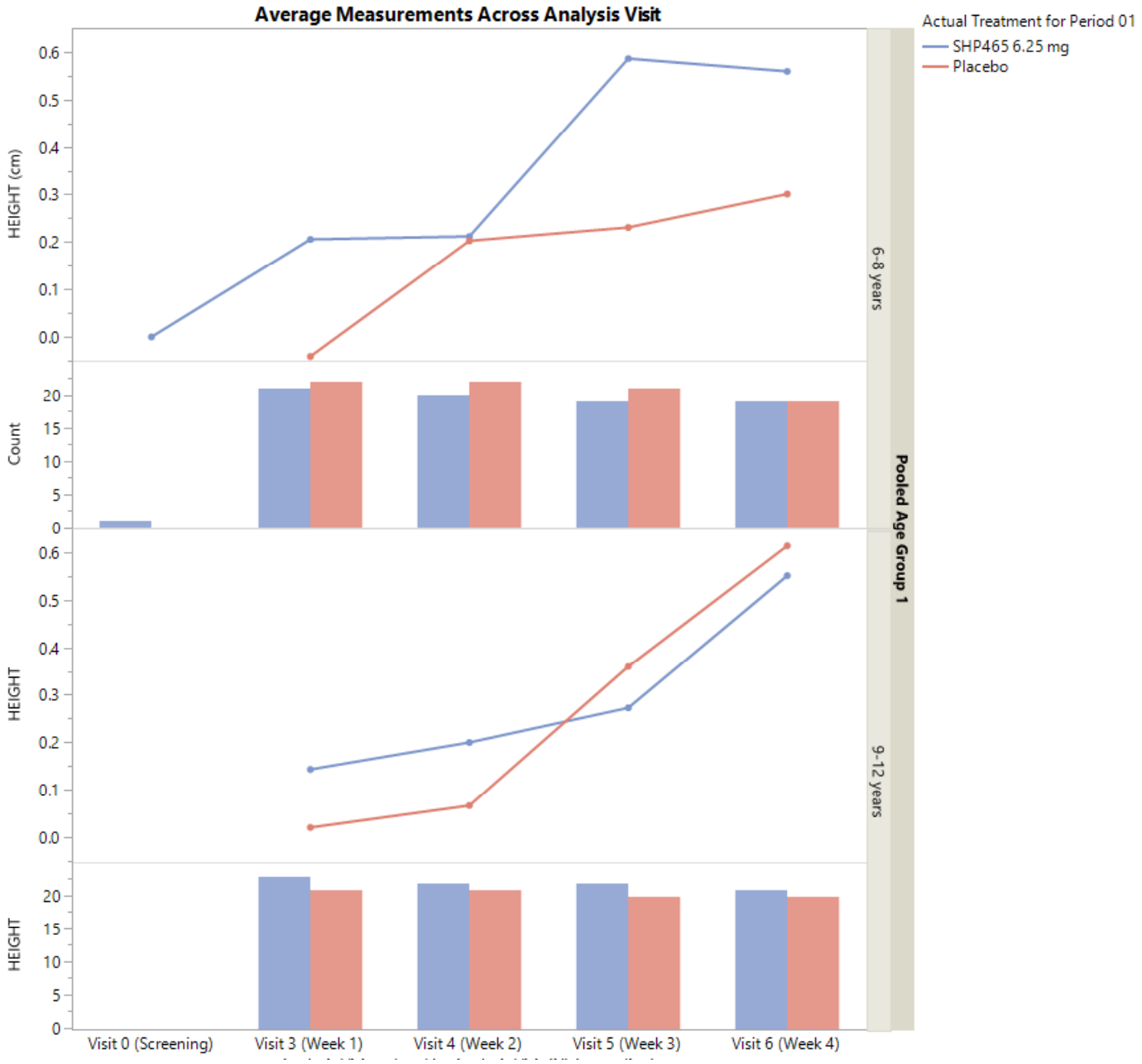
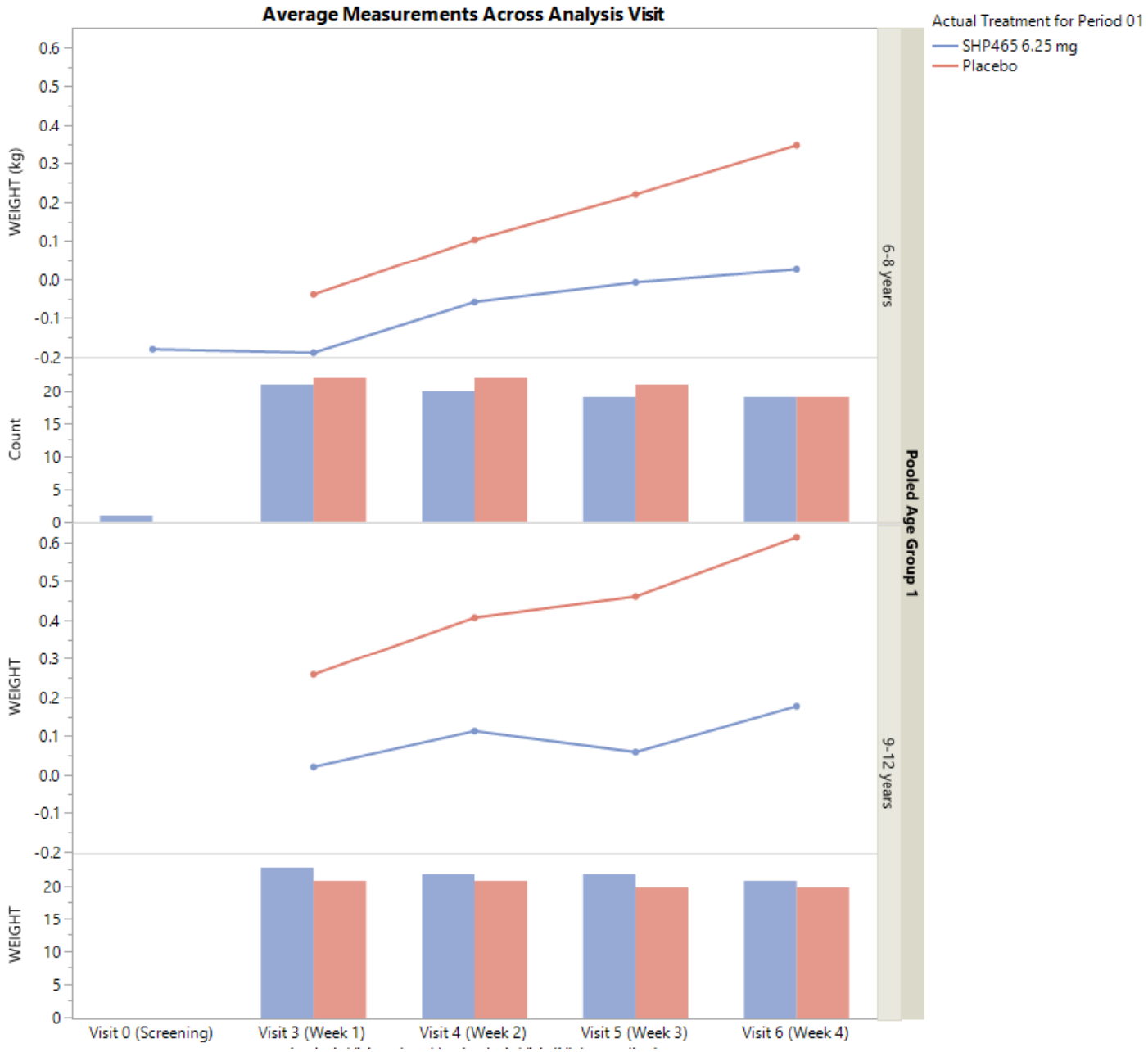


Figure 4: Change in baseline mean weight by age group (Study SHP465-309)



(Source: Clinical reviewer created using JMP Clinical 7.0)

5.2.7. Specific Safety Studies/Clinical Trials

Study SHP465-308 was designed to be a 12-month open-label safety extension trial of patients age 4- to 12-years who participated in the PK study (SHP465-112) and the efficacy trial (SHP465-309). The extension study was terminated by the Applicant with FDA's concurrence due to lack of efficacy of SHP465.

The Study 308 safety data set includes 63 patients enrolled from the previous trials (Group A) and 77 patients (Group B) enrolled directly (total n=140). There was an even distribution of age groups 4- to 5-years and 6- to 12-years (n=70 each).

As described in Section 5.2.2 of this review and Table 6, below, the duration of exposure to SHP465 6.25 mg averages 6-months (26 weeks) among the cohorts in Study 308. Although the study was planned for 12-months, the duration is adequate for long-term safety assessments.

Table 6: Exposure Duration by Cohort in SHP465-308

Duration of exposure	Group A from 112 (SHP465 6.25 mg)	Group A from 309 (placebo)	Group A from 309 (SHP465 6.25 mg)	Group B direct (SHP465 6.25 mg)	Average duration of exposure
N	19	22	22	77	140
Days Mean (SD)	119 (60)	215 (76)	202 (104)	185 (110)	180
Weeks (Mean (SD))	17 (9)	31 (11)	29 (15)	26 (16)	26

(Source: Adapted Table 5, page 46 of SHP465-308 CSR)

The most frequently reported (≥2%) AEs were weight decreased (6.4%), headache (5.7%), decreased appetite (5.0%), diarrhea (5.0%), irritability (3.6%), and vomiting (3.6%). The clinical reviewer focused the review on the long-term effects on insomnia, decreased appetite, weight loss, and psychiatric AEs, as listed in Table 7. Insomnia was not a reason for discontinuation.

Table 7: AEs of interest is SHP465-308

AE term	Group A (4-5 years) N	Group A (6-12 years) N	Group B (4-5 years) N	Group B (6-12 years) N (%)	Total (N=140)
Weight decreased	0	3	1	5	9 (6.4)
Decreased appetite	0	1	3	3	7 (5.0)
Insomnia	1	1	1	1	4 (2.9)
Irritability/affect lability	1	5	2	0	8 (5.7)

(Source: Modified Table 7, page 50 of SHP465-308 CSR)

The older children (6- to 12-years) reported more AEs than the 4- to 5-year-olds. In Table 7, most decreased weight- and appetite-related AEs were reported in patients directly enrolled in the long-term open-label study. Of the nine patients reporting weight decreased, eight were

reported in the 6- to 12-year age group (n=3 Group A; n=5 Group B) and one patient in the 4- to 5-year age group (Group B). More AEs occur when starting treatment of stimulants. For example, only one patient in Group A (6- to 12-years) reported decreased appetite. In contrast, in the directly enrolled Group B, three patients in each age group reported decreased appetite (n=6).

Narratives were provided in the CSR for each patient in Table 7. Two patients (1.4%) discontinued from the trial due to weight decreased or decreased appetite. The patient who discontinued for decreased appetite on Day 10 was a 7-year-old male from Group B. Subject (b) (6) complained of weight loss (≥5%) on day 58 with duration of 37 days and on day 94 (≥ 10%) and ongoing at the time the subject left the study. One patient reported >7% weight loss. The percent changes in weight were not recorded for the other patients reporting weight loss.

Although baseline growth parameters (height, weight, BMI) were listed in the vital signs dataset, monthly weights were not provided for the clinical reviewer to graph over time. However, the Applicant described the change from baseline in the growth parameters by enrollment group and age. Table 8 lists the negative change in body mass index, with the largest decrease in the youngest patients. If the dose of SHP465 6.25 mg was high enough to treat ADHD compared to placebo, more weight loss over time would be expected. Therefore, maintaining the limitation of use for patient 13-years and above with the approved doses should be upheld.

Table 8: Change in BMI from baseline to patient's final visit (SHP465-308)

	Group A (4-5 yr)	Group A (6-12 yr)	Group B (4-5 yr)	Group B (6-12 yr)
N	19	44	51	26
BMI (kg/m^2) Median	-0.85	-0.32	-0.22	-0.08
Min, max	-3.0, 0.4	-2.4, 2.3	-4.8, 4.3	-3.0, 4.1

(Source: Modified from Table 18, page 70 of SHP465-308 CSR)

5.2.8. Additional Safety Explorations

Pediatrics and Assessment of Effects on Growth

As described in Sections 5.2.5 and 5.2.6, there was not an appreciable impact on growth over the 4-week study. Refer to Section 5.2.7 of this review for the assessment of growth from the open-label safety study (SHP465-308).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Controlled Substances Staff (CSS) recommends no change to Section 9, Drug Abuse and Dependence, of the label. CSS agrees with the proposed changes to Section 8.4, Pediatric Use, recommended by DPP.

CSS Conclusions:

- The requested PMR and PWR have, from CSS' perspective, been fulfilled.
- Mydayis, or SHP465, contains mixed amphetamine salts listed in Schedule II of the CSA. The Applicant has not requested a change in schedule.
- The Applicant did not conduct nonclinical or clinical abuse related studies for SHP465.
- There were no AEs from the pediatric clinical studies that are related to abuse.
- The absence of any abuse-related AEs may be related to Study SHP465-309 not demonstrating clinical efficacy over placebo, suggesting a sub-therapeutic dosage in this pediatric population.
- There was no evidence of abuse, misuse, or diversion of SHP465 in any of the clinical trials.

5.2.9. Integrated Assessment of Safety

The safety of SHP465 6.25 mg was important because of the severe insomnia and decreased appetite seen with higher doses in the registration trial for the age group 6- to 12-years. In study SHP465-309, SHP465 6.25 mg/day demonstrated adequate safety during the 4-week efficacy trial compared to placebo. The open-label long-term in pediatric patients 4- to 12-years showed AEs expected with MAS ER (e.g. insomnia, affect lability). The decreased appetite and weight loss were reported most often and had the largest impact on the 4- to 5-year-olds. Although one patients discontinued the study early due to weight loss or decreased appetite, there was less growth impact than in the higher, approved doses.

5.3. Conclusions and Recommendations

The review team unanimously recommends that SHP465 6.25 mg not be approved because of lack of efficacy. Language about the failed study will be added to the professional labeling in Section 8.4. No changes to the existing safety information in labeling is recommended because there were minimal dose-related AEs from the SHP465 6.25 mg dose compared to those in the placebo group.

6 Pediatrics

This supplement was submitted in response to both PREA PMRs (PMR 3224-1, 3224-4, and 3224-5) and a PWR issued for the evaluation of a lower dose of SHP465 (6.25 mg) in pediatric patients 4 to 12 years of age. Of note, a higher dose of SHP465 (12.5 mg titrated to 25 mg) was previously evaluated and data were submitted as part of the original NDA. The higher dose was not approved in patients 6 to 12 years of age due to higher incidence of adverse events, including insomnia and loss of appetite; therefore, a limitation of use was in included in the product label.

For this supplement, the Applicant conducted a randomized double-blind efficacy and safety study of SHP465 6.25 mg once a day in patients 6 to 12 years of age with ADHD (PMR 3224-5). The primary efficacy analysis demonstrated lack of benefit as compared to placebo. Given the findings at the lower dose, the long-term safety study in patients 4 to 12 years of age (PMR 3224-4) was stopped and available safety data were submitted for review by the Agency in this supplement. The Applicant also submitted data from the completed PK study in patients 4 to 5 years of age (PMR 3224-1). In the context of the above data, the indication will not be expanded and the current limitation of use for patients under 12 years of age will remain in the labeling. A brief summary of the new data in patients 4 to 12 years of age will be described under section 8.4, reflecting that a safe and effective dose could not be established in this age group. The Applicant has completed the studies that were required in the PREA PMR (3224-1,3224-4, and 3224-5); these PREA PMR should be considered fulfilled.

7 Labeling Recommendations

7.1. Prescription Drug Labeling

The Applicant proposed this change to Section 8.4 Pediatrics in the labeling:

> *MYDAYIS has been studied for the treatment of ADHD in children 6 to 12 years old in two placebo controlled safety and efficacy trials. In the first trial,* (b) (4) *Children 6 to 12 years of age experienced higher rates of adverse reactions in some cases compared to patients 13 years and older, including higher rates of insomnia (30% versus 8%) and appetite decreased (43% versus 22%). In addition, amphetamine systemic exposures (both d- and l-) in patients 6 to 12 years of age following a single dose were higher than those observed in adults at the same dose (72-79% higher C_{max} and approximately 83% higher AUC).*
>
> *In the second trial,* (b) (4)

(b) (4)

The review team recommends this language:

> *MYDAYIS has been studied for the treatment of ADHD in pediatric patients 6 to 12 years in two placebo controlled safety and efficacy trials. In the first trial, pediatric patients 6 to 12 years experienced higher rates of adverse reactions in some cases compared to patients 13 years and older, including higher rates of insomnia (30% versus 8%) and appetite decreased (43% versus 22%). In addition, amphetamine systemic exposures (both d- and l-) in pediatric patients 6 to 12 years following a single dose were higher than those observed in adults at the same dose (72-79% higher C_{max} and approximately 83% higher AUC). A second trial evaluated a lower dose than those approved for pediatric patients ages 13 to 17 years; efficacy was not demonstrated for the lower dose. Therefore, a safe and effective dose cannot be established in pediatric patients 12 years and younger.*

8 Division Director (Clinical) Comments

Given that efficacy was not demonstrated for the 6.25 mg dose in pediatric patients ages 6 to 12 years, the Limitation of Use statement in approved labeling will remain. Safety findings are included in section 8.4; however, the new findings will not be included as they would only serve to undermine the LoU statement. With these studies, the Applicant has fulfilled their PREA post-marketing requirements. Having fulfilled the terms of the Pediatric Written Request, we will also grant an additional 6 months of exclusivity per the Best Pharmaceuticals for Children Act.

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/s/

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