# CLINICAL REVIEW

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|---|---|
| Application Type | NDA |
| Application Number(s) | 022063 |
| Priority or Standard | Standard |
| Submit Date(s) | 12/20/16 |
| Received Date(s) | 12/20/16 |
| PDUFA Goal Date | 6/20/17 |
| Division / Office | Division of Psychiatry Products/ODE 1 |
| Reviewer Name(s) | Nancy Dickinson, PharmD. |
| Review Completion Date | 5/19/17 |
| Established Name | Mixed salts of a single-entity amphetamine |
| (Proposed) Trade Name | Mydayis |
| Therapeutic Class | stimulant |
| Applicant | Shire |
| Formulation(s) | Extended release capsule |
| Dosing Regimen | Once daily in morning |
| Indication(s) | Attention deficit hyperactivity disorder (ADHD) |
| Intended Population(s) | Adults, pediatrics 6-17 years |

Template Version: March 6, 2009

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

The efficacy and safety of SHP465 (mixed salts of a single-entity amphetamine extended release capsule) are adequate to recommend approval for the treatment of attention deficit hyperactivity disorder (ADHD). SHP465 was studied in pediatric patients 6 to 17 years and adults. I recommend limiting the approved indication to pediatric patients 13 years and above because patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of adverse reactions, mainly insomnia and decreased appetite.

## 1.2 Risk Benefit Assessment.

ADHD is primarily a childhood disorder that may extend into adulthood. The prevalence of ADHD in pediatrics is about 9%, staying relatively stable over the past three decades using adequate diagnoses (Polanczyk, 2014). The prevalence in adults is 2.5% (Simon, 2009).

Fortunately, there are many highly effective pharmacological options to treat ADHD, most of these are stimulants. Stimulant preparations can be quick-acting (within 30 minutes) and short lasting (four to six hours) or longer lasting (eight to 12 hours). The Agency's drug use data demonstrates that adults *and* children are currently using 8- or 12-hour extended-release stimulants followed by a 4-hour immediate-release dosage form. Because patients are already using stimulants for 16 hours a day, it appears that taking one capsule in the morning may be beneficial for some patients with ADHD; the proposed product was designed to provide 16-hour symptom relief.

Benefit: SHP465 has the same active moiety as the highly efficacious Adderall XR (mixed salts of a single-entity amphetamine extended release capsule); there is no surprise that SHP465 demonstrates robust efficacy in adults and pediatrics.

Risk: SHP465 has the expected adverse events of a stimulant. See Section 7. During the drug's development, Shire lowered the proposed dose strengths, leading to increased tolerability in adult and adolescent (13 to 17 years) patients.

In general, the risk-benefit ratio is considered favorable in patients over 13 years old. For children under 13 years (i.e., 6 to 12 years), there is a small portion of children with severe ADHD (e.g., sequelae of fetal alcohol syndrome) for whom a 16-hour stimulant may be necessary, especially if those patients are already taking an extended-release

stimulant followed by an immediate-release one. The risk-benefit ratio of once daily SHP465 is considered favorable in the younger children with severe attention deficit hyperactivity disorder who are already taking stimulants multiple times a day.

However, for most children less than 12 years old with ADHD, the risk-benefit ratio of SHP465 is less certain. As noted in this review, there was a concerning incidence of insomnia and decreased appetite reported in the 6 to 12 year old age group during clinical development. Given that there are only 24 hours in a day, there are only eight hours for sleep left in the day if patients take a 16-hour stimulant; this is clearly insufficient for children in this age group to rest, grow, and not be irritable. The American Academy of Pediatrics and the American Academy of Sleep Medicine currently recommend for children in this age group to sleep nine to 12 hours per 24 hours on a regular basis to promote optimal health. Additionally, SHP465 causes decreased appetite that may contribute to long-term growth suppression and weight loss from a chronically taken stimulant.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS is recommended.

## 1.4 Recommendations for Postmarket Requirements and Commitments

A postmarketing requirement (PMR) addressing the Pediatric Research Equity Act (PREA) requirement to ensure a pediatric-appropriate formulation is recommended to ensure a lower dose (6.25mg) of SHP465 is available for pediatric patients within two years post approval.

Shire submitted a Pediatric Study Plan in their NDA resubmission, December 20, 2016, to study SHP465 in 4 to 5 year old preschool attention deficit hyperactivity disorder patients and to manufacture a lower dose formulation, 6.25mg. The lowest dose of SHP465 to be approved in this application is 12.5mg.

Prior to the NDA resubmission, on November 3, 2016, Shire submitted a Proposed Pediatric Study Request (PPSR). On, February 27, 2017, the Agency issued an inadequate letter denoting the need for the pediatric study plan to address decreased appetite and insomnia in the preschool population, based on preliminary review of the clinical study report for 6 to 12 years in the NDA (SHP465-305). On March, 17, 2017, Shire submitted a revised PPSR including an updated pediatric study plan. That PPSR is currently under review. The Applicant may decide not to pursue the PPSR if the timing for when the approval of NDA 22063 and the pediatric exclusivity do not align.

Therefore, a PMR to formulate a 6.25mg dose and to evaluate its safety and efficacy in the 4 to 5 year old preschool population is important. Additionally, we will require a PMR to evaluate the 6.25mg dose of SHP465 for the 6 to 12 year old ADHD population. In Section 7.2.1, I will discuss my concerns about the plasma concentration levels of the pediatric patients compared to adults receiving SHP465 12.5mg.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

SHP465 (proposed trade name: Mydayis) is an extended-release capsule of mixed salts of a single-entity amphetamine. It was previously known as SPD465. It is an oral product comprised of four amphetamine salts: dextro- and levoamphetamine sulfate, dextroamphetamine saccharate, and amphetamine aspartate monohydrate. The ratio of *d*- to *l*- isomers is three to one (3:1). The extended-release capsule contains three types of drug-releasing beads, which provide immediate-release, pulsatile delayed-release, and delayed, extended-release of the mixed amphetamine salts. The mixed salts of a single-entity amphetamine are the same active ingredient in Adderall XR. SHP465 is intended to last for sixteen hours.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

All of the drug products listed below are approved for ADHD in children over 6 years old, adolescents, and adults.

**Table 1: Drugs approved for attention deficit hyperactivity disorder**

| **Stimulants** | **Non-stimulant** |
|---|---|
| Drug name | Drug name |
| amphetamine | atomoxetine |
| mixed salts of a single-entity amphetamine | clonidine |
| dextroamphetamine | guanfacine |
| dexmethylphenidate | |
| lisdexamfetamine | |
| methylphenidate | |

[Source: Reviewer created]

## 2.3 Availability of Proposed Active Ingredient in the United States

Currently, the active ingredients in SHP465, mixed salts of a single-entity amphetamine, are available under the trade name Adderall and Adderall XR. Both formulations are approved for the treatment of ADHD in children, adolescents, and adults.

## 2.4 Important Safety Issues With Consideration to Related Drugs

The stimulants for the treatment of ADHD have class warnings that are applicable to SHP465. The boxed warning about abuse and dependence of stimulants warns about choosing patients who are less likely to abuse stimulants. The class warnings about serious cardiovascular reactions, including sudden death, are applicable, especially to adult patients. The warnings about heart rate increases are relevant to both pediatric patients and adults for SHP465. The class warning for seizure was not present in newly approved extended-release amphetamines; however, based on clinical trial data for SHP465, the seizure warning will be present in this label. Finally, the class warning about growth suppression is applicable to pediatric patients, as weight loss and decreased appetite was prominent in the Phase 3 SHP465 pediatric trial.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

*Regulatory History of IND 066329*

- December 4, 2002: SPD465 was submitted as an Investigational New Drug (IND) 066329. No clinical holds were placed during the IND Phases of clinical development program.
- November 18, 2003: Shire met with the Agency on to discuss Phase 2 and Phase 3 development of SHP465 (formerly named SPD465). Three points were agreed to at that meeting.
    - Shire may seek approval for four dosing strengths (12.5, 25, 37.5, and 50mg) with the initial NDA submission, (b) (4)
    - (b) (4)
    - Further, the Agency informed Shire that a Pediatric Written Request for adolescents aged 13 to 17 would not be issued, following advice from the Office of Counter Terrorism and Pediatric Drug Development that SHP465 would not provide a significant public health benefit over existing therapies.
- November 11, 2004: The Agency issued a letter in response to a Special Protocol Assessment on study SHP465-301. The proposed (b) (4) .

- November 18, 2005: Shire met with the Agency regarding the clinical implications of changes to the formulation of SHP465 that were needed to limit the size of the capsules below size (b) (4) capsules. Size (b) (4) capsules (b) (4) . Hence, Shire reported that an additional Phase 2 study, Study SHP465-203, would establish the duration of effect in adults with the intended market formulation at the 25mg strength. The Agency agreed that duration of effect at the 25mg dose would translate to higher dose strengths.
- March 8, 2006: At a pre-NDA meeting, the Agency stated we would allow for consideration of a 14- to 16-hour duration of effect labeling claim for the adult dose ranges of 12.5mg to (b) (4) if the claim was supported by the data submitted to the NDA.

*Regulatory History of the Original NDA (022063)*

- July 21, 2006: The original NDA 022063 was submitted to FDA and filed September 5, 2006.
- August 29, 2006, September 7, 18, 29, 2006, October 9, 2006, November 9, 14, 17, 29, 2006, January 22, 31, 2007, March 7, 2007 and April 10 and 27, 2007: Dates of amendments submitted to NDA 022063.
- April 2007: Shire sought a PREA partial waiver from pediatric studies for children less than age 12 as "clinicians are not likely to prescribe SHP465 in children 12 years of age and below due to the long duration of effect, potentially leaving younger children to stay awake past their bedtime." (Source: FDA Clinical Review April 15, 2007)
- May 18, 2007: The Agency issued an Approvable letter for original NDA 022063. The following major issues were outstanding:
    a. Clinical Pharmacology dissolution studies must be completed according to certain specifications.
    b. The Division of Medication Error Prevention and Analysis (DMEPA) was concerned with Adderall XR and SHP465 having the same established name and asked Shire to plan an educational campaign to discern the 12-hour product from the 16-hour product.
    c. Update the Periodic Safety Report with cases of abuse, misuse, and diversion.
    d. Revised draft labeling did not include the proposed 37.5 mg and 50 mg strengths because the Agency stated there was no additional efficacy at these higher doses and there were additional adverse events associated with these higher doses. However if new information relating to the safety or effectiveness of SHP465 becomes available, revision of the labeling may be required.
    e. Postmarketing Commitment for studying (b) (4)
    f. Postmarketing Commitment for studying (b) (4)

- May 24, 2007: Shire submitted a notice of intent to file an amendment to support approval but did not progress this activity further due to a business decision.

*Regulatory History of Class 2 Resubmission of NDA 022063*

- April 25, 2014: The Agency provided Written Responses Only (WRO) comments in which they classified Shire's response to the SHP465 2007 Approvable Letter as a Class 2 resubmission of the original NDA 022063.
- Items addressed from the May 18, 2007, Approvable letter:
  a. Dissolution studies completed.
  b. Agreement on the educational plan for discerning between the three formulations of mixed salts of single-entity amphetamine (i.e., Adderall, Adderall XR, and the proposed product, Mydayis).
  c. Agreement on a voluntary risk management plan (not a REMS) to address abuse, misuse, and diversion.
  d. Agreement on Shire's proposed study SHP465-306 to address safety and efficacy of 12.5, 25, 37.5, and 50mg doses in adults. (b) (4)
  e. (b) (4) After seven years since the 2007 Approvable letter, the Agency already has data on cardiovascular risk of amphetamines.
- August 4, 2014: A teleconference was held to discuss SHP465 and the need for pediatric premarketing studies before making a Class 2 resubmission.
- June 17, 2015: The Agency issued meeting minutes from the cancelled June 8, 2015, Type C meeting. There was final agreement on the Phase 3 study in adults (Study SHP465-306) and discussion of pathways for NDA resubmission.
- July 27, 2015: WRO comments issued to Shire regarding adequacy of the abuse potential evaluation.
- February 13, 2016: WRO comments issued to Shire's questions regarding the effects of alcohol on the bioavailability of the drug product, studies comparing the pharmacokinetics of several dosages of SHP465 and Adderall XR to clarify the recommended dose range and abuse potential, and additional product stability data for 48 months and less to address concerns about the dose range proposal planned for NDA resubmission.
- July 14, 2016: A Type C meeting was held to obtain the Agency's concurrence on the presentation and content of the NDA resubmission.
- December 20, 2016: Shire resubmitted NDA 22063; a 6-month review clock started.
- January 17, 2017: The Agency issued an acknowledgment letter of the Class 2 NDA resubmission.

*Proprietary Name*

Shire's original NDA submission contained a proposed trade name (b) (4). The NDA resubmission and formal Proprietary Name Request for Review dated January 17, 2017, contains a different proposed trade name, Mydayis. The trade name Mydayis is acceptable to DMEPA.

See Section 2.6 for a table of studies submitted and reviewed under the original NDA 22063. The Applicant submitted seven Phase 1 studies in adults; three Phase 2 studies, one in adolescents (SHP465-202) and two in adults; and three Phase 3 trials in adults.

This review will concentrate on the two new Phase 3 trials in the December 20, 2016, resubmission.

## 2.6 Other Relevant Background Information

**Table 2: Studies Reviewed in Original NDA July 2006**

| Type of Study | Study ID | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | No. of Subjects Enrolled | Healthy Subjects or Diagnosis | Duration of Tx |
|---|---|---|---|---|---|---|---|
| BA/BE | 101 | Assess PK profiles and bioequivalence of 3 SHP465 delayed- release (DR) bead prototypes vs. ADDERALL | Phase 1, randomized, open- label, 4-way crossover, 4 periods | •SHP465 12.5 mg 1×12.5 mg DR bead prototype 1,1×12.5 mg DR bead prototype 2,1×12.5 mg DR bead prototype 3 •1×10 mg (tablet) ADDERALL l Capsule, oral Pilot formulation | 12 | Healthy Adults (fasting) | 4 single doses (Periods 1-4; 7-day washout between periods) |
| BA/BE | 102 | Assess PK profiles of 3 SHP465 DR composite formulations vs. ADDERALL XR Safety, tolerability, effect of food on bioavailability | Phase 1, randomized, open- label, 4-way crossover, 5 periods | •1×20 mg ADDERALL XR and 2×5 mg Capsule C (fed) •1×15 mg Capsule A and 3×5 mg Capsule C (fed) •1×15 mg Capsule B and 3×5 mg Capsule C (fed) •1×20 mg ADDERALL XR followed by 1×10 mg ADDERALL 8 h later Capsule, oral Pilot formulation | 20 | Healthy Adults 18-55 years, inclusive | 5 single doses (Periods 1-4 fed; Period 5 fasted; 7-day washout between periods) |

| Type of Study | Study ID | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | No. of Subjects Enrolled | Healthy Subjects or Diagnosis | Duration of Tx |
|---|---|---|---|---|---|---|---|
| PK | 103 | Assess PK profile vs. ADDERALL XR<br>Safety | Phase 1, randomized, open-label, single-dose, 2-treatment crossover 2 periods | •SHP465 37.5 mg 1×37.5 mg (fasted)<br>•1×25 mg ADDERALL XR (fasted) followed by 1×12.5 mg MAS IR 8 h later<br>Capsule, oral<br>Intended to market formulation | 20 | Healthy Adults 18-55 years, inclusive | 2 single doses (Periods 1,2; 7-day washout between periods) |
| BA | 105 | Assess the effect of a high-fat meal on bioavailability relative to fasted state<br>Safety and tolerability | Phase 1, randomized, open-label, 3-way crossover 3 periods | •SHP465 50 mg 1×50 mg (fasted), 1×50 mg (fed high fat meal),1×50 mg (fasted, sprinkled 1 tbsp applesauce) Capsule, oral<br>Intended to market formulation | 16 | Healthy Adults 18-55 years, inclusive | 3 single doses (Periods 1-3; 7-day washout between periods) |
| PK | 106 | Assess dose proportionality<br>Safety and tolerability | Phase 1, open-label, single-ascending doses, 4 periods | •SHP465 12.5-75 mg 1×12.5 mg,1×37.5 mg,1×50 mg, 1×75 mg<br>Capsule, oral<br>Intended to market formulation | 28 | Healthy Adults 18-55 years, inclusive | Single dose (4 planned periods, 7-day washout between periods) |

| Type of Study | Study ID | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | No. of Subjects Enrolled | Healthy Subjects or Diagnosis | Duration of Tx |
|---|---|---|---|---|---|---|---|
| PK | 107 | Assess PK and dose proportionality following repeat-dose administration<br>Safety and tolerability | Phase 1, open-label, incomplete block randomization 4-treatment, dose escalating<br>3 periods | •SHP465 12.5-75 mg<br>1×12.5 mg,1×25 mg,1×50 mg, 1x75 mg<br>Period 1: SHP465 12.5 mg/day for 7 days<br>Period 2: SHP465 25 mg/day for 7 days or SHP465 50 mg/day for 7 days<br>Period 3: SHP465 75 mg/day for 7 days<br>Capsule, oral<br>Intended to market formulation | 20 | Healthy Adults<br>18-55 years, inclusive | 21 days (three 7- day dosing periods) |
| PK | 110 | Assess PK and dose proportionality following repeat-dose administration<br>Safety and tolerability | Phase 1, open-label, incomplete block randomization<br>4-treatment,<br>dose escalating<br>3 periods | •SHP465 12.5-75 mg<br>1×12.5 mg, 1×25 mg,<br>1×50 mg, 1×75 mg<br>Period 1: SHP465 12.5 mg/day for 7 days<br>Period 2: SHP465 25 mg/day for 7 days or SHP465 50 mg/day for 7 days<br>Period 3: SHP465 75 mg/day for 7 days<br>Capsule, oral<br>Intended to market formulation | 18 | Healthy adults<br>18-55 years, inclusive | 21 days<br>(three<br>7-day dosing periods) |

| Type of Study | Study ID | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | No. of Subjects Enrolled | Healthy Subjects or Diagnosis | Duration of Tx |
|---|---|---|---|---|---|---|---|
| PD, Efficacy | 201 | Assess the duration of efficacy (DOE) vs. placebo and immediate-release amphetamine formulation (AMPH IR) Safety | Phase 2, randomized, double-blind, placebo and active-controlled, 3-treatment arm crossover 3 periods | •SHP465 25-75 mg 1×25 mg (Days 1-3) then 2×25 mg (Days 4-7) OR 1×37.5 mg (Days 1-3) then 2×37.5 mg (Days 4-7) •AMPH-IR 2×12.5 mg (Days 1-7) •2×Placebo (Days 1-7) Capsule, oral R&D formulation | 86 | Adults 18-55 years, inclusive with ADHD | 3 weeks |
| PD, Efficacy | 202 | Assess DOE vs. placebo and AMPH IR Safety | Phase 2, randomized, double-blind, placebo and active-controlled, 3-treatment crossover 3 periods | •SHP465 25 or 50 mg 1×25 mg (Days 1-7) OR 1×25 mg (Days 1-3) then 2×25 mg (Days 4-7) •AMPH-IR 1×12.5 mg (Days 1-7) •Placebo (Days 1-7) Capsule, oral R&D formulation | 84 | Adolescents13 to 17 years, inclusive with ADHD | 21 days (three 7-day periods) |
| PD, Efficacy | 203 | Assess DOE Safety | Phase 2, randomized, double-blind, placebo-controlled, 2-treatment crossover 2 periods | •SHP465 25 mg 1×25 mg (Days 1-7) •1×Placebo (Days 1-7) Capsule, oral Intended to market formulation | 79 | Adults 18-55 years, inclusive with ADHD | 2 weeks (two 7-day dosing periods) |

| Type of Study | Study ID | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | No. of Subjects Enrolled | Healthy Subjects or Diagnosis | Duration of Tx |
|---|---|---|---|---|---|---|---|
| Efficacy | 301 | Short term; Efficacy and Safety | Phase 3, randomized placebo-controlled, parallel-group stepwise dose optimization | •SHP465 12.5-75 mg 1×12.5 mg, 1×25 mg, 1×37.5 mg, 1×50 mg, 1×62.5 mg and 2×37.5 mg (Days 1-7)<br>•2×Placebo (Days 1-7) Capsule, oral<br>Intended to market formulation | 274 (137 SHP465, 137 placebo) | Adults 18-55 years, inclusive with ADHD | 7 weeks |
| Efficacy | 303 | Short term; Efficacy & Safety | Phase 3, randomized, double-blind, placebo-controlled, parallel-group, forced dose titration | •SHP465 25-75 mg 1×25, 1×37.5, 1×50, 2×37.5 mg daily<br>•2×Placebo daily<br>Capsule, oral<br>Intended to market formulation | 412 (308 SHP465, 104 placebo) | Adults 18-55 years, inclusive with ADHD | 6 weeks |
| Efficacy | 304 | Long term; Efficacy & Safety | Phase 3, Open-label | •SHP465 12.5-75 mg 1×12.5, 1×25, 1×37.5, 1×50, 2×37.5 mg daily<br>Capsule, oral<br>Intended to market formulation | 505 (324 SHP465, 181 placebo) | Adults 18-55 years, inclusive with ADHD | 12 months |

(Source: Derived from 5.2 Tabular Listing of Clinical Studies, Table 1, pages 1-6)

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

This NDA resubmission was submitted in Electronic Common Technical Document (eCTD) format. All sections/modules appear complete. The submission was reasonably well organized and paginated to allow for an acceptable review. Subject unique identifiers are not duplicated in the patient data, indicating data integrity.

## 3.2 Compliance with Good Clinical Practices

The clinical trials in the NDA resubmission, SHP465-111, 305, and 306, were monitored by an external Contract Research Organization (CRO) according to the principles of Good Clinical Practice (GCP).

The Office of Scientific Investigations (OSI), Division of Clinical Compliance Evaluation, inspected four clinical investigation sites. The sites were chosen based on the high numbers of INDs (20 to 60) for each investigator and high enrollment of subjects in studies SHP465-306 and 305. None of the four investigators had deviations from regulations. OSI concluded that Drs. Murphy, Greenbaum, Arnold, and Weisler adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. Table 3 includes detailed information on the clinical investigators and sites.

**Table 3: Inspection of Four Clinical Sites**

| Name of Clinical Investigator Address, Site # | Protocol # and Subject # | Inspection Date | Classification |
|---|---|---|---|
| William R. Murphy, M.D.<br>4601 W. 109th Street, Suite 208<br>Overland Park, KS 66211<br>SHP465-305 (Site #2)<br>SHP465-306 (Site #101) | SHP465-305<br>13 randomized<br><br>SHP465-306<br>9 randomized | 3/15/2017 to 3/21/2017 | Preliminary classification: NAI |
| Michael Greenbaum, M.D.<br>Capstone Clinical Research<br>1880 W. Winchester Road, Suite 204<br>Libertyville, IL 60048<br>SHP465-305 (Site #9)<br>SHP465-306 (Site #102) | SHP465-305<br>7 randomized<br><br>SHP465-306<br>11 randomized | 04/19/2017 to 04/26/2017 | Preliminary classification: NAI |

| Name of Clinical Investigator Address, Site # | Protocol # and Subject # | Inspection Date | Classification |
|---|---|---|---|
| Valerie Arnold, M.D.<br>Clinical Neuroscience Solution, INC<br>6401 Poplar Avenue, Suite 420<br>Memphis, TN 38119<br>SHP465-305 (Site #13)<br>SHP465-306 (Site #120) | SHP465-305<br>8 randomized<br><br>SHP465-306<br>12 randomized | 3/13/2017<br>to<br>3/15/2017 | NAI |
| Richard H. Weisler, M.D.<br>PA & Associates<br>700 Spring Forest Rd., Suite 125<br>Raleigh, NC 27609<br>SHP465-306 (Site #137) | SHP465-306<br>6 randomized | 01/30/2017<br>to<br>02/03/2017 | Preliminary classification: NAI |

### 3.3 Financial Disclosures

The Applicant certified that 467 clinical investigators did not have financial arrangements with Shire, nor were Shire employees. The six clinical investigators with financial disclosures were all related to grants, equipment compensation, retainer, or honoraria received from Shire after February 2, 1999.

The Applicant reports that study design of double-blind, randomized, placebo-controlled helped minimize potential bias. Additionally, the protocols and investigators were reviewed by the Institutional Review Board prior to study initiation.

See Appendix Section 9.4 for the completed Clinical Investigator Financial Disclosure review template. There are no concerns about investigators and financial disclosure.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The Office of Pharmaceutical Quality made an approval recommendation regarding SHP465.

The naming convention for the established name of SHP465 was clarified for the label by the chemistry reviewer. It is Mydayis (mixed salts of a single-entity amphetamine extended release capsule), for oral use, CII.

## 4.2 Clinical Microbiology

No new clinical microbiology data was submitted with this NDA.

## 4.3 Preclinical Pharmacology/Toxicology

No new preclinical data was submitted with this NDA.

## 4.4 Clinical Pharmacology

Dissolution studies from the May 18, 2007, Approvable letter were completed and submitted.

This NDA resubmission contains a new pediatric (6 to 17 years) pharmacokinetic (PK) study, SHP465-111. See Section 5.3.

### 4.4.1 Mechanism of Action

Amphetamines are in the pharmacological class of central nervous system stimulants. Although the precise mechanism of action of amphetamines in humans remains unknown, animal and in vitro studies have shown that amphetamines act via presynaptic release of dopamine and noradrenergic amines in the presynaptic neuron, leading to an increase intrasynaptic concentration of the amines. The net result is increased noradrenergic activity and dopaminergic activity in the brain leading to its desired CNS effects of increased attention, as well as increased alertness and anorexia. (Mark Ritter, 2007)

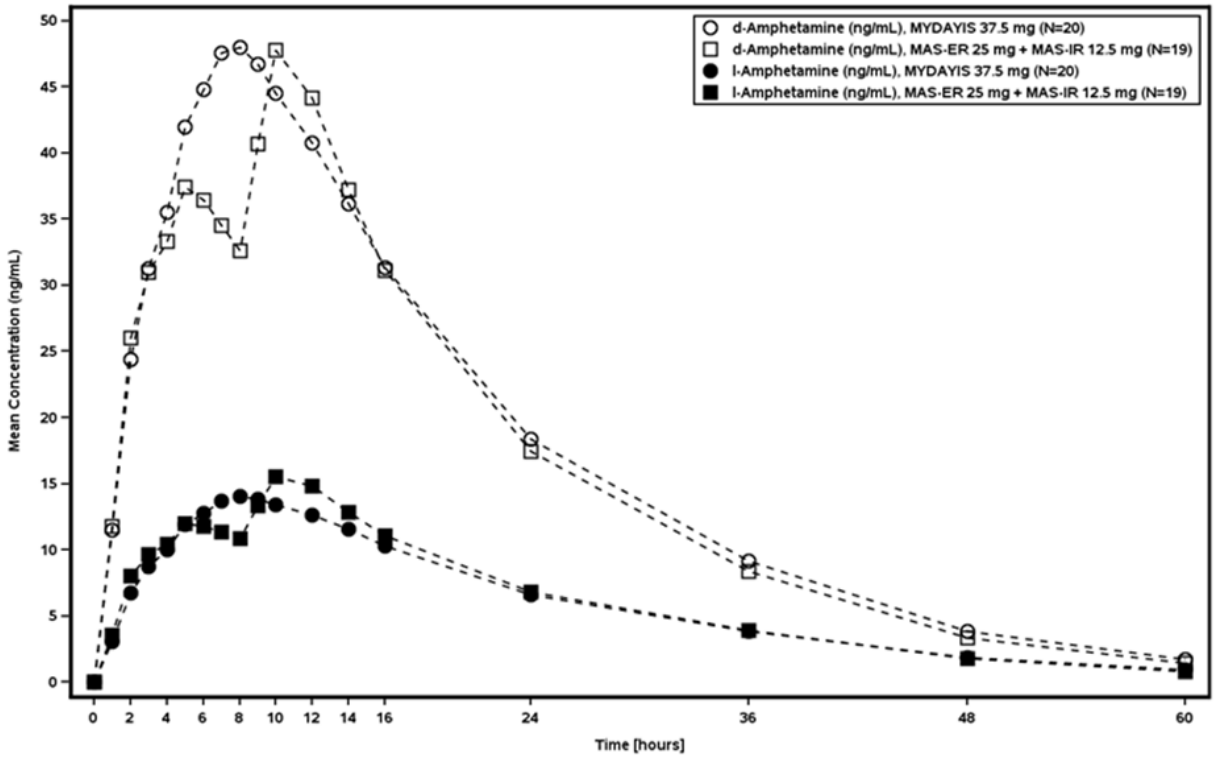
### 4.4.2 Pharmacodynamics

Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The result of increased noradrenergic release leads to an increase in sympathetic tone to various organs and body systems. Amphetamine use increases sympathetic tone to the cardiovascular system (i.e., increase alpha 1 activity-vasoconstriction; increased beta 1-activtiy-increased heart contractility, chronotropic and bathmotropic effects).

### 4.4.3 Pharmacokinetics

Both in adults and pediatric patients, SHP465 has plasma levels which mimic the *d*- and *l*- amphetamine pharmacokinetics (PK) levels from an eight-hour extended release capsule (Adderall XR) followed by four-hour immediate release tablet (Adderall). See Figure 1 for the SHP465 25mg and 37.5mg. The dose proportionality is linear; therefore, the 12.5mg and 25mg doses in pediatric patients have a similar area under the curve (AUC).

**Figure 1: Mean plasma concentrations of 37.5mg in adults of d- and l-amphetamine 16-hour capsule compared to 8-hour capsule + 4-hour tablet**




(Source: Draft Labeling Text submitted 12/20/16 to NDA 22063)

For additional information, refer to the Clinical Pharmacology Review for this NDA.

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

The following table summarizes the studies providing clinical data in support of this application.

**Table 4: Trial Summary for Studies in NDA 22063 Resubmission**

| Type of Study | Study ID | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | No. of Subjects Enrolled | Healthy Subjects or Diagnosis | Duration of Tx |
|---|---|---|---|---|---|---|---|
| PK | 111 | Evaluate the PK of *d*-amphetamine and *l*-amphetamine Safety and tolerability | Phase 1, open-label, single-dose | •SHP465 12.5-25 mg<br>Children 6-12 years<br>1×12.5 mg<br>Adolescents 13-17 years<br>1×25 mg<br>Capsule, oral<br>Intended to market formulation | 28 | Children and adolescents 6-17 years with ADHD | Single dose |
| Efficacy | 305 | Efficacy, safety, and tolerability | Phase 3, randomized, double-blind, placebo-controlled, dose titration | •SHP465 12.5-25 mg<br>1×12.5, 1×25 mg daily<br>•1×Placebo daily<br>Capsule, oral<br>Intended to market formulation | 263 (132 SHP465; 131 placebo) | Children and Adolescents 6-17 Years with ADHD | 4 weeks |
| Efficacy | 306 | Efficacy, safety, and tolerability | Phase 3, randomized, double-blind, parallel-group, placebo-controlled, forced-dose titration<br>4 periods | •SHP465 12.5-37.5 mg daily<br>1×12.5 mg,<br>1×37.5 mg (12.5 mg Week 1, 1×25 mg Week 2, and 1×37.5 mg Weeks 3-4).<br>•1×Placebo daily<br>Capsule, oral<br>Intended to market formulation | 275 (184 SHP465; 91 placebo) | Adults 18-55 years, inclusive with ADHD | 4 weeks |

(Source: Derived from 5.2 Tabular Listing of Clinical Studies, Table 1, pages 1-6)

## 5.2 Review Strategy

This review focuses on the safety and efficacy of the two Phase 3 trials in the NDA resubmission.

The adult efficacy data is primarily from the Phase 3 adult study, SHP465-306. The adult safety data was pooled from studies SHP465-301, 303, and 306. The adult indication is also supported by short and long-term data from studies SHP465-301, 303, and 304, submitted to and reviewed in the original NDA.

The pediatric efficacy and safety data for ages 6-12 years and 13-17 years is derived from the Phase 3 pediatric study, SHP465-305.

## 5.3 Discussion of Individual Studies/Clinical Trials

As displayed in Section 5.1, Table 3, three new clinical trial study reports were in the NDA resubmission.

The pediatric pharmacokinetic (PK) study, SHP465-111, was a single-dose study but provided no efficacy or safety data. No serious adverse events or deaths occurred during the PK study. Overall, 27 subjects of 28, completed the study. One subject (Subject 001-1005) was withdrawn from the study due to inability to establish an indwelling catheter; this subject was not included in the PK analysis set due to insufficient and interpretable primary PK data.

See Review of Efficacy in Section 6 and Review of Safety in Section 7 for information on Studies SHP465-305 and 306.

# 6 Review of Efficacy

***Efficacy Summary Studies SHP465-306 and SHP465-305***

Mixed salts of a single-entity amphetamine are known to be 80% effective for the treatment of attention deficit hyperactivity disorder (Stein, 2011). The immediate release version of the drug entity was approved in 1960 and the extended release capsule (Adderall XR) was approved in 2001. Both dosage forms are approved for adults and pediatric patients (6 to 17 years). Shire developed SHP465 using the same ratio of mixed salts of a single-entity amphetamine combined in a sixteen-hour extended release capsule.

Unsurprisingly, SHP465 demonstrated robust efficacy in both the adult and pediatric populations. The NDA resubmission contained new clinical data in studies SHP465-306 and 305. In adults, Study SHP465-306, the reduction from baseline in Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) with prompts total score was significantly greater in the SHP465 12.5 mg and the SHP465 37.5 mg treatment groups compared with the placebo treatment group ($p<0.001$). In pediatric patients, Study SHP465-305, the reduction from baseline in Attention Deficit Hyperactivity Disorder Rating Scale, DSM-IV version (ADHD-RS-IV) total score was significantly greater in the SHP465 treatment group (12.5 or 25 mg) compared with the placebo treatment group ($p<0.001$).

*Dosage Strengths*
In the NDA resubmission dating December 20, 2016, Shire proposes labeling claims for SHP465 in the following dose strengths: 12.5, 25, 37.5, and 50mg. The efficacy of SHP465 50mg was evaluated in Phase 3 trials in adults (SHP465-301 and 303). Those studies were reviewed in the 2006 original NDA by Dr. Mark Ritter. The 50mg dose demonstrated efficacy over placebo.

According to the original NDA clinical reviewer, study SHP465-303 evaluated dose response, including the 50mg and 75mg strengths. In that study, the 75mg dose was not clearly superior for the treatment of adult ADHD symptoms. Additionally, the 75mg arm had many subject dropouts, presumably due to adverse events. Hence, the Agency required Shire to evaluate a new lower dose in adults (i.e., 12.5mg in study SHP465-306).

I agree with Shire's decision (b) (4)

## 6.1 Indication

The proposed indication for SHP465 is for the treatment of ADHD in patients 6 years and older.

### 6.1.1 Methods

Both 4-week efficacy trials were adequately designed.

*Objectives*
The primary objective of both studies, SHP465-306 and 305, was to evaluate the efficacy of each SHP465 dose administered daily at 7:00 (± two hours) in the morning compared to placebo in the treatment of adults (18-55 years of age) or pediatric patients

(6-17 years of age) diagnosed with attention-deficit hyperactivity disorder. The primary measure of efficacy was the clinician administered ADHD Rating Scale (ADHD-RS).

The key secondary objective of both studies, SHP465-306 and 305, was to evaluate the efficacy of each SHP465 dose compared to placebo using a global clinical measure of improvement, the Clinical Global Impression –Improvement (CGI-I).

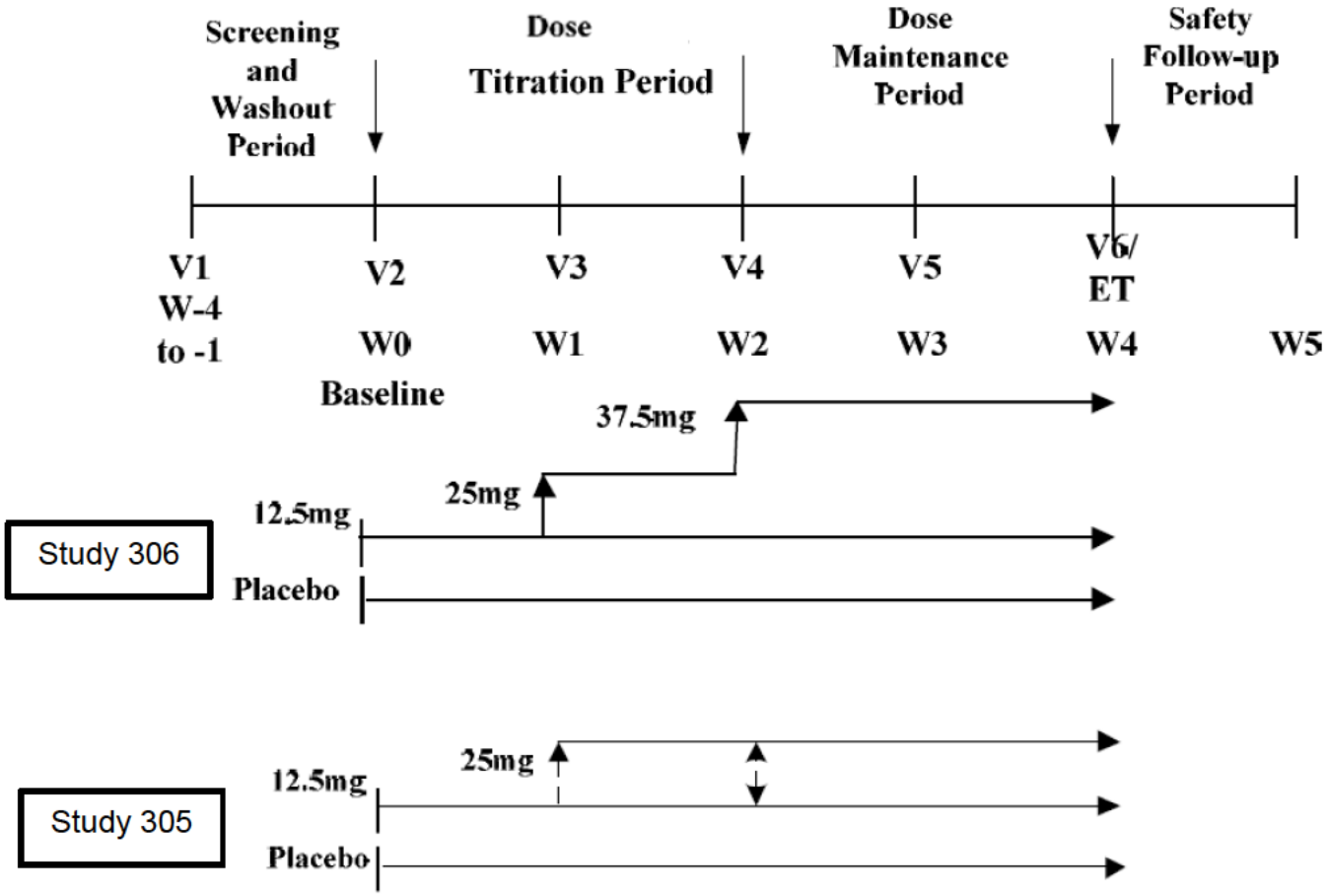
*Design of Study SHP465-306*
The Phase 3, randomized, double-blind, multicenter, placebo-controlled, forced-dose titration, safety and efficacy study of SHP465 in adults aged 18-55 years with ADHD took place in 43 centers in the United States.

The four-week study consisted of four periods: Screening and washout, forced-dose titration (two weeks), dose maintenance (two weeks), and safety follow-up. The patients were randomized to 12.5mg group, forced-dose titration group up to 37.5mg, or placebo. See Figure 2 for a design flow diagram.

*Design of Study SHP465-305*
The Phase 3, randomized, double-blind, multi-center, placebo-controlled, dose-optimization, safety and efficacy study of SHP465 in children and adolescents aged 6-17 years with ADHD took place in 36 centers in the United States.

The four-week study consisted of four periods: Screening and washout, dose optimization (two weeks), dose maintenance (two weeks), and safety follow-up. The patients were randomized to SHP465 or placebo. Randomization was stratified to facilitate balance of treatment allocation within each age group (6-12 years and 13-17 years). In the SHP465 group, the starting dose was 12.5mg and increased to 25mg. See Figure 2 for a design flow diagram.

**Figure 2: Study Design Flow Chart (SHP465-306 and 305)**




(Source: Derived from 5.3.5.1 Protocols for SHP465-306 and 305)

*Study Population SHP465-306*

Key inclusion criteria:

- Met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for ADHD
- Baseline score (at Visit 2) of ≥ 28 on the adult ADHD-RS with prompts (total score).
- 18 to 55 years of age
- Satisfactory medical assessment without clinically significant or relevant abnormalities
- Minimum level of intellectual functioning as determined at screening (Visit 1)

Key exclusion criteria:

- Significant comorbid Axis I or Axis II psychiatric diagnoses as established by the Mini-International Neuropsychiatric Interview (MINI)
- Risk for suicide as judged by investigator

- History of substance abuse or dependence disorder
- Body Mass Index (BMI) of <18.5 kg/$m^2$ or ≥ 40 kg/$m^2$
- Chronic or acute illness or condition that could confound the safety assessment results. (Mild, stable asthma was not excluded)
- History of seizure disorder other than febrile seizures or current tic disorder
- Hypertension with systolic blood pressure >139 mmHg or average sitting diastolic blood pressure >89 mmHg. (Well-controlled mild hypertension treated by a single antihypertensive agent was not excluded)
- Known history or family history of various cardiovascular diseases, including arrhythmia
- Previous failure to respond to amphetamine
- Sedating antihistamines, decongestant sympathomimetics and monoamine oxidase inhibitors were excluded

*Study Population SHP465-305*
Key inclusion criteria:

- Met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for ADHD
- Baseline score (at Visit 2) of ≥ 28 on the ADHD-RS-IV total score.
- 6 to 17 years of age
- Currently not taking ADHD therapy or was not completely satisfied with any aspect of their current ADHD therapy.

Key exclusion criteria:

- Significant comorbid Axis I or Axis II psychiatric diagnoses
- Comorbid DSM-IV-TR diagnosis of conduct disorder
- Risk for suicide as judged by investigator
- History of seizure disorder other than febrile seizures or current tic disorder
- Sedating antihistamines, decongestant sympathomimetics and monoamine oxidase inhibitors were excluded

### 6.1.2 Demographics

*Study SHP465-306:*
The demographic data on the adult study population is generalizable to the ADHD population. There were 152 males and 123 females who completed the study (275 total). The patients in Study SHP465-306 were evenly distributed among treatment groups. There were 80 subjects (89.9%) in the placebo treatment group, 80 subjects (87.0%) in the SHP465 12.5mg treatment group, and 76 subjects (84.4%) in the SHP465 37.5mg treatment group who completed the study. The race and ethnicity distribution mimics the ADHD population, with Caucasian/white being most prominent. See Table 5.

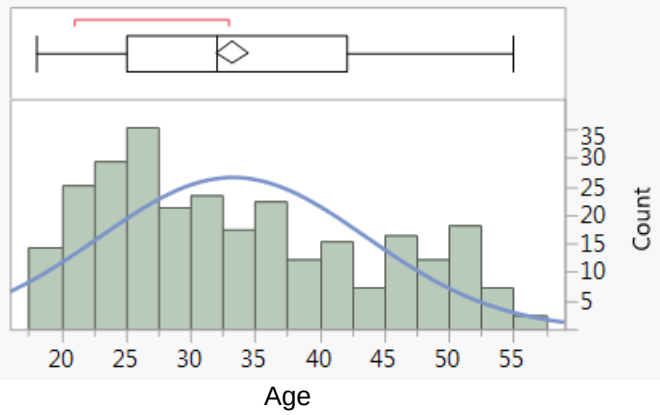
The normal distribution of age was 33.3 years, which appears reasonable (see Figure 3 and Table 5). Table 6 contains weight, height, and body mass index means, which are also generalizable to the adult ADHD population.

**Table 5: Subject demographics in adults (SHP465-306) #1**

| | PLACEBO | | SHP465 12.5mg | | SHP465 37.5mg | |
|---|---|---|---|---|---|---|
| **SEX** | **N** | **% of Total** | **N** | **% of Total** | **N** | **% of Total** |
| F | 47 | 17.09% | 35 | 12.73% | 41 | 14.91% |
| M | 44 | 16.00% | 57 | 20.73% | 51 | 18.55% |
| **RACE** | | | | | | |
| AMERICAN INDIAN OR ALASKA NATIVE | 2 | 0.73% | 0 | 0.00% | 1 | 0.36% |
| ASIAN | 2 | 0.73% | 1 | 0.36% | 4 | 1.45% |
| BLACK OR AFRICAN AMERICAN | 6 | 2.18% | 10 | 3.64% | 7 | 2.55% |
| MULTIPLE | 5 | 1.82% | 4 | 1.45% | 4 | 1.45% |
| NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER | 1 | 0.36% | 1 | 0.36% | 1 | 0.36% |
| OTHER | 0 | 0.00% | 0 | 0.00% | 2 | 0.73% |
| WHITE | 75 | 27.27% | 76 | 27.64% | 73 | 26.55% |
| **ETHNIC** | | | | | | |
| HISPANIC OR LATINO | 14 | 5.09% | 10 | 3.64% | 12 | 4.36% |
| NOT HISPANIC OR LATINO | 77 | 28.00% | 82 | 29.82% | 80 | 29.09% |

(Source: Reviewer-created from Tabulation STDM Data, Study SHP465-306)

**Figure 3: Age Distribution**




(Sources: Reviewer-created from Tabulation STDM Data, Study SHP465-306)

**Table 6: Subject demographics in adults (SHP465-306) #2**

| | PLACEBO Mean (SD) | SHP465 12.5mg Mean (SD) | SHP465 37.5mg Mean (SD) |
|---|---|---|---|
| **AGE (years)** | 34.5 (11) | 33.0 (10) | 32.0 (10) |
| **WEIGHT (kg)** | 82.8 (17) | 84.4 (19) | 83.9 (21) |
| **HEIGHT (cm)** | 171.6 (11) | 173.1 (10) | 173 (12) |
| **BMI (kg/m2)** | 28.1 (5) | 27.9 (5) | 27.8 (6) |

(Source: Derived 5.3.5.1 Study Report SHP465-306, page 61)

*Study SHP465-305*

The demographic data of the 264 subjects in the pediatric study population (6 to 17 years) is generalizable to the ADHD population. Both treatment groups were balanced regarding gender and race (see Table 7). For ethnicity, there were 213 subjects identifying themselves as Non-Hispanic or Latino and 51 Hispanic or Latino subjects.

Table 8 includes weight, height, and body mass index, which appear generalizable to the pediatric ADHD population. The age groups were fairly balanced among treatments, but there were more subjects in the 13 to 17 year old group (N=78), than the 6 to 12 age group (N=54).

**Table 7: Subject demographics in pediatric patients by age group (SHP465-305) #1**

| | Placebo | | | | SHP465 | | | |
|---|---|---|---|---|---|---|---|---|
| | AGEGR1 | | | | AGEGR1 | | | |
| | Age Group=13-17 years | | Age Group=6-12 years | | Age Group=13-17 years | | Age Group=6-12 years | |
| **SEX** | **N** | **% of Total** | **N** | **% of Total** | **N** | **% of Total** | **N** | **% of Total** |
| F | 32 | 9.79% | 28 | 8.56% | 53 | 16.21% | 31 | 9.48% |
| M | 38 | 11.62% | 18 | 5.50% | 54 | 16.51% | 73 | 22.32% |
| **RACE** | | | | | | | | |
| BLACK OR AFRICAN AMERICAN | 8 | 2.45% | 4 | 1.22% | 25 | 7.65% | 21 | 6.42% |
| MULTIPLE | 6 | 1.83% | 4 | 1.22% | 7 | 2.14% | 16 | 4.89% |
| OTHER | 1 | 0.31% | 1 | 0.31% | 4 | 1.22% | 3 | 0.92% |
| WHITE | 55 | 16.82% | 37 | 11.31% | 71 | 21.71% | 64 | 19.57% |

(Source: Reviewer-created from Analysis Dataset Adam, ADAE, Study SHP465-305)

**Table 8: Subject demographics in pediatric patients by age group (SHP465-305) #2**

| | 6 to 12 years (N= 54) | | 13 to 17 years (N=78) | |
|---|---|---|---|---|
| | **PLACEBO** Mean (SD) | **SHP465** Mean (SD) | **PLACEBO** Mean (SD) | **SHP465** Mean (SD) |
| **AGE (years)** | 9.1 (2) | 9.1 (2) | 14.7 (2) | 14.7 (1) |
| **WEIGHT (kg)** | 41.6 (12) | 36.5 (11) | 62.0 (15) | 59.5 (13) |
| **HEIGHT (cm)** | 142.1 (12) | 139.7 (11) | 164.8 (11) | 164.7 (10) |
| **BMI (kg/m2)** | 20.2 (3) | 18.3 (3) | 22.5 (4) | 21.8 (3) |

(Source: Reviewer-created from Analysis Dataset Adam, ADAE, Study SHP465-305, and SHP465-305 Study Report, page 62.)

### 6.1.3 Subject Disposition

*Study SHP465-306*

The disposition of adults was appropriately explained by the Applicant. There were 80 subjects (89.9%) in the placebo treatment group, 80 subjects (87.0%) in the SHP465 12.5mg treatment group, and 76 subjects (84.4%) in the SHP465 37.5mg treatment group who completed the study. The most common reasons for early termination were adverse events occurring in seven subjects in the SHP465 12.5mg treatment group and five subjects in the SHP465 37.5mg treatment group. It is not surprising that adverse events were the reason for discontinuations and not because of lack of efficacy. See Table 9 for more information.

**Table 9: Subject Disposition SHP465-306**

| | Treatment Group | | | |
|---|---|---|---|---|
| **Population Description** | **Placebo** | **SHP465 12.5** | **SHP465 37.5** | **Total** |
| Screened Set | | | | 369 |
| Screen Failures | | | | 94 |
| Randomized Set | 91 | 92 | 92 | 275 |
| Lost to follow up | 1 | 0 | 2 | 3 |
| Other | 1 | 0 | 0 | 1 |
| Safety Set | 89 | 92 | 90 | 271 |
| Adverse Event | 0 | 2 | 1 | 3 |
| Protocol Violation | 1 | 0 | 0 | 1 |
| Withdrawal by | 1 | 1 | 1 | 3 |
| Subject Other | 1 | 0 | 0 | 1 |
| Full Analysis Set | 86 | 89 | 88 | 263 |
| Adverse Event | 0 | 5 | 4 | 9 |
| Protocol Violation | 1 | 0 | 0 | 1 |
| Withdrawal by | 2 | 2 | 4 | 4 |
| Subject Lost to | 1 | 1 | 0 | 2 |
| Follow up | 1 | 0 | 0 | 1 |
| Lack of Efficacy | 1 | 1 | 4 | 6 |
| Completed Study | 80 | 80 | 76 | 236 |

(Source: 5.3.5.1 SHP465-306 Synopsis)

*Study SHP465-305*

Of the 264 randomized subjects (132 subjects were randomized to the placebo treatment group and 132 subjects were randomized to the SHP465 treatment group), 263 were included in the safety set. One subject randomized to the placebo group was lost to follow-up prior to study drug administration. 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 (N=4) in the placebo treatment group and adverse events (N=11) in the SHP465 treatment group.

### 6.1.4 Analysis of Primary Endpoint(s)

The Agency's Biostatics Reviewer, Yang Wang, Ph.D., replicated the Applicant's efficacy analyses and agrees with me that Study SHP465-306 and 305 have robust efficacy results. There were no statistical issues in the NDA resubmission.

*Study SHP465-306*

The primary efficacy variable was the change from baseline in the ADHD-RS with prompts total score at Visit 6 (Week 4). The primary efficacy endpoint was analyzed using a linear mixed-effects model for repeated measures (MMRM). The primary comparison of interest was at Visit 6 (Week 4) for each of the SHP465 doses compared with placebo. The mean (SD) baseline ADHD-RS with prompts total scores were 40.5 (6.52) for the placebo treatment group, 39.8 (6.38) for the SHP465 12.5mg treatment group, and 39.9 (7.07) for the SHP465 37.5mg treatment group. The mean (SD) Visit 6 (Week 4) ADHD-RS with prompts total scores were 29.2 (13.12) for the placebo treatment group, 21.6 (12.96) for the SHP465 12.5mg treatment group, and 15.8 (11.43) for the SHP465 37.5mg treatment group. The LS mean (95% CI) change from baseline in ADHD-RS total score for Visit 6 (Week 4) was -10.4 (-13.0, -7.8) for the placebo treatment group, -18.5 (-21.1, -15.9) for the SHP465 12.5mg treatment group, and -23.8 (-26.5, -21.2) for the SHP465 37.5mg treatment group. The reduction from baseline in ADHD-RS with prompts total score was significantly greater in the SHP465 12.5 mg and the SHP465 37.5mg 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) and the effect size was 0.67 for the SHP465 12.5 mg treatment group. The difference in LS mean (95% CI) was -13.4 (-17.1, -9.7), and the effect size was 1.11 for the SHP465 37.5mg treatment group.

**Table 10: Summary of Primary Endpoint Statistics**

| 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 | -10.4 | -18.5 | -23.8 |
| Difference of LS mean change from baseline (95% CI) SHP465 vs placebo | | -8.1 (-11.7, -4.4) | -13.4 (-17.1, -9.7) |
| Effect size | | 0.67 | 1.11 |
| p-value | | p<0.001 | p<0.001 |

(Source: 5.3.5.1 SHP465-306 Study Report Body, page 68)

*Study SHP465-305*

The primary efficacy variable was the change from baseline in the ADHD-RS-IV Total Score at Visit 6 (Week 4). The primary efficacy endpoint was analyzed using a linear MMRM. The mean (SD) baseline ADHD-RS-IV Total Scores were 40.0 (6.96) for the placebo treatment group and 39.0 (6.95) for the SHP465 treatment group. The mean (SD) ADHD-RS-IV Total Scores at Visit 6 (Week 4) were 28.2 (13.71) for the placebo treatment group and 17.3 (11.78) for the SHP465 treatment group. The LS mean (95% CI) change from baseline in ADHD-RS-IV Total Score was -10.8 (-13.0, -8.5) for the placebo treatment group and -20.7 (-22.9, -18.5) for the SHP465 treatment group. The reduction from baseline in ADHD-RS-IV Total Score was 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), and the effect size was 0.80, favoring SHP465 treatment.

**Table 11: Summary of Primary Endpoint Statistics**

| 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 | -10.8 | -20.7 |
| Difference of LS mean change from baseline (95% CI) SHP465 vs placebo | | -9.9 (-13.0, -6.8) |
| Effect size | | 0.80 |
| p-value | | <0.001 |

(Source: 5.3.5.1 SHP465-305 Study Report Body, page 71)

### 6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoint for studies SHP465-306 and 305 was the CGI-I.

*Study SHP465-306*

At Visit 6 (Week 4), the CGI-I scores for the SHP465 12.5mg and SHP465 37.5mg treatment groups were 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) and the effect size was 0.68 for the SHP465 12.5mg treatment; the difference in LS mean (95% CI) was -1.2 (-1.6, -0.9) for the SHP465 37.5mg treatment and the effect size was 1.11, both favoring SHP465 treatment.

*Study SHP465-305*
At Visit 6 (Week 4), the CGI-I score for the SHP465 treatment group was significantly lower compared with the placebo treatment group ($p<0.001$). The difference in LS mean (95% CI) was -0.8 (-1.1, -0.5), and the effect size was 0.65, favoring SHP465 treatment.

### 6.1.6 Other Endpoints

No other endpoints were analyzed.

### 6.1.7 Subpopulations

No statistically significant differences were observed between efficacy for gender and race for neither study, SHP465-306 nor 305.

One analysis of interest is the primary efficacy age subgroup analysis in study SHP465-305. The total scores on the ADHD-RS-IV were compared between the 6 to 12 year old (children) age group and the 13 to 17 year old (adolescents) 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 the placebo group.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Section 6.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Phase 2 Duration of Effect (DOE) trials of SHP465 were reviewed in the 2006 original NDA. SHP465 demonstrated 16 hours of efficacy compared to placebo for both adolescents (13-17 years) and adults.

### 6.1.10 Additional Efficacy Issues/Analyses

None.

# 7 Review of Safety

## ***Safety Summary***

The adult population safety evaluation of the NDA resubmission for SHP465 is based on the pooled Integrated Summary of Safety (ISS) and the Phase 3 study SHP465-306. The pediatric safety data is from Study SHP465-305.

Mixed salts of a single-entity amphetamine extended release capsule is a known entity and its safety profile is well-characterized and consistent with the known safety profile of other stimulants. Unsurprisingly, there is significant overlap in the safety profile of the proposed product and the labeled safety information described in the Adderall and Adderall XR package inserts. However, because of the longer duration of effect of SHP465 (16 hours), insomnia appears to be more problematic in the proposed product for the pediatric and the adult populations.

Insomnia has a greater impact in pediatric patients, especially the 6 to 12 age group. These children need nine to twelve hours sleep per 24 hours on a regular basis to promote optimal health (American Academy of Pediatrics, 2016). This safety review focuses primarily on adverse events identified in the pediatric population. Potential growth suppression in younger children (6 to 12) is the most concerning adverse event with SHP465 and is plausible based on 1. Insomnia based lack of growth hormone secreted during Rapid Eye Movement (REM) sleep and 2. decreased appetite reported with SHP465.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of the adult population was evaluated using the ISS and the safety set from SHP465-306. The ISS consisted of adverse event data from the Phase 3 studies, SHP465-301, 303, and 306.

The pediatric safety evaluation is derived from study SHP465-305 adverse event data.

### 7.1.2 Categorization of Adverse Events

The Applicant coded investigator terms to preferred terms (PT) using MedDRA 18.1 in the NDA resubmission. The accuracy of coding was assessed by examining the reported term to the body system term (AEBODSYS) through the lowest level terms (AELLT). I included some other terms to mean “insomnia”, such as initial insomnia, sleep disturbance, middle insomnia, etc. My evaluation of the adverse event preferred term data was consistent with Shire’s adverse event tables in the proposed draft

labeling. However, I was undecided about including adverse events with an occurrence rate of 1.9%, which Shire rounded up to 2% because the 1.9% cases were only one subject's report. Of note, I do think it is important to list the one case of seizure. See section 7.3 for more information.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Integrated Safety Data, SHP465-301, 303, 306 in adults was reviewed (studies 301 and 303 were reviewed in the original NDA application and will not be discussed here). Unsurprisingly, adverse events consistent with sympathomimetic drugs were reported more in the doses of 50mg or higher. Examples of sympathomimetic adverse events are increased blood pressure and tachycardia.

## 7.2 Adequacy of Safety Assessments

The safety assessments were adequate for studies SHP465-306 and 305. The Post Sleep Questionnaire (PSQ) was important to assess insomnia in the pediatric patients in order to quantify how severe and for how many days or weeks the insomnia endured. See Appendix 9.5 for the Table of Safety Assessments.

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Discussion of the extent of drug exposure for mixed salts of a single-entity amphetamine extended release capsule is limited in this review because of the extensive data already known about the drug. Further, in the original NDA, adult safety data was reviewed from Phase 3 trials of SHP465 at higher doses than study SHP465-306.

There is some concern that the 12.5mg starting dose in 6 to 12 year old pediatric patients is too high. However, 12.5mg is the lowest available dose of SHP465. Refer to the Office of Clinical Pharmacology, Division of Pharmacometrics reviewer's review for a boxplot comparison of adult and 7 to 12 year olds plasma Cmax concentration data from SHP465 12.5mg. Shire plans to develop a 6.25mg, which would allow greater dosing flexibility.

### 7.2.2 Explorations for Dose Response

Study SHP465-303, an adult dose response trial, was reviewed in the 2006 original NDA. See Section 6 for discussion.

### 7.2.3 Special Animal and/or In Vitro Testing

None.

### 7.2.4 Routine Clinical Testing

Clinical laboratory testing was adequate and is listed in Table 17, Table of Safety Assessments in Appendix 9.5. Both the adult study and the pediatric study had the same schedule of safety assessments.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the to-be-approved label and the Clinical Pharmacologist's review. I did not identify any issues.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There is extensive data on the class of extended-release stimulants. SHP465 is the longest-acting one reviewed thus far by the Agency. The adverse events identified with SHP465 are expected.

## 7.3 Major Safety Results

### 7.3.1 Deaths

No deaths occurred in either study, SHP465-306 nor SHP465-305.

### 7.3.2 Nonfatal Serious Adverse Events

In study SHP465-306 in adults, no serious adverse events were reported.

One nonfatal serious adverse event occurred in study SHP465-305. In the placebo group, a 16-year-old female, ID 002-0019, with history of depression attempted suicide and was withdrawn from the study. It is highly unlikely that this serious adverse event was related to SHP465 because the subject received placebo and had a history of depression.

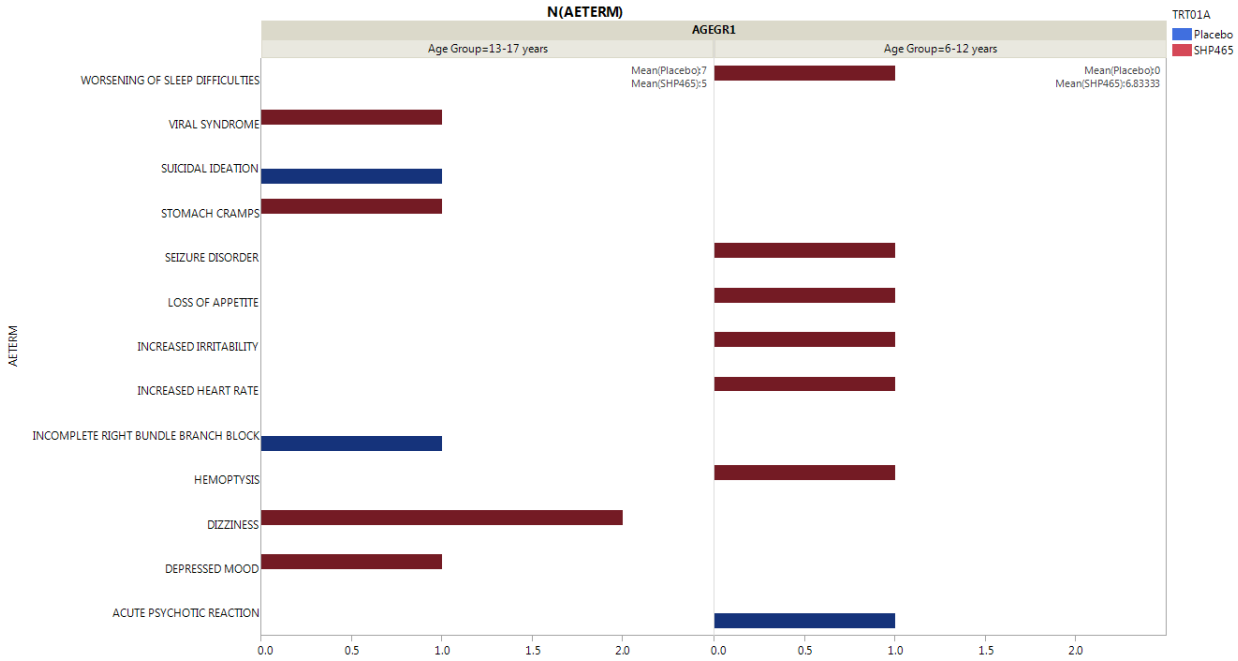
### 7.3.3 Dropouts and/or Discontinuations

The number of dropouts and discontinuations in both the adult and pediatric studies were more in the SHP465 treatment groups compared to the placebo groups.

In study SHP465-306, seven subjects (7.6%) in the SHP465 12.5mg treatment group had drug withdrawn due to an adverse event, five (5.6%) in the SHP465 37.5mg treatment group had drug withdrawn due to an adverse event, and no subjects in the placebo treatment group had drug withdrawn due to an adverse event.

The pediatric trial, SHP465-305, also had more discontinuations in the SHP465 group than the placebo group. Figure 4 shows 8% (7/78) drug withdrawn in 13 to 17 year old group and 13% (7/54) drug withdrawn in 6 to 12 year group and the adverse event leading to discontinuation per placebo or SHP465 treatment group. Of note, the reasons for discontinuation in the younger children in the SHP465 group were each one patient per adverse event: sleep difficulty, seizure, decrease appetite, irritability, increased heart rate, and hemoptysis. I believe that if the sample size was larger and able to be compared among pediatric age groups that there would be more dropouts in 6 to 12 year olds due to insomnia, irritability (because of lack of sleep), and decreased appetite leading to weight loss. Those adverse events are less tolerated (by caregivers) in younger patients, in my opinion.

**Figure 4: Pediatric Discontinuations by Age Group**




(Source: Reviewer-created from Study SHP465-305 ADAE data)

### 7.3.4 Significant Adverse Events

*Study SHP465-306*

The adverse events in Study 306 in adults are consistent with the general safety profile of stimulants. Table 12 is a report of adverse event occurrence over two percent (>2%) in adults. The most frequent adverse events attributed to SHP465 are insomnia, decreased appetite, and dry mouth. There were no significant differences in adverse events between males and females.

Because study SHP465-306 evaluated lower doses (12.5, 25, and 37.5mg) in adults than in the original submission (12.5 to 75mg), the cardiovascular safety concerns from the original NDA about doses higher than 50mg per day were alleviated.

Interestingly, Shire added erectile dysfunction to their proposed label Adverse Reaction >2% table. I will delete that listing in the label. According to my analysis of the ISS, erectile dysfunction was reported seven times in six adults. That is the same amount of reports as tooth pain and leg cramps which are not >2%. See Table 13.

Of note, in the adult study, no positive suicidal ideation was reported on the Columbia Suicide Severity Rating Scale (C-SSRS).

**Table 12: Adverse Event Occurrence >2% in Adults, Study SHP465-306**

| | Description of Actual Arm | | | |
|---|---|---|---|---|
| | PLACEBO | SHP465 12.5mg | SHP465 37.5mg | Total |
| | Count (%) | Count (%) | Count (%) | Count (%) |
| Total | N=91 | N=92 | N=92 | N=275 |
| Gastrointestinal disorders | 3 (3.3%) | 15 (16.3%) | 21 (22.8%) | 39 (14.2%) |
| Constipation | 1 (1.1) | 4 (4.3) | 2 (2.2) | 7 (2.5) |
| Dry mouth | 3 (3.3) | 13 (14.1) | 20 (21.7) | 36 (13.1) |
| General disorders and administration site conditions | 3 (3.3%) | 4 (4.3%) | 3 (3.3%) | 10 (3.6%) |
| Fatigue | 3 (3.3) | 4 (4.3) | 3 (3.3) | 10 (3.6) |
| Infections and infestations | 7 (7.7%) | 8 (8.7%) | 9 (9.8%) | 24 (8.7%) |
| Nasopharyngitis | 3 (3.3) | 5 (5.4) | 4 (4.3) | 12 (4.4) |
| Upper respiratory tract infection | 4 (4.4) | 3 (3.3) | 5 (5.4) | 12 (4.4) |
| Investigations | 3 (3.3%) | 3 (3.3%) | 1 (1.1%) | 7 (2.5%) |
| Blood pressure increased | 3 (3.3) | 3 (3.3) | 1 (1.1) | 7 (2.5) |
| Metabolism and nutrition disorders | 4 (4.4%) | 18 (19.6%) | 27 (29.3%) | 49 (17.8%) |
| Decreased appetite | 4 (4.4) | 18 (19.6) | 27 (29.3) | 49 (17.8) |
| Nervous system disorders | 6 (6.6%) | 10 (10.9%) | 14 (15.2%) | 30 (10.9%) |
| Headache | 4 (4.4) | 6 (6.5) | 12 (13) | 22 (8) |
| Somnolence | 3 (3.3) | 4 (4.3) | 2 (2.2) | 9 (3.3) |
| Psychiatric disorders | 4 (4.4%) | 30 (32.6%) | 24 (26.1%) | 58 (21.1%) |
| Anxiety | 1 (1.1) | 6 (6.5) | 4 (4.3) | 11 (4) |
| Bruxism | | 1 (1.1) | 5 (5.4) | 6 (2.2) |
| Depressed mood | 1 (1.1) | 4 (4.3) | 1 (1.1) | 6 (2.2) |
| Initial insomnia | 1 (1.1) | 4 (4.3) | 6 (6.5) | 11 (4) |
| Insomnia | 1 (1.1) | 13 (14.1) | 10 (10.9) | 24 (8.7) |
| Irritability | | 5 (5.4) | 4 (4.3) | 9 (3.3) |

(Source: Reviewer-created from study data SHP465-306 using JMP Clinical 6.0)

**Table 13: Pooled Adult Safety Data, >2% Adverse Events**

| Body System | Adverse Reaction | MYDAYIS (N= 626) | Placebo (N= 328) |
|---|---|---|---|
| Nervous System | | | |
| | Anxiety | 7% | 3% |
| | Feeling Jittery | 2% | 1% |
| | Agitation | 2% | 0% |
| | Bruxism | 2% | 0% |
| Psychiatric disorders | | | |
| | Insomnia | 31% | 8% |
| | Depression | 3% | 0% |
| Metabolism and nutritional disorders | | | |
| | Decreased Appetite | 30% | 4% |
| | Weight Decreased | 9% | 0% |
| Gastrointestinal System | | | |
| | Dry Mouth | 23% | 4% |
| | Diarrhea | 3% | 1% |
| Cardiovascular System | | | |
| | Heart Rate Increased | 9% | 0% |
| | Palpitations | 4% | 2% |
| Genitourinary System | | | |
| | Dysmenorrhea | 4% | 2% |
| | Erectile dysfunction | 2% | 1% |

(Source: Created from proposed label adverse event table in draft label submitted December 20, 2016)

*Study SHP465-305*

SHP465 is a sixteen-hour extended release stimulant. As mentioned in the Safety Summary, insomnia and decreased appetite are concerning in a pediatric population. The younger age group (6 to 12 years) of pediatric patients was more susceptible to adverse events than the 13 to 17 year old group.

Table 14 indicates that decreased appetite occurred in 43% of the 6 to 12 year olds and that weight decreased in three patients (these children are expected to gain weight as they are growing). This was a 4-week trial, so when considering chronic use of SHP465 in pediatrics, there is likelihood of weight loss leading to growth suppression.

Over 25% of the pediatric patients (or their caregivers) reported insomnia. Shire states that the insomnia is time limited. However, it had great enough impact that one patient dropped out due to the insomnia and another patient dropped out due to a seizure, possibly induced by lack of sleep.

**Table 12: Adverse Events in 6 to 12 year olds- Study SHP465-305**

| | | Description of Actual Arm | | | |
|---|---|---|---|---|---|
| | | SHP465 N=54 | | PLACEBO N=53 | |
| **Body System or Organ Class** | **Dictionary-Derived Term** | **Count** | **%** | **Count** | **%** |
| Metabolism and nutrition disorders | Decreased appetite | 23 | 42.6% | 4 | 7.5% |
| Psychiatric disorders | Insomnia | 11 | 20.4% | . | . |
| | Initial insomnia | 4 | 7.4% | 1 | 1.9% |
| | Irritability | 4 | 7.4% | . | . |
| Investigations | Heart rate increased | 4 | 7.4% | 1 | 1.9% |
| | Weight decreased | 3 | 5.6% | . | . |
| | Weight increased | . | . | 3 | 5.7% |
| Nervous system disorders | Headache | 6 | 11.1% | 2 | 3.8% |
| | Dizziness | 3 | 5.6% | . | . |
| Gastrointestinal disorders | Nausea | 3 | 5.6% | 1 | 1.9% |
| | Vomiting | 3 | 5.6% | . | . |
| Infections and infestations | Pharyngitis streptococcal | 1 | 1.9% | 2 | 3.8% |
| Respiratory, thoracic and mediastinal disorders | Oropharyngeal pain | . | . | 3 | 5.7% |

(Source: Reviewer-created from ADAE.xpt data study SHP465-305)

A 12 year old male (ID 038-0002), experienced a seizure on day 23 of SHP465 treatment. He was withdrawn from the study and was started on levetiracetam. The patient had no prior history of seizure disorder. I disagree with the investigator's assertion that the seizure was not related to study drug.

The notable adverse event in 13 to 17 year old group taking SHP465 was 22% decreased appetite leading to weight loss in four patients. Insomnia (5%) was not as prominent in this age group although it occurred at the rate twice of placebo (see Table 15).

**Table 13: Adverse Events in 13 to 17 year olds- Study SHP465-305**

| | | Description of Actual Arm | | | |
|---|---|---|---|---|---|
| | | SHP465 | | PLACEBO | |
| | | N=78 | | N=79 | |
| Body System or Organ Class | Dictionary-Derived Term | Count | % | Count | % |
| Nervous system disorders | Headache | 10 | 12.8% | 13 | 16.5% |
| Metabolism and nutrition disorders | Decreased appetite | 17 | 21.8% | 5 | 6.3% |
| Gastrointestinal disorders | Nausea | 6 | 7.7% | 3 | 3.8% |
| | Abdominal pain upper | 3 | 3.8% | 1 | 1.3% |
| Psychiatric disorders | Irritability | 5 | 6.4% | 2 | 2.5% |
| | Insomnia | 4 | 5.1% | 2 | 2.5% |
| General disorders | Fatigue | 2 | 2.6% | 3 | 3.8% |
| Infections and infestations | Upper respiratory tract infection | 3 | 3.8% | 2 | 2.5% |
| Investigations | Weight decreased | 4 | 5.1% | 1 | 1.3% |

(Source: Reviewer-created from ADAE.xpt data study SHP465-305)

### 7.3.5 Submission Specific Primary Safety Concerns

The adverse events identified in the NDA resubmission are primarily from the ADAE.xpt dataset from study SHP465-305 and the ISS, ADAE.xpt. I used JMP 13.0 and JMP Clinical 6.0 to quantify the events discussed in other safety sections of this review and verify the Applicant's proposed adverse event label. These evaluations revealed no unexpected adverse events from SHP465 and its well-known active moiety.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The adverse events are groups by patient age group.

The most common (>5%) adverse events reported in adults, 18 to 55 years old, taking SHP465 were insomnia (31%), decreased appetite (30%), dry mouth (23%), decreased weight (9%), heart rate increased (9%), and anxiety (7%).

In adolescents, 13 to 17 years old, the most common adverse events reported were decreased appetite (13%), nausea (5%), and insomnia (5%).

Finally, in children, 6 to 12 years old, the most common adverse events reported were decreased appetite (43%), insomnia (28%), heart rate increased (7%), irritability (7%), nausea (6%), dizziness (6%), and weight decreased (6%).

### 7.4.2 Laboratory Findings

Laboratory assessments (biochemistry, endocrinology, hematology, and urinalysis) were collected at screening. The results were reviewed prior to enrolling subjects in study SHP465-306 and 305. Laboratory assessments were collected a second and third time, at baseline and at the end of trial (EOT).

### 7.4.3 Vital Signs

As expected with stimulants, increased blood pressure, and pulse rate are reported in both study SHP465-306 and 305. The adult patients had a greater increase from baseline than the pediatric patients did. In addition, adults usually have more cardiovascular risk factors, which can make the sympathomimetic adverse events more concerning. Table 16 indicates a dose proportional increase in pulse rate in adults.

**Table 14: Pulse Rate Increase, Study SHP465-306**

| **Parameter**<br>Time point [mean (SD)]<br>Min, Max | **Treatment Group** | | |
|---|---|---|---|
| | **Placebo** | **SHP465 12.5 mg** | **SHP465 37.5 mg** |
| **Pulse Rate (bpm)** | | | |
| Change from baseline | 0.1 (8.35) | 3.3 (10.52) | 7.1 (11.48) |
| Min, Max | -21, 23 | -25, 24 | -23, 38 |

(Source: Derived from SHP465-306 study report, Table 33, page 99.)

### 7.4.4 Electrocardiograms (ECGs)

*Study SHP465-306*
None of the ECG findings resulted in a clinically significant ECG interpretation or ECG-related treatment-emergent adverse event.

*Study SHP465-305*
There were no clinically meaningful changes in mean ECG or QTc-related parameters.

### 7.4.5 Special Safety Studies/Clinical Trials

Not conducted.

### 7.4.6 Immunogenicity

No data regarding immunogenicity were submitted with this NDA.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Not conducted.

### 7.5.2 Time Dependency for Adverse Events

Not conducted.

### 7.5.3 Drug-Demographic Interactions

None.

### 7.5.4 Drug-Disease Interactions

Amphetamine class warnings and precautions list drug-disease interactions in the SHP465 label. However, because of patient exclusion criteria in the SHP465 trials, few drug-disease interactions were reported with SHP465. For example, subjects with existing cardiovascular disease were excluded. Subjects with pre-existing psychosis or bipolar I disorder were excluded because it is known that amphetamine may induce psychosis or mania. Interestingly, a patient, ID 005-0007, in study SHP465-305 did have an acute psychotic episode, but he was taking placebo and psychosis was not study drug related, in my opinion. See Section 7 for additional safety data.

### 7.5.5 Drug-Drug Interactions

No new drug-drug interactions were submitted with this NDA. The SHP465 label does contain amphetamine class drug interactions.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No human carcinogenicity studies were submitted with this NDA.

### 7.6.2 Human Reproduction and Pregnancy Data

No human reproduction/pregnancy data was submitted with this NDA.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Amphetamines have a class Warning and Precaution about suppression of growth. See Section 7.3.4 for pediatric safety data on growth.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

(b) (4) prepared the Abuse Potential Report, dated November 14, 2016, for this NDA.

The abuse potential of SHP465 is consistent with the characterization of amphetamine being a high potential for abuse. No human abuse potential studies of SHP465 were performed because any results generated would not add significantly to understanding the abuse potential of an extended-release amphetamine product. Marketed amphetamine extended-release formulations, including mixed amphetamine salts, are abused at a rate comparable to extended release methylphenidate products. According to the report, abusers are known to use multiple tablets of lower dose strengths to reach their desired psychoactive effect; a higher amphetamine dose (e.g., 50 mg) would not present a new risk. SHP465 will be Schedule II.

## 7.7 Additional Submissions / Safety Issues

One additional safety issue arose surrounding the proprietary and established name of SHP465. Shire submitted the proprietary name Mydayis, which was acceptable from a medication errors perspective and not found to be promotional by Office of Prescription Drug Promotion. In the DMEPA Proprietary Name Review dated April 13, 2017, there is concern about risk of confusion for the currently marketed Adderall XR and Mydayis, which have different PK profiles. Both drugs have the same established name, including “extended release capsule”, an overlapping 25mg strength, and the same (once daily) frequency of administration.

In order to prevent errors and within our regulatory purview, DMEPA took steps to address their concern. In the 2007 Approvable Letter, DMEPA requested that Shire plan for an educational campaign upon launch of Mydayis to differentiate the 12-hour and the 16-hour forms of mixed salts of a single-entity amphetamine extended-release capsules. DMEPA is also contacting the Office of Generic Drugs to inform them of the potential for confusion in case an abbreviated new drug application is submitted for Adderall XR or Mydayis in the future.

# 8 Postmarket Experience

At this time, Adderall and Adderall XR spontaneous MedWatch safety reports are being monitored by the Office of Surveillance and Epidemiology/Division of Pharmacovigilance 1 (OSE/DPV1). Adderall and Adderall XR do not have new safety issues associated with the drug entity, mixed salts of a single-entity amphetamine extended release capsule. That is the same active moiety contained in SHP465.

# 9 Appendices

## 9.1 Literature Review/References

In the 2007 Approvable Letter, the Agency requested that Shire provide updated reports on the world archival literature pertaining to the safety of SHP465. In our April 25, 2014, Type C Written Responses Only, we agreed with Shire's proposal to provide a world literature update similar to that provided for the annual report for Adderall XR based on general amphetamine use because SHP465 is not marketed in any country. Shire submitted a literature review with 83 references with updates on mixed amphetamine salts. Their methodology to conduct the literature review was adequate.

## 9.2 Labeling Recommendations

Labeling meetings were held March 27, April 18, and May 2, 2017. The major areas discussed from a clinical standpoint were:

- Add information about the 16-hour duration to sections before the Clinical Pharmacology section 12
- Rearrange the Adverse Reactions leading to discontinuation section
- Remove (b) (4) from the Clinical Studies section 14
- DMEPA suggested adding duplicative language about potential for overdose by substitution based on milligram per milligram
- Add class amphetamine warning about lowering the seizure threshold due to one case in a pediatric patient with no prior history
- Change the time of dosage from (b) (4) to “upon awakening”

## 9.3 Advisory Committee Meeting

Because the evaluation of the safety data did not reveal unexpected safety issues for mixed salts of a single-entity amphetamine extended release capsule, and because the design and results of the efficacy trials did not pose particular concerns, this application was not presented to an Advisory Committee.

## 9.4 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 022063

Submission Date(s): 12/20/16

Applicant: Shire

Product: SHP465 (mixed salts of a single-entity amphetamine extended release capsule)

Reviewer: Nancy Dickinson, PharmD

Date of Review: 3/17/17

Covered Clinical Study (Name and/or Number): SHP465-111
SHP465-305
SHP465-306

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes X | No ☐ (Request list from applicant) |
| Total number of investigators identified: 467 | | |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 6<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes X | No ☐ (Request details from applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes X | No ☐ (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes N/A | No ☐ (Request explanation from applicant) |

The six clinical investigators with financial disclosures were all related to grants, equipment compensation, retainer, or honoraria received from Shire after February 2, 1999. The amounts of payments were listed for each of the six investigators.

Shire reports that the designs of Studies SHP465-305 and 306 minimized the potential for bias by any investigator. By the study design, there was no single investigator or sub-investigator who had influence that could affect the results of the trial. The key factors included in the study design which minimize potential bias are:

1. Both studies, SHP465-305 and 305 were double-blind and placebo-controlled.
   The actual treatment given to individual subjects is determined by a randomization schedule. In no instance should an investigator treating patients in these trials have known the sequence of potential treatment assignments. Per protocol, the randomization code in these trials was not to be broken except in emergency situations, where the identification of the investigational product was required for further treatment of the subject.
2. All trial protocols were reviewed and approved by the Institutional Review Board (IRB) before its initiation in order to ensure that financial interests of the trial investigators did not compromise the protection of research subjects.
3. The clinical trials were monitored by an external Contract Research Organization (CRO) according to the principles of Good Clinical Practice (GCP).

According to Form FDA 3454, there were no primary or sub-investigators who were Applicant employees. The Applicant certified there were no financial arrangements with the clinical investigators listed on Form FDA 3454.

## 9.5 Safety Assessment Table Study SHP465-306 and 305

**Table 15: Safety Assessments Study SHP465-306 and 305**

| Visit | Screening and Washout | | Baseline | Dose Optim/Titrate | | Dose Maintenance | | Safety Follow-up |
|---|---|---|---|---|---|---|---|---|
| | 1 | Telephone Call | 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** |
| Inclusion/exclusion criteria | X | X | X | | | | | |
| Demographics | X | | | | | | | |
| Randomly assigned to treatment | | | X | | | | | |
| Medical and medication history | X | | | | | | | |
| Physical examination | X | | X | | | | X | |
| Vital sign measurements | X | | X | X | X | X | X | |
| Height and body mass index | X | | | | | | | |
| Body weight | X | | X | X | X | X | X | |
| Clinical laboratory assessments | X | | X | | | | X | |
| Urine drug screen | X | | X | | | | | |
| Serum pregnancy test | X | | X | | | | | |
| Urine pregnancy test | | | X | | | | X | |
| Electrocardiogram (12-lead) | X | | X | | X | | X | |
| ADHD-RS-IV or ADHDRS prmts | | | X | X | X | X | X | |
| CGI-S | | | X | | | | | |
| CGI-I | | | | X | X | X | X | |
| Post Sleep Questionnaire | X | | X | X | X | X | X | |

| Visit | Screening and Washout | | Baseline | Dose Optim/Titrate | | Dose Maintenance | | Safety Follow-up |
|---|---|---|---|---|---|---|---|---|
| | 1 | Telephone Call | 2 | 3 | 4 | 5 | 6/ET | Telephone Call |
| C-SSRS baseline version | X | | | | | | | |
| C-SSRS since last visit version | | | X | X | X | X | X | |
| AEs and concomitant meds | X | X | X | X | X | X | X | X |

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/s/

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NANCY C DICKINSON
06/20/2017

JAVIER A MUNIZ
06/20/2017