Office of Clinical Pharmacology Review

NDA	022063
Link to EDR	\\CDSESUB1\evsprod\NDA022063\0022
Submission Date	12/20/2016
Submission Class	Priority (Class 2 Resubmission)
Brand Name	Mydayis®
Generic Name	Mixed salts of a single entity amphetamine
Dosage Form and Strength	Extended Release Capsule 12.5 mg, 25 mg, 37.5 mg and 50 mg
Route of Administration	Oral
Proposed Indication	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant	Shire
Related IND	66,329
OCP Review Team	Kofi A. Kumi, Ph.D., Michael Bewernitz, Ph.D., Kevin Krudys, Ph.D., Hao Zhu, Ph.D.
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1. Executive Summary

This NDA is a Class 2 Resubmission for a triple-bead amphetamine extended release product (SHP465) by Shire Pharmaceuticals. It is a complete response to an approvable letter that was issued for NDA 22063 in May 2007. Even though the sponsor notified the Agency in May of 2007 of intent to file an amendment to support approval, they decided not to pursue the development of SHP465 at that time for business reasons. The sponsor has reactivated the development program for SHP465 and is currently seeking approval for SHP465 under the tradename of Mydayis® for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

SHP465 is a once-daily, triple-bead, sustained-release, single-entity mixed amphetamine salt (MAS) product for oral administration. The first 2 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; these 2 beads are similar formulations using the same manufacturing processes as for Adderall XR which is manufactured by the same Sponsor and approved for ADHD. The third bead is unique to the triple-bead MAS and 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. Adderall XR reportedly lasts about 12 hours. The need for a longer duration of symptom coverage was justified by multiple reports that, in clinical practice, Adderall XR is supplemented after 8 hours with MAS immediate release (IR) to extend the duration of action to last during waking hours.

The clinical development program consisted of 16 clinical studies, 13 of which were included in the original NDA, and 3 of which (i.e., one PK trial in pediatric patients aged 6-17 years, one efficacy and safety trial in pediatric patients aged 6-17 years, and one efficacy and safety trial in adults aged 18-55 years) are new and included in this resubmission. A population pharmacokinetic analysis report was also included in this resubmission.

The key review issues are: 1) is the exposure after administration of SHP465 similar to the reference drug, Adderall XR plus the administration of MAS IR after 8 hours? 2) Is the proposed dosing regimen appropriate? 3) Should SHP465 to be administered with or without food? 4) Are there dose adjustments in renal impairment patients or patients receiving a gastric pH modulator?

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 022063 and supports the approval of the SHP465 for the treatment of Attention Deficit Hyperactivity Disorder. OCP supports limiting the use of SHP465 to patients 13 years and older. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	Substantial evidence of effectiveness was demonstrated in registration trials in adults and pediatric patients. The uniqueness of this formulation is that the duration of action after administration of SHP465 is about 16 hours compared to about 12 hours for currently approved mixed amphetamine salts extended release formulations.
General Dosing Instructions	Overall, the proposed dosing is acceptable in adults and pediatric

	patients 13 years and older. The proposed doses are not recommended for pediatric patients 6 to 12 years of age. The recommended starting dose in adults 18 to 55 years is 12.5 mg once daily in the morning upon awakening. Dosage may be adjusted in increments of 12.5 mg no sooner than weekly to a maximum dose of 50 mg/day. The recommended starting dose in pediatric patients 13 to 17 years old is 12.5 mg daily in the morning upon awakening. Dosage may be adjusted in increments of 12.5 mg no sooner than weekly to a maximum dose of 25 mg/day Doses may be taken with or without food. However, in order to ensure consistent clinical response, patients should endeavor to take SHP465 either with food always or without food consistently. The whole content of a capsule may be sprinkled on an apple sauce and the whole amount of apple sauce should be administered.
Dosing in specific patients	Dose adjustments are not recommended in patients with mild and moderate renal impairment. Dose in patients with severe renal impairment should start with at least half the recommended dose and further adjustment made based on clinical response, since exposures would be higher at the recommended doses. SHP465 is not recommended for patients with End Stage Renal Disease (ESRD). Increased gastric pH due to concomitant use of a gastric pH modulator may change the exposure and pharmacokinetic profile of amphetamine. Frequently monitoring patients for changes in clinical effect is recommended. Adjust therapy based on clinical response.
Bridge between the to be marketed and approved reference drug	D- and l- amphetamine exposures (AUC, Cmax) are similar (i.e., meeting BE criteria), even though the pharmacokinetic profiles are different, after administration of equal doses of SHP465 and Adderall XR + Adderall IR 8 hours later.

OCP recommends that the Sponsor pursue a lower than 12.5 mg strength post-marketing to allow better starting dose in pediatric patients 6-12 years. A lower dosage strength may facilitate the use of SHP465 in pediatric patients 6 – 12 years old since the current recommended doses result in higher incidence of adverse events such as insomnia and decreased appetite. Refer to medical review for details of adverse event profile after administration of SHP.

1.2 Post-Marketing Requirements and Commitments

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐PMC ☑PMR	Pharmacokinetics (PK) in children 4-5 years old	There is an increasing use of amphetamines in children 4 -5 years old. Therefore, a PK study in this age group will inform dosing and assist in the design of safety monitoring plan in the safety and efficacy study that is being required by medical division.	A PK study to fully describe the shape of the concentration-time curve.

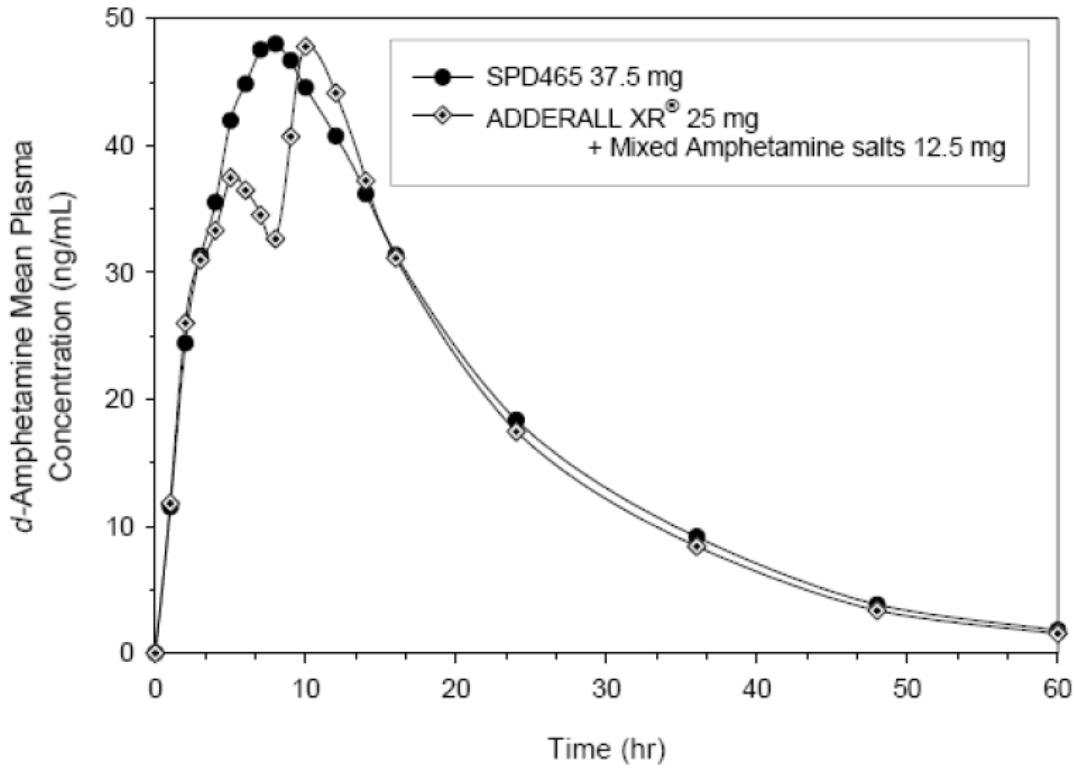
2. Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

SHP465 is a new formulation of amphetamine, a stimulant used to treat Attention Deficit Hyperactivity Disorder (ADHD). SHP465 is a once-daily, triple-bead, mixed amphetamine salt (MAS) combination comprised of sulfate salts of dextroamphetamine and amphetamine with dextroamphetamine saccharate and amphetamine aspartate monohydrate. The first 2 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. These 2 beads are similar using the same manufacturing processes as for Adderall XR. The third bead is unique to the triple-bead MAS and provides an additional delayed-dose of MAS. Adderall XR, is manufactured by the same Sponsor and approved for the treatment of ADHD. However, the duration of effect is about 12 hours. SHP465 is designed to last up to 16 hours. The relative bioavailability study was conducted to compare SHP465 with Adderall XR used in combination with MAS IR given 8 hours later. The pharmacokinetic properties were investigated in single dose and multiple dose studies conducted in healthy adult subjects and pediatric patients.

Pharmacokinetic comparison between SHP465 and Adderall XR + MAS IR
SHP465 37.5 mg, and ADDERALL XR 25 mg followed by mixed amphetamine salts IR 12.5 mg administered 8 hours later, were similar (i.e. met BE criteria) with respect to Cmax and AUC of *d*- and *l*-amphetamine, even though the pharmacokinetic profiles are different (Figure 1 and Table 1). The mean time to maximum d- and l-amphetamine concentration (Tmax) was about 8 hours and 10 hours for SHP465 and Adderall XR + MAS IR, respectively. The elimination half-lives of *d*-amphetamine (10.1 and 9.7 hours for SHP465 and Adderall XR, respectively) and *l*-amphetamine (12.5 and 11.7 hours for SHP465 and Adderall XR, respectively) were similar.

Figure 1: Mean *d*-Amphetamine Plasma Concentrations Over Time After a Single Dose, under fasting conditions, of SPD465 or ADDERALL XR



Source: Dr. Andre Jackson review (DARRTS Date: 4/24/2007)

Table 1: Plasma Pharmacokinetic Parameters for d-Amphetamine after a Single Dose of SHP465 or Adderall XR + Mixed Amphetamine Salts (IR) Administered 8 hours later- PK Population

Parameters	SPD465 37.5mg (A)			ADDERALL XR® 25mg + 12.5mg MAS (B)			Exponentiated LS Mean Ratio % (A)/(B)	90% CI
	n	Mean (±SD)	LS Mean	n	Mean (±SD)	LS Mean		
C_{max} (ng/mL)	20	50.3 (7.5)	49.7	19	49.3 (7.4)	49.2	101.0	(96.9, 105.3)
T_{max} (hr)	20	8.2 (2.0)	--	19	9.7 (2.1)	--	--	--
$AUC_{(0\text{-last})}$ (ng*hr/mL)	20	1058.0 (184.5)	1042.4	19	997.9 (172.9)	1000.8	104.2	(100.2, 108.3)
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	20	1084.9 (196.2)	1067.8	19	1019.5 (181.3)	1022.5	104.4	(100.3, 108.7)
$T_{1/2}$ (hr)	20	10.1 (1.3)	--	19	9.7 (1.2)	--	--	--

Source: Dr. Andre Jackson review (DARRTS Date: 4/24/2007)

Pharmacokinetics of SHP465

The Sponsor utilized population PK analyses to estimate apparent clearance and apparent volume of distribution for both d-amphetamine and l-amphetamine utilizing sparse and rich PK data obtained from adults as well as pediatric patients age 7 to 17 years. The apparent clearance of d-amphetamine and l-amphetamine is 25.2 L/h and 23.7 L/h, respectively. Following a 12.5 mg single dose of SHP465, for both d-amphetamine and l-amphetamine, children (age 7-12 years) have 44% higher and 77 - 83% higher C_{max} than adolescents (age 13-17 years) or adults, respectively. Also, for this dose, children also have a 39-46% higher and 101-102% higher $AUC_{0\text{-}24}$ than adolescents or adults, respectively, receiving the same dose. For both isomers, the apparent clearance and apparent volume increase as body weight increases. There was no significant relationship between age and gender on the Cl/F and V/F of d- or l-amphetamine, after adjusting body weight.

The exposures to both *d*- and *l*-amphetamine, as presented by Cmax and AUC(0-24) at steady state, increased with increasing SHP465 doses. The increases were dose-proportional across the dose range of 12.5 to 75 mg. Consumption of a high fat meal slows SHP465 absorption (increases median Tmax by about 5 hours) but does not affect the Cmax and AUC. Therefore, SHP465 can be taken without regard to meals. However, given the shape of pharmacokinetic profile change with high fat meal and the strong concentration-response relationship, patients should be advised to take the dose constantly either with food or without food to ensure consistent clinical response over time.

SHP465 pharmacokinetics (Cmax and AUC data for both *d*- and *l*-amphetamine) are not affected by whether the capsule was consumed intact or if the contents of the capsule were sprinkled onto an apple sauce.

There was an approximately 1.5-fold increase in the exposures to both *d*- and *l*-amphetamine following the seventh daily SHP465 dose when compared with a single oral dose of 12.5 mg. Based on statistical comparisons of predose *d*- and *l*-amphetamine concentrations, steady-state was attained between Day 5 and 8 of dosing.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

SHP465 is to be administered once daily with or without food. The content of the capsule can be sprinkled on an apple sauce and administered. Patients should be consistent on taking the product either with or without food every time to ensure consistent clinical response over time.

The recommended starting dose in adults 18 to 55 years is 12.5 mg once daily in the morning upon awakening. Dosage may be adjusted in increments of 12.5 mg no sooner than weekly to a maximum dose of 50 mg/day.

The recommended starting dose in children 13 to 17 years old is 12.5 mg daily in the morning upon awakening. Dosage may be adjusted in increments of 12.5 mg no sooner than weekly to a maximum dose of 25 mg/day

Sponsor provided efficacy and safety results from Phase 3 trials (Studies 305 and 306) in order to support the proposed therapeutic dose regimens. Please refer to the medical officer's review for Agency's evaluation and conclusions

2.2.2 Therapeutic Individualization

Dosing in Renal Impairment

No dedicated renal impairment studies were conducted with SHP465, which contains both d- and l-amphetamine. The sponsor referred to a study conducted with lisdexamphetamine, which may be converted to d-amphetamine, as the basis for recommending dosing of SHP465 in patients with renal impairment.

The disposition of *d*-amphetamine after administration of lisdexamphetamine (Vyvanse ® manufactured by the same sponsor) is expected to be similar to that after administration of SHP465 if the pharmacokinetics of lisdexamphetamine is unaffected by renal impairment. A renal impairment study conducted with lisdexamphetamine in subjects with various degrees of renal impairment indicated the exposures to *d*-amphetamine and lisdexamphetamine were not significantly increased in patients with mild to moderate renal impairment. Patients with severe renal impairment showed approximately 2 fold increase in d-amphetamine with no apparent increase in lisdexamphetamine exposure. The lisdexamphetamine and d-amphetamine data collected from ESRD subjects are limited and with high variability. Some subjects showed a high concentration of lisdexamphetamine with extremely low concentration of amphetamine, suggesting possible inability of these patients to convert lisdexamphetamine to amphetamine in

this population. Some subjects demonstrated high pre-dose lisdexamphetamine concentration level with no clear explanation. Hence, the data in ESRD is inconclusive to make dosing recommendation.

The effect of renal impairment on exposure to l-amphetamine in adults and pediatric patients aged 13 -17 years is not known. Mechanistically, if the changes in d-amphetamine observed in patients with mild to severe renal impairment receiving lisdexamphetamine is mainly due to glomerular filtration, we would anticipate that l-amphetamine show similar change with d-amphetamine. It is possible that metabolic enzymes and renal active transporters may be involved in the elimination of d- or l-amphetamine. These enzymes and renal active transporters may show selectivity on different stereoisomers which may be enhanced in patients with compromised renal function. The pharmacokinetic profiles of d- and l-amphetamine with a consistent ratio across various time points do not appear to directly suggest the existence of this selectivity. It is still feasible that the selectivity may be more apparent in patients with compromised renal function than in patients with normal renal function. However, it is to note that l-amphetamine seems to account for approximately 25% of the total circulating amphetamine (d- and l-amphetamine in combination). Therefore, we anticipate that the total amphetamine exposure change may follow similar trend (at least qualitatively) with d-amphetamine in patients with mild to severe renal impairment, even though there might be some quantitative deviation.

Overall, the recommendations for dosage adjustment in patients with compromised renal function following the administration of SHP465 may be derived mainly based on *d*-amphetamine changes in various renal impairment patients, which are (1) no dosage adjustment in patients mild to moderate renal impairment, (2) reduced dose initially by half in patients with severe renal impairment (Given the uncertainty of the quantitative change on total amphetamine, further dosage adjustment may be required), and (3) no recommendation of usage in ESRD.

Dosing in Hepatic Impairment Patients
Formal studies in patients with hepatic impairment were not conducted.

2.3 Outstanding Issues

The review team voiced concerns regarding tolerability of the proposed 12.5 mg starting dose in pediatric patients, particularly in children 6 to 12 years of age, observed in Phase 3 trials. In the Phase 3 trial, the incidence of adverse events such as insomnia and loss of appetite are higher in pediatric patients 6 -12 years than adults and pediatric patients 13 – 17 years old. Higher exposures were observed in pediatric patients 6 -12 years than in adults or pediatric patients 13 - 17 years. Refer to medical review for details of adverse events profile. While data were not available to assess exposure-safety relationship, single-dose PK determined that children experienced greater C_{max} and a greater AUC_{0-24} for both amphetamine isomers following administration of single 12.5 mg Mydayis capsules (median d-amphetamine C_{max} of 27.6 ng/mL and 16.71 ng/mL, in children and adults, respectively; median d-amphetamine AUC_{0-24} of 419 hr*ng/mL and 226 hr*ng/mL, in children and adults, respectively). However, as there is not currently a lower dose level available, and as it is not appropriate to recommend splitting the

12.5 mg capsule, a dose reduction below 12.5 mg during initiation cannot be recommended. Therefore, SHP465 is not recommended for use in pediatric patients 6 -12 years of age. OCP supports the decision to limit the use of SHP465 in patients 13 years and older. In addition, OCP recommends that the sponsor pursues a lower dose level post-marketing

Pharmacokinetic Studies in Children 4 -5 years old. This study would be requested as a Post Marketing Requirement (PMR)

2.4 Summary of Labeling Recommendations

General dosing recommendation is acceptable for patients 13 years and above.

Not recommended for use in pediatric patients 12 years and younger.

Adult patients with severe renal impairment patients (GFR 15 – < 30 mL/min/1.73 m^2) should start at the recommended starting dose with a maximum of dose of at least half of the recommended dose for patients without renal impairment.

It is recommended that pediatric patients with severe renal impairment take 12.5 mg per day if tolerable. Dose escalation is not recommended in pediatric patients 13 – 17 years with severe renal impairment.

Not recommended for use in patients with ESRD (GFR < 15 mL/min/1.73 m^2) .

Caution should be exercised when administering a pH modulator (e.g., proton pump inhibitor or H2 blocker) concomitantly with SHP465. Frequent monitoring is recommended and therapy adjusted based on clinical response.

SHP465 can be administered with or without food; however, patients should be advised to take it constantly either with or without food for consistent clinical response.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

This submission is a complete response to an approvable letter that was issued for NDA 22063 in May 2007. The approvable letter tentatively approved 12.5 and 25 mg SHP465 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The clinical development program consisted of 16 clinical studies, 13 of which were included in the original NDA, and 3 of which are new and included in this resubmission. The resubmission includes the following studies

Study SHP-111: A Phase 1, open-label study of the pharmacokinetics of d- and l-amphetamine after a single oral dose of SHP465 12.5 mg or 25 mg administered to children and adolescents aged 6 to 17 years with ADHD.

Study SHP465-305: A Phase 3, randomized, double-blind, multicenter, placebo controlled, dose-optimization, safety and efficacy study of SHP465 in children and adolescents aged 6 to 17 years with ADHD.

Study SHP465-306: A Phase 3, randomized, double-blind, multicenter, placebo-controlled, forced-dose titration, safety and efficacy study of SHP465 in adults aged 18 to 55 years with ADHD.

A population PK analysis was also included in the resubmission. No formal drug-drug interaction studies (regarding pharmacokinetics and pharmacodynamics) were conducted. The sponsor stated that all information on drug-drug interaction potential of amphetamine is potentially applicable to SHP465.

SHP465 is a once-daily, triple-bead, sustained release, single-entity, mixed amphetamine salt product for oral administration, and is comprised of sulfate salts of dextro- and levo-amphetamine, with dextroamphetamine saccharate and amphetamine aspartate monohydrate. SHP465 capsules contain 3 types of drug-releasing beads, which provide immediate release (IR), pulsatile delayed release (DR1), and delayed sustained release (DR2) of the mixed amphetamine salts. The first 2 beads are similar formulation with the same manufacturing process as to Adderall XR. The third bead is unique to the triple-bead MAS and provides an additional delayed-dose of MAS. The sponsor developed SHP465 sustained release formulation to provide a once-daily preparation designed to provide symptom coverage up to 16 hours post-administration.

In addition to Phase 1 formulation studies and completed Phase 2 duration studies in adults and adolescents to demonstrate duration of effect between 2 and 16 hours; two pivotal Phase 3 studies were included in the original NDA (SPD465-301 and SPD465-303) that evaluated the efficacy and safety of different dose regimens of SHP465 in adults. SPD465-301 used a double-blind design, and all subjects completed a dose-optimization phase of SHP465 doses starting at 12.5 mg up to 75 mg followed by a dose-maintenance phase. This sequence was designed to maximize symptom control while minimizing adverse events (AEs). Study SPD465-303 used a forced-dose design in which adults were randomized to either SHP465 (25, 50, or 75 mg) or placebo. Study SPD465-304 was conducted to assess long-term safety (out to 1 year) and maintenance of efficacy of doses.

The 3 additional clinical studies included in the resubmission were designed to further explore the dose range in adults and evaluate the pharmacokinetics, safety, and efficacy beyond the classroom study of SHP465 in adolescents to the broader pediatric population (6-17 years old). Study SHP465-111 assessed pharmacokinetic properties in single dose and multiple doses of 12.5 and 25 mg in children and adolescent patients with ADHD. Studies SHP465-305 and SHP465-306 assessed the efficacy and safety of SHP465 in subjects diagnosed with ADHD. Study SHP465-306 was conducted in adults aged 18-55 years and evaluated fixed doses of 12.5 and 37.5 mg, and SHP465-305 was conducted in children and adolescents aged 6-17 years and evaluated SHP465 fixed doses of 12.5 and 25 mg.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	Amphetamine is non-catecholamine sympathomimetic amines. Exact mechanism of action in ADHD is not known
Active moieties	Mixed Amphetamine Salts: Neutral sulfate salts of dextroamphetamine and amphetamine, amphetamine aspartate monohydrate
QT Prolongation	The potential of QT prolongation after administration of amphetamine products is not known.
General Information	
Bioanalysis	LC/MS/MS Assay Range: 0.5 – 75 ng/mL; 0.1 – 100 ng/mL
Drug Exposure at steady state following the therapeutic dosing regimen	Steady state reached between Day 5 and 8
Maximum tolerated dose or exposure	75 mg
Dose Proportionality	12.5 mg to 75 mg
Accumulation	R = 1.5
Absorption	Time to maximum concentration (Tmax) about 8 hours Effect of Food: Tmax delayed by about 5 hours but Cmax and AUC for both d and l-amphetamine not affected after administration with a high fat meal. Co-administration with apple sauce did not affect exposure or prolong Tmax.
Distribution	Protein Binding about 40%
Elimination	Mean T ½ is approximately 10 – 12.5 hours Metabolism: CYP2D6, Flavin containing monooxygenase 3 (FMO) and dopamine β-hydroxylase Amphetamine is not inhibitor in vitro of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in human hepatic microsomal suspensions, nor was it an in vitro inducer of CYP1A2, CYP2B6 or CYP3A4/5 in cultured fresh human hepatocytes. Amphetamine is not an in vitro substrate for permeability glycoprotein (P-gp) in vitro inhibitor of P-gp. Excretion: Renal

3.3 Clinical Pharmacology Questions

3.3.1 To what extend does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

In all 3 Phase 2 studies, the efficacy and duration of effect were determined using the PERMP, a skill-adjusted math test administered before and at 2, 4, 8, 12, 14, and 16 hours after dosing in the controlled environment of either an Adult Work Place Laboratory setting or a classic classroom analog.

The primary efficacy endpoint for the Phase 2 studies submitted in the original application was the average PERMP total scores over Classes 1-6 and at each time point from 2 through 16 hours post dose in the PERMP total scores. In the Phase 3 studies, the primary efficacy outcome was based on clinician administered ADHD-RS-IV total scores, which were assessed weekly during the 6-week double-blind treatment period. SHP465 demonstrated a significant treatment effect in each of the 3 randomized treatment groups (25, 50, or 75 mg) compared with placebo on the primary efficacy endpoint, ADHD-RS-IV total score ($p<0.0001$) and key secondary efficacy endpoint, CGI-I ($p<0.0001$).

Study SHP465-306, the new safety and efficacy study, examined the efficacy and safety of SHP465 (forced-dose titration) vs placebo in adults with ADHD. In this parallel-group, double-blind, Phase 3 study, subjects were randomized 1:1:1 to receive SHP465 12.5 mg, SHP465 37.5 mg, or placebo daily for a 4-week treatment period. The primary measure of efficacy was the clinician-administered adult ADHD-RS with prompts. The primary efficacy analysis demonstrated significantly greater symptom reduction and clinical improvement at Visit 6 (Week 4) from baseline in subjects diagnosed with ADHD and receiving treatment with both SHP465 12.5 and 37.5 mg compared with subjects receiving placebo. The difference from placebo was larger in the SHP465 37.5 mg than in the 12.5 mg treatment group. According to the sponsor, the doses studied were adequate to demonstrate efficacy of SHP. Please refer to Agency's medical review for details of the efficacy and safety analysis.

3.3.2 Is the proposed general dosing regimen appropriate?

Yes, the proposed dosing regimen is acceptable for patients 13 years and older. However, it does not appear to be appropriate to use SHP464 in pediatric patients 6 to 12 years of age with the currently proposed dosing regimen because for a given dose, exposures in these children are higher than pediatric children 13 -17 years and adults. Also, insomnia and loss of appetite are higher in pediatric patients 13 -17 years and adults.

The proposed dosing regimen in patients 13 years and older is acceptable. Based on the clinical pharmacology properties and efficacy and safety observations of SHP465, the recommended starting dose of 12.5 mg once daily in the morning for adults and pediatric patients 13 -17 years old who are either starting treatment for the first time or switching from another medication regimen is appropriate. Dosage may be adjusted in increments of 12.5 mg no sooner than weekly up to a maximum dose of 50 mg/day, based on the therapeutic needs and response in adult patients. The maximum dose in pediatric patients is 25 mg/day. The dose can be taken with or

without food. However, patients are advised to constantly take either with or without food in order to ensure consistent clinical response over time. The content of a capsule can be sprinkled on apple sauce and the whole amount should be taken.

We recommend that SHP465 not be used in pediatric patients 6 to 12 years of age. There are concerns regarding the tolerability issues which may arise from administering the same initial dose during titration, 12.5 mg once daily, to children 6 to 12 years of age as is proposed for adults. A single dose of 12.5 mg SHP465 produced higher Cmax and AUC_{0-24} values in children 6 to 12 years of age than in adults (Figure 2 and Figure 3). The same trend of higher C_{max} and AUC_{0-24} in pediatric patients 6 to 12 years of age compared to adults is seen for the l-amphetamine isomer as well.

Figure 2: Comparison of d-amphetamine C_{max} Distribution following a Single 12.5 mg Capsule Administered to adults or Pediatric Patients age 7 to 12 years.

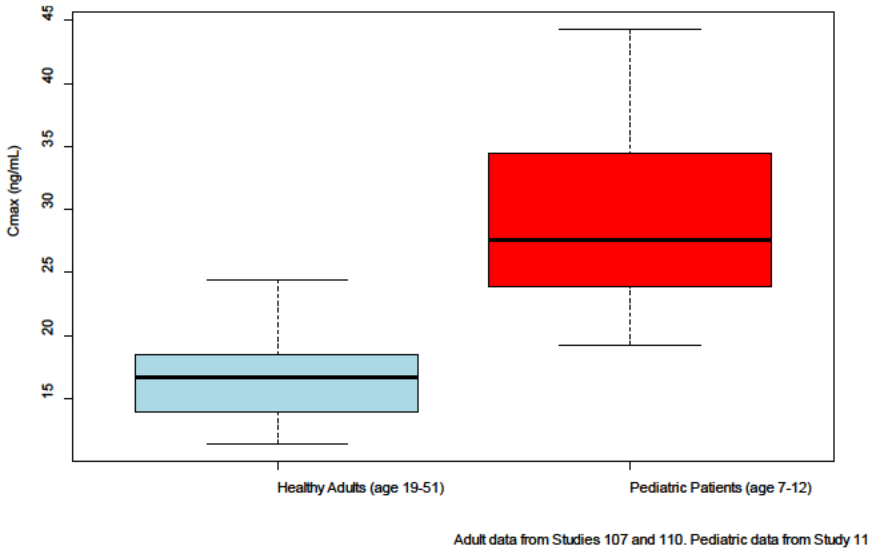
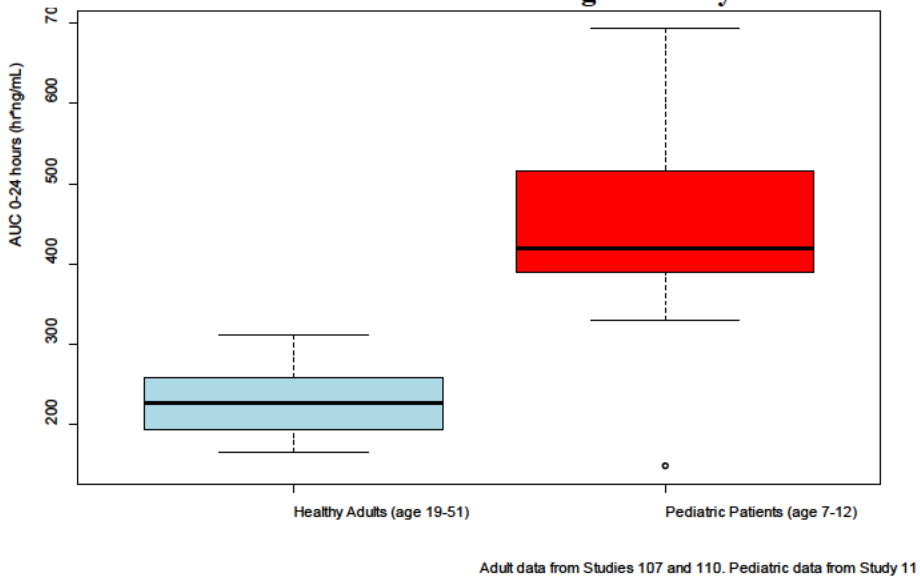


Figure 3: Comparison of d-amphetamine AUC_{0-24} Distribution following a Single 12.5 mg Capsule Administered to adults or Pediatric Patients age 7 to 12 years.



Consistent with the increased exposure in pediatric patients 6 to 12 years of age, it was observed in Phase 3 studies that the incidence of adverse events such as insomnia and loss of appetite were higher in pediatric patients aged 6 -12 years old compared to adults or pediatric patients age 13 -17 years. Unfortunately, there is insufficient data to formally assess the relationship between adverse event rate and amphetamine exposure as PK data were not collected in the phase 3 trials.

A reduced starting dose for pediatric patients 6 to 12 years of age is not feasible, because a strength lower than 12.5 mg is not available. In addition, it was not appropriate to recommend consuming half of a capsule as there is no guarantee that "splitting" a capsule contents would result in a 50/50 split of each of the 3 types of beads in each capsule (IR beads, delayed-IR beads, and XR beads).

Other products in this class generally allow for a reduction of initial dosage if tolerability is an issue. For example, such a statement is available in Adderall (amphetamine) XR label (01/2017 version) which states: "In children with ADHD who are 6-12 years of age and are either starting treatment for the first time or switching from another medication, start with 10 mg once daily in the morning; …. When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 5 mg once daily in the morning."

In summary, the general dosing regimen in patients 13 years and above is acceptable. However, we feel that it is prudent to limit the use of SHP465 to patients 13 years and older based on both higher exposures and incidence of adverse events in pediatric patients 6 -12 years than patients 13 years and above until data on using a lower starting dose in this patient population is

available. Furthermore, we recommend that the Sponsor pursue a lower dosage strength post-marketing.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Yes

No dose adjustment based on age, gender, body weight, and race

Renal Impairment

No dedicated renal impairment studies were conducted with SHP465, which contains both d- and l-amphetamine. The sponsor referred to a study conducted with lisdexamphetamine, which may be converted to d-amphetamine, as the basis for recommending dosing of SHP465 in patients with renal impairment.

The disposition of *d*-amphetamine after administration of lisdexamphetamine (Vyvanse ® manufactured by the same sponsor) is expected to be similar to that after administration of SHP465 if the pharmacokinetics of lisdexamphetamine is unaffected by renal impairment. A renal impairment study conducted with lisdexamphetamine in subjects with various degrees of renal impairment indicated the exposures to *d*-amphetamine and lisdexamphetamine were not significantly increased in patients with mild to moderate renal impairment. Patients with severe renal impairment showed approximately 2 fold increase in d-amphetamine with no apparent increase in lisdexamphetamine exposure. The lisdexamphetamine and d-amphetamine data collected from ESRD subjects are limited and with high variability. Some subjects showed a high concentration of lisdexamphetamine with extremely low concentration of amphetamine, suggesting possible inability of these patients to convert lisdexamphetamine to amphetamine in this population. Some subjects demonstrated high pre-dose lisdexamphetamine concentration level with no clear explanation. Hence, the data in ESRD is inconclusive to make dosing recommendation.

The effect of renal impairment on exposure to l-amphetamine in adults and pediatric patients aged 13 -17 years is not known. Mechanistically, if the changes in d-amphetamine observed in patients with mild to severe renal impairment receiving lisdexamphetamine is mainly due to glomerular filtration, we would anticipate that l-amphetamine show similar change with d-amphetamine. It is possible that metabolic enzymes and renal active transporters may be involved in the elimination of d- or l-amphetamine. These enzymes and renal active transporters may show selectivity on different stereoisomers which may be enhanced in patients with compromised renal function. The pharmacokinetic profiles of d- and l-amphetamine with a consistent ratio across various time points do not appear to directly suggest the existence of this selectivity. It is still feasible that the selectivity may be more apparent in patients with compromised renal function than in patients with normal renal function. However, it is to note that l-amphetamine seems to account for approximately 25% of the total circulating amphetamine (d- and l-amphetamine in combination). Therefore, we anticipate that the total amphetamine exposure change may follow similar trend (at least qualitatively) with d-

amphetamine in patients with mild to severe renal impairment, even though there might be some quantitative deviation.

Overall, the recommendations for dosage adjustment in patients with compromised renal function following the administration of SHP465 may be derived mainly based on *d*-amphetamine changes in various renal impairment patients, which are (1) no dosage adjustment in patients mild to moderate renal impairment, (2) reduced dose initially by half in patients with severe renal impairment (Given the uncertainty of the quantitative change on total amphetamine, further dosage adjustment may be required), and (3) no recommendation of usage in ESRD.

Hepatic Impairment

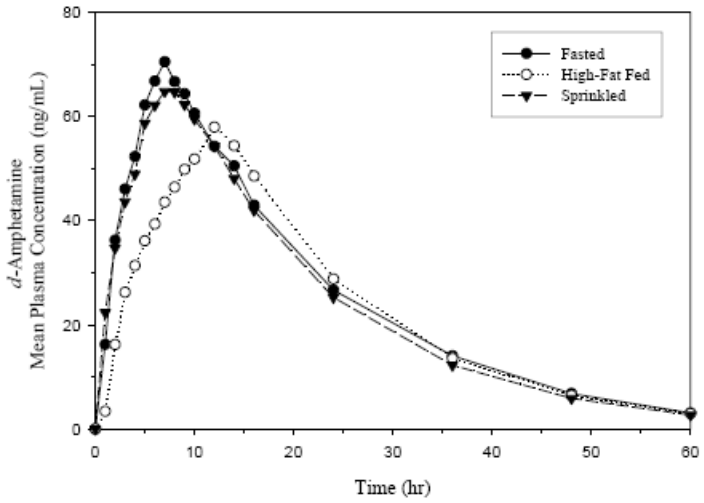
Formal pharmacokinetic studies for hepatic impairment effect have not been conducted for SHP465. Limited data in 3 hepatic impairment men from the literature showed that after oral administration of ^{14}C-5 mg amphetamine, about 90% of the ^{14}C was excreted in the urine in 3 to 4 days. About 60-65% of the ^{14}C was excreted in 1 day, 30% as unchanged drug, 21% as total benzoic acid and 3% as 4-hydroxyamphetamine

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

High fat food did not significantly affect the amphetamine exposure with 15% reduction in Cmax and 10% change in AUC by average. However, it altered the shape of pharmacokinetic profiles by prolonging Tmax from 7 to 12 hours. We consider that SHP465 can be administered with or without food. However, since amphetamine shows a strong concentration-effect relationship, patients may be advised to establish a consistent pattern to take this product with or without food to ensure consistent clinical response.

Sprinkling of SHP465 on applesauce had no effect on any PK parameters of both d- and l-amphetamine. Visual inspection does not reveal significant difference in shape of the concentration –time profile when the contents of the capsule is sprinkled on apple sauce and taken compared to when it is administered as a whole capsule in the fasting condition. High fat meal resulted in similar concentration-time profile but the peak concentration was lower and time to peak concentration was delayed. Please refer to Clinical Pharmacology review in DARRTS dated 4/24/2007 by Dr. Andre Jackson for details of study.

Figure 4: Mean *d*-Amphetamine Plasma Concentrations over Time after a Single 50mg Dose of SPD465 - PK Population



Source: Dr. Andre Jackson's review

Table 2: Statistical Analysis of Plasma d-Amphetamine Following a Single Dose Administration of 50 mg SHP465 with or without food

Parameter	Exponentiated LS Means			Ratio of LS Means		90% CI	
	Fasted (A)	High-Fat Meal (B)	Sprinkled (C)	B/A	C/A	B/A	C/A
C_{max} (ng/mL)	69.6	59.4	66.7	85.3	95.8	80.4, 90.5	90.3, 101.6
$AUC_{(0\text{-}inf)}$ (hr*ng /mL)	1528.3	1392.5	1463.7	91.1	95.8	86.7, 95.8	91.1, 100.6
$AUC_{(0\text{-}last)}$ (hr*ng/mL)	1484.2	1350.3	1424.5	91.0	96.0	86.7, 95.5	91.5, 100.7

Source: Dr. Andre Jackson's review

Table 3: Statistical Analysis of Plasma l-Amphetamine Following a Single Dose Administration of 50 mg SHP465 with or without food

Parameter	Exponentiated LS Means			Ratio of LS Means		90% CI	
	Fasted (A)	High-Fat Meal (B)	Sprinkled (C)	B/A	C/A	B/A	C/A
C_{max} (ng/mL)	20.4	17.4	19.8	85.2	96.9	80.2, 90.6	91.2, 103.0
$AUC_{(0\text{-}inf)}$ (hr*ng/mL)	522.3	463.4	495.0	88.7	94.8	83.9, 93.9	89.6, 100.3
$AUC_{(0\text{-}last)}$ (hr*ng/mL)	492.2	436.1	468.1	88.6	95.1	83.8, 93.7	90.0, 100.5

Source: Dr. Andre Jackson's review

CYP2D6 is known to be involved in the metabolism of Amphetamine to 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations (different types of metabolizers) in amphetamine metabolism are a possibility. Potential pharmacokinetic drug interactions (DDI) involved in CYP2D6 cannot be excluded. Frequent monitoring is recommended.

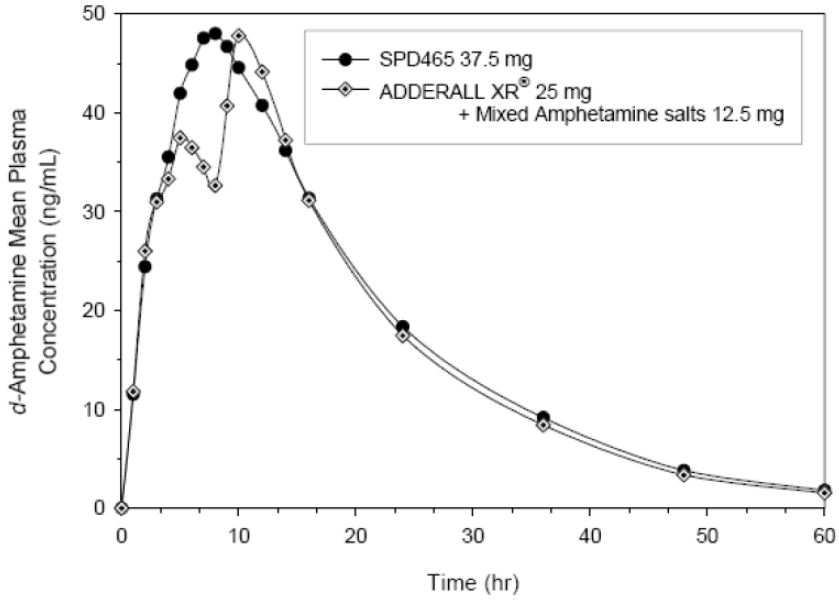
No formal clinical studies have been conducted between SHP465 and proton pump inhibitors. The sponsor referenced a clinical study (Study SPD489-113) conducted between Adderall XR and Vyvanse with and without omeprazole. The study (SPD489-113) was a Phase 1, open-label, randomized, 4-period crossover drug interaction study to evaluate the pharmacokinetic profiles of Vyvanse and Adderall XR when each is administered alone and in combination with the proton pump inhibitor omeprazole in healthy adult volunteers. Adderall XR 20 mg, single dose was administered concomitantly with the proton pump inhibitor, omeprazole (40 mg once daily for 14 days), the median Tmax of *l*–amphetamine was decreased by 1.25 hours (from 4 to 2.75 hours), and the median Tmax of *d*–amphetamine was decreased by 2.5 hours (from 5.5 to 3 hours), compared to Adderall XR administered alone. The study indicated that the shape of the concentration time profile can be affected by concomitant use of omeprazole, even though the AUC and Cmax values of each moiety were unaffected. As indicated previously, the first 2 beads in SHP465 are similar to those in Adderall XR. The third delayed release bead in SHP465 is designed to release amphetamine at pH 7. Therefore, it is possible that the shape pharmacokinetic profile of amphetamine following the administration of SHP465 can be altered because of the increased drug release from the first 2 beads under elevated gastric pH. Given the level of exposure and shape of pharmacokinetic change observed with Adderall XR, frequent monitoring of patients for changes in clinical effect is recommended if SHP465 is used in combination with a gastric pH modulator (e.g., a H_2 blocker or a proton pump inhibitor). Adjust therapy based on clinical response.

3.3.5 Are the Exposures to d- and l- amphetamine after SHP465 and Adderall XR + Adderall IR similar?

Yes.
In the original submission, the sponsor submitted a single-dose, fasting, 2-period crossover, single-center study involving 19 healthy adult subjects between the ages of 18 and 55 years was conducted to compare the exposure and shape of pharmacokinetic profiles of SPD465 and Adderall XR+mixed amphetamine IR. This study was reviewed by Dr. Andre Jackson and put in DARRTS on 4/24/2007.

The 90% CIs for Cmax and AUC ratios of d-amphetamine and l-amphetamine meet bioequivalence criteria when SHP 465 is compared to Adderall XR + mixed amphetamine IR formulation given 8 hours later. However, the shapes of the pharmacokinetic profiles are different.

Figure 5: Mean *d*-Amphetamine Plasma Concentrations Over Time After a Single Dose, under fasting conditions, of SPD465 or ADDERALL XR - PK Population



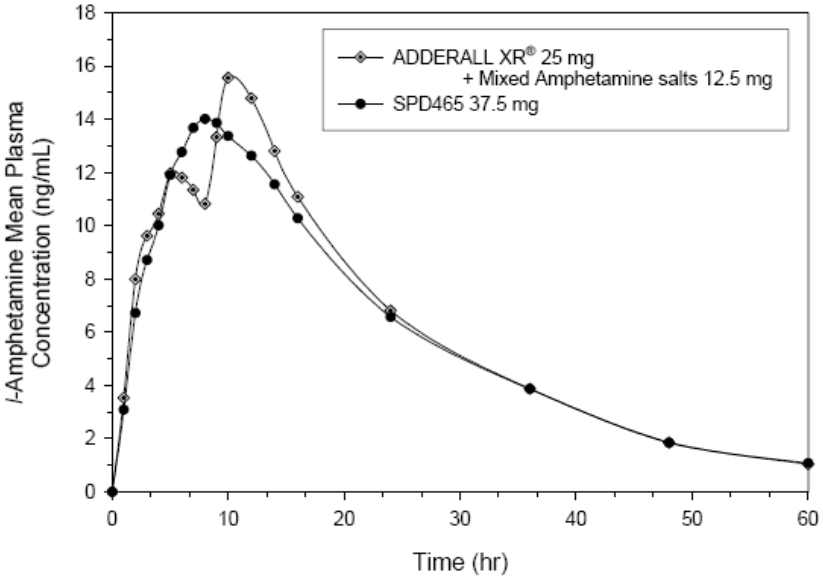
Source: Dr. Andre Jackson's Review, 4/24/2007

Table 4: Plasma Pharmacokinetic Parameters for d-Amphetamine after a Single Dose of SHP465 or Adderall XR + Mixed Amphetamine Salts (IR) Administered 8 hours later- PK Population

Parameters	SPD465 37.5mg (A)			ADDERALL XR® 25mg + 12.5mg MAS (B)			Exponentiated LS Mean Ratio % (A)/(B)	90% CI
	n	Mean (±SD)	LS Mean	n	Mean (±SD)	LS Mean		
C_{max} (ng/mL)	20	50.3 (7.5)	49.7	19	49.3 (7.4)	49.2	101.0	(96.9, 105.3)
T_{max} (hr)	20	8.2 (2.0)	--	19	9.7 (2.1)	--	--	--
$AUC_{(0\text{-last})}$ (ng*hr/mL)	20	1058.0 (184.5)	1042.4	19	997.9 (172.9)	1000.8	104.2	(100.2, 108.3)
$AUC_{(0\text{-Inf})}$ (ng*hr/mL)	20	1084.9 (196.2)	1067.8	19	1019.5 (181.3)	1022.5	104.4	(100.3, 108.7)
$T_{1/2}$ (hr)	20	10.1 (1.3)	--	19	9.7 (1.2)	--	--	--

Source: Dr. Andre Jackson's review

Figure 6: Mean *l*-Amphetamine Plasma Concentrations Over Time After a Single Dose, under fasting conditions, of SPD465 or ADDERALL XR- PK Population



Source: Dr. Andre Jackson's review

Table 5: Plasma Pharmacokinetic Parameters for l-Amphetamine after a Single Dose of SHP465 or Adderall XR + Mixed Amphetamine Salts Administered 8 hours later- PK Population

Parameters	SPD465 37.5mg (A)			ADDERALL XR® 25mg + 12.5mg MAS (B)			Exponentiated LS Mean Ratio % (A)/(B)	90% CI
	n	Mean (±SD)	LS Mean	n	Mean (±SD)	LS Mean		
C_{max} (ng/mL)	20	14.7 (2.2)	14.6	19	16.0 (2.3)	16.0	90.9	(87.5, 94.4)
T_{max} (hr)	20	8.4 (2.1)	--	19	10.7 (1.3)	--	--	--
$AUC_{(0\text{-last})}$ (ng*hr/mL)	20	353.5 (66.0)	347.6	19	364.1 (66.5)	364.6	95.3	(91.0, 99.8)
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	20	372.8 (73.5)	365.9	19	382.3 (69.0)	383.9	95.3	(91.2, 99.6)
$t_{1/2}$ (hr)	20	12.5 (1.7)	--	19	11.7 (1.6)	--	--	--

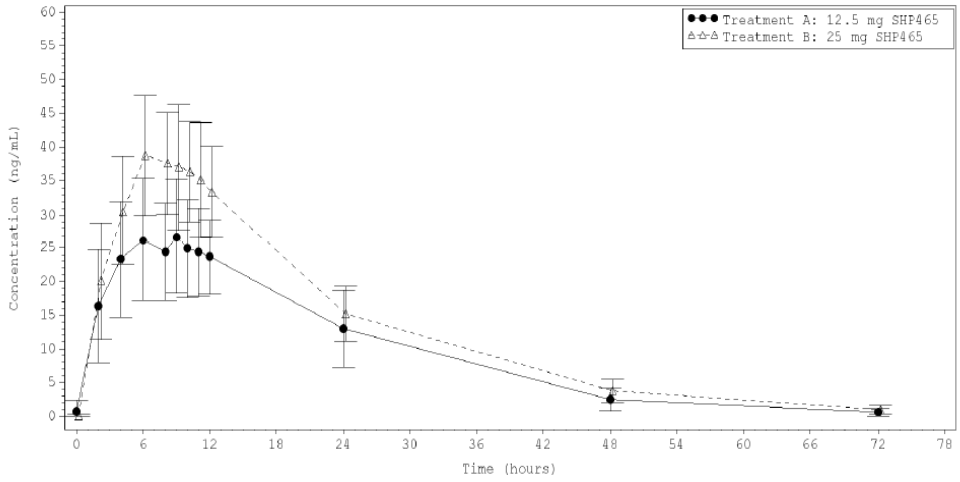
Source: Dr. Andre Jackson's review

3.3.6 What are the Pharmacokinetic characteristics of d- and l- amphetamine after administration of SHP465 to pediatric patients 6 – 12 and 13 -17 years old and how do they compare to Adults?

After correcting for dose, the mean Cmax and AUC d-amphetamine were about 44% and 46%, respectively higher in children 6 -12 years than adolescents 13 -17 years old. The mean Tmax of *d*-amphetamine was 9.30 h in children and 7.50 h in adolescents and the mean T ½ was 9.9 h in children and 11.4 h in adolescents. Similar trend was seen for l-amphetamine.

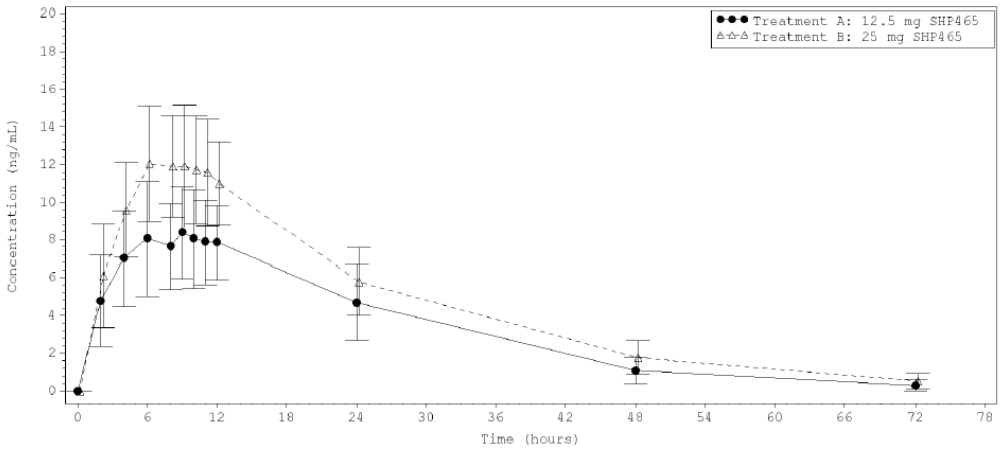
A Phase 1, open-label study (SHP465-111) of the pharmacokinetics of *d*- and *l*-amphetamine after a single oral dose of SHP465 12.5 mg or 25 mg administered to children and adolescents aged 6-17 years with attention-Deficit Hyperactivity Disorder was conducted by the Sponsor and included in this re-submission. The following are main results of study.

Figure 7: Mean (±SD) *d*-amphetamine Plasma Concentrations After a Single Dose of SHP465



Source: Study SHP465-111

Figure 8: Mean (±SD) l-amphetamine Plasma Concentrations After a Single Dose of SHP465



Source: Study SHP465-111

Table 6: Summary of d-amphetamine Pharmacokinetic Parameters by Age Group

Age Group	Statistic	C_{max} (ng/mL)	t_{max} (h)	AUC_{inf} (ng·h/mL)	AUC_{last} (ng·h/mL)	CL/F (L/h)	λ_z (1/h)	$t_{1/2}$ (h)	V_z/F (L)
6-12 years	n	13	13	11[a]	13	11[a]	11[a]	11[a]	11[a]
	Mean (SD)	29.22 (7.260)	9.304 (4.9015)	651.97 (174.282)	643.59 (161.727)	15.3 (3.81)	0.0722 (0.01279)	9.9091 (1.92783)	217.0 (61.79)
	Geometric mean	28.43	8.523	631.90	625.46	14.8	0.0711	9.7513	208.7
	Median	27.60	8.000	588.08	585.66	15.9	0.0680	10.1994	199.8
	%CV	24.8	52.7	26.7	25.1	25.0	17.7	19.5	28.5
	Min, Max	19.2, 44.3	6.00, 24.00	440.6, 970.3	435.3, 925.7	10, 21	0.048, 0.092	7.520, 14.334	129, 313
13-17 years	n	14	14	14	14	14	14	14	14
	Mean (SD)	40.57 (9.255)	7.496 (1.4454)	892.57 (209.378)	875.23 (200.093)	22.1 (5.23)	0.0628 (0.01172)	11.3666 (1.95137)	353.8 (65.24)
	Geometric mean	39.63	7.367	870.17	854.17	21.5	0.0619	11.2057	348.3
	Median	37.95	8.000	869.04	863.72	21.6	0.0633	10.9513	349.2
	%CV	22.8	19.3	23.5	22.9	23.7	18.7	17.2	18.4
	Min, Max	27.3, 58,5	6.00, 10.00	564.4, 1279.6	555.4, 1233.1	15, 33	0.047, 0.093	7.479, 14.808	264, 466

AUC_{inf}=area under the curve extrapolated to infinity; AUC_{last}= area under the curve from the time 0 to the last measurable concentration; C_{max}= maximum concentration occurring at t_{max}; CL/F=total body clearance for extravascular administration; λ_z=first order rate constant associated with the terminal (log-linear) portion of the curve; CV=coefficient of variation; max=maximum; min=minimum; SD=standard deviation; t_{max}= time of maximum observed concentration during a dosing interval; $t_{½}$=terminal half-life; V_z/F= volume of distribution based on the terminal phase following extravascular administration

[a] Due to insufficient information, elimination for 2 subjects cannot be characterized.

Source: Study SHP465-111

Table 7: Summary of l-amphetamine Pharmacokinetic Parameters by Age Group

Age Group	Statistic	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (ng·h/mL)	AUC_{last} (ng·h/mL)	CL/F (L/h)	λ_z (1/h)	$t_{1/2}$ (h)	V_z/F (L)
6-12 years	n	13	13	12	13	12	12	12	12
	Mean (SD)	9.31 (2.374)	10.081 (4.6566)	225.09 (65.252)	222.06 (59.833)	14.9 (4.02)	0.0614 (0.01336)	11.8145 (2.76544)	251.5 (80.93)
	Geometric mean	9.04	9.381	216.91	214.68	14.4	0.0601	11.5393	239.8
	Median	8.98	9.000	204.23	203.89	15.3	0.0593	11.6954	231.0
	%CV	25.5	46.2	29.0	26.9	26.9	21.7	23.4	32.2
	Min, Max	6.2, 14.1	6.00, 24.00	148.3, 353.1	144.4, 322.1	9, 21	0.038, 0.086	8.098, 18.199	139, 397
13-17 years	n	14	14	14	14	14	14	14	14
	Mean (SD)	12.88 (3.205)	7.738 (1.7332)	326.09 (92.866)	314.37 (84.161)	20.6 (5.85)	0.0551 (0.01245)	13.1525 (2.90674)	377.0 (83.04)
	Geometric mean	12.52	7.561	314.43	304.10	19.9	0.0539	12.8605	368.8
	Median	12.55	8.000	321.14	309.71	19.5	0.0564	12.2827	352.1
	%CV	24.9	22.4	28.5	26.8	28.4	22.6	22.1	22.0
	Min, Max	8.1, 18.5	6.00, 11.00	186.8, 543.5	182.6, 496.7	11, 33	0.036, 0.086	8.071, 19.440	280, 515

AUC_{inf}=area under the curve extrapolated to infinity; AUC_{last}= area under the curve from the time 0 to the last measurable concentration; C_{max}= maximum concentration occurring at t_{max}; CL/F=total body clearance for extravascular administration; λ_z=first order rate constant associated with the terminal (log-linear) portion of the curve; CV=coefficient of variation; max=maximum; min=minimum; SD=standard deviation; t_{max}= time of maximum observed concentration during a dosing interval; $t_{½}$=terminal half-life; V_z/F= volume of distribution based on the terminal phase following extravascular administration

Source: Study SHP465-111

Comparison of pharmacokinetic parameters between age groups is provided in the following table. Please note the difference in doses administered to the different age groups.

Table 8: Pharmacokinetic Parameters of d- and l-amphetammine (Mean [SD]) by Age

		d-amphetamine			*l*-amphetamine		
Population (age range; N)	Dose (mg)	T_{max} (hour)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	T_{max} (hour)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)
Adults (19-52; 20)	37.5	8.2 (2.0)	50.3 (7.5)	1085 (196)	8.4 (2.1)	14.7 (2.2)	373 (73.5)
Adolescents (13-17; 14)	25	8.0* [6.0, 10.0]	40.6 (9.26)	893 (209)	8.0* [6.0, 10]	12.9 (3.21)	326 (92.9)
Children (6-12; 13)	12.5	8.0* [6.0, 24.0]	29.2 (7.26)	652 (174)	9.0* [6.0, 24]	9.31 (2.37)	225 (65.3)

*median

Source: Clinical Pharmacology Summary

The mean half-life of d-amphetamine for Adults (19 -52 years), Adolescents (13 – 17 years), Children (6 -12 years) was 10.1, 11.4 and 9.9 years, respectively. The mean half-life of l-amphetamine for Adults (19 – 52 years), Adolescents (13 – 17 years) and Children (6-12 years) 12.5, 13.2 and 11.8 hours, respectively.

PK data were available from 74 adult patients and 28 pediatric patients (age 7-17 years). Sponsor built separate population PK models for d-amphetamine and l-amphetamine. Sponsor's population PK analyses resulted in apparent clearance for a 70 kg person of 25.2 L/h and 23.7 L/h for d- and l-amphetamine. Weight was the only covariate included in the final model. Weight-based allometric scaling was used to model the relationship of apparent clearance with weight as well as apparent volume of distribution with weight for both isomers.

4. Appendices

4.1 Summary of Bioanalytical Method Validation and Performance

Table 5 Summary of QPS-42-1379, TR-02-029, and TR-03-032 Validation Reports (*d*-Amphetamine)

Parameter	QPS-42-1379	TR-02-029	TR-03-032
Date of Report	03 Nov 2014	17 Apr 2003	16 Sep 2003
Analyte	*d*-Amphetamine	*d*-Amphetamine	*d*-Amphetamine
Matrix	K^2-EDTA Human Plasma	Na-EDTA Human Plasma	Na-EDTA Human Plasma
Assay Method	LC-MS/MS	LC-MS/MS	LC-MS/MS
Internal Standard (IS)	(±)-Amphetamine-d_5	*d*-Amphetamine-d_6	*d*-Amphetamine-d_6
Analytical Method Type	LC-MS/MS	LC-MS/MS	LC-MS/MS
Extraction Method	Liquid-liquid	Liquid-liquid	Liquid-liquid
Sample Volume	200 µL	20-50 µL	20-50 µL
QC Concentrations	0.1, 0.3, 4, 40, and 80 ng/mL	1.5, 20.0, and 60.0 ng/mL	1.5, 20.0, and 60.0 ng/mL
Standard Curve Concentrations	0.1, 0.2, 1, 3, 10, 30, 90, and 100 ng/mL	0.5, 1.0, 2.0, 5.0, 15.0, 25.0, 50.0, and 75.0 ng/mL	0.5, 1.0, 2.0, 5.0, 15.0, 25.0, 50.0, and 75.0 ng/mL
Lower Limit of Quantitation	0.100 ng/mL	0.500 ng/mL	0.500 ng/mL
Upper Limit of Quantitation	100 ng/mL	75.0 ng/mL	75.0 ng/mL
Average Recovery of Analyte (%)	62.6	66.6	NR
Average Recovery of Internal Standard (%)	NA[a]	NR	NR
Analytical QC Intraday Precision Range (%CV)	0.7-3.9	0.4-6.7	0.3-4.4
Analytical QC Intraday Accuracy Range (%RE)	-7.4-3.0	90.7-114.3	96.7-101.7
Analytical QC Interday Precision Range (%CV)	2.4-2.8	0.7-5.2	1.1-3.0
Analytical QC Interday Accuracy Range (%RE)	-6.1-2.0	94.0-111.6	99.3-100.9
Stock Solution Stability in Methanol	Refer to COA[b]	6 Hours at Ambient temperature	Reported in TR-02-029
Benchtop Stability in Plasma	24 Hours at Ambient Temperature	24 Hours at Ambient Temperature	Reported in TR-02-029
Freeze/Thaw Stability in Plasma	5 Cycles at -20°C and -70°C	4 Cycles	Reported in TR-02-029
Benchtop Stability in Whole Blood	2 Hours at Ambient Temperature	NR	NR
Long-term Storage Stability in Plasma	77 Days at -20°C and -70°C	39 Months at -70°C	Reported in TR-02-029
Dilution Integrity	1000 ng/mL diluted 20-fold	60 ng/mL diluted 10-fold	Reported in TR-02-029
Selectivity	≤20.0% LLOQ for analyte; ≤5.0% for IS	≤20.0% LLOQ for analyte; ≤5.0% for IS	Reported in TR-02-029

Table 6 Summary of QPS-42-1379, TR-02-029, and TR-03-032 Validation Reports (*l*-Amphetamine)

Parameter	QPS-42-1379	TR-02-029	TR-03-032
Date of Report	03 Nov 2014	17 Apr 2003	16 Sep 2003
Analyte	*l*-Amphetamine	*l*-Amphetamine	*l*-Amphetamine
Matrix	K_2-EDTA Human Plasma	Na-EDTA Human Plasma	Na-EDTA Human Plasma
Assay Method	LC-MS/MS	LC-MS/MS	LC-MS/MS
Internal Standard (IS)	(±)-Amphetamine-d_5	*l*-Amphetamine-d_6	*l*-Amphetamine-d_6
Analytical Method Type	LC-MS/MS	LC-MS/MS	LC-MS/MS
Extraction Method	Liquid-liquid	Liquid-liquid	Liquid-liquid
Sample Volume	200 µL	20-50 µL	20-50 µL
QC Concentrations	0.1, 0.3, 4, 40, and 80 ng/mL	1.5, 20.0, and 60.0 ng/mL	1.5, 20.0, and 60.0 ng/mL
Standard Curve Concentrations	0.1, 0.2, 1, 3, 10, 30, 90, and 100 ng/mL	0.5, 1.0, 2.0, 5.0, 15.0, 25.0, 50.0, and 75.0 ng/mL	0.5, 1.0, 2.0, 5.0, 15.0, 25.0, 50.0, and 75.0 ng/mL
Regression Model Used for Concentration Calculations	Weighted Linear	Quadratic	Weighted Linear
Lower Limit of Quantitation	0.100 ng/mL	0.500 ng/mL	0.500 ng/mL
Upper Limit of Quantitation	100 ng/mL	75.0 ng/mL	75.0 ng/mL
Average Recovery of Analyte (%)	62.7	52.1	NR
Average Recovery of Internal Standard (%)	NA[a]	NR	NR
Analytical QC Intraday Precision Range (%CV)	0.8-4.5	0.5-6.6	0.3-4.4
Analytical QC Intraday Accuracy Range (%RE)	-7.3-5.3	90.7-113.3	96.7-101.7
Analytical QC Interday Precision Range (%CV)	1.9-3.9	0.7-4.2	1.1-3.0
Analytical QC Interday Accuracy Range (%RE)	-5.5-3.8	91.3-111.0	99.3-100.9
Stock Solution Stability in Methanol	Refer to COA[b]	6 Hours at Ambient temperature	Reported in TR-02-029
Benchtop Stability in Plasma	24 Hours at Ambient Temperature	24 Hours at Ambient Temperature	Reported in TR-02-029
Freeze/Thaw Stability in Plasma	5 Cycles at -20°C and -70°C	4 Cycles	Reported in TR-02-029
Benchtop Stability in Whole Blood	2 Hours at Ambient Temperature	NR	NR
Long-term Storage Stability in Plasma	77 Days at -20°C and -70°C	39 Months at -70°C	Reported in TR-02-029
Dilution Integrity	1000 ng/mL diluted 20-fold	60 ng/mL diluted 10-fold	Reported in TR-02-029
Selectivity	≤20.0% LLOQ for analyte; ≤5.0% for IS	≤20.0% LLOQ for analyte; ≤5.0% for IS	Reported in TR-02-029

Source: Summary of Biopharmaceutics Studies and Analytical Methods

4.2 Clinical Pharmacokinetics

Clinical Pediatric Study Report

Study Report #: SHP465-111 Study Period: 10/6/15 – 11/13/15

Study Sites:
Houston Clinical Trials 3701 Kirby Dr., Suite 570 Houston, TX 77098
Principal Investigator: Alain Katic, MD

QPS MRA 6141 Sunset Dr., Suite 301 Miami, FL 33143
Principal Investigator: Americo F. Padilla, MD

Center for Psychiatry and Behavioral Medicine, Inc. 7351 Prairie Falcon Rd, Suite 160
Las Vegas, NV 89128

Principal Investigator: Ann Childress, MD

Analytical Site: (b) (4)

Principal Scientist: (b) (4)

EDR Link: \\CDSESUB1\evsprod\NDA022063\0022\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\shp465-111

Title: A Phase 1, Open-label Study of the Pharmacokinetics of *d*- and *l*-amphetamine After a Single Dose of SHP465 12.5 mg or 25 mg Administered to Children and Adolescents Aged 6-17 Years With Attention-Deficit Hyperactivity Disorder (ADHD)

Objective: The primary objective of this study was to evaluate the pharmacokinetics of *d*-amphetamine and *l*-amphetamine in children and adolescents aged 6-17 years with ADHD after a single oral dose of SHP465 12.5 mg or 25 mg.
The secondary objective of this study was to assess the safety and tolerability of SHP465 in children and adolescents aged 6-17 years with ADHD after a single oral dose of SHP465 12.5 mg or 25 mg.

Study Design:

Design: Phase 1, open-label, single-dose study. The study consisted of a screening period, a treatment period, and a follow-up period. After screening and a 7-day washout period, the eligible subjects were stratified into 2 age groups	
Screening: 28 days	Washout: 7-days prior to dosing
Stratification: 2 age groups: children (6-12 years) and adolescents (13-17 years) with approximately 6 males and 6 females per age group.	
Number of Subjects: 36 subjects were screened and 28 subjects were enrolled in the study. Overall, 27 subjects completed the study. One subject (001-1005) was withdrawn from the	

study due to inability to establish indwelling catheter
Main Inclusion Criteria: Study subjects were 6-17 years old with primary diagnosis of ADHD and had no clinically significant relevant abnormalities of medical history, physical examination, 12-lead electrocardiogram (ECG) or clinical/laboratory evaluations at the screening visit. The subjects had to meet the Diagnostic and Statistical Manual of Mental Disorder, Fifth edition (DSM-5), criteria for a primary diagnosis of ADHD based on an accepted ADHD diagnostic instrument and documented in the subject's medical record and was adequately controlled with an amphetamine-based product.
Major Exclusion Criteria: Concomitant ADHD medication other than an amphetamine-based product, having a DSM-5 diagnosis of conduct disorder, being underweight or overweight, having a known history of hypertension, seizure, chronic or current tic disorder, or current Tourette's disorder, or having a family history of sudden cardiac death or ventricular arrhythmia.
Treatments: Single oral dose of 12.5 mg capsule in children aged 6-12 years or 25 mg capsule in adolescents aged 13-17 years. Subjects fasted for 8 hours before administration of investigational product on Day 1 and for 2 hours post dose. Batch Numbers: 12.5 mg SHP465 manufacturer lot number AD6032A; 25 mg SHP465 manufacturer lot number AD6033A
PK Sampling Times: Predose, 2, 4, 6, 8, 10, 11, 12, 24, 48, 72 hours post dose

Analytical Method:

Analyte	d- and l-amphetamine
Method	LC-MS/MS
Matrix	Plasma
Range	0.1 to 100 ng/mL
Performance	Assay Performance of d-Amphetamine Quality Control Samples in Human Plasma d-Amphetamine Nominal Concentration, ng/mL Low QC, 0.3 / Mid QC, 4 / Mid QC, 40 / High QC, 80 %CV: 12.0 / 4.6 / 2.8 / 5.1 %Bias: -3.0 / -7.0 / -2.3 / 2.0 Assay Performance of l-Amphetamine Quality Control Samples in Human Plasma l-Amphetamine Nominal Concentration, ng/mL Low QC, 0.3 / Mid QC, 4 / Mid QC, 40 / High QC, 80 %CV: 15.1 / 4.3 / 5.2 / 7.0 %Bias: -7.0 / -8.0 / -3.0 / 0.6
Reviewer Comment	The analytical method and validation are acceptable

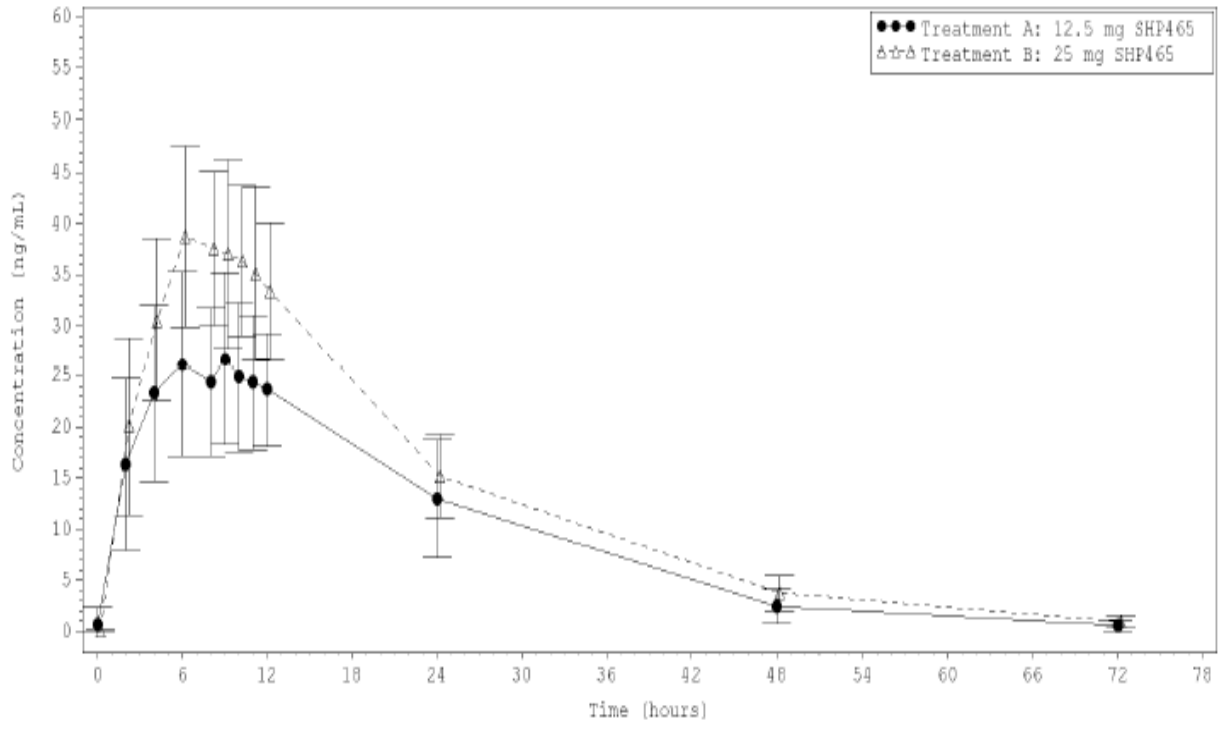
Statistical Method: The safety analysis set consisted of all subjects who had taken at least 1 dose of investigational product and had at least 1 post dose safety assessment.
The PK analysis set consisted of all subjects in the safety analysis set for whom the primary PK data were considered sufficient and interpretable.

Study Population

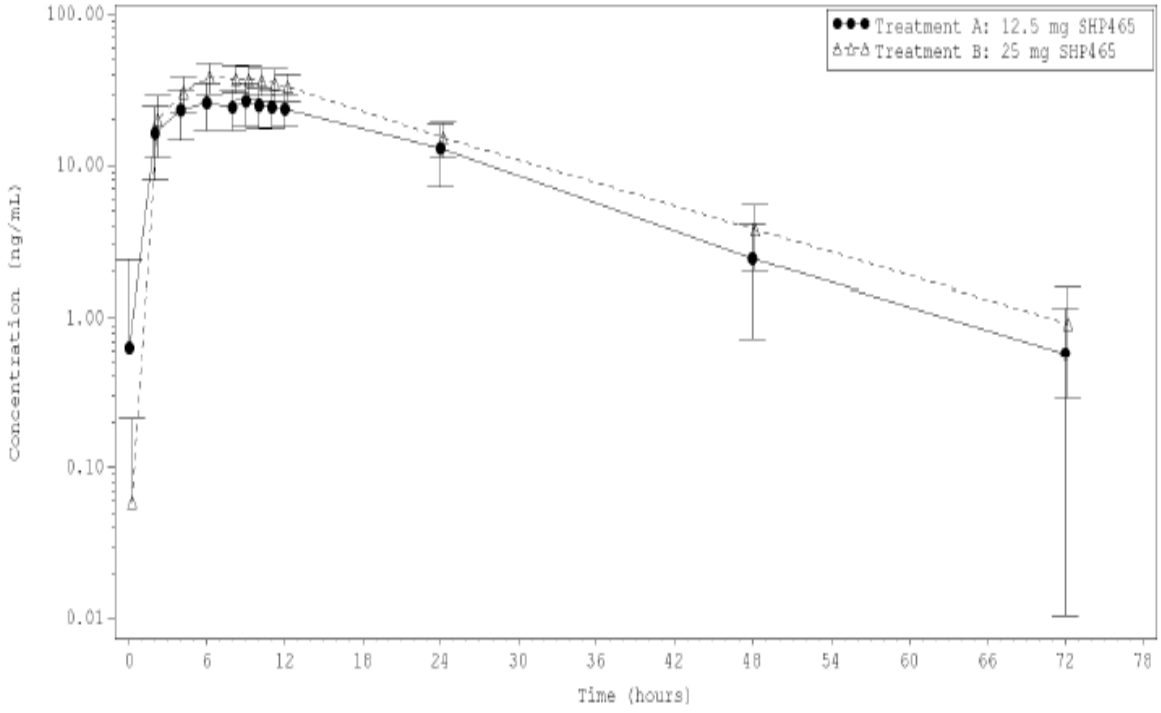
Randomized/Completed/Discontinued due to AE	28/27/0
Mean Overall Age [Median (range)] years Children (6-12 years) Adolescents (13-17 years)	12.3 [12.3 (7, 17).- Total 10.2 [10.5 (7,12)] 14.4 [14.0 (13,17)]
Male/Female	16/12
Race (Caucasian/Black/other)	13/13/2
Overall Weight (±SD) kg Children Adolescents	48.8 (15.53) 37.03 (7.63) 59.94 (12.66)

Results:

Mean (±SD) d-amphetamine Plasma Concentration After Single Dose of SHP465



Mean (±SD) d-amphetamine Plasma Concentration After Single Dose of SHP465 (Log Scale)



Summary of d-amphetamine Pharmacokinetic Parameters by Age Group

Age Group	Statistic	C_{max} (ng/mL)	t_{max} (h)	AUC_{inf} (ng·h/mL)	AUC_{last} (ng·h/mL)	CL/F (L/h)	λ_z (1/h)	$t_{1/2}$ (h)	V_z/F (L)
6-12 years	n	13	13	11[a]	13	11[a]	11[a]	11[a]	11[a]
	Mean (SD)	29.22 (7.260)	9.304 (4.9015)	651.97 (174.282)	643.59 (161.727)	15.3 (3.81)	0.0722 (0.01279)	9.9091 (1.92783)	217.0 (61.79)
	Geometric mean	28.43	8.523	631.90	625.46	14.8	0.0711	9.7513	208.7
	Median	27.60	8.000	588.08	585.66	15.9	0.0680	10.1994	199.8
	%CV	24.8	52.7	26.7	25.1	25.0	17.7	19.5	28.5
	Min, Max	19.2, 44.3	6.00, 24.00	440.6, 970.3	435.3, 925.7	10, 21	0.048, 0.092	7.520, 14.334	129, 313
13-17 years	n	14	14	14	14	14	14	14	14
	Mean (SD)	40.57 (9.255)	7.496 (1.4454)	892.57 (209.378)	875.23 (200.093)	22.1 (5.23)	0.0628 (0.01172)	11.3666 (1.95137)	353.8 (65.24)
	Geometric mean	39.63	7.367	870.17	854.17	21.5	0.0619	11.2057	348.3
	Median	37.95	8.000	869.04	863.72	21.6	0.0633	10.9513	349.2
	%CV	22.8	19.3	23.5	22.9	23.7	18.7	17.2	18.4
	Min, Max	27.3, 58,5	6.00, 10.00	564.4, 1279.6	555.4, 1233.1	15, 33	0.047, 0.093	7.479, 14.808	264, 466

AUC_{inf}=area under the curve extrapolated to infinity; AUC_{last}= area under the curve from the time 0 to the last measurable concentration; C_{max}= maximum concentration occurring at t_{max}; CL/F=total body clearance for extravascular administration; λ_z=first order rate constant associated with the terminal (log-linear) portion of the curve; CV=coefficient of variation; max=maximum; min=minimum; SD=standard deviation; t_{max}= time of maximum observed concentration during a dosing interval; $t_{½}$=terminal half-life; V_z/F= volume of distribution based on the terminal phase following extravascular administration

[a] Due to insufficient information, elimination for 2 subjects cannot be characterized.

Summary of d-amphetamine Dose-normalized and Body Weight-normalized Pharmacokinetic Parameters by Age Group

Age Group	Statistic	C_{max} (ng/mL/mg)	AUC_{inf} (ng·h/mL/mg)	AUC_{last} (ng·h/mL/mg)	CL/F (L/h/kg)	V_z/F (L/kg)
6-12 years	n	13	11[a]	13	11[a]	11[a]
	Mean (SD)	3.12 (0.774)	69.54 (18.590)	68.65 (17.251)	0.4 (0.09)	5.8 (0.85)
	Geometric mean	3.03	67.40	66.72	0.4	5.7
	Median	2.94	62.73	62.47	0.4	5.8
	%CV	24.8	26.7	25.1	21.3	14.8
	Min, Max	2.0, 4.7	47.0, 103.5	46.4, 98.7	0, 1	4, 7
13-17 years	n	14	14	14	14	14
	Mean (SD)	2.16 (0.494)	47.60 (11.167)	46.68 (10.672)	0.4 (0.10)	6.0 (0.91)
	Geometric mean	2.11	46.41	45.56	0.4	5.9
	Median	2.02	46.35	46.06	0.4	5.8
	%CV	22.8	23.5	22.9	25.3	15.1
	Min, Max	1.5, 3.1	30.1, 68.2	29.6, 65.8	0, 1	4, 7

AUC_{inf}=area under the curve extrapolated to infinity; AUC_{last}= area under the curve from the time 0 to the last measurable concentration; C_{max}= maximum concentration occurring at t_{max}; CL/F=total body clearance for extravascular administration; CV=coefficient of variation; max=maximum; min=minimum; SD=standard deviation; V_z/F= volume of distribution based on the terminal phase following extravascular administration

[a] Due to insufficient information, elimination for 2 subjects cannot be characterized.

Summary of d-amphetamine Dose-normalized and Body Weight-normalized Pharmacokinetic Parameters by Gender

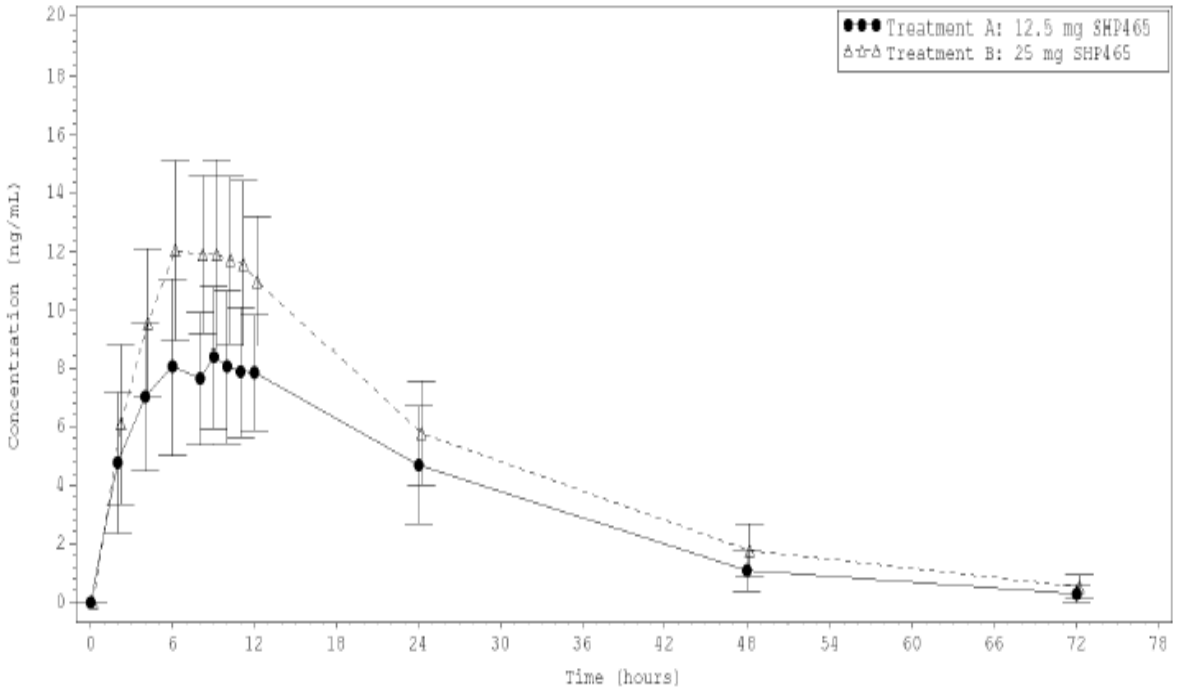
Gender	Statistic	C_{max} (ng/mL/mg)	AUC_{inf} (ng·h/mL/mg)	AUC_{last} (ng·h/mL/mg)	CL/F (L/h/kg)	V_z/F (L/kg)
Female	n	12	11	12	11	11
	Mean (SD)	2.55 (0.541)	57.28 (18.443)	58.21 (18.182)	0.4 (0.11)	5.7 (0.85)
	Geometric mean	2.50	54.89	55.76	0.4	5.6
	Median	2.46	53.41	53.48	0.4	5.5
	%CV	21.2	32.2	31.2	29.4	14.9
	Min, Max	1.9, 3.7	30.1, 103.5	29.6, 98.7	0, 1	4, 7
Male	n	15	14	15	14	14
	Mean (SD)	2.68 (0.969)	57.24 (18.894)	56.49 (18.223)	0.4 (0.08)	6.1 (0.88)
	Geometric mean	2.53	54.54	53.94	0.4	6.0
	Median	2.55	52.37	52.50	0.4	6.3
	%CV	36.1	33.0	32.3	18.3	14.5
	Min, Max	1.5, 4.7	33.7, 93.0	33.3, 92.6	0, 1	4, 7

AUC_{inf}=area under the curve extrapolated to infinity; AUC_{last}= area under the curve from the time 0 to the last measurable concentration; C_{max}= maximum concentration occurring at t_{max}; CL/F=total body clearance for extravascular administration; CV=coefficient of variation; max=maximum; min=minimum; SD=standard deviation; V_z/F= volume of distribution based on the terminal phase following extravascular administration

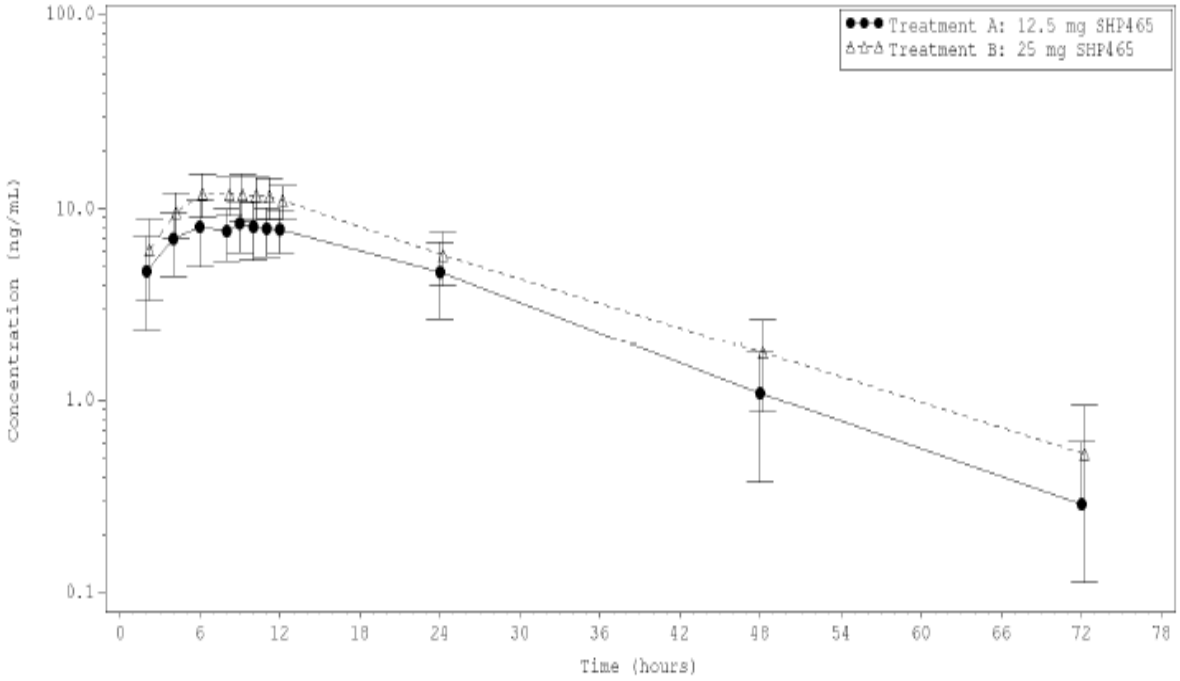
After correcting for dose, the exposure at the unit dose was lower in adolescents than children. After correcting for body weight, CL/F and Vz/F were similar between the age groups. No influence of gender on PK was observed.

L-amphetamine

Mean (±SD) l-amphetamine Plasma Concentration After Single Dose of SHP465



Mean (±SD) l-amphetamine Plasma Concentration After Single Dose of SHP465 (Log Scale)



Summary of l-amphetamine Pharmacokinetic Parameters by Age Group

Age Group	Statistic	C_{max} (ng/mL)	T_{max} (h)	AUC_{inf} (ng·h/mL)	AUC_{last} (ng·h/mL)	CL/F (L/h)	λ_z (1/h)	$t_{1/2}$ (h)	V_z/F (L)
6-12 years	n	13	13	12	13	12	12	12	12
	Mean (SD)	9.31 (2.374)	10.081 (4.6566)	225.09 (65.252)	222.06 (59.833)	14.9 (4.02)	0.0614 (0.01336)	11.8145 (2.76544)	251.5 (80.93)
	Geometric mean	9.04	9.381	216.91	214.68	14.4	0.0601	11.5393	239.8
	Median	8.98	9.000	204.23	203.89	15.3	0.0593	11.6954	231.0
	%CV	25.5	46.2	29.0	26.9	26.9	21.7	23.4	32.2
	Min, Max	6.2, 14.1	6.00, 24.00	148.3, 353.1	144.4, 322.1	9, 21	0.038, 0.086	8.098, 18.199	139, 397
13-17 years	n	14	14	14	14	14	14	14	14
	Mean (SD)	12.88 (3.205)	7.738 (1.7332)	326.09 (92.866)	314.37 (84.161)	20.6 (5.85)	0.0551 (0.01245)	13.1525 (2.90674)	377.0 (83.04)
	Geometric mean	12.52	7.561	314.43	304.10	19.9	0.0539	12.8605	368.8
	Median	12.55	8.000	321.14	309.71	19.5	0.0564	12.2827	352.1
	%CV	24.9	22.4	28.5	26.8	28.4	22.6	22.1	22.0
	Min, Max	8.1, 18.5	6.00, 11.00	186.8, 543.5	182.6, 496.7	11, 33	0.036, 0.086	8.071, 19.440	280, 515

AUC_{inf}=area under the curve extrapolated to infinity; AUC_{last}= area under the curve from the time 0 to the last measurable concentration; C_{max}= maximum concentration occurring at t_{max}; CL/F=total body clearance for extravascular administration; λ_z=first order rate constant associated with the terminal (log-linear) portion of the curve; CV=coefficient of variation; max=maximum; min=minimum; SD=standard deviation; t_{max}= time of maximum observed concentration during a dosing interval; $t_{½}$=terminal half-life; V_z/F= volume of distribution based on the terminal phase following extravascular administration

Summary of l-amphetamine Dose-normalized and Body Weight-normalized Pharmacokinetic Parameters by Age Group

Age Group	Statistic	C_{max} (ng/mL/mg)	AUC_{inf} (ng·h/mL/mg)	AUC_{last} (ng·h/mL/mg)	CL/F (L/h/kg)	V_z/F (L/kg)
6-12 years	n	13	12	13	12	12
	Mean (SD)	2.98 (0.760)	72.03 (20.881)	71.06 (19.147)	0.4 (0.09)	6.7 (1.31)
	Geometric mean	2.89	69.41	68.70	0.4	6.6
	Median	2.87	65.35	65.24	0.4	6.4
	%CV	25.5	29.0	26.9	22.0	19.6
	Min, Max	2.0, 4.5	47.5, 113.0	46.2, 103.1	0, 1	5, 10
13-17 years	n	14	14	14	14	14
	Mean (SD)	2.06 (0.513)	52.18 (14.859)	50.30 (13.466)	0.4 (0.11)	6.3 (0.97)
	Geometric mean	2.00	50.31	48.66	0.3	6.3
	Median	2.01	51.38	49.55	0.3	6.3
	%CV	24.9	28.5	26.8	29.8	15.3
	Min, Max	1.3, 3.0	29.9, 87.0	29.2, 79.5	0, 1	4, 8

AUC_{inf}=area under the curve extrapolated to infinity; AUC_{last}= area under the curve from the time 0 to the last measurable concentration; C_{max}= maximum concentration occurring at t_{max}; CL/F=total body clearance for extravascular administration; CV=coefficient of variation; max=maximum; min=minimum; SD=standard deviation; V_z/F= volume of distribution based on the terminal phase following extravascular administration

Summary of l-amphetamine Dose-normalized and Body Weight-normalized Pharmacokinetic Parameters by Gender

Gender	Statistic	C_{max} (ng/mL/mg)	AUC_{inf} (ng·h/mL/mg)	AUC_{last} (ng·h/mL/mg)	CL/F (L/h/kg)	V_z/F (L/kg)
Female	n	12	11	12	11	11
	Mean (SD)	2.44 (0.523)	62.74 (21.528)	62.31 (19.585)	0.3 (0.11)	5.9 (0.72)
	Geometric mean	2.39	59.67	59.51	0.3	5.8
	Median	2.43	58.05	56.76	0.3	5.9
	%CV	21.4	34.3	31.4	32.9	12.2
	Min, Max	1.7, 3.5	29.9, 113.0	29.2, 103.1	0, 1	4, 7
Male	n	15	15	15	15	15
	Mean (SD)	2.55 (0.960)	60.31 (19.894)	58.68 (19.556)	0.4 (0.08)	6.9 (1.17)
	Geometric mean	2.39	57.43	55.85	0.4	6.9
	Median	2.39	52.09	51.17	0.4	6.8
	%CV	37.6	33.0	33.3	20.7	16.9
	Min, Max	1.3, 4.5	33.9, 98.5	33.2, 97.7	0, 1	5, 10

AUC_{inf}=area under the curve extrapolated to infinity; AUC_{last}= area under the curve from the time 0 to the last measurable concentration; C_{max}= maximum concentration occurring at t_{max}; CL/F=total body clearance for extravascular administration; CV=coefficient of variation; max=maximum; min=minimum; SD=standard deviation; V_z/F= volume of distribution based on the terminal phase following extravascular administration

Lower exposure to *l*-amphetamine than to *d*-amphetamine was observed, which approximately corresponded to the dose ratio (3:1) between *d*- and *l*-amphetamine. After correcting for body weight, CL/F and Vz/F were similar between the age groups. No influence of gender was observed.

Safety

Was there any death or serious adverse events? No

The sponsor stated that overall, 3 TEAEs were reported by 3 subjects (10.7%), of which 2 TEAEs were of mild severity and 1 TEAE was of moderate severity: cough which was assessed to be related to investigational product (IP) but resolved on the same day, increased hepatic enzyme which was rated as not related to IP and headache which was rated as related to IP. The sponsor reported that the increased hepatic enzyme resolved without any corrective measures.

Summary
The study evaluated pharmacokinetics, safety, and tolerability of SHP465 in children aged 6-12 years and adolescents aged 13-17 years with ADHD after a single oral dose of SHP465 12.5 mg or 25 mg. After correcting for dose, the mean Cmax and AUC d-amphetamine were about 44% and 46%, respectively higher in children than adolescents

suggesting that the exposure at the unit dose was lower in adolescents than children. Similar results were observed for l-amphetamine. Lower exposure to *l*-amphetamine than to *d*-amphetamine was observed, which approximately corresponded to the dose ratio (3:1) between *d*- and *l*-amphetamine. The mean tmax of *d*-amphetamine was 9.30 h in children and 7.50 h in adolescents and the mean T ½ was 9.91 h in children and 11.37 h in adolescents. After correcting for body weight, CL/F and Vz/F were similar between the age groups.

Three Treatment Emergent Adverse Events (TEAEs) were reported; none were severe and 1 TEAE was reported as related to SHP465 by the investigator. No deaths or treatment-emergent SAEs were reported during the study; no subject discontinued the study due to a TEAE.

Reviewer Comments

The study was designed to evaluate the pharmacokinetics of d-amphetamine and l-amphetamine after administration of a single dose of SHP465 in pediatric patients for children aged 6-12 years and adolescents aged 13-17 years. To exclude any effects of concomitant ADHD medication on the PK of SHP465, all eligible subjects discontinued their ongoing ADHD medications from 7 days prior to dosing on Day 1.The design was adequate to compare exposure levels in pediatric patients. The method of analysis is adequate. Exposure in children is greater than adolescents when adjusted for dose in this study. Clearance and volume of distribution appear similar when adjusted for weight of children and adolescents. Tmax occurred at about 2 hours later in children 6 – 12 years compared to adolescents 13 -17 years.

4.3 Population PK and/or PD Analyses

A population PK model was developed to characterize the PK of d-amphetamine and l-amphetamine in adult volunteers as well as pediatric patients with ADHD. and to assess the effect of covariates on Mydayis PK. Sponsor utilized PK data from n=74 healthy adult subjects and n=28 pediatric ADHD patients containing 2918 d-amphetamine and 2918 l-amphetamine concentrations (2786 and 2764 measurements that were not BLQ for d- and l-amphetamine).

The following table summarizes the studies included in the population PK model generation.

Table 4.3.1: Clinical Trials Included in the Population PK Dataset

Study	Number of Subjects	Dose (mg)	Population
SPD465-103	20	37.5	adult
SPD465-105	16	50	adult
SPD465-107	20	12.5	adult
SPD465-110	18	12.5, 25, 50, 75	adult
SHP465-111	28	12.5, 25	pediatric

Source: page 16 of 389 in shr0301.pdf, sequence 0022, module 5335

SHP465-103 (adult): Phase 1 study to compare PK of a single 37.5 mg Mydayis capsule with PK of a single administration of Adderall XR® 25 mg + mixed amphetamine salts IR 12.5 mg in n=19 healthy adult subjects. Plasma concentrations for D- and L-amphetamine were determined prior to the first dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours post-dose for each treatment.

SHP465-105 (adult): Phase 1 study to assess the effect of a high-fat meal on the bioavailability 50 mg Mydayis dose in n=16 healthy adult subjects. Plasma concentrations for D- and L-amphetamine were determined prior to the first dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours post-dose for each treatment period.

SHP465-107 (adult): Phase 1, 3-period, 4-treatment study to assess the safety, tolerability, and PK of escalating Mydayis dose levels (from 12.5 to 75 mg) in n=20 healthy adults. Initial dose level is 12.5 mg once daily for 7 days. Afterwards, half the subjects escalate to 25 mg once daily for 7 days and other half of the subjects escalate to 50 mg once daily. In Period 3, patients were increased to 75 mg once daily for 7 days. Sparse PK samples were collected on Days 5 and 6 of each treatment period. PK samples were collected at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours post-dose on Days 1 and 7 of each treatment period.

[*Reviewer comment: Sponsor states that Study 107 was terminated due to a disruption in study drug dosing and pharmacokinetic analysis was performed for the 12.5 mg dose level administered. Study 110 is appears to be an attempt to gather the data that was not collected in Study 107.*]

SHP465-110 (adult): Same design as Study 107 except n=18 healthy subjects were enrolled.

SHP465-111 (pediatric): Phase 1, multicenter, open-label study to assess PK and safety of d-amphetamine and l-amphetamine of single-doses of 12.5 or 25 mg Mydayis administered to n=27 patients age 6-17 years after an 8-hour fast. Plasma concentrations for D- and L-amphetamine were determined pre dose and at 2, 4, 6, 8, 9, 10, 11, 12, 24, 48, and 72 hours post-dose.

Methodology: Sponsor utilized nonlinear mixed effects modeling using NONMEM software Version 7 Level 3 (Icon Development Solutions, Hanover, MD). Sponsor developed separate models with the same structure for D-amphetamine and L-amphetamine. Sponsor assessed model adequacy and decisions to increase model complexity using visual inspection of diagnostic scatter plots, successful convergence of minimization routing, plausibility of parameter estimates, precision of parameter estimates, and correlation between model parameter estimation errors < 0.95.

Absorption and Distribution: Sponsor utilized a dual zero-1st order absorption model. A zero-order (infusion) process parameterized with infusion durations D1 and D3 was used to describe transport of drug into the depots (compartments 1 and 3). F1 and F3 are the bioavailability for the two depots (where F1 + F3 = 1). However, the absolute bioavailability is not known.

A first-order process was used to describe absorption from the depots into the central compartment (compartment 2). Sponsor also estimated a separate first-order absorption rate constant from a depot (compartment 3) into the central compartment for study 110 ($Ka3_{110}$) in order to explore an apparent effect of study number on the PK of both isomers.

The food effect on amphetamine PK (a delay in T_{max} without any relevant effect on extent of absorption) was modelled by allowing the presence of food to increase the duration (D1) of the infusion into a depot (compartment 1).

Elimination: Sponsor utilized a linear elimination process to describe the disappearance from the central compartment. The elimination model is parameterized in terms of apparent clearance and apparent volume of distribution.

Covariates: Sponsor determined that weight was the main covariate affecting PK of both isomers. Weight-based allometric scaling was applied to both apparent clearance and apparent volume of distribution.

The final model parameters for D-amphetamine model and the L-amphetamine model are shown in the following tables.

Table 4.3.2: Population PK Parameters for Final D-Amphetamine Model (Run 56)

parameter	estimate	NONMEM 95% CI
$CL/F(\theta_1)$	25.2 L/h	23.1, 27.4
$\cdot (WT/70)^{0.75}$		
$\cdot CLeff_{FEMALE}(\theta_{10})$	0.999	0.900, 1.11
$V/F(\theta_2)$	419 L	402, 436
$\cdot (WT/70)^{1}$		
$\cdot Veff_{FEMALE}(\theta_{11})$	0.936	0.873, 1.00
$Ka1(\theta_3)$	0.765 h^{-1}	0.529, 1.11
$Ka3(\theta_4)$	1.40 h^{-1}	0.711, 2.74
$Ka3_{110}(\theta_8)$	4.73 h^{-1}	0.987, 22.7
$D1(\theta_5)$	0.702 h	0.463, 1.06
$D1_{FED}(\theta_9)$	13.6 h	10.2, 18.2
$D3(\theta_6)$	7.18 h	6.66, 7.74
$F1(\theta_7)$	0.385	0.343, 0.428
$F3$	0.615	0.572, 0.657
$\Omega^{1.1} CL/F$	0.0349 (%CV=18.7)	0.0186, 0.0511
$\Omega^{2.1} COV_{CL/F-V/F}$	0.0103 (r=0.498)	0.00106, 0.0195
$\Omega^{2.2} V/F$	0.0122 (%CV=11.1)	0.00427, 0.0202
$\Omega^{3.1} COV_{CL/F-Ka1}$	-0.000460 (r=-0.00527)	−0.0446, 0.0437
$\Omega^{3.2} COV_{V/F-Ka1}$	0.00115 (r=0.0223)	−0.0279, 0.0302
$\Omega^{3.3} Ka1$	0.218 (%CV=46.7)	0, 0.470
$\Omega^{4.1} COV_{CL/F-Ka3}$	0.0150 (r=0.0682)	−0.111, 0.141
$\Omega^{4.2} COV_{V/F-Ka3}$	-0.0470 (r=-0.360)	−0.129, 0.0354
$\Omega^{4.3} COV_{Ka1-Ka3}$	0.0172 (r=0.0312)	−0.292, 0.326
$\Omega^{4.4} Ka3$	1.39 (%CV=118)	0, 3.13
$\Omega^{5.1} COV_{CL/F-D1}$	0.0345 (r=0.730)	−0.0162, 0.0853
$\Omega^{5.2} COV_{V/F-D1}$	0.0200 (r=0.713)	−0.0224, 0.0624
$\Omega^{5.3} COV_{Ka1-D1}$	0.0269 (r=0.227)	−0.148, 0.202
$\Omega^{5.4} COV_{Ka3-D1}$	-0.149 (r=-0.497)	−0.500, 0.203
$\Omega^{5.5} D1$	0.0642 (%CV=25.3)	0, 0.207
$\sigma^{1.1} prop$	0.0282 (%CV=16.8)	0.0271, 0.0293
$\sigma^{2.2} add$	0.250 (SD=0.500)	0.107, 0.392

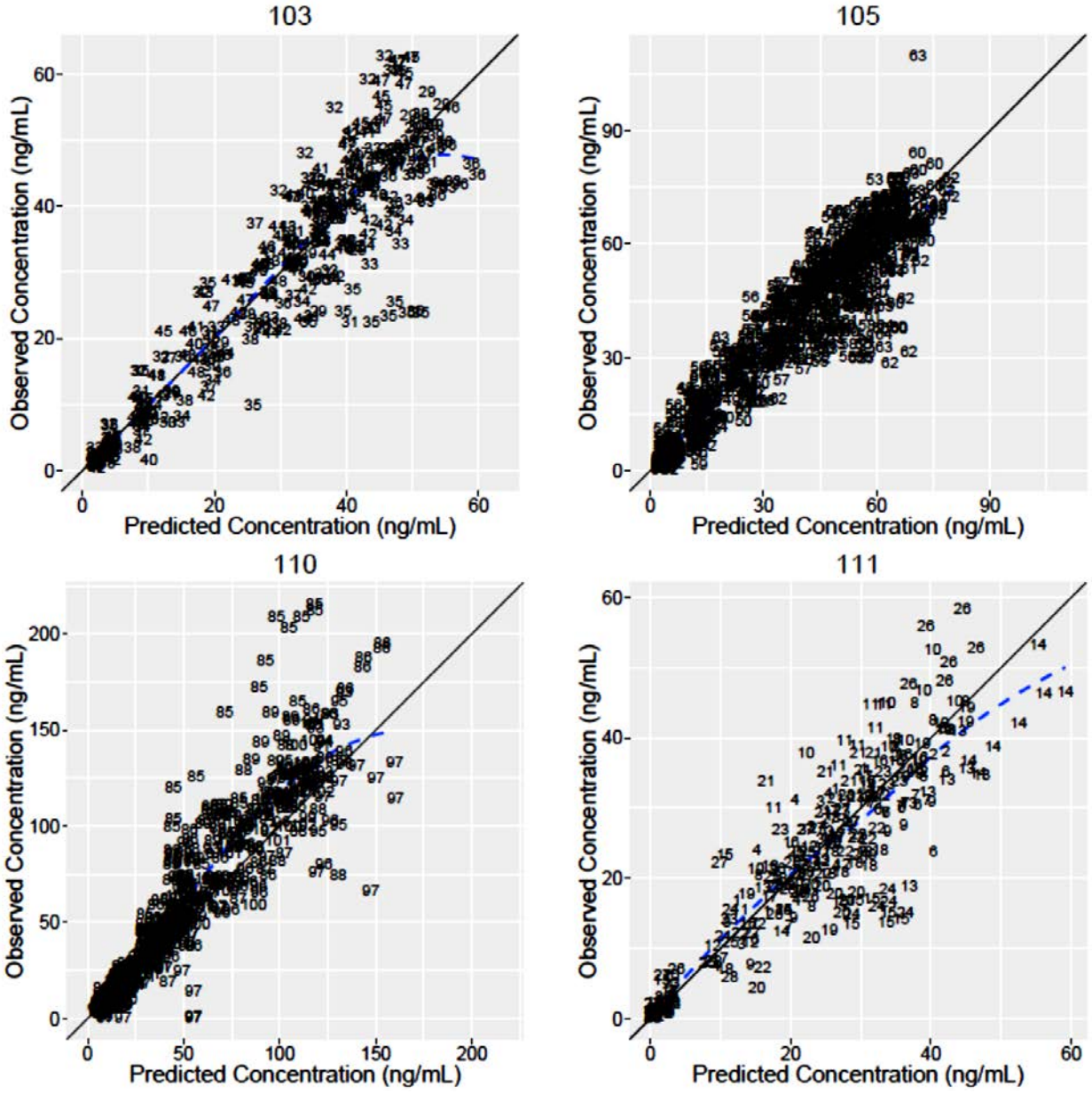
CL/F = clearance, $CLeff_{FEMALE}$ = multiplier to determine CL/F in females, V/F = central volume, $Veff_{FEMALE}$ = multiplier to determine V/F in females, Ka1 = absorption rate constant cmpt. one, Ka3 = absorption rate constant compt. three, $Ka3_{110}$ = absorption rate constant compt. three (Study 110), D1 = duration compt. one, $D1_{FED}$ = duration compt. one (FED), D3 = duration compt. three, F1 = bioavailablity compt. one, F3 = bioavailablity compt. three, WT = baseline weight, Ω = interindividual variance (%CV), σ = residual variance (proportional (prop) or additive (add)), r = correlation, COV = covariance, %CV = percent coefficient of variation.

(*source: population PK report shr0301.pdf, page 46 of 389*)

Sponsor indicates that, based on covariate analysis results, sex is not expected to be a clinically relevant covariate for D-amphetamine PK.

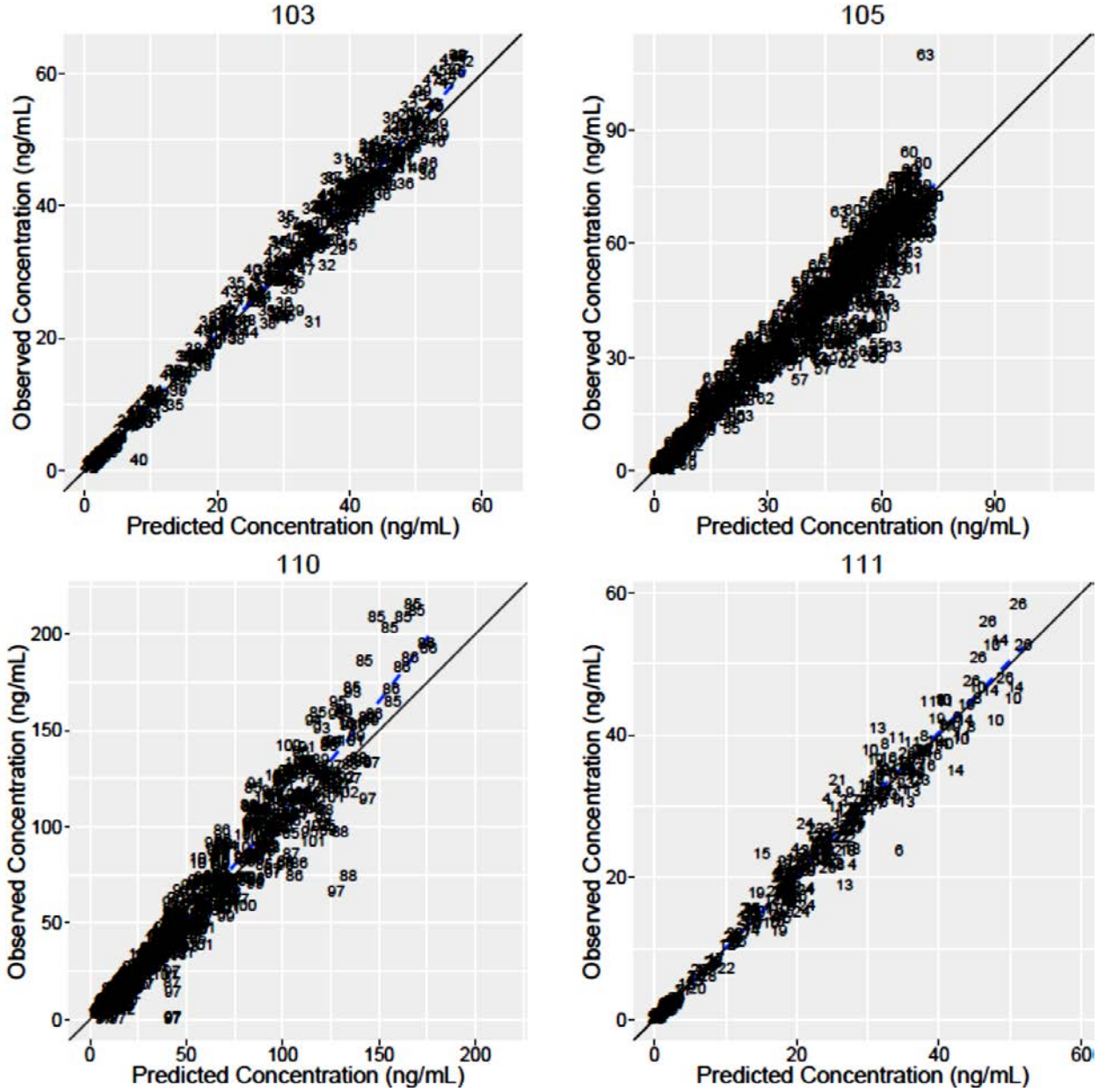
The following diagnostic plots were utilized to guide the development of the models for D-amphetamine.

Figure 4.3.1: PRED vs DV by Study – (Model 56, Final D-amphetamine Model)



(*source: population PK report shr301.pdf, page 116 of 389*)

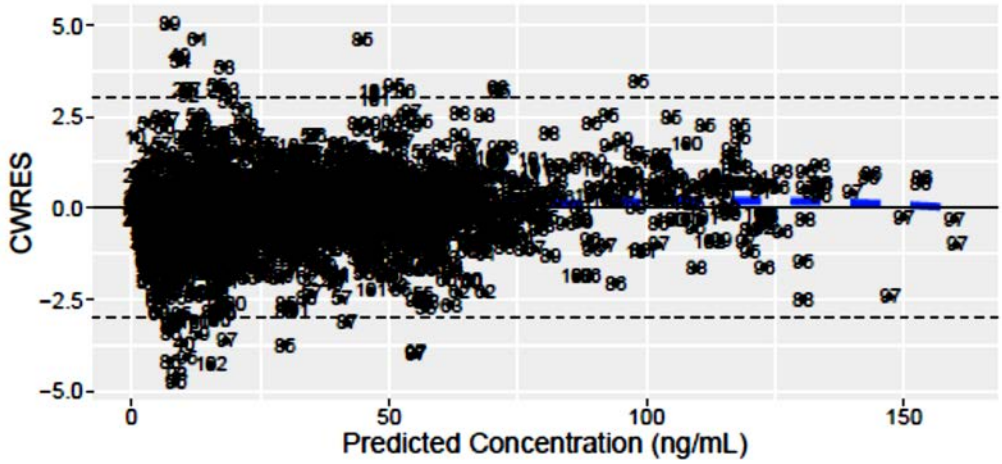
Figure 4.3.2: IPRE vs DV – (Model 56, Final D-amphetamine Model)



(*source: population PK report shr301.pdf, page 117 of 389*)

[*Reviewer comment: While some bias may be present in study 110, the Sponsor's analyses did not identify any covariates to explain the apparent "study effect" phenomena.*]

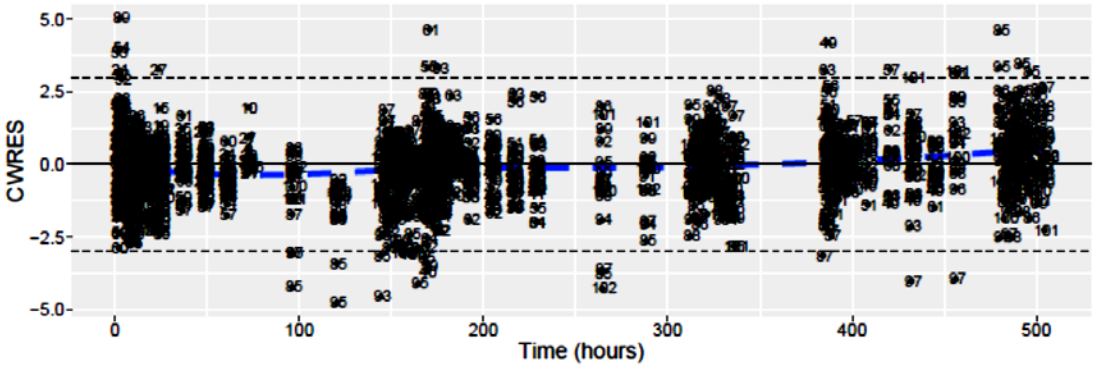
Figure 4.3.3: CWRES vs PRED – (Model 56, Final D-amphetamine Model)



Conditional weighted residuals are plotted versus d-amphetamine population predictions. Values are indicated by black circles and marked with patient ID. The blue dashed line is a loess smooth. A solid black line at $y = 0$ and dashed lines at $y = 3$ and $y = -3$ are included as references.

(*source: population PK report shr301.pdf, page 119 of 389*)

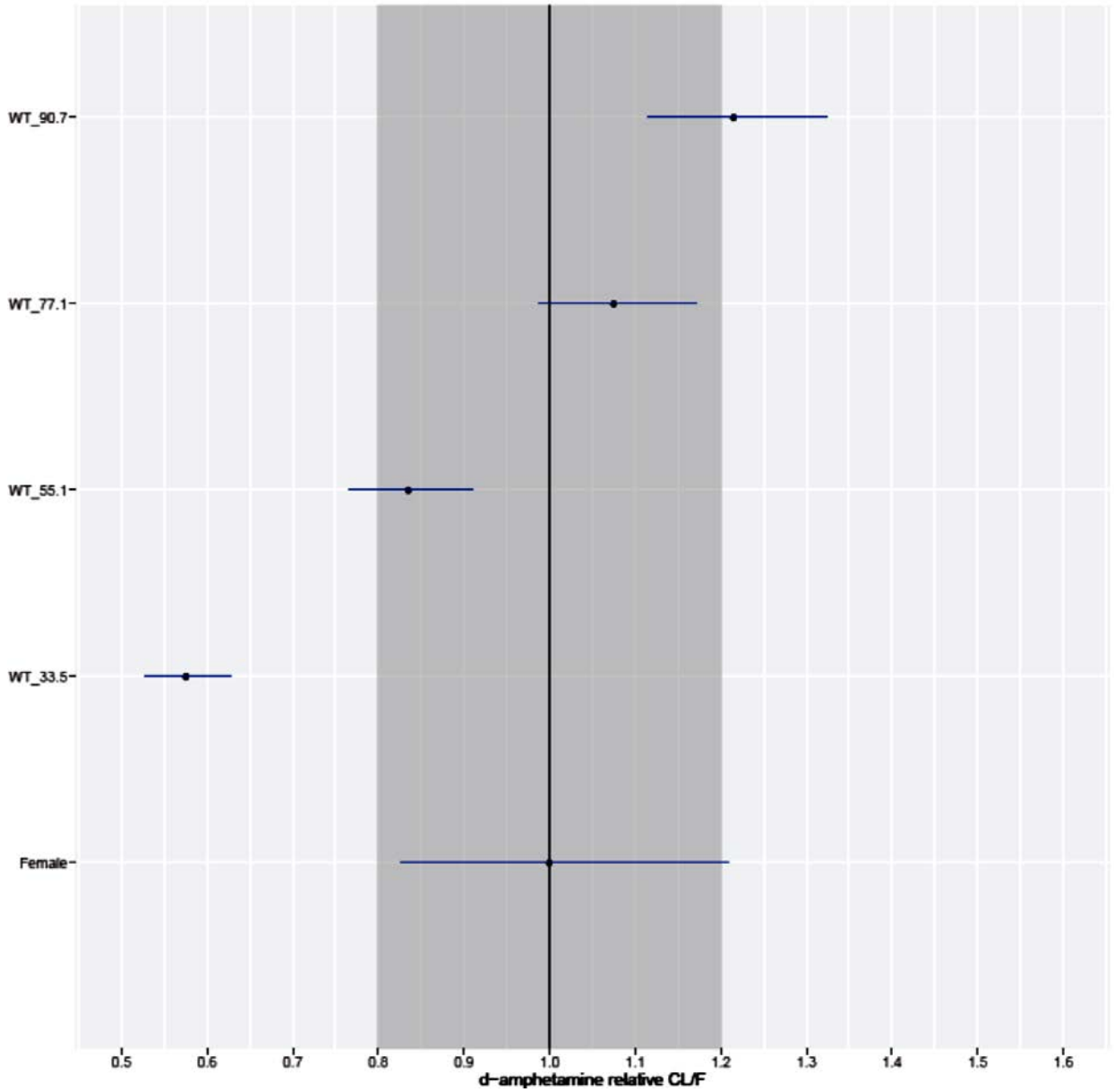
Figure 4.3.4: CWRES vs TIME – (Model 56, Final D-amphetamine Model)



(*source: population PK report shr301.pdf, page 121 of 389*)

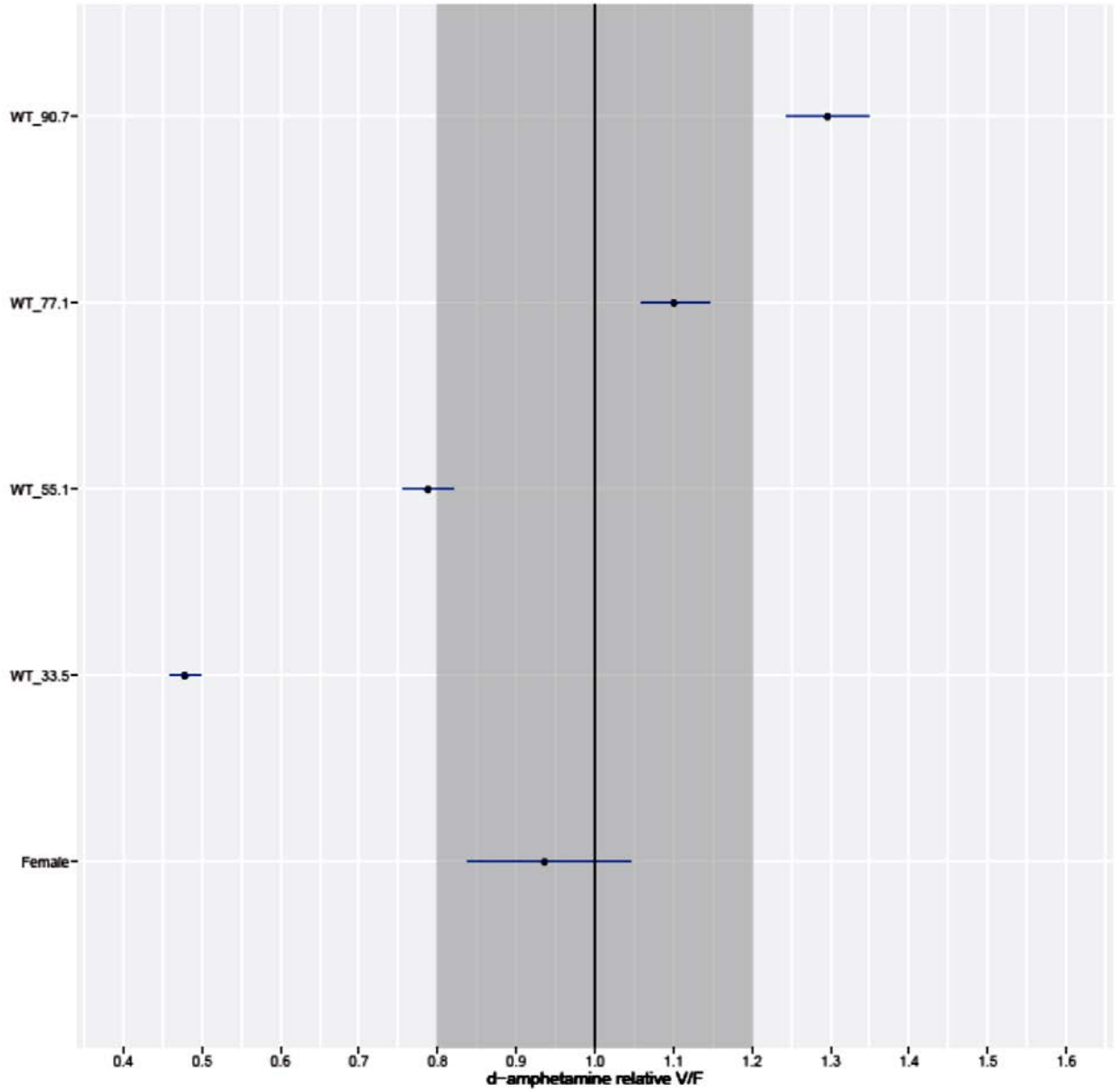
[*Reviewer comment: Based on the residual plots, there is no apparent bias for the D-amphetamine model throughout the dosing interval or across the range of observed concentrations.*]

Figure 4.3.5: ETA CL vs Weight – (Model 56, Final D-amphetamine Model)



(*source: population PK report shr301.pdf, page 137 of 389*)

Figure 4.3.6: ETA V vs Weight – (Model 56, Final D-amphetamine Model)



(*source: population PK report shr301.pdf, page 138 of 389*)

[*Reviewer comment: The plots of eta CL versus weight and eta V versus weight support the inclusion of weight as a covariate for CL and V for D-amphetamine.*]

Table 4.3.3: Population PK Parameters for Final L-Amphetamine Model (Run 308)

parameter	estimate	NONMEM 95% CI
$CL/F(\theta_1)$	23.7 L/h	21.6, 26.0
$\cdot (WT/70)^{0.75}$		
$\cdot CLeff_{FEMALE}(\theta_{10})$	1.01	0.903, 1.13
$V/F(\theta_2)$	483 L	463, 504
$\cdot (WT/70)^1$		
$\cdot Veff_{FEMALE}(\theta_{11})$	0.939	0.873, 1.01
$Ka1(\theta_3)$	0.506 h^{-1}	0.377, 0.677
$Ka3(\theta_4)$	1.63 h^{-1}	0.806, 3.31
$Ka3_{110}(\theta_8)$	11.4 h^{-1}	0.501, 260
$D1(\theta_5)$	0.280 h	0.0682, 1.15
$D1_{FED}(\theta_9)$	10.4 h	4.44, 24.4
$D3(\theta_6)$	7.40 h	6.84, 8.01
$F1(\theta_7)$	0.450	0.395, 0.505
$F3$	0.550	0.495, 0.605
$\Omega^{1.1} CL/F$	0.0463 (%CV=21.5)	0.0253, 0.0673
$\Omega^{2.1} COV_{CL/F-V/F}$	0.0104 (r=0.447)	$6.31e-05$, 0.0208
$\Omega^{2.2} V/F$	0.0117 (%CV=10.8)	0.00468, 0.0188
$\Omega^{3.1} COV_{CL/F-Ka1}$	-0.0138 (r=-0.166)	−0.0455, 0.0178
$\Omega^{3.2} COV_{V/F-Ka1}$	-0.00351 (r=-0.0836)	−0.0224, 0.0153
$\Omega^{3.3} Ka1$	0.150 (%CV=38.8)	0.0191, 0.282
$\Omega^{4.1} COV_{CL/F-Ka3}$	0.0547 (r=0.192)	−0.113, 0.222
$\Omega^{4.2} COV_{V/F-Ka3}$	-0.0514 (r=-0.359)	−0.151, 0.0478
$\Omega^{4.3} COV_{Ka1-Ka3}$	0.0628 (r=0.122)	−0.196, 0.321
$\Omega^{4.4} Ka3$	1.75 (%CV=132)	0, 3.77
$\Omega^{5.5} D1$	0.380 (%CV=61.6)	0, 0.953
$\sigma^{1.1} prop$	0.0253 (%CV=15.9)	0.0245, 0.0262
$\sigma^{2.2} add$	0.0581 (SD=0.241)	0.0358, 0.0804

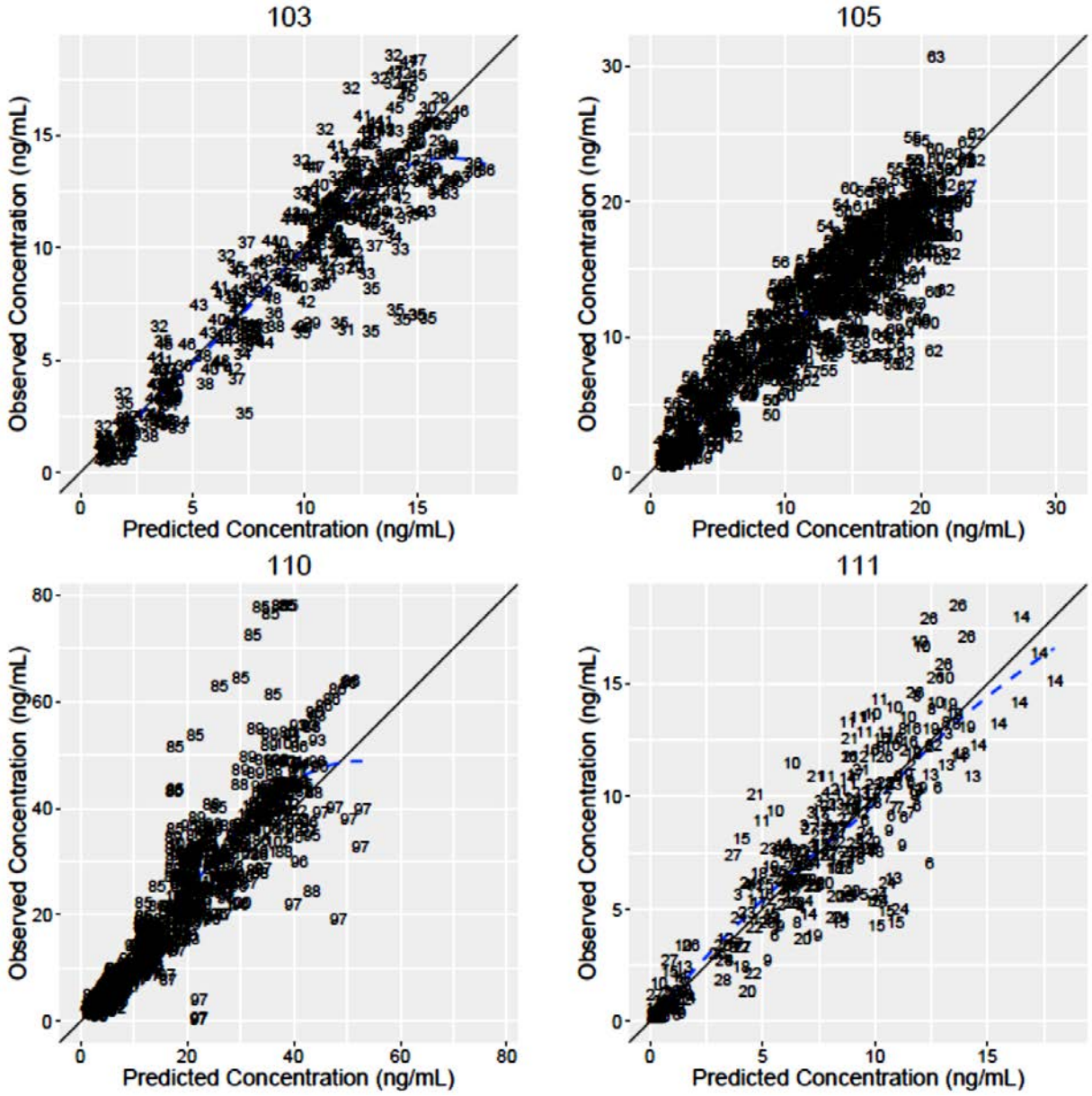
CL/F = clearance, $CLeff_{FEMALE}$ = multiplier to determine CL/F in females, V/F = central volume, $Veff_{FEMALE}$ = multiplier to determine V/F in females, Ka1 = absorption rate constant cmpt. one, Ka3 = absorption rate constant compt. three, $Ka3_{110}$ = absorption rate constant compt. three (Study 110), D1 = duration compt. one, $D1_{FED}$ = duration compt. one (FED), D3 = duration compt. three, F1 = bioavailablity compt. one, F3 = bioavailablity compt. three, WT = baseline weight, Ω = interindividual variance (%CV), σ = residual variance (proportional (prop) or additive (add)), r = correlation, COV = covariance, %CV = percent coefficient of variation.

(*source: population PK report shr0301.pdf, page 60 of 389*)

Sponsor indicates that, based on covariate analysis results, sex is not expected to be a clinically relevant covariate for L-amphetamine PK.

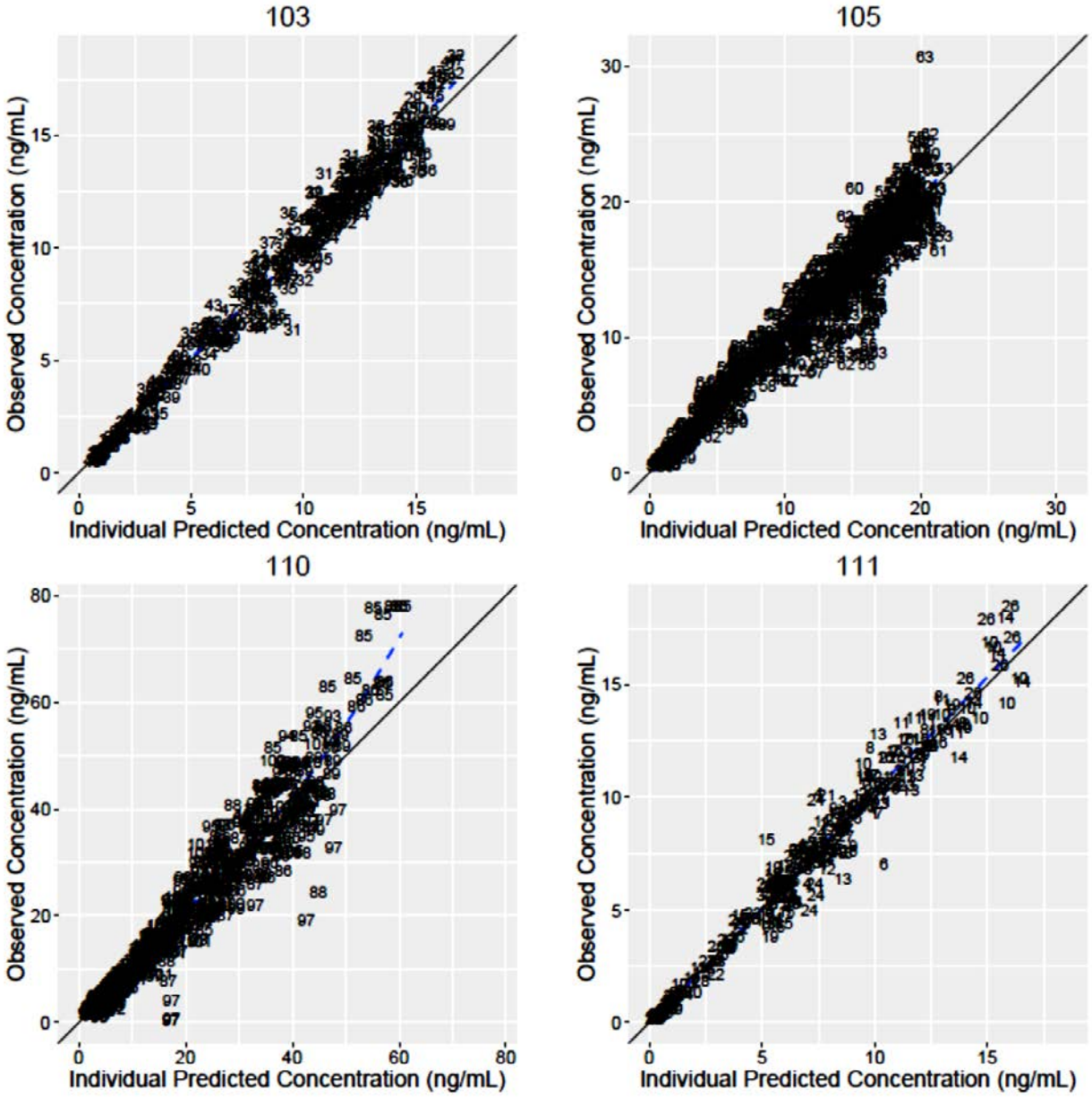
The following diagnostic plots were utilized to guide the development of the models for L-amphetamine.

Figure 4.3.7: PRED vs DV by Study – (Model 308, Final L-amphetamine Model)



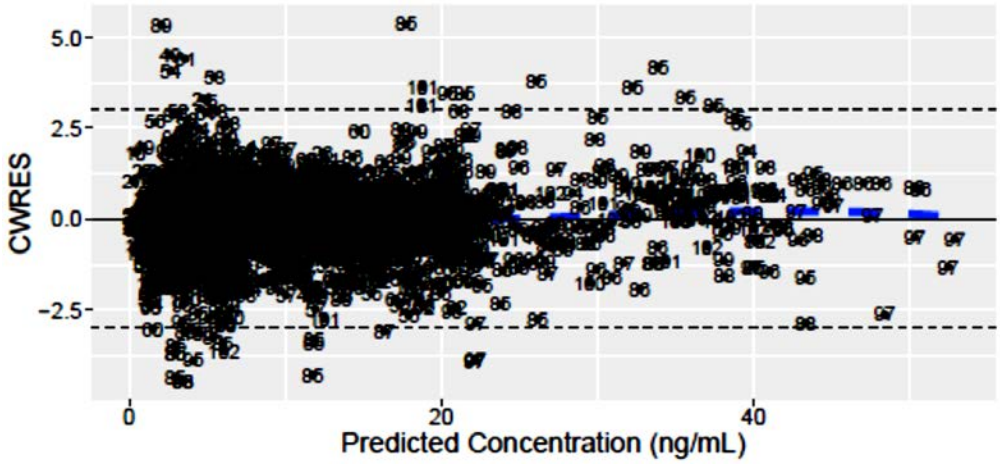
(*source: population PK report shr301.pdf, page 172 of 389*)

Figure 4.3.8: IPRE vs DV by Study – (Model 308, Final L-amphetamine Model)



(*source: population PK report shr301.pdf, page 173 of 389*)

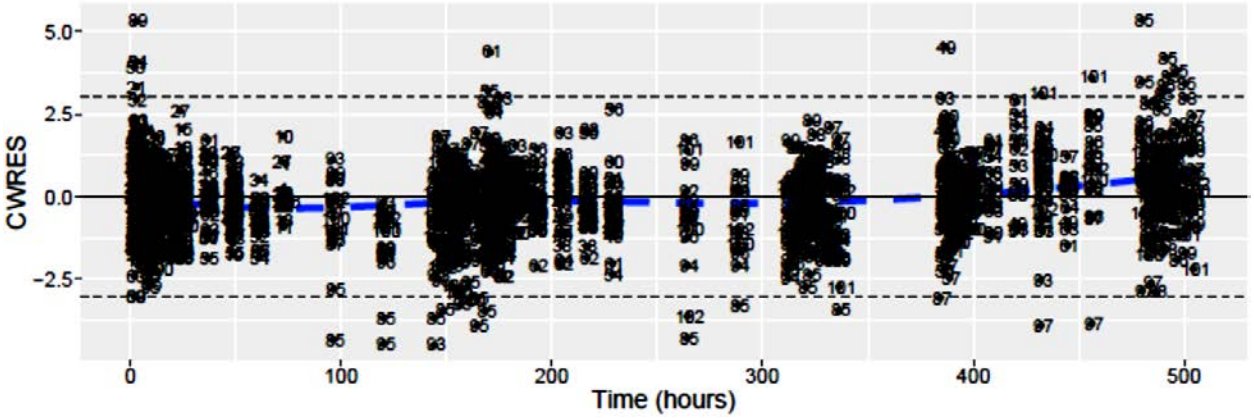
Figure 4.3.9: CWRES vs PRED – (Model 308, Final L-amphetamine Model)



Conditional weighted residuals are plotted versus l-amphetamine population predictions. Values are indicated by black circles and marked with patient ID. The blue dashed line is a loess smooth. A solid black line at y = 0 and dashed lines at y = 3 and y = -3 are included as references.

(*source: population PK report shr301.pdf, page 175 of 389*)

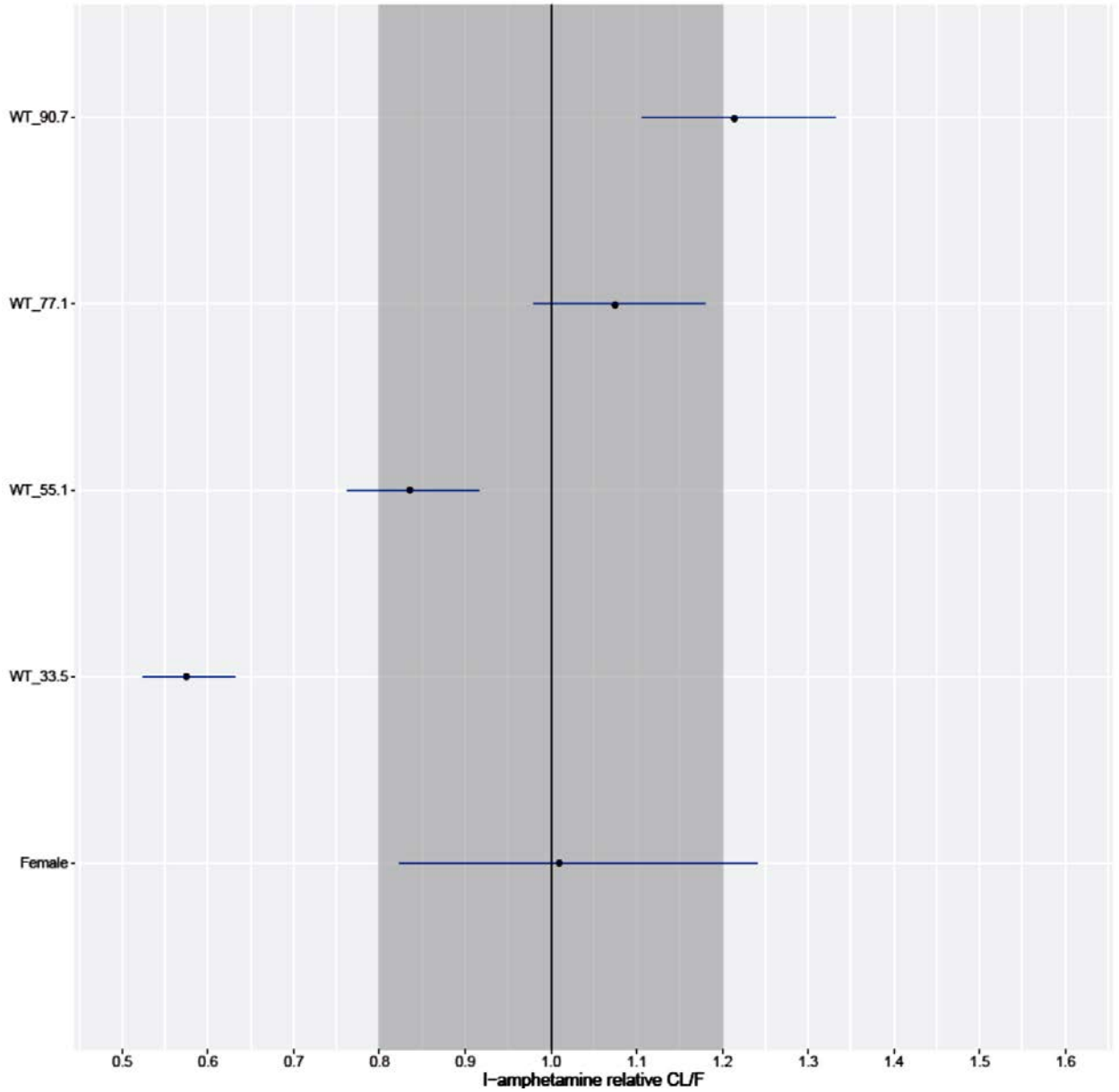
Figure 4.3.10: CWRES vs TIME – (Model 308, Final L-amphetamine Model)



Conditional weighted residuals are plotted versus time (hours) for l-amphetamine. Values are indicated by black circles and marked with patient ID. The blue dashed line is a loess smooth. A solid black line at y = 0 and dashed lines at y = 3 and y = -3 are included as references.

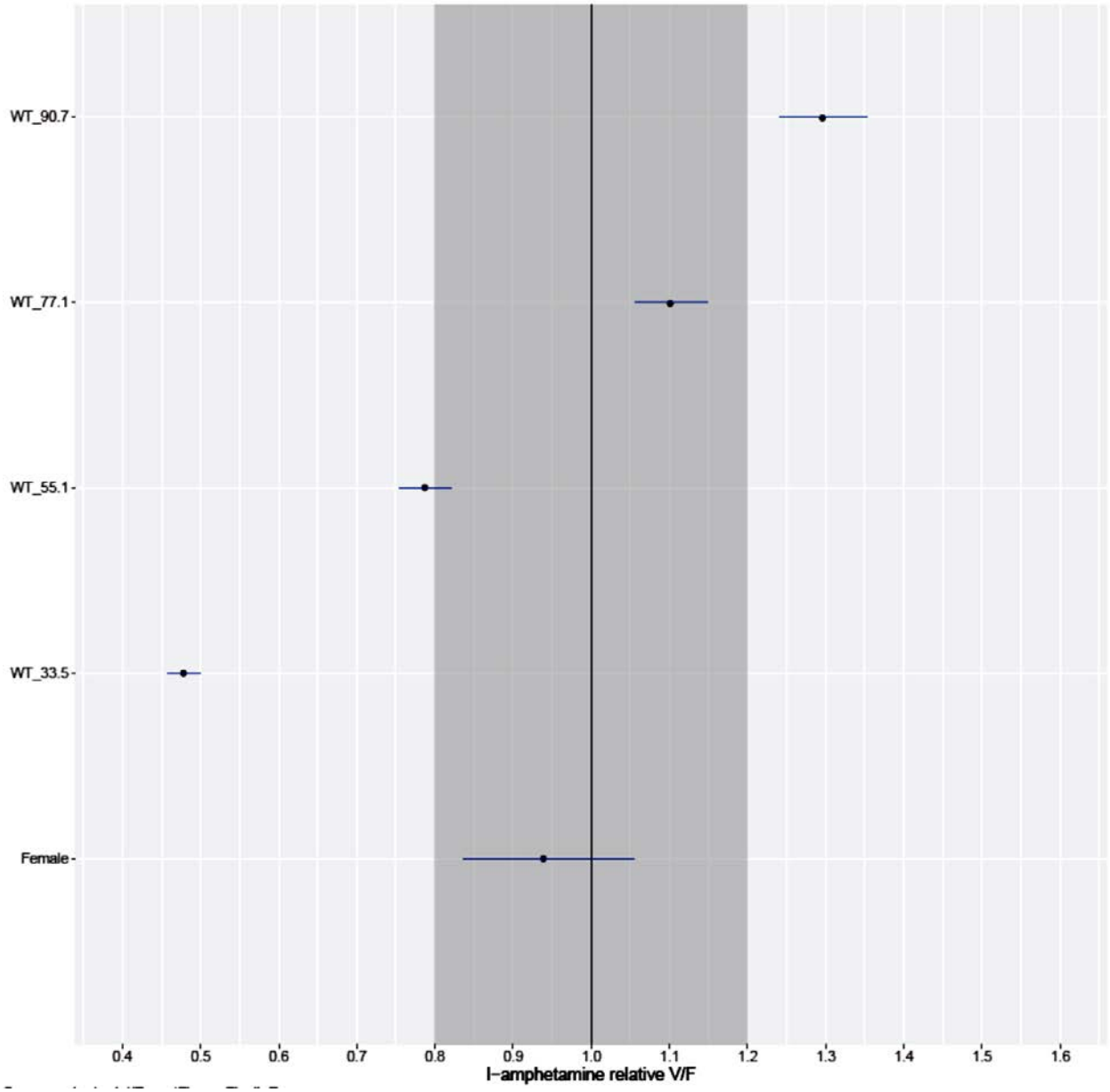
(*source: population PK report shr301.pdf, page 177 of 389*)

Figure 4.3.11: ETA CL vs Weight – (Model 308, Final L-amphetamine Model)



(*source: population PK report shr301.pdf, page 193 of 389*)

Figure 4.3.12: ETA V vs Weight – (Model 308, Final L-amphetamine Model)



(*source: population PK report shr301.pdf, page 194 of 389*)

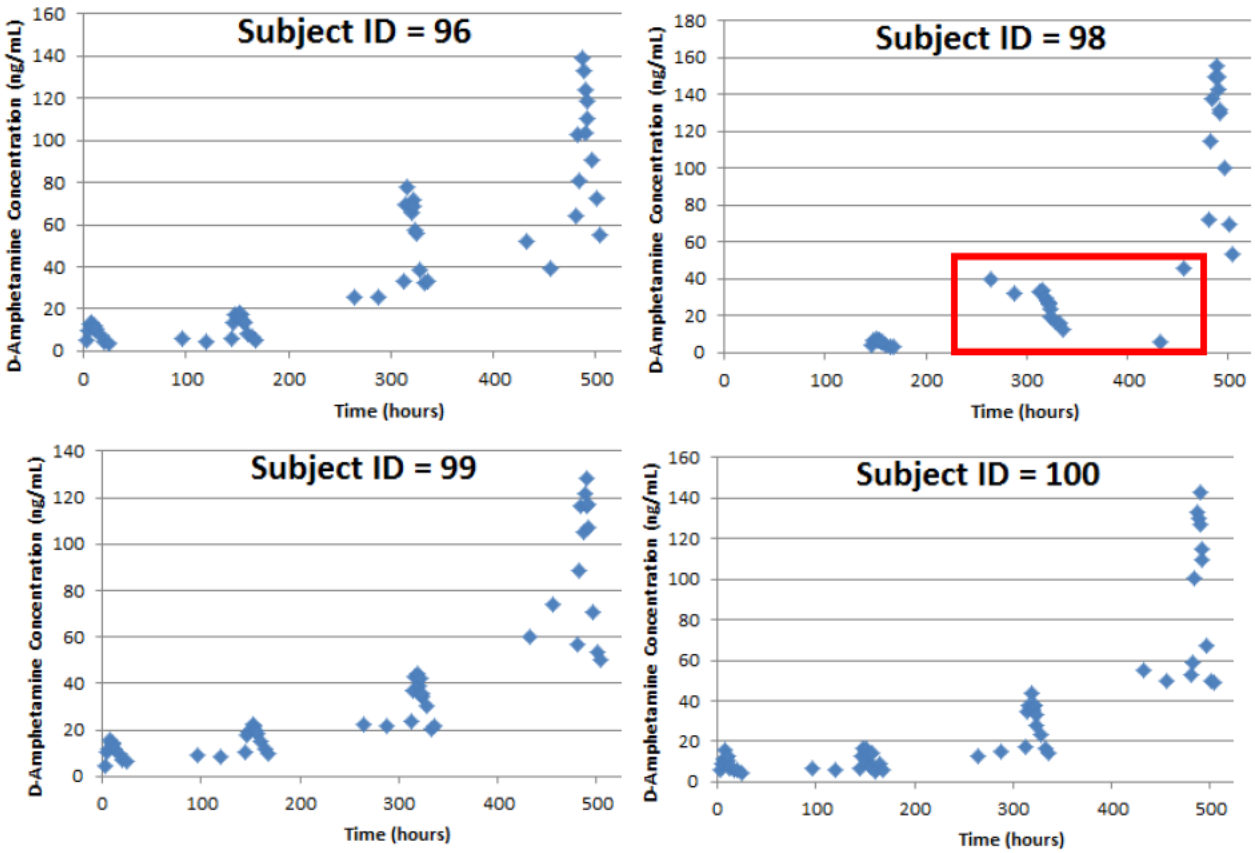
[*Reviewer comment: The plots of eta CL versus weight and eta V versus weight support the inclusion of weight as a covariate for CL and V for L-amphetamine.*]

Effect of Study 107: For both isomers Study 107 demonstrated CL/F 27.3% higher than other studies in the analyses. Sponsor reports that there is no covariates that could explain the difference from other studies. Overall Sponsor concludes that there is no clear explanation for this apparent between-study variation in CL/F.

[*Reviewer comment: Sponsor indicates that Study 107 was terminated due to a disruption in study drug dosing and PK data were only available from the 12.5 mg dose level (clinical-pharmacology.pdf, page 7 of 49). Study 111 has the same design as Study 107 but provided PK data from all arms (12.5 mg initial dose, escalation to 25 mg, escalation to 37.5 mg, and final escalation to 50 mg). In addition, as there is a 27.3% higher clearance in this study with no apparent explanation, and since there is incomplete data from this study, it is acceptable to exclude patients from this study in the population PK analyses. Sponsor also indicates that Study 110 had a faster absorption rate constant from Depot 2 (compartment 3).*]

Subject ID=98: Sponsor indicates that subject ID=98 in Study 110 had a very unusual PK profile during the 3rd sampling period which appeared as if this patient missed their dose. Sponsor indicates that a review of the source data did not indicate any issues. Overall, Sponsor determined that PK data from ID=98 should be excluded from population PK analyses.

Figure* 4.3.13*: Individual PK Profiles from Subjects Enrolled Study 110



[*Reviewer comment: The PK profile for subject ID=98 was visually compared with other subjects.*

This reviewer agrees with the Sponsor that Subject 98 has an unusual PK profile around 3rd rich PK sampling period (indicated with the red box in the figure above). The profile doesn't appear to be consistent with the general trend observed with other patients. Overall, it is reasonable to remove subject 98 from PK analyses.]

Sponsor reports that the apparent clearance estimated from their population PK analyses for D-amphetamine (25.2 L/h) is comparable to a value reported in Roberts et al., 2015 (28.7 L/h for D-amphetamine).

[Reviewer's comment: ***Overall, the Sponsor's model is acceptable****.]*

Reviewer Analyses*: Sponsor proposed inclusion of a table section 12.3 of the label (Table 5 in the Sponsor's proposed label, located in the Absorption subheading) that provided a comparison of PK following a single 25 mg dose to adolescent patients age 13 to 17 years and PK of a single 12.5 mg dose to child patients age 6 to 12 years. However, OCP proposed removal of this table as comparing the PK of two different age groups receiving two different dose levels doesn't appear relevant to the medical professionals. Instead, OCP proposed a comparison of the same dose level, 12.5 mg, in pediatric patients (grouped into children age < 12 years and adolescents age 13 to 17 years) versus adults. PK data were available from n=13 children and n=20 adults following administration of a 12.5 oral capsule. Adolescent patients did not have single-dose PK data for the 12.5 mg dose level but rather the 25 mg dose level. As OCP has previously determined that Mydayis PK are proportional from 12.5 mg to 75 mg as part of the review of the original submission (see the clinical pharmacology review of NDA 022063 signed on 04/24/2007), then PK for a 12.5 mg single dose to adolescent patients could be predicted by scaling the PK data from the 25 mg single dose. The results are shown in the table below.*

Table 4.3.4: D- and L-Amphetamine Exposure Following a Single 12.5 mg Mydayis Capsule Administered to Children, Adolescents, and Adults.

Isomer	*Exposure Metric*	*Children (Age 7 to 12 years)*	*Adolescents (age 13-17 years)**	*Adults*	*Ratio of Child PK / Adolescent PK*	*Ratio of Child PK / Adult PK*
D-amphetamine	*C_{max} (ng/mL)*	*29.22*	*20.29*	*16.5*	*1.44*	*1.77*
	*AUC_{0-24} (hr*ng/mL)*	*460*	*315*	*227*	*1.46*	*2.03*
L-amphetamine	*C_{max} (ng/mL)*	*9.31*	*6.44*	*5.08*	*1.44*	*1.83*
	*AUC_{0-24} (hr*ng/mL)*	*149*	*107*	*74*	*1.39*	*2.01*

** PK data were not available for single doses of 12.5 mg Mydayis administered to adolescent patients. However, PK data were provided following administration of a single 25 mg Mydayis dose to adolescent patients. Mydayis demonstrates proportional PK from 12.5 mg to 75 mg for both C_{max} and AUC_{0-24}. Adolescent exposure at 12.5 mg was predicted by scaling the observed PK data acquired following a single 25 mg Mydayis to adolescent patients.*

<u>D-isomer</u>: Following a 12.5 mg dose children having a 44% and 77% higher C_{max} than adolescents and adults, respectively (see the table above for details). The AUC_{0-24} for children receiving this dose is 46% and 103% higher than for adolescents and adolescents and adults, respectively.

<u>L-isomer</u>: Following a 12.5 mg dose children having a 44% and 83% higher C_{max} than adolescents and adults, respectively. The AUC_{0-24} for children receiving this dose is 39%% and 101% higher than for adolescents and adolescents and adults, respectively.

Based on these analyses, the following text was proposed by OCP for addition into section 12.3, Specific Populations – Age:

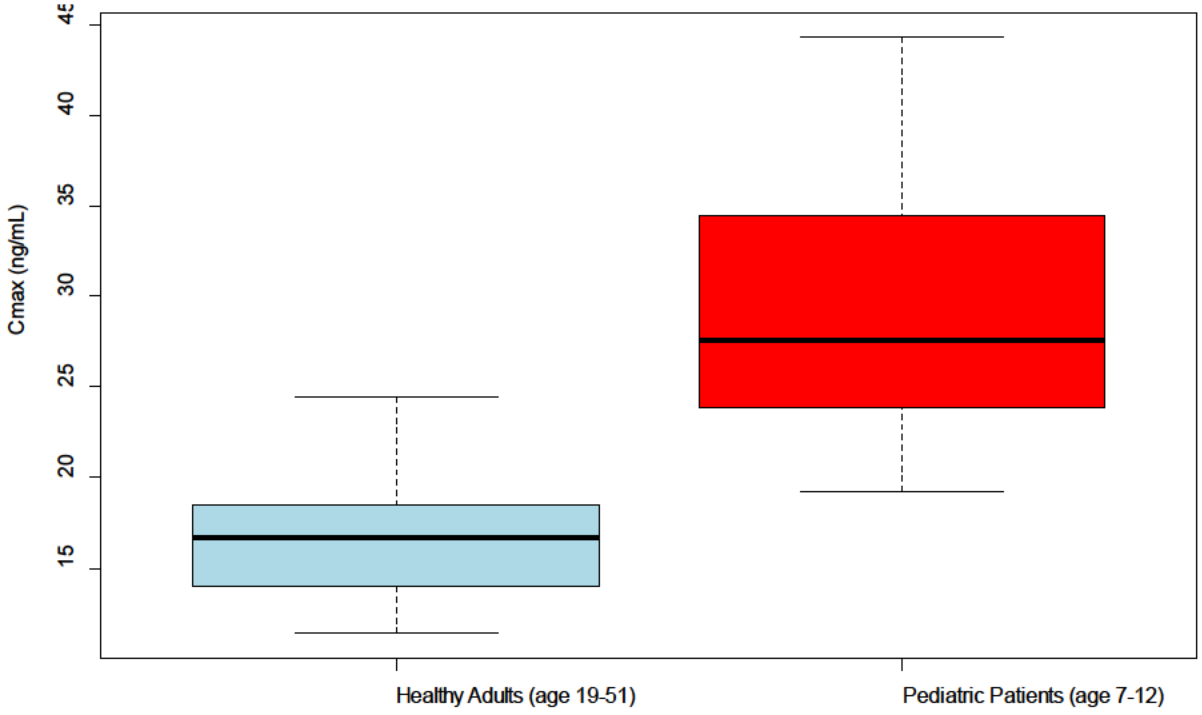
> *"A single 12.5 mg MYDAYIS capsule administered to patients age 7 to 12 years (n=13) produces a 77-83% higher Cmax for d- and l-amphetamine, and an approximately 100% higher AUC for d- and l-amphetamine, compared to a single 12.5 mg MYDAYIS capsule administered to adults (age 19 to 51 years).*
>
> *Pharmacokinetic (PK) data acquired from patients age 13 to 17 years (n=14) who received a single 25 mg MYDAYIS capsule was scaled (based on PK proportionality) and compared with PK data from patients 7 to 12 years (n=13) who received a single 12.5 mg MYDAYIS capsule. Based on PK proportionality, a single 12.5 mg MYDAYIS capsule would produce a 44% higher Cmax for d- and l-amphetamine, and a 39%-46% higher AUC for d-and l-amphetamine in patients age 7 to 12 years compared to patients age 13 to 17 years."*

4.4 Pharmacometric Assessment of Starting Dose

Key Question: Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

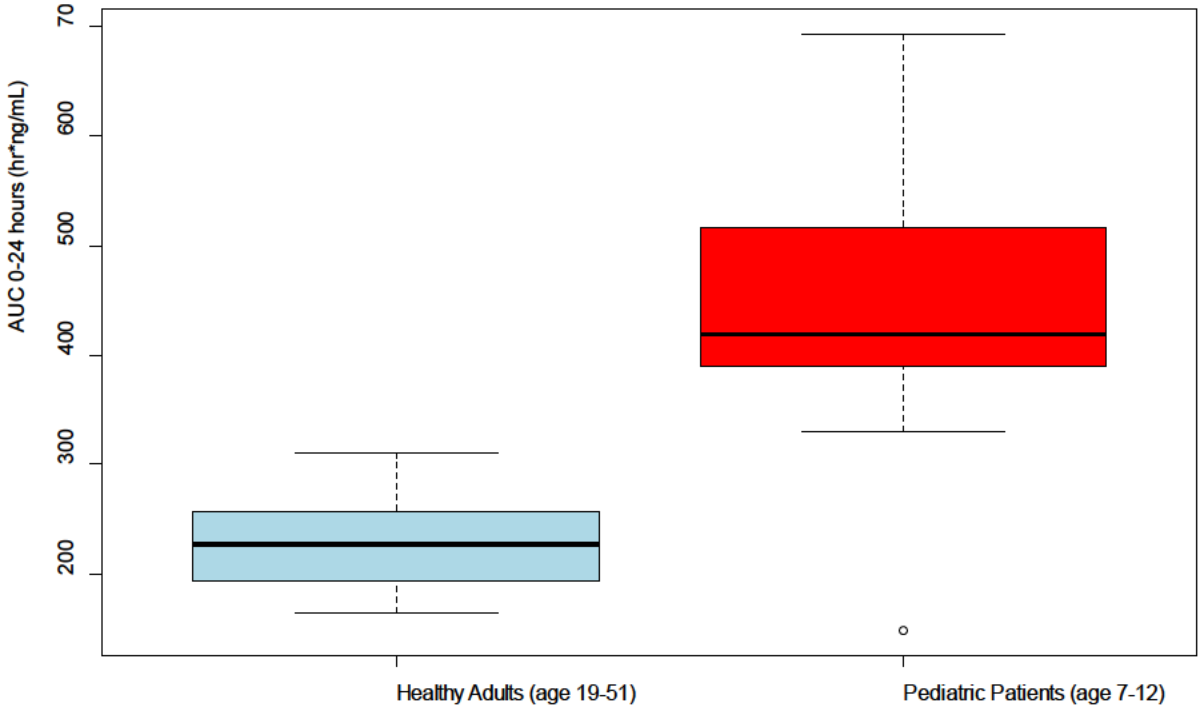
OCP initially had concerns regarding tolerability issues which may arise from administering the same initial dose during titration, 12.5 mg once daily, to children as is proposed for adults. The medical officer indicated that weight loss and insomnia were two adverse events of concern in the Phase 3 trials. In addition to concerns about adverse event rates in children, single doses of 12.5 mg MYDAYIS produced higher Cmax values and higher AUC_{0-24} values in than in adults when receiving a single 12.5 mg dose (please see figures below).

Figure 4.4.1: Comparison of D-amphetamine C_{max} Distribution following a Single 12.5 mg Capsule Administered to adults or Pediatric Patients age 7 to 12 years.



Adult data from Studies 107 and 110. Pediatric data from Study 11

Figure 4.4.2: Comparison of D-amphetamine AUC_{0-24} Distribution following a Single 12.5 mg Capsule Administered to adults or Pediatric Patients age 7 to 12 years.



Adult data from Studies 107 and 110. Pediatric data from Study 11

[*Reviewer comment: The same trend of higher C_{max} and AUC_{0-24} in pediatric patients compared to adults is seen for the L-amphetamine isomer as well.*]

There is insufficient data to formally assess the relationship between adverse event rate and amphetamine exposure as PK data were not collected in the phase 3 trials.

After internal discussion, it was noted that while some children may not be able to tolerate the 12.5 mg once daily initial dose, there is currently no feasible way to lower the initial dose as there is not currently a lower dose level than 12.5 mg. In addition the team decided it was not appropriate to recommend consuming half of a capsule as there is no guarantee that "splitting" a capsule contents would result in a 50/50 split of each of the 3 types of beads in each capsule (IR beads, delayed-IR beads, and XR beads).

We point out that other products in this class allow for a reduction of initial dosage if tolerability is an issue. For example, such a statement is available in Adderall (amphetamine) XR label (01/2017 version) which states:

> *"In children with ADHD who are 6-12 years of age and are either starting treatment for the first time or switching from another medication, start with 10 mg once daily in the morning; .... When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 5 mg once daily in the morning."*.

As such, OCP recommends that the Sponsor pursue a lower dose level post-marketing.

Please refer to the medical officer's review for detailed discussion regarding the efficacy and safety data submitted to support the proposed therapeutic dose regimen.

4.5 References

Roberts, J.K., Cook, S.F., Stockmann, C., Rollins, D.E.,Wilkins, D.G. and Sherwin, C.M.T. A Population Pharmacokinetic Analysis of Dextroamphetamine in the Plasma and Hair of Healthy Adults. Clin Drug Investig 35 (2015):633–43.

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Amphetamine ER Capsules
PRIMARY REVIEWER: Andre Jackson
NDA: 22063/SPD465
TYPE: NDA
FORMULATION: ER CAPSULES LA ADDERALL XR
STRENGTH: 12.5 mg, 25 mg, 37.5 mg and 50 mg
APPLICANT: SHIRE
Submission Dates: July 21, 2006

INDICATIONS: ATTENTION DEFICIT DISORDER IN ADULTS

EXECUTIVE SUMMARY

There are currently three medications, ADDERALL XR(Shire Development Inc.), atomoxetine (STRATTERA, Eli Lilly and Company), and dexmethylphenidate hydrochloride (Focalin XR™, Novartis), that are approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD in adults. SPD465 is once daily, three component, extended-release, single-entity amphetamine product designed to provide a duration of therapeutic effect of 14-16 hours. The four active ingredients in SPD465 are mixed salts of single entity amphetamine, the identical active ingredients found in ADDERALL and ADDERALL XR. The formulation of SPD465 is based on the formulation of ADDERALL XR capsules. ADDERALL XR capsules contain immediate-release (IR) beads (first component) and pulsatile delayed-release (DR1) beads (second component) that are designed to give a double-pulsatile delivery of amphetamines in order to prolong the duration of therapeutic effect relative to ADDERALL tablets (IR formulation of mixed amphetamine salts).

The rationale for the development of SPD465 (Long Acting Adderall XR) is to enable primarily adult and adolescent ADHD patients to benefit from ADHD symptom control throughout the entire day and to extend those benefits into the early evening hours, following a single morning dose.

The following studies were done by the firm to characterize the in vivo performance of their product in comparison to Adderall XR.

Study	Formulation
SPD465 – 101: Characterize the PK profiles of three delayed-release beads prototypes for SPD465 compared to Adderall®	Pilot formulation-NR
SPD465 - 102: assess PK profile of 3 delayed release composite formulations of SPD465 when administered with food compared to a reference treatment of 20 mg dose of Adderal XR® followed by 10mg dose of Adderall administered 8hours later	Pilot formulation-NR
SPD465 – 103: Evalaute the PK Profile of 37.5 mg SPD465 Product relative to and Adderall XR 25 mg + mixed amphetamine salts (MAS) IR 12.5 mg	Intend to market

SPD465 – 105: Assess the effect of a high fat meal on the bioavailability of SPD465 50 mg relative to the fasted state	Intend to market
SPD465 – 106: Evaluate dose proportionality of single ascending doses of SPD465 with the dose range of 12.5 to 75 mg.	Intended to market (early termination)-NR
SPD465 – 107: Describe the PK of SPD465 following repeat-dose administration over the range of doses from 12.5 to 75 mg	Intended to market (early termination)-NR
SPD465 – 110: Describe the PK of SPD465 following repeat-dose administration over the range of doses from 12.5 to 75 mg	Intend to market (repeat of SPD465-107)

NR-Not reviewed because formulation was a pilot or the vivo study was terminated prior to concluding [106-Health Canada suspended sales of Adderall XR.; 107-Terminated due to a disruption in study drug dosing.]

The following studies were done by the firm to support their Clinical data.

The firm did 3 clinical studies:

1. SPD465-201 (duration of effect, adolescents)
2.SPD465-202 (duration of effect adult) studies
3.SPD465-203 (duration of effect in adults).

SPD465-202 examined the duration of effect and safety of SPD465 (25 or 50mg) vs placebo in adolescents (13-17 years old) with ADHD. AMPH IR (12.5mg) was included as an active comparator for assay sensitivity. In this Phase II crossover study with three 1-week treatment periods of daily dosing, all subjects were to receive all treatments (SPD465, AMPH IR,placebo)

SPD465-203 examined the duration of effect and safety of SPD465 25mg vs placebo in adults with ADHD. In this Phase II crossover study with two 1-week treatment periods of daily dosing, all subjects were to receive both treatments (SPD465 and placebo). The study was designed to show differences between SPD465 25mg and placebo.

RECOMENDATIONS:

1.The study **SPD465 – 103** showed that for NDA 22063 (i.e., Long Acting Adderall XR) the 37.5 mg formulation is BE to Adderall XR 25 mg + mixed amphetamine salts (MAS) IR 12.5 mg.

2. The firm's proposed dissolution methodology is acceptable to OCP however their specifications should be changed to allow a (b) (4) % range which can be easily met. The final dissolution method and FDA specifications for all strengths are:

Table 1: Conditions for Dissolution Testing of SPD465 Capsules i	
Apparatus	USP II, paddles
Paddle Speed	50 RPM
Media	Media 1: pH 1.1 ± 0.1, Dilute HCl Media 2: pH 6.0 ± 0.1, Phosphate Buffer Media 3: pH 7.5 ± 0.1, Phosphate Buffer
Temperature	37.0°C ± 0.5°C
Dissolution Volume	1) 750mL Dilute HCl for the first 2 hours 2) 950mL pH 6.0 Phosphate Buffer for the 3rd hour 3) 1000mL pH 7.5 Phosphate Buffer for the remainder
Dissolution Specifications for SPD465 Capsules	
Time (hours)	Percent Dissolved
2	(b) (4)
3	
10	

COMMENTS TO THE SPONSOR:

1. The firm's proposed dissolution methodology is acceptable to OCP however their specifications should be changed to allow a (b) (4) % range which can be easily met. The final dissolution method and FDA specifications for all strengths are:

Table 2: Conditions for Dissolution Testing of SPD465 Capsules ii	
Apparatus	USP II, paddles
Paddle Speed	50 RPM
Media	Media 1: pH 1.1 ± 0.1, Dilute HCl Media 2: pH 6.0 ± 0.1, Phosphate Buffer Media 3: pH 7.5 ± 0.1, Phosphate Buffer
Temperature	37.0°C ± 0.5°C
Dissolution Volume	4) 750mL Dilute HCl for the first 2 hours 5) 950mL pH 6.0 Phosphate Buffer for the 3rd hour 6) 1000mL pH 7.5 Phosphate Buffer for the remainder
Dissolution Specifications for SPD465 Capsules	
Time (hours)	Percent Dissolved
2	(b) (4)
3	

10	(b) (4)

2.The firm should conduct studies to investigate in vitro dose-dumping in the presence of alcohol.

The current dissolution method is:

Apparatus	USP II, paddles
Paddle Speed	50 RPM
Media	Media 1: pH 1.1 ± 0.1, Dilute HCl Media 2: pH 6.0 ± 0.1, Phosphate Buffer Media 3: pH 7.5 ± 0.1, Phosphate Buffer
Temperature	37.0oC ± 0.5oC

The sponsor should perform dissolution studies for all SPD 465 strengths using the current dissolution conditions with the addition of 0%, 5%, 20% and 40% of ethanol to the dissolution media.

3. These studies should be completed and submitted to this NDA within 3 months.

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INTRODUCTION

The longer acting stimulant preparations (eg ADDERALL XR and methylphenidate [CONCERTA, Alza Pharmaceuticals]) are designed to provide duration of effect up to 12 hours. However, clinicians have noted that there are a substantial proportion of patients treated with these formulations who require additional treatment with a short-acting stimulant to extend the therapeutic duration later in the day. For patients currently taking long-acting stimulant formulations and who require duration of clinical benefit beyond 10-12 hours, the clinical dosing paradigm is that of frequent augmentation of the morning long-acting formulation, typically at 8-10 hours post-dose, with a smaller dose of the same immediate release (IR) medication. Clinicians in the ADHD field have indicated that they consider this augmentation strategy most relevant to the "longer day demands" of adults and adolescents, rather than school age, pediatric patients (ages 6-12).

QUESTION BASED REVIEW

IS THE NEW 37.5 MG SPD465 FORMULATION BE TO THE CURRENTLY MARKETED ADDERALL XR 25 MG + MIXED AMPHETAMINE SALTS IR 12.5 MG ADMINISTERED 8 HOURS LATER ?

A single-dose, fasting, 2-period crossover, single-center study involving 19 healthy adult subjects between the ages of 18 and 55 years was done to investigate the bioequivalence of SPD465 and Adderall XR+mixed amphetamine IR.

Table 7: Plasma Pharmacokinetic Parameters for *d*-Amphetamine After a Single Dose of SPD465 or ADDERALL XR® + Mixed Amphetamine Salts Administered 8 Hours Later – PK Population

Parameters	SPD465 37.5mg (A)			ADDERALL XR® 25mg + 12.5mg MAS (B)			Exponentiated LS Mean Ratio % (A)/(B)	90% CI
	n	Mean (±SD)	LS Mean	n	Mean (±SD)	LS Mean		
C_{max} (ng/mL)	20	50.3 (7.5)	49.7	19	49.3 (7.4)	49.2	101.0	(96.9, 105.3)
T_{max} (hr)	20	8.2 (2.0)	--	19	9.7 (2.1)	--	--	--
$AUC_{(0\text{-last})}$ (ng*hr/mL)	20	1058.0 (184.5)	1042.4	19	997.9 (172.9)	1000.8	104.2	(100.2, 108.3)
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	20	1084.9 (196.2)	1067.8	19	1019.5 (181.3)	1022.5	104.4	(100.3, 108.7)
$T_{1/2}$ (hr)	20	10.1 (1.3)	--	19	9.7 (1.2)	--	--	--

Figure 1. Mean *d*-Amphetamine Plasma Concentrations Over Time After a Single Dose, under fasting conditions,of SPD465 or ADDERALL XR - PK Population

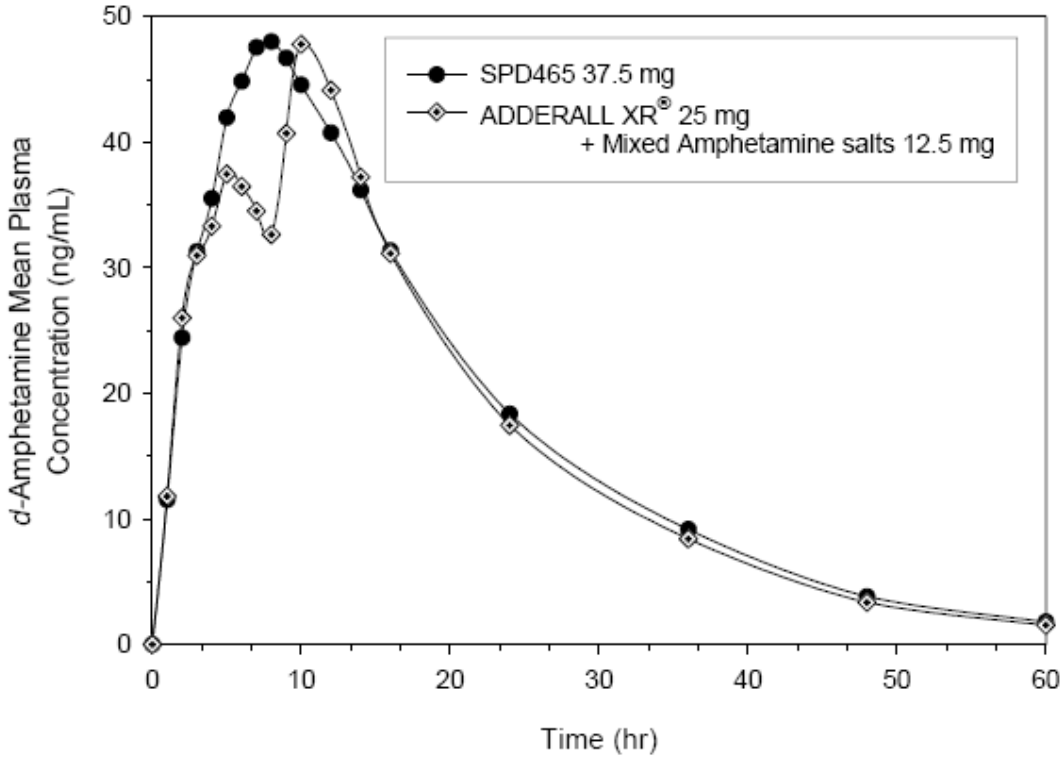


Figure 2. Mean *l*-Amphetamine Plasma Concentrations Over Time After a Single Dose, under fasting conditions, of SPD465 or ADDERALL XR® - PK Population

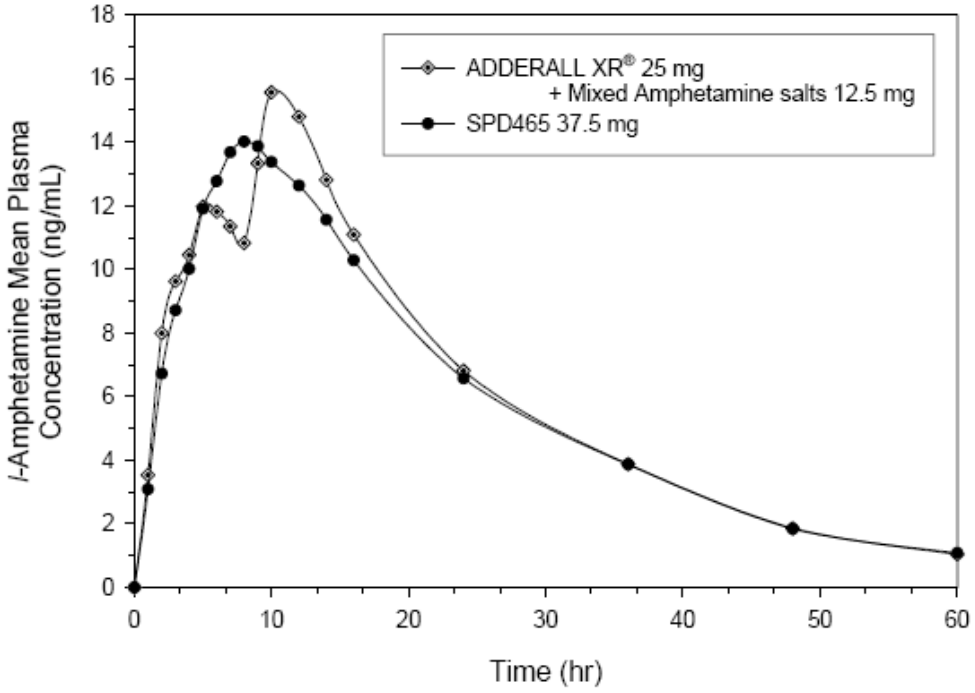


Table 8: Plasma Pharmacokinetic Parameters for *l*-Amphetamine After a Single Dose of SPD465 or ADDERALL XR® + Mixed Amphetamine Salts Administered 8 Hours Later – PK Population

Parameters	SPD465 37.5mg (A)			ADDERALL XR® 25mg + 12.5mg MAS (B)			Exponentiated LS Mean Ratio % (A)/(B)	90% CI
	n	Mean (±SD)	LS Mean	n	Mean (±SD)	LS Mean		
C_{max} (ng/mL)	20	14.7 (2.2)	14.6	19	16.0 (2.3)	16.0	90.9	(87.5, 94.4)
T_{max} (hr)	20	8.4 (2.1)	--	19	10.7 (1.3)	--	--	--
$AUC_{(0\text{-last})}$ (ng*hr/mL)	20	353.5 (66.0)	347.6	19	364.1 (66.5)	364.6	95.3	(91.0, 99.8)
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	20	372.8 (73.5)	365.9	19	382.3 (69.0)	383.9	95.3	(91.2, 99.6)
$t_{1/2}$ (hr)	20	12.5 (1.7)	--	19	11.7 (1.6)	--	--	--

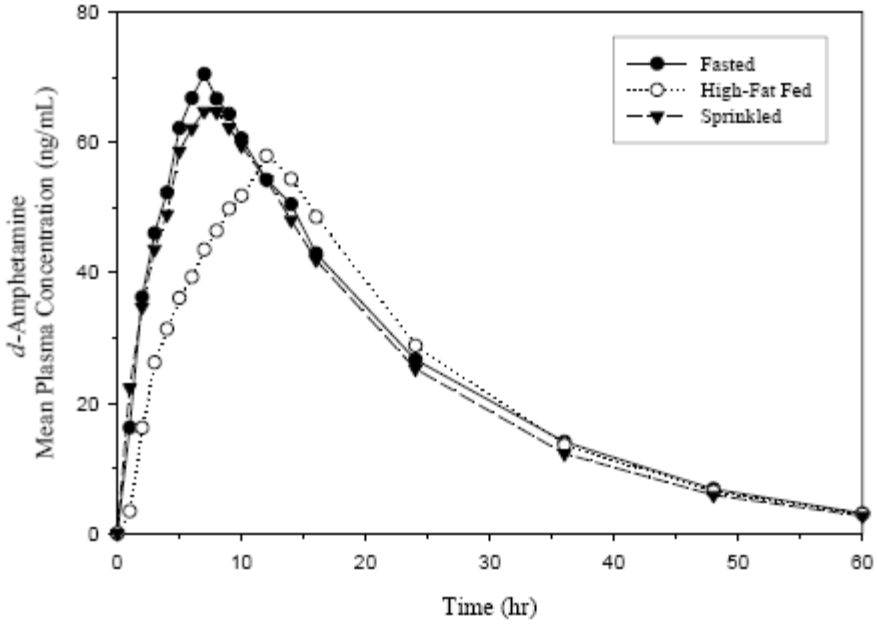
Results for the 90% CI for d-amphetamine and l-amphetamine indicate that both species are BE for SPD465 when compared to Adderall XR+mixed amphetamine IR formulation given 8 hours later.

WHAT IS THE EFFECT OF FOOD ON THE BIOAVAILABILITY OF THE SPD465 FORMULATION?

A three way crossover study was done in 14 subjects. The treatments were :

Treatment A = SPD465 50mg intact capsule after fasting at least 10 hours
Treatment B = SPD465 50mg intact capsule following a standard high-fat meal
Treatment C = SPD465 50mg capsule contents sprinkled on applesauce

Figure 3. Mean *d*-Amphetamine Plasma Concentrations over Time After a Single 50mg Dose of SPD465 - PK Population



L-amphetamine curves were similar but with levels approximately 3x smaller.

Table 8: Statistical Analysis Results of Plasma *d*-Amphetamine Following a Single Dose Administration of 50mg SPD465 - PK Population							
Parameter	Exponentiated LS Means			Ratio of LS Means		90% CI	
	Fasted (A)	High-Fat Meal (B)	Sprinkled (C)	B/A	C/A	B/A	C/A
C_{max} (ng/mL)	69.6	59.4	66.7	85.3	95.8	80.4, 90.5	90.3, 101.6
$AUC_{(0\text{-}inf)}$ (hr*ng /mL)	1528.3	1392.5	1463.7	91.1	95.8	86.7, 95.8	91.1, 100.6
$AUC_{(0\text{-}last)}$ (hr*ng/mL)	1484.2	1350.3	1424.5	91.0	96.0	86.7, 95.5	91.5, 100.7

Table 10: Statistical Analysis Results of Plasma *l*-Amphetamine Following a Single Dose Administration of 50mg SPD465 - PK Population							
Parameter	Exponentiated LS Means			Ratio of LS Means		90% CI	
	Fasted (A)	High-Fat Meal (B)	Sprinkled (C)	B/A	C/A	B/A	C/A
C_{max} (ng/mL)	20.4	17.4	19.8	85.2	96.9	80.2, 90.6	91.2, 103.0
$AUC_{(0\text{-}inf)}$ (hr*ng/mL)	522.3	463.4	495.0	88.7	94.8	83.9, 93.9	89.6, 100.3
$AUC_{(0\text{-}last)}$ (hr*ng/mL)	492.2	436.1	468.1	88.6	95.1	83.8, 93.7	90.0, 100.5

Source: Section 12.1, Table 2.3
Note: 14 subjects received Fasted (A) and 16 subjects each received Fed (B) and Sprinkled (C)
LS=Least squares
(A) SPD465 50mg fasted subjects
(B) SPD465 50mg high-fat fed subjects
(C) SPD465 50mg sprinkled on applesauce

d-amphetamine
The effect of a high fat meal was to decrease the Cmax by 15%, AUC by 10% and to increase the time for Tmax from 7 to 12 hrs. On the other hand the sprinkling of SDP 465 on applesauce had no effect on any pk parameter. 90% CI for both parameters were within 80-125% of the fasted study for both treatments (i.e., food and sprinkles).

l-amphetamine
The effect of a high fat meal was to decrease the Cmax by 15%, AUC by 13% and to increase the time for Tmax from 7.5 to 12 hrs. On the other hand the

sprinkling of SDP 465 on applesauce had no effect on any pk parameter. 90% CI for both parameters were within 80-125% of the fasted study for both treatments (i.e., food and sprinkles).

ARE THE PHARMACOKINETICS OF SPD465 LINEAR FOLLOWING MULTIPLE DOSE ADMINISTRATION?

A Phase I, open-label, incomplete block randomization, three-period, four treatment, dose escalating study investigating the safety, tolerability, and PK of SPD465 administered at steady state was conducted in 20 subjects. The study was conducted at a single center in 20 healthy male and female subjects between the ages of 18 and 55.

Doses over the range of 12.5 to 75 mg /day for 7 days.

Results from the study were:

Statistical Analysis of Dose Proportionality of Cmax and AUC(0-24)
(PK Population)

Analyte	PK Parameter	Slope	90% Confidence Interval
d-Amphetamine	Cmax (ng/mL)	1.0777	[1.0152, 1.1402]
	AUC (0-24) (hr*ng/mL)	1.0999	[1.0361, 1.1636]
l-Amphetamine	Cmax (ng/mL)	1.0711	[1.0118, 1.1303]
	AUC (0-24) (hr*ng/mL)	1.0868	[1.0264, 1.1472]

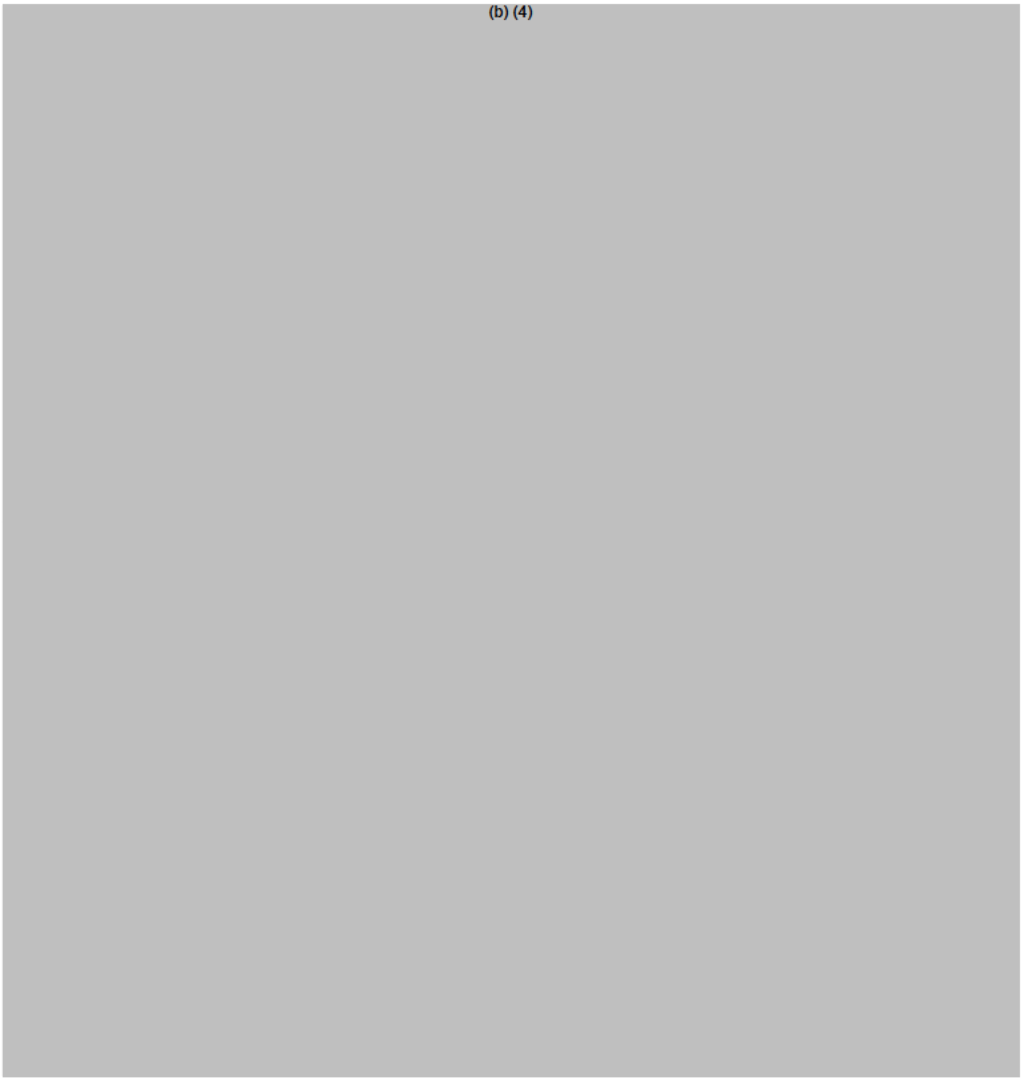
The slope of the regression line was ~1 and the 90% CI based upon the power model included 1 which indicates that the drug exhibits a linear increase in Cmax and AUC (tau) with increasing dose.

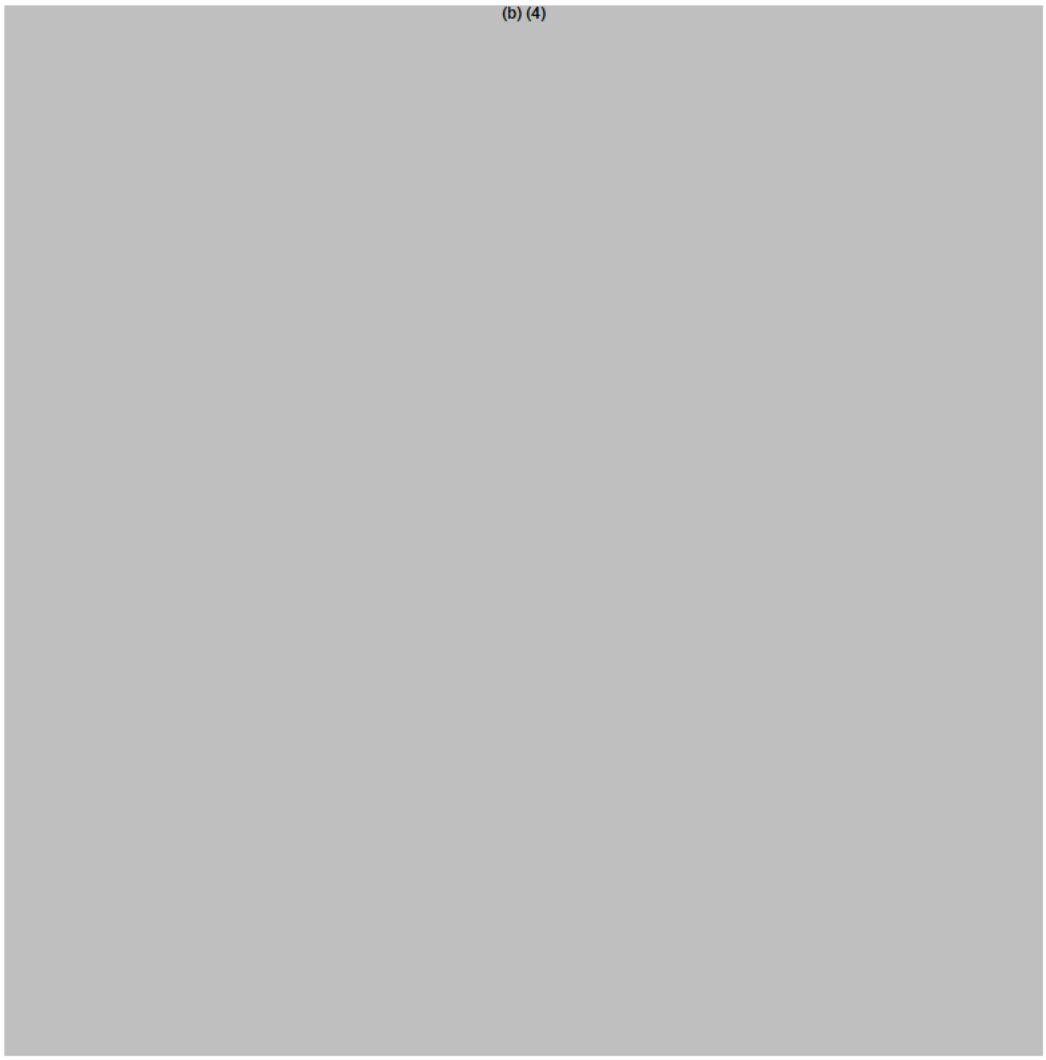
FORMULATION

Clinical study 203 was done with the intended to be marketed formulation. The overall quantitative formulation of the capsules and its manufacturing process are identical to that of 201 and 202 clinical supplies. The study 203 design is similar to that of 201 and 202 (main difference being in the strengths studied). All strengths had 3 types of beads immediate release, pulsatile delayed release and delayed extended release.

COMPOSITION

FORMULATION:




(b) (4)

DISSOLUTION:

Four strengths of SPD 465 were tested including batches of the formulations used in clinical studies SPD465-201 and SPD465-203 and biostudies. These dissolution conditions and specifications are included in Table 3, method, and Table 4 sponsor's specifications, respectively. Dissolution data for the SPD465 formulations used in clinical studies SPD465-201 and SPD465-203 are presented in Table 5. and in the other tables for the other strengths used in the biostudies.

Table 3: Conditions for Dissolution Testing of SPD465 Capsules [iii]	
Apparatus	USP II, paddles
Paddle Speed	50 RPM
Media	Media 1: pH 1.1 ± 0.1, Dilute HCl Media 2: pH 6.0 ± 0.1, Phosphate Buffer Media 3: pH 7.5 ± 0.1, Phosphate Buffer
Temperature	37.0°C ± 0.5°C
Dissolution Volume	7) 750mL Dilute HCl for the first 2 hours 8) 950mL pH 6.0 Phosphate Buffer for the 3rd hour 9) 1000mL pH 7.5 Phosphate Buffer for the remainder

TABLE WITH FIRM'S PROPOSED DISSOLUTION SPECIFICATIONS

Table 4: Dissolution Specifications for SPD465 Capsules	
Time (hours)	Percent Dissolved
2	(b) (4)
3	
10	

Table 5: Dissolution Data for SPD465 Capsules used in SPD465-201 and SPD465-203			
Time (hr.)	In-vitro Dissolution (% Dissolved)[iv]		
	SPD465-201		SPD465-203
	25mg capsule Mean ± SD, (Range)[v]	37.5mg capsule Mean ± SD, (Range)[vi]	25mg capsule Mean ± SD, (Range)[vii]
0	0	0	0
2	**34 ± 0.4, (34-35)**	**34 ± 0.6, (33-35)**	**34 ± 0.8, (33-35)**
3	**64 ± 1.0, (62-65)**	**62 ± 1.5 (60-64)**	**63 ± 1.8, (61-66)**
4	66 ± 0.5, (66-67)	65 ± 0.9, (64-66)	69 ± 3.8, (65-75)
6	77 ± 1.0, (76-78)	73 ± 1.2, (72-75)	77 ± 4.5, (74-86)
8	88 ± 1.6, (86-90)	84 ± 2.0, (82-87)	89 ± 4.7, (83-97)
10	**94 ± 1.7, (92-96)**	**90 ± 2.3, (87-93)**	**90 ± 2.7, (87-94)**
12	97 ± 1.3, (96-99)	93 ± 1.8, 91-95)	94 ± 5.3, (88-100)
14	99 ± 1.4, (97-101)	95 ± 1.4, (93-96)	94 ± 3.2, (90-99)

SD = standard deviation
Specification time points presented in Bold font.
Dissolution data for each lot presented in this table conforms to L1.

The 12.5 mg was used in study SPD465-110, the 37.5 mg lot was used in study SPD465-103 and the 50 mg was used in study SPD465-105.

DISSOLUTION DATA FOR THE 12.5 MG CAPSULES

Specification: Time (hours) % Dissolved (b) (4)
2
3
10

Vessel	% Dissolved							
	2.00 hr	3.00 hr	4.00 hr	6.00 hr	8.00 hr	10.00 hr	12.00 hr	14.00 hr
[redacted]	34	67	71	81	94	99	101	102
[redacted]	35	69	73	83	93	100	103	105
[redacted]	33	65	69	78	88	93	91	99
[redacted]	36	70	75	89	101	104	105	100
5	35	64	69	73	89	93	96	97
6	35	66	71	82	91	96	99	100
[redacted]	33	64	69	73	88	93	91	97
[redacted]	36	70	75	89	101	104	105	105
[redacted]	35	67	71	81	93	98	99	101

DISSOLUTION DATA FOR THE 37.5 MG CAPSULES

Specification: Time (hours) % Dissolved (b) (4)
2
3
10

Vessel	% Dissolved							
	2.00 hr	3.00 hr	4.00 hr	6.00 hr	8.00 hr	10.00 hr	12.00 hr	14.00 hr
1	34	65	69	80	89	94	98	100
2	33	64	69	80	90	94	97	99
3	34	64	69	80	88	93	95	97
4	36	65	69	78	87	93	96	98
5	34	66	71	82	92	96	99	100
6	34	64	71	83	93	98	100	101
Min	33	64	69	78	87	93	95	97
Max	36	66	71	83	93	98	100	101
Mean	34	65	70	81	90	95	98	99

DISSOLUTION DATA FOR THE 50 MG CAPSULES

Vessel	% Dissolved							
	2.00 hr	3.00 hr	4.00 hr	6.00 hr	8.00 hr	10.00 hr	12.00 hr	14.00 hr
1	34	62	71	84	95	100	102	103
2	33	59	68	78	89	95	98	100
3	34	58	69	81	92	98	101	102
4	34	60	71	83	94	99	102	103
5	35	57	71	81	91	97	100	102
6	35	61	70	80	91	97	99	100
Min	33	57	68	78	89	95	98	100
Max	35	62	71	84	95	100	102	103
Mean	34	60	70	81	92	98	100	102

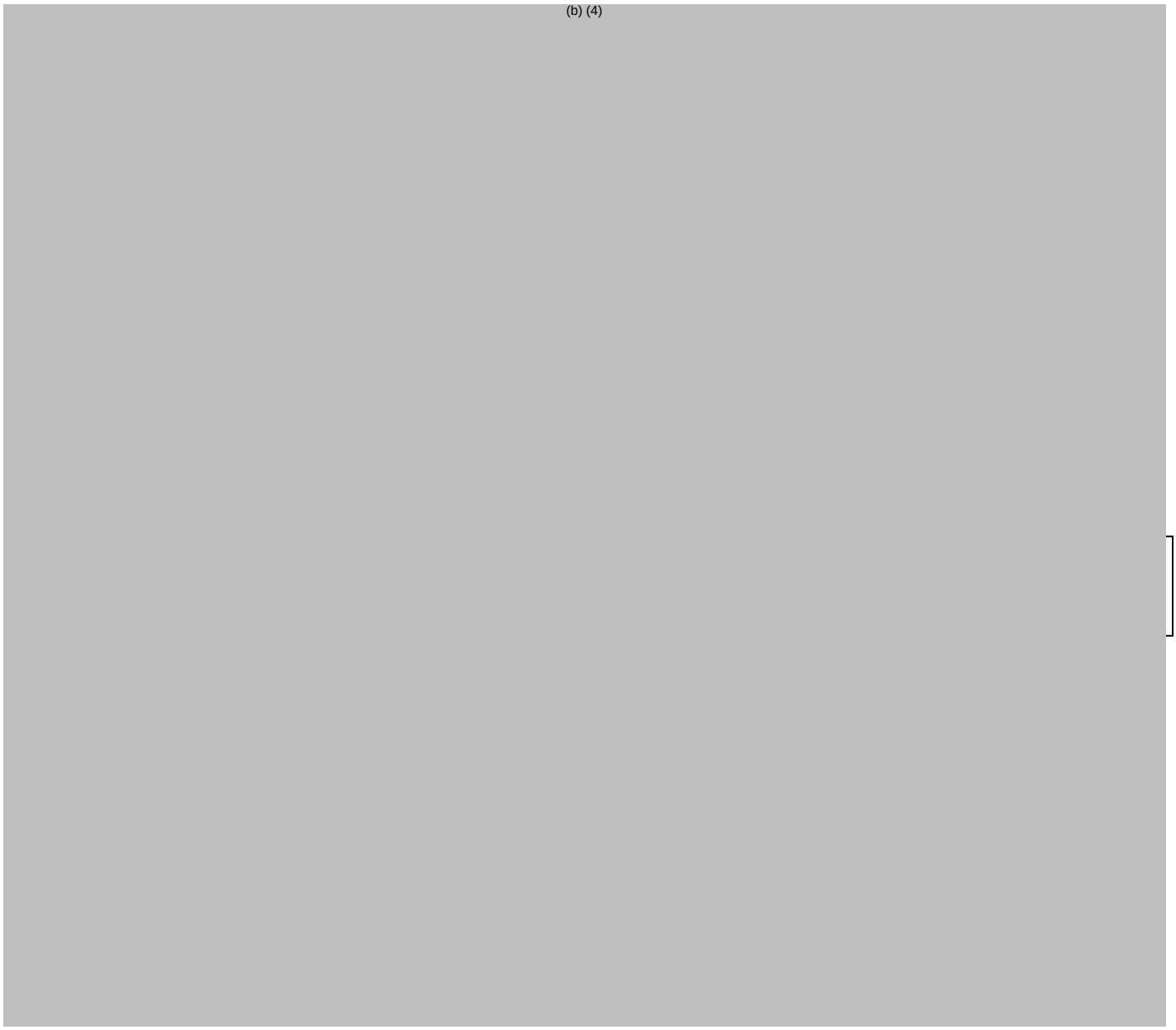
FDA METHOD AND SPECIFICATIONS:

Dissolution Specifications for SPD465 Capsules	
Time (hours)	Percent Dissolved (b) (4)
2	
3	
10	

FIRM'S PROPOSED LABEL

(b) (4)

(b) (4)



FDA PROPOSED LABEL

12 CLINICAL PHARMACOLOGY

12.1 Pharmacodynamics

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not fully established. Amphetamines are thought to block the reuptake of

norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space[84].

12.2 Pharmacokinetics

Pharmacokinetic studies of [TRADENAME] have been conducted in healthy adult subjects. [TRADENAME] contains d-amphetamine and l-amphetamine salts in the ratio of 3:1. [TRADENAME] exhibits linear dose proportionality over the range of 12.5 mg to 75 mg. Steady-state is achieved by Day 7 of dosing with no unexpected accumulation[85].

The time to reach maximum plasma concentration (T_{max}) for [TRADENAME] is about 8 hours.

A single dose of [TRADENAME] 37.5 mg capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to ADDERALL XR® 25 mg followed by 12.5 mg immediate release amphetamine administered 8 hours later[87].

The mean elimination half-lives for d-amphetamine and l-amphetamine in adults are 10 to 13 hours, respectively[89].

Food does not affect the extent of absorption of d-amphetamine and l-amphetamine for [TRADENAME], but prolongs T_{max} by 5 hours (from 7.0 hrs at fasted state to 12.0 hrs after a high-fat meal) for d-amphetamine and 4.5 hours (from 7.5 hours at fasted state to 12 hours after a high-fat meal) for l-amphetamine after administration of [TRADENAME] 50 mg. Opening the capsule and sprinkling the contents on applesauce results in comparable absorption and exposure to the intact capsule taken in the fasted state[90].

SIGNATURES

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Division Director DCP1
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cc: NDA 22-063, HFD-860(Mehta, Baweja, Jackson)
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DETAILED STUDY REPORTS

ASSAY VALIDATION

ANALYTICAL SECTION

What bioanalytical method was used to assess concentration?

Assay Validation – Based upon a weighted quadratic regression model

Parameter	` D-amphetamine	L-amphetamine
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection	LC\ Mass Spectrometric \ Mass Spectrometric Detection
Number of Freeze-thaw	4 Cycles QC's 1.5 ng/ml 60 ng/ml	4 Cycles QC's 1.5 ng/ml 60 ng/ml
Benchtop Stability at RT	24hrs	24hrs
Long term at –20° C	39 months	39 months
Extraction Recovery Low Med High	 61.8% @ 1.5 ng/ml 66% @ 20 ng/ml 71.6% @ 60 ng/ml	 44% @ 1.5 ng/ml 54% @ 20 ng/ml 59% @ 60 ng/ml

The firm had initially decided to use a quadratic equation for validation of precision and accuracy but later decided that a linear regression was better. The LC/MS/MS assay for analyzing d-amphetamine and l-amphetamine in human sodium EDTA plasma was validated successfully using a linear curve. All the acceptance criteria were met as outlined in the Amendment to Validation Protocol. The validation data reported here demonstrated that the current configuration of the LC-MS system provides precise, accurate and reproducible data for the assay method when employing a weighted linear regression model to define the calibration curve. All the acceptance criteria were met as outlined in the Amendment.

DETAILED STUDY REPORTS

Study-SPD465-103

TITLE: A PHASE I PHARMACOKINETIC STUDY IN HEALTHY ADULT VOLUNTEERS TO EVALUATE THE PHARMACOKINETIC PROFILE OF A 37.5MG SPD465 PRODUCT RELATIVE TO AN ADDERALL XR® 25MG + MIXED AMPHETAMINE SALTS IR 12.5MG

STUDY INITIATION DATE: 17 Nov 2004

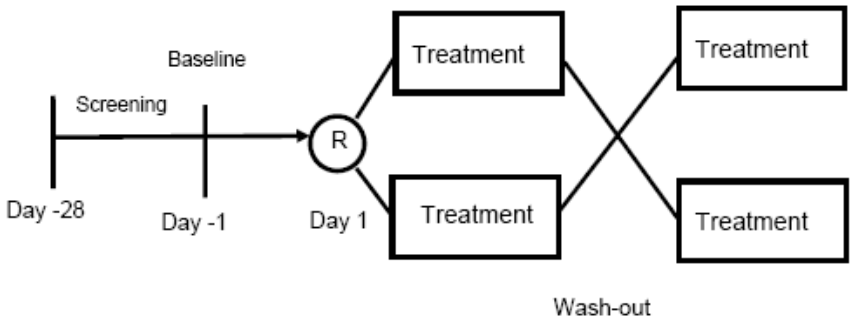
STUDY COMPLETION DATE: 22 December 2004

STUDY OBJECTIVES
The primary objective of this study was to assess the PK of a SPD465 37.5mg product (Treatment A) compared to a reference treatment of a 25mg dose of ADDERALL XR® followed by a 12.5mg dose of mixed amphetamine salts IR administered 8 hours later (Treatment B).

METHODS

Overall Study Design and Plan - Description
This was a Phase I, open-label, randomized, single-dose, 2-period crossover, single-center study involving healthy adult subjects between the ages of 18 and 55 years, inclusive. On Study Day 1 of each period, subjects were to be administered a single dose of SPD465 37.5mg or 25mg ADDERALL XR® followed by mixed amphetamine salts IR 12.5mg 8 hours later according to the randomization schedule.

Figure 1: Study Design Flow Chart



Selection of doses in the study
This study was designed to evaluate the PK of a SPD465 37.5mg product compared to a

reference treatment. The reference treatment was a 25mg dose of ADDERALL XR$_v$ followed by a 12.5mg dose of mixed amphetamine salts IR administered 8 hours later. The reference treatment was designed to mimic the clinical practice of providing extended coverage by supplementing a morning dose of ADDERALL XR$_v$ with a dose of mixed amphetamine salts IR 8 hours later in order to increase the duration of action.

Table 2: Description and Batch Number Information of Investigational Products

Treatment	Study Drug	Dose	Batch #
Treatment A	Capsule A*	1x37.5mg Capsule A	Capsule A: A03549
Treatment B	ADDERALL XR® + Capsule B†	1x25mg ADDERALL XR® followed by 1x12.5mg Capsule B 8 hours later	ADDERALL XR®: A02936B Capsule B: B03043a

Demographics

Table 6: Subject Demographics and Baseline Characteristics – Safety Population

Characteristic	Category/Parameter	Sequence AB (N=10)	Sequence BA (N=10)	Total (N=20)
Age (years)	Mean (±SD)	28.7 (6.63)	31.3 (10.80)	30.0 (8.83)
	Median (min-max)	28.0 (21-37)	27.5 (22-50)	27.5 (21-50)
Gender, n (%)	Male	4 (40%)	4 (40%)	8 (40%)
	Female	6 (60%)	6 (60%)	12 (60%)
Ethnicity, n (%)	Hispanic/Latino	1 (10%)	0 (0%)	1 (5%)
	Not Hispanic/Latino	9 (90%)	10 (100%)	19 (95%)
Race, n (%)	White	10 (100%)	8 (80%)	18 (90%)
	Black/African-American	0 (0%)	2 (20%)	2 (10%)
Weight (kg)	Mean (±SD)	71.6 (7.26)	76.1 (12.38)	73.8 (10.15)
	Median (min-max)	71.0 (62-82)	71.0 (61-97)	71.0 (61-97)
Height (cm)	Mean (±SD)	173.5 (5.75)	171.7 (10.10)	172.6 (8.05)
	Median (min-max)	174.0 (165-185)	168.9 (158-188)	172.7 (158-188)
BMI (kg/m^2)	Mean (±SD)	23.74 (1.972)	25.75 (2.173)	24.75 (2.267)
	Median (min-max)	23.70 (20.1–26.9)	25.90 (22.7–29.2)	25.10 (20.1–29.2)

Plasma Sample Collection and Handling

Blood samples for the determination of plasma *d*- and *l*-amphetamine concentrations were collected 30 minutes prior to drug administration (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours after dosing

Pharmacokinetic Data Analysis

The primary outcome measures in this Phase 1 study were comprised of PK parameters calculated from plasma concentrations of *d*- and *l*-amphetamine by non-compartmental techniques using WinNonlin$_v$ Professional version 4.1 or higher. All calculations were based on actual sampling times. Calculated PK parameters included the following:

C_{max} Maximum plasma concentration

t_{max} Time of maximum plasma concentration

λ_z Terminal phase rate constant
$t_{½}$ Terminal half-life
$AUC_{(0\text{-last})}$ Area under the plasma concentration-time curve from Time 0 to last measured time
$AUC_{(0\text{-inf})}$ Area under the plasma concentration-time curve from Time 0 to infinity

All available *d*- and *l*-amphetamine plasma concentration data from subjects were evaluated for PK unless the data were impacted by a significant protocol deviation or vomiting immediately following oral dosing.

Statistical Analysis of Pharmacokinetic Parameters
Pharmacokinetic parameters were compared between treatment groups using an analysis of variance (ANOVA) with sequence, period, and treatment as fixed effects, and subject nested within sequence as a random effect. This analysis was performed for the natural log transformations of C_{max}, $AUC_{(0\text{-inf})}$, and $AUC_{(0\text{-last})}$ using SAS PROC MIXED.

ANALYTICAL

Clinical study began:
Sample analysis completed: January 5, 2005
Longest Possible Storage- 60 days

Parameter	D-Amphetamine	L-Amphetamine
Method	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL	0.5 ng/mL
Linearity (Standard curve samples)	0.5ng/ml-75 ng/ml	0.5ng/ml-75 ng/ml
Quality Control (QC) Samples	1.5 ng/mL 20.0 ng/ml 60.0 ng/ml	1.5 ng/mL 20.0 ng/ml 60.0 ng/ml
Precision of Standards (%CV)	10.6%@0.5 ng/ml 0.5 %@ 75 ng/ml	1.2 %@0.5 ng/ml 0.6 %@ 75 ng/ml
Precision of QC Samples (%CV)	7% @ 1.5 ng/ml 5%@20.6 ng/ml 4%@ 61 ng/ml	6.5 %@ 1.5 ng/ml 4.8 %@20.6 ng/ml 4.4 %@ 61 ng/ml
Accuracy of Standards (%)	94 %@0.5 ng/ml 100 %@ 75 ng/ml	89.2 %@0.5 ng/ml 99.7 %@ 75 ng/ml
Accuracy of QC Samples (%)	101%@1.5 ng/ml 98%@20.6 ng/ml 99 %@ 61 ng/ml	101 %@1.5 ng/ml 98 %@20.6 ng/ml 99 %@ 61 ng/m l

RESULTS

Figure 1. Mean *d*-Amphetamine Plasma Concentrations Over Time After a Single Dose, under fasting conditions,of SPD465 or ADDERALL XR - PK Population

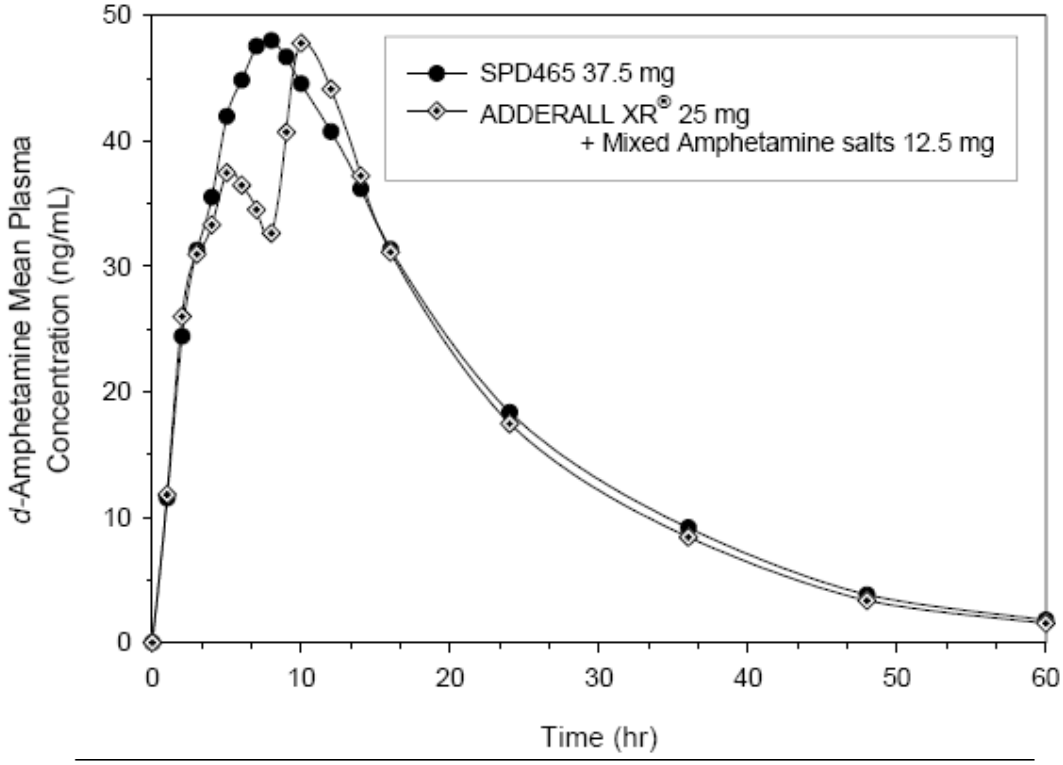


Table 7: Plasma Pharmacokinetic Parameters for *d*-Amphetamine After a Single Dose of SPD465 or ADDERALL XR® + Mixed Amphetamine Salts Administered 8 Hours Later – PK Population

Parameters	SPD465 37.5mg (A)			ADDERALL XR® 25mg + 12.5mg MAS (B)			Exponentiated LS Mean Ratio % (A)/(B)	90% CI
	n	Mean (±SD)	LS Mean	n	Mean (±SD)	LS Mean		
C_{max} (ng/mL)	20	50.3 (7.5)	49.7	19	49.3 (7.4)	49.2	101.0	(96.9, 105.3)
T_{max} (hr)	20	8.2 (2.0)	--	19	9.7 (2.1)	--	--	--
$AUC_{(0\text{-last})}$ (ng*hr/mL)	20	1058.0 (184.5)	1042.4	19	997.9 (172.9)	1000.8	104.2	(100.2, 108.3)
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	20	1084.9 (196.2)	1067.8	19	1019.5 (181.3)	1022.5	104.4	(100.3, 108.7)
$T_{1/2}$ (hr)	20	10.1 (1.3)	--	19	9.7 (1.2)	--	--	--

Figure 2. Mean *l*-Amphetamine Plasma Concentrations Over Time After a Single Dose, under fasting conditions, of SPD465 or ADDERALL XR® - PK Population

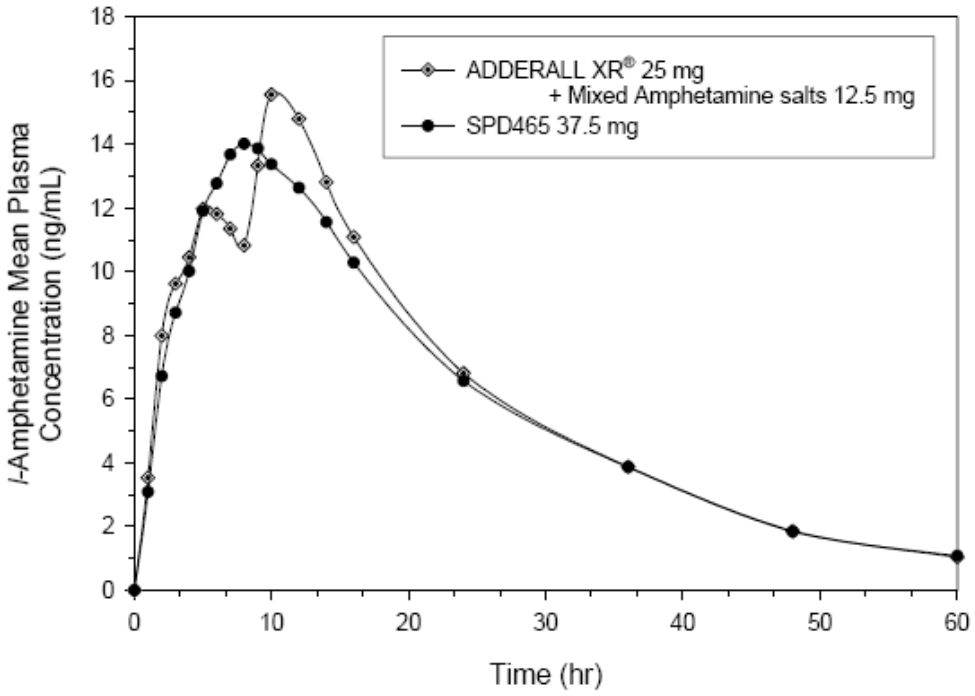


Table 8: Plasma Pharmacokinetic Parameters for *l*-Amphetamine After a Single Dose of SPD465 or ADDERALL XR® + Mixed Amphetamine Salts Administered 8 Hours Later – PK Population

Parameters	SPD465 37.5mg (A)			ADDERALL XR® 25mg + 12.5mg MAS (B)			Exponentiated LS Mean Ratio % (A)/(B)	90% CI
	n	Mean (±SD)	LS Mean	n	Mean (±SD)	LS Mean		
C_{max} (ng/mL)	20	14.7 (2.2)	14.6	19	16.0 (2.3)	16.0	90.9	(87.5, 94.4)
T_{max} (hr)	20	8.4 (2.1)	--	19	10.7 (1.3)	--	--	--
$AUC_{(0\text{-last})}$ (ng*hr/mL)	20	353.5 (66.0)	347.6	19	364.1 (66.5)	364.6	95.3	(91.0, 99.8)
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	20	372.8 (73.5)	365.9	19	382.3 (69.0)	383.9	95.3	(91.2, 99.6)
$t_{1/2}$ (hr)	20	12.5 (1.7)	--	19	11.7 (1.6)	--	--	--

Source: Section 12.1, Table 2.2, Table 2.3
MAS=mixed amphetamine salts
LS=Least squares
-- not determined
(A) SPD465 37.5mg
(B) ADDERALL XR® 25mg + mixed amphetamine salts IR 12.5mg administered 8 hours later

Comment:

d-amphetamine:

Exposure to *d*-amphetamine was similar following administration of SPD465 and

ADDERALL XR + mixed amphetamine salts IR administered 8 hours later , as determined from mean Cmax (50.3ng/mL and 49.3ng/mL, respectively), mean AUC(0-last) (1058.0ng*hr/mL and 997.9ng*hr/mL, respectively), and mean AUC(0-inf) (1084.9ng*hr/mL and 1019.5ng*hr/mL, respectively). The 90% CI of the test-to-reference ratios on LS mean values for Cmax, AUC(0-last) and AUC(0-inf) were 96.9-105.3, 100.2-108.3, and 100.3-108.7, respectively, and were fully contained within the bioequivalence range of 80%-125%.

l-amphetamine
Mean *l*-amphetamine C_{max} following the dose of SPD465 was slightly lower (approximately 10%) than the value obtained after the ADDERALL XR® + mixed amphetamine salts IR dose (14.7ng/mL and 16.0ng/mL, respectively). Means for $AUC_{(0\text{-}last)}$ (353.5ng*hr/mL and 364.1ng*hr/mL, respectively) and $AUC_{(0\text{-}inf)}$ (372.8ng*hr/mL and 382.3ng*hr/mL, respectively) were comparable between SPD465 and ADDERALL XR® + mixed amphetamine doses. The 90% CI of the test-to-reference ratios on LS Mean values for C_{max}, $AUC_{(0\text{-}last)}$, and $AUC_{(0\text{-}inf)}$ values were 87.5-94.4, 91.0-99.8, and 91.2-99.6, respectively, and were fully contained within the bioequivalence range of 80%–125%.

The elimination half lives of *d*-amphetamine (10.1 hr and 9.7 hr) and *l*-amphetamine (12.5 hr and 11.7 hr) were similar following treatment with SPD465 37.5mg and ADDERALL XR® 25mg + mixed amphetamine salts IR 12.5mg administered 8 hours later, respectively.

Study-SPD465-105

TITLE:

A PHASE I STUDY TO EVALUATE THE PHARMACOKINETIC PROFILE OF SPD465 50MG UNDER FED, FASTED, AND SPRINKLED CONDITIONS IN HEALTHY ADULT VOLUNTEERS

STUDY INITIATION DATE: December 27, 2004
STUDY COMPLETION DATE: January 26, 2005

STUDY OBJECTIVES

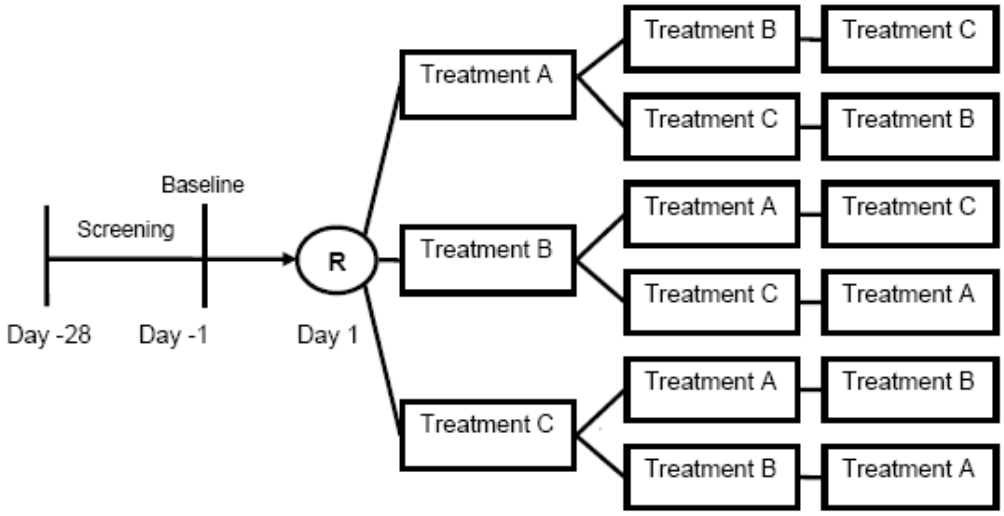
The primary objective of this study was to assess the effect of a high-fat meal on the bioavailability of SPD465 50mg relative to the fasted state

Secondary Objectives
The secondary objectives were to:
1. Assess the bioavailability of SPD465 50mg after the contents of the product were sprinkled on applesauce relative to the fasted state.

Overall Study Design and Plan - Description

This was a Phase I, open-label, randomized, single-dose, 3-period crossover, single-center study involving healthy adult subjects between the ages of 18 and 55 years, inclusive. Each subject was to be randomly assigned to a sequence in which he or she received each of the three treatments.

Figure 1: Study Design Flow Chart



Treatment A = SPD465 50mg intact capsule after fasting at least 10 hours
Treatment B = SPD465 50mg intact capsule following a standard high-fat meal
Treatment C = SPD465 50mg capsule contents sprinkled on applesauce

METHODS

Demographics

Table 6: Subject Demographics and Baseline Characteristics of All Subjects

		Sequence						
		ABC (N=2)	ACB (N=2)	BAC (N=3)	BCA (N=3)	CAB (N=3)	CBA (N=3)	Total (N=16)
Age (years)	Mean (±SD)	50.5 (0.71)	20.0 (1.41)	39.0 (13.00)	28.7 (13.28)	34.3 (9.45)	25.7 (9.87)	32.8 (12.51)
	Median (min, max)	50.5 (50, 51)	20.0 (19, 21)	46.0 (24, 47)	21.0 (21, 44)	31.0 (27, 45)	21.0 (19, 37)	29.0 (19, 51)
Gender N (%)	Male	0 (0.0)	1 (50.0)	1 (33.3)	3 (100.0)	2 (66.7)	2 (66.7)	9 (56.3)
	Female	2 (100.0)	1 (50.0)	2 (66.7)	0 (0.0)	1 (33.3)	1 (33.3)	7 (43.8)
Ethnicity N (%)	Hispanic/Latino	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Not Hispanic/Latino	2 (100.0)	2 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	16 (100.0)
Race N (%)	White	2 (100.0)	2 (100.0)	3 (100.0)	3 (100.0)	2 (66.7)	3 (100.0)	15 (93.8)
	Black/African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (6.3)
Weight (kg)	Mean (±SD)	68.5 (3.82)	82.8 (14.42)	73.1 (13.43)	72.0 (4.54)	76.5 (10.78)	70.8 (14.33)	73.7 (10.16)
	Median (min, max)	68.5 (66, 71)	82.8 (73, 93)	66.7 (64, 89)	70.3 (69, 77)	73.5 (68, 89)	64.9 (60, 87)	70.8 (60, 93)
Height (cm)	Mean (±SD)	162.6 (0.00)	189.3 (16.19)	171.9 (16.34)	174.4 (8.15)	172.7 (11.61)	173.5 (6.39)	173.8 (11.62)
	Median (min, max)	162.6 (163, 163)	189.3 (178, 201)	165.1 (160, 191)	177.8 (165, 180)	170.2 (163, 185)	172.7 (168, 180)	171.5 (160, 201)
BMI (Kg/m^2)	Mean (±SD)	26.0 (1.63)	23.3 (0.07)	24.6 (1.45)	23.8 (2.39)	25.7 (1.96)	23.5 (3.21)	24.5 (2.05)
	Median (min, max)	26.0 (24.8, 27.1)	23.3 (23.2, 23.3)	24.5 (23.2, 26.1)	24.3 (21.2, 25.9)	25.9 (23.7, 27.6)	21.9 (21.4, 27.2)	24.4 (21.2, 27.6)

Plasma Sample Collection and Handling

Blood samples for the determination of plasma *d*- and *l*-amphetamine concentrations were to be collected 30 minutes prior to drug administration (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours after dosing in each treatment period.

Pharmacokinetic Data Analysis

The primary outcome measures in this Phase 1 study were comprised of PK parameters calculated from plasma concentrations of *d*- and *l*-amphetamine by non-compartmental techniques using WinNonlin$_{v}$ Professional version 4.1 or higher[15]. All calculations were based on actual sampling times. Calculated PK parameters included the following:

C_{max} Maximum plasma concentration

t_{max} Time of maximum plasma concentration

$AUC_{(0\text{-}last)}$ Area under the plasma concentration-time curve from Time 0 to last measured time

$AUC_{(0\text{-}inf)}$ Area under the plasma concentration-time curve from Time 0 to infinity

λ_z Terminal phase rate constant

$t_{½}$ Terminal half-life

Statistical Analysis of Pharmacokinetic Parameters

The PK parameters were compared between treatment groups using an analysis of variance (ANOVA) with sequence, period, and treatment as fixed effects, and subject nested within sequence as a random effect. This analysis was performed for the natural logtransformations of C_{max}, $AUC_{(0\text{-}inf)}$, and $AUC_{(0\text{-}last)}$ using SAS PROC MIXED.

For C_{max}, $AUC_{(0\text{-}inf)}$, and $AUC_{(0\text{-}last)}$, exponentiated least squares (LS) means for each treatment were obtained by taking the antilog of the LS means on the log scale. Ratios of the exponentiated LS means for the test treatment relative to the reference treatment and 90% confidence intervals (CIs) of the ratios were provided. The 90% confidence intervals were obtained by taking the antilog of the 90% confidence intervals for the

difference between the LS means on the log scale. If these confidence intervals fell within the limits of 80-125 percent, the absence of food effect was claimed.
To investigate the primary objective (ie to evaluate the impact of a standard high-fat meal on the plasma PK of *d*- and *l*-amphetamine), SPD465 administered following a high-fat meal was compared to SPD465 administered following at least a 10-hour fast, with fasting administration as the reference. To investigate the secondary pharmacokinetic objective (ie to evaluate the impact of SPD465 sprinkled on applesauce), SPD465 administered after sprinkled on applesauce was compared to SPD465 administered after at least a 10-hour fast, with the fasting administration as the reference.

ANALYTICAL

Clinical study began: December 27, 2004
Sample analysis completed: March 11, 2005
Longest Possible Storage- 90 days

Parameter	D-Amphetamine	L-Amphetamine
Method	LC-MS/MS	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL	0.5 ng/mL
Linearity (Standard curve samples)	0.5ng/ml-75 ng/ml	0.5ng/ml-75 ng/ml
Quality Control (QC) Samples	1.5 ng/mL 20.0 ng/ml 60.0 ng/ml	1.5 ng/mL 20.0 ng/ml 60.0 ng/ml
Precision of Standards (%CV)	2.6%@0.5 ng/ml 0.8 %@ 75 ng/ml	4.6%@0.5 ng/ml 1.1 %@ 75 ng/ml
Precision of QC Samples (%CV)	8% @ 1.5 ng/ml 8%@20.6 ng/ml 5 %@ 61 ng/ml	6 %@ 1.5 ng/ml 8 %@20.6 ng/ml 4 %@ 61 ng/ml
Accuracy of Standards (%)	91 %@0.5 ng/ml 99 %@ 75 ng/ml	91 %@0.5 ng/ml 99 %@ 75 ng/ml
Accuracy of QC Samples (%)	102%@1.5 ng/ml 99%@20.6 ng/ml 100 %@ 61 ng/ml	103 %@1.5 ng/ml 102 %@20.6 ng/ml 99 %@ 61 ng/m l

RESULTS

Figure 1. Mean *d*-Amphetamine Plasma Concentrations over Time After a Single 50mg Dose of SPD465 - PK Population

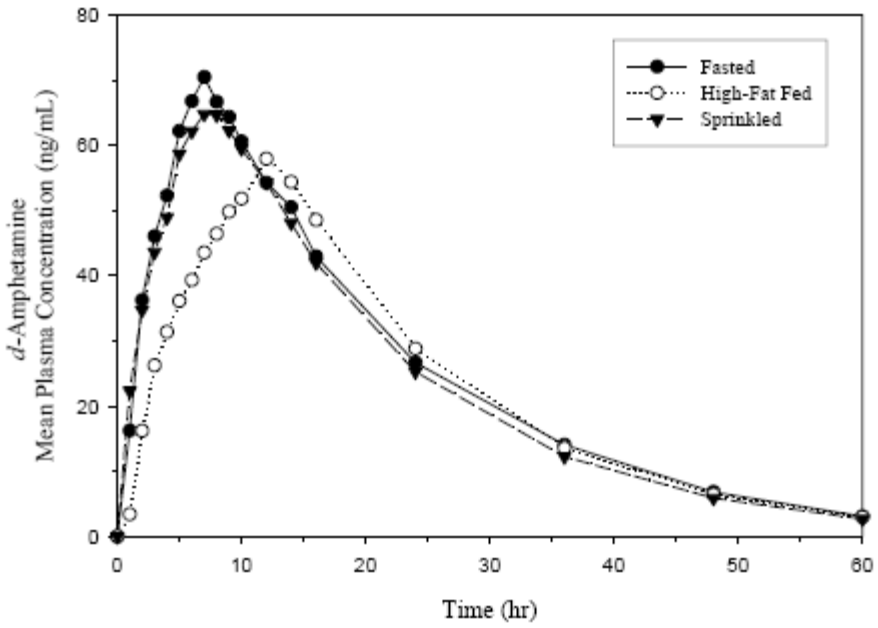


Table 7: *d*-Amphetamine Plasma Pharmacokinetic Parameters Following a Single Dose Administration of 50mg SPD465 - PK Population

Parameter	Statistic	Treatment		
		Fasted (A)	High-Fat Meal (B)	Sprinkled (C)
	N	14	16	16
C_{max} (ng/mL)	Mean (SD)	72.3 (13.7)	60.0 (7.1)	67.3 (7.7)
T_{max} (hr)	Median (Min, Max)	7.0 (6.0, 10.0)	12.0 (8.0, 14.0)	7.5 (5.0, 9.0)
$AUC_{(0\text{-last})}$ (hr*ng /mL)	Mean (SD)	1531.9 (292.4)	1382.6 (289.9)	1450.8 (253.3)
$AUC_{(0\text{-inf})}$ (hr*ng /mL)	Mean (SD)	1589.5 (360.0)	1433.8 (339.5)	1497.9 (300.8)
$t_{1/2}$ (hr)	Mean (SD)	10.9 (2.6)	10.5 (2.1)	10.6 (2.2)

Table 8: Statistical Analysis Results of Plasma *d*-Amphetamine Following a Single Dose Administration of 50mg SPD465 - PK Population							
Parameter	Exponentiated LS Means			Ratio of LS Means		90% CI	
	Fasted (A)	High-Fat Meal (B)	Sprinkled (C)	B/A	C/A	B/A	C/A
C_{max} (ng/mL)	69.6	59.4	66.7	85.3	95.8	80.4, 90.5	90.3, 101.6
$AUC_{(0\text{-}inf)}$ (hr*ng /mL)	1528.3	1392.5	1463.7	91.1	95.8	86.7, 95.8	91.1, 100.6
$AUC_{(0\text{-}last)}$ (hr*ng/mL)	1484.2	1350.3	1424.5	91.0	96.0	86.7, 95.5	91.5, 100.7

Figure 2. Mean *l*-Amphetamine Plasma Concentrations over Time After a Single 50mg Dose of SPD465 - PK Population

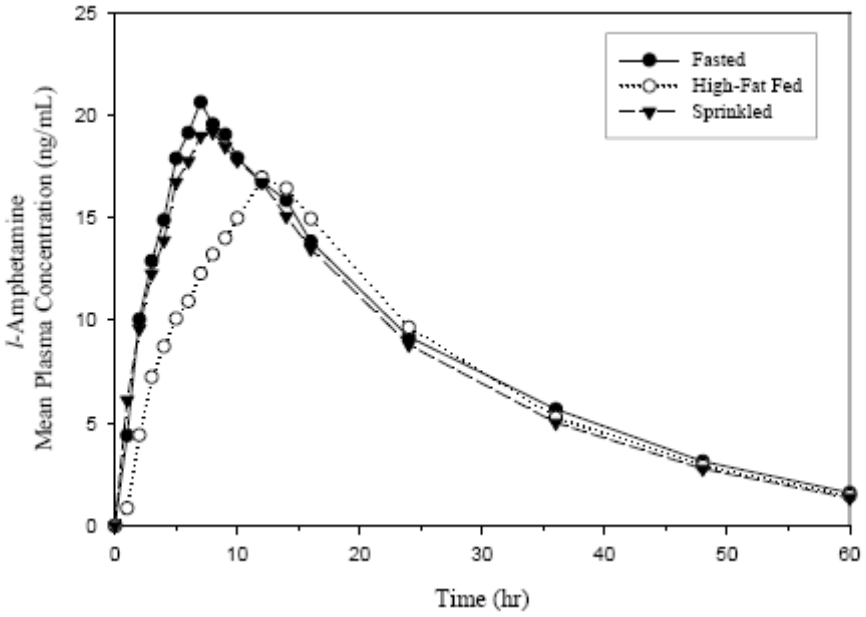


Table 9: /-Amphetamine Plasma Pharmacokinetic Parameters Following a Single Dose Administration of 50mg SPD465 - PK Population

Parameter	Statistic	Treatment		
		Fasted (A)	High-Fat Meal (B)	Sprinkled (C)
	N	14	16	16
C_{max} (ng/mL)	Mean (SD)	21.1 (3.7)	17.6 (2.2)	20.0 (2.5)
T_{max} (hr)	Median (Min, Max)	7.5 (6.0, 12.0)	12.0 (8.0, 14.0)	8.0 (5.0, 12.0)
$AUC_{(0\text{-last})}$ (hr*ng/mL)	Mean (SD)	506.9 (107. 9)	448.3 (107.8)	479.2 (100.8)
$AUC_{(0\text{-inf})}$ (hr*ng/mL)	Mean (SD)	545.2 (147.9)	481.7 (138.4)	511.4 (127.1)
$t_{1/2}$ (hr)	Mean (SD)	13.6 (3.7)	12.8 (3.3)	13.0 (3.2)

Source: Section 12.1, Table 2.2
(A) SPD465 50mg fasted subjects
(B) SPD465 50mg high-fat fed subjects
(C) SPD465 50mg sprinkled on applesauce

Table 10: Statistical Analysis Results of Plasma /-Amphetamine Following a Single Dose Administration of 50mg SPD465 - PK Population

Parameter	Exponentiated LS Means			Ratio of LS Means		90% CI	
	Fasted (A)	High-Fat Meal (B)	Sprinkled (C)	B/A	C/A	B/A	C/A
C_{max} (ng/mL)	20.4	17.4	19.8	85.2	96.9	80.2, 90.6	91.2, 103.0
$AUC_{(0\text{-inf})}$ (hr*ng/mL)	522.3	463.4	495.0	88.7	94.8	83.9, 93.9	89.6, 100.3
$AUC_{(0\text{-last})}$ (hr*ng/mL)	492.2	436.1	468.1	88.6	95.1	83.8, 93.7	90.0, 100.5

Source: Section 12.1, Table 2.3
Note: 14 subjects received Fasted (A) and 16 subjects each received Fed (B) and Sprinkled (C)
LS=Least squares
(A) SPD465 50mg fasted subjects
(B) SPD465 50mg high-fat fed subjects
(C) SPD465 50mg sprinkled on applesauce

Comment:
d-amphetamine

The exposure to *d*-amphetamine, as described by C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ was highest in fasted subjects, slightly lower in subjects receiving the drug sprinkled on applesauce and lowest in subjects pretreated with a high-fat meal. The 90% CI of the test-to-reference ratios, with fasted as the reference treatment, were within the acceptable bioequivalence range of 80%-125% indicating that although the exposure was slightly lower when the drug was given with food, there was bioequivalence across the different conditions.

l-amphetamine

The exposure to *l*-amphetamine, as described by C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$, was highest in fasted subjects, slightly lower when SPD465 was given sprinkled on applesauce, and lowest following a high-fat meal. As observed for *d*-amphetamine, the 90% CI of the test-to-reference ratios of LS means were within the acceptable bioequivalence range of 80%-125% indicating that there were no differences across the 3 treatments.
Tmax was delayed by 4.5 hr with food.

Study-SPD465-110

TITLE:

An Open-label, Incomplete Block Randomization, Three-Period, Four-Treatment, Dose Escalating Study of the Safety, Tolerability, and Pharmacokinetics of SPD465 Administered at Steady State in Healthy Adult Subjects

STUDY INITIATION DATE: December 1, 2005
STUDY COMPLETION DATE: January 15, 2006

STUDY OBJECTIVES
Primary Objective
The primary objective of this study was to describe the PK of SPD465 following repeat-dose administration over the range of doses from 12.5 to 75mg.

Secondary Objectives
The secondary objectives were to:

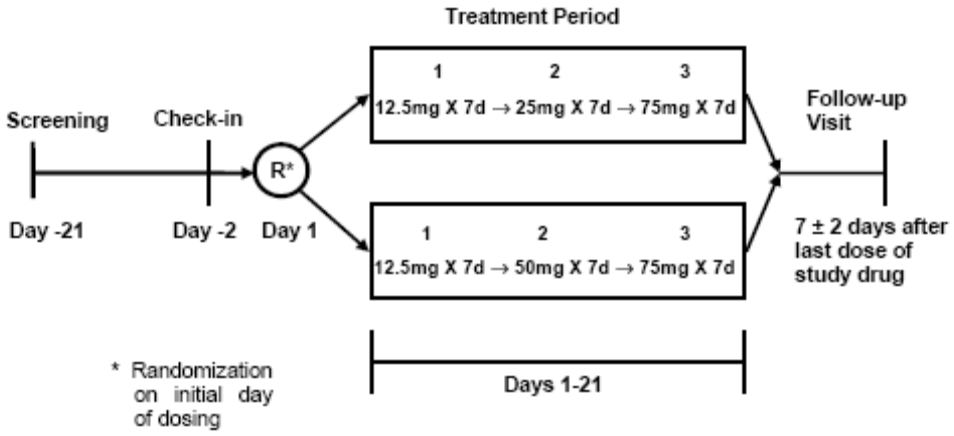
- Assess the safety and tolerability of SPD465 following repeat-dose administration up to 75mg.
- Evaluate the dose-proportionality of SPD465 following repeat-dose administration.

Overall Study Design and Plan - Description
This was a Phase I, open-label, incomplete block randomization, three-period, four treatment, dose escalating study of the safety, tolerability, and PK of SPD465 administered at steady state. The study was conducted at a single center.
Twenty healthy male and female subjects between the ages of 18 and 55 that were considered eligible based on the inclusion and exclusion criteria were to participate in the study. The study consisted of screening, check-in, treatment, and follow-up periods.

A single blood sample from each subject for the determination of plasma *d*- and *l*-amphetamine concentrations was to be collected prior to dosing on Days 5 and 6 of each treatment period. Serial blood samples for the determination of plasma *d- and l*-amphetamine concentrations were to be collected at specified times on days of intensive PK sampling (Day 1 of Period 1 and on Day 7 of each treatment period). During days of intensive PK sampling, vital signs (oral temperature at pre-dose only; BP, HR,

respiratory rate [RR]), and 12-lead ECG measurements were to be obtained pre-dose and at 2, 4, 8, 10, and 12 hours post-dose and pre-dose on other days as specified.

Figure 1: Study Design Flow Chart



METHODS

Demographics

Table 1.2.1 Subject Demographics and Baseline Characteristics by Treatment Sequence (Safety Population)

Characteristic	Statistic	12.5mg/25mg/75mg (N=10)	12.5mg/50mg/75mg (N=8)	Total (N=18)
Age (yrs)	N	10	8	18
	Mean (SD)	34.3 (10.58)	28.1 (6.20)	31.6 (9.22)
	Median	35.5	29.0	30.0
	Min, Max	18, 48	19, 37	18, 48
Gender N (%)	Male	8 (80.0)	5 (62.5)	13 (72.2)
	Female	2 (20.0)	3 (37.5)	5 (27.8)
Ethnicity N (%)	Hispanic/Latino	2 (20.0)	1 (12.5)	3 (16.7)
	Not Hispanic/Latino	8 (80.0)	7 (87.5)	15 (83.3)
Race N (%)	White	5 (50.0)	2 (25.0)	7 (38.9)
	Black/African American	5 (50.0)	6 (75.0)	11 (61.1)
	Native Hawaiian/Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)
	American Indian/Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)	N	10	8	18
	Mean (SD)	74.6 (9.45)	78.1 (10.74)	76.2 (9.41)
	Median	76.5	74.0	74.5
	Min, Max	57, 84	63, 93	57, 93

Cross Reference: Listing 2.2

Plasma Sample Collection and Handling

Plasma concentrations of *d*- and *l*-amphetamine of SPD465 were to be measured at the following timepoints:
• Day 1 of Period 1 and Day 7 of each treatment period prior to dosing and at 2, 4, 6, 8, 9, 10, 11, 12, 16, 20, and 24 hours following dose administration.
• On Days 5 and 6, a single blood sample pre-dosing.
During each treatment period, blood samples for bioanalytical analysis of *d*- and *l*-amphetamine were to be collected from the antecubital vein via direct venipuncture or indwelling catheter into a Vacutainer tube containing ethylenediaminetetraacetic acid (EDTA) as the anticoagulant.

Pharmacokinetic Data Analysis

Statistical Analysis of Pharmacokinetic Parameters
Pharmacokinetic measurements
Calculated PK parameters included the following:
C_{max} Maximum plasma concentration
t_{max} Time of maximum plasma concentration
AUC_{0-24} Area under the plasma concentration-time curve from Time 0 to Time 24 hours
CL/F Apparent oral clearance
CL/F/Wt Weight adjusted apparent oral clearance
C_{min} Minimum plasma concentration

R Accumulation ratio AUC_{0-24}/AUC_{0-24}
Area under the plasma concentration-time curve from Time 0 to Time 24 hours on Day 7 at 25mg, 50mg, and 75mg relative to the AUC_{0-24} on Day 7 at 12.5mg

Dose proportionality was analyzed using the power model. For the *d*- and *l*-amphetamine analytes, the natural log transformed C_{max} and AUC_{0-24} parameters were analyzed using PROC MIXED in SAS and a mixed effects model with a fixed effect for natural log transformed dose and a random effect for subject. The estimated slope for the log-dose fixed effect was reported with a 90% CI.

Assessment of Steady State

For each subject in each study period, predose plasma concentrations on Day 5, 6, 7 and the Day 7 24 hour plasma concentration were tested using a multiple range test to see if the subject was at steady-state.

Clinical study began: **December 1, 2005**
Sample analysis completed: January 10, 2006
Longest Possible Storage- 30 days

Parameter	D-Amphetamine	L-Amphetamine
Method	LC-MS/MS	

Sensitivity/LOQ	0.5 ng/mL	0.5 ng/mL
Linearity (Standard curve samples)	0.5ng/ml-75 ng/ml	0.5ng/ml-75 ng/ml
Quality Control (QC) Samples	1.5 ng/mL 20.0 ng/ml 60.0 ng/ml	1.5 ng/mL 20.0 ng/ml 60.0 ng/ml
Precision of Standards (%CV)	3%@0.5 ng/ml 1.2%@ 75 ng/ml	3.8%@0.5 ng/ml 0.9 %@ 75 ng/ml
Precision of QC Samples (%CV)	5 @ 1.5 ng/ml 4@20.6 ng/ml 2%@ 61 ng/ml	2.5@.5 ng/ml 4.5 %@20.6 ng/ml 1.3 %@ 61 ng/ml
Accuracy of Standards (%)	112%@0.5 ng/ml 101%@ 75 ng/ml	91 %@0.5 ng/ml 99 %@ 75 ng/ml
Accuracy of QC Samples (%)	95%@1.5 ng/ml 95@20.6 ng/ml 99 %@ 61 ng/ml	94.8 %@1.5 ng/ml 96 %@20.6 ng/ml 100 %@ 61 ng/m l

RESULTS

Figure 1. Mean *d*-Amphetamine Plasma Concentrations over Time After Seven Once-Daily Oral Doses of SPD465 to Healthy Subjects

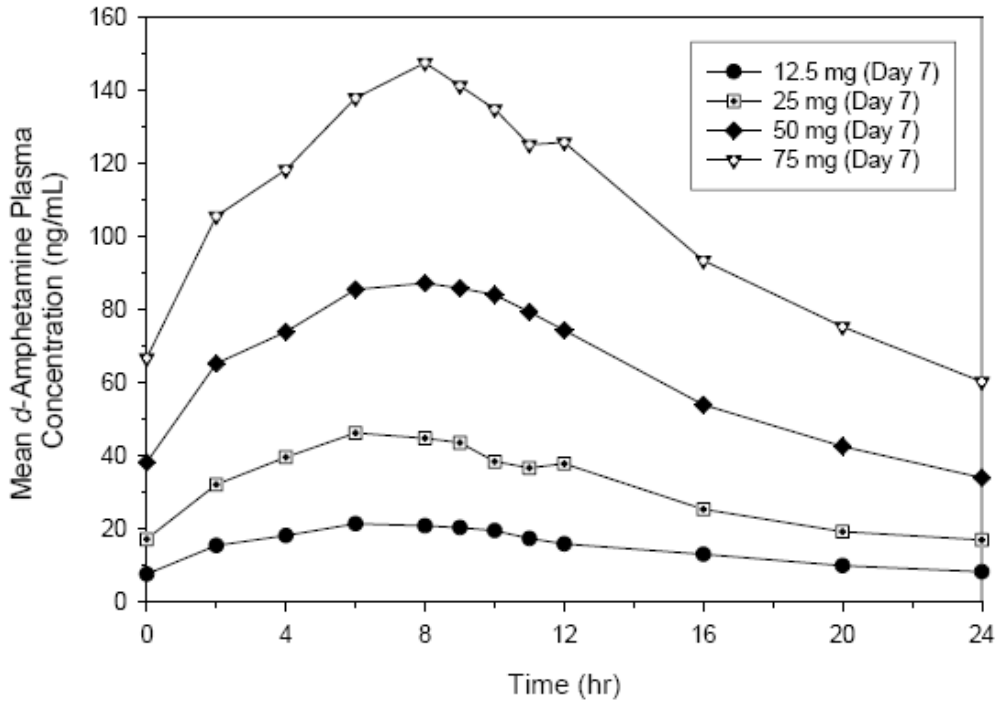


Table 1: *d*-Amphetamine Plasma Pharmacokinetic Parameters Following Single and Seven Once-Daily Oral SPD465 Doses to Healthy Subjects

Parameter	Statistic	Single Dose (Day 1)	Multiple Dose (Day 7)			
		12.5mg N=18*	12.5mg N=18*	25mg N=9	50mg N=8	75mg N=17*
C_{max} (ng/mL)	Mean (SD)	17.0 (2.9)	22.4 (5.8)	48.5 (4.6)	94.2 (32.1)	153.5 (24.6)
T_{max} (hr)	Median (Min, Max)	8.0 (6.0, 9.0)	6.0 (2.0, 10.1)	8.0 (6.0, 9.0)	6.0 (4.0, 12.1)	8.0 (6.0, 12.0)
AUC_{0-24} (hr*ng /mL)	Mean (SD)	248.5 (45.3)	351.3 (87.5)	742.0 (77.5)	1499.7 (504.9)	2526.2 (495.1)
C_{min} (ng/mL)	Mean (SD)	--	7.6 (2.9)	17.2 (5.6)	38.2 (10.5)	66.8 (23.8)
CL/F (L/hr)	Mean (SD)	39.0 (7.2)	29.5 (13.5)	25.5 (2.8)	29.5 (16.6)	22.9 (3.7)
CL/F/Wt (L/hr/kg)	Mean (SD)	0.51 (0.09)	0.40 (0.18)	0.35 (0.05)	0.40 (0.23)	0.31 (0.06)
R	Mean (SD)	--	1.4 (0.3)	--	--	--
AUC_{0-24}/ AUC_{0-24} 12.5mg	Mean (SD)	--	--	2.2 (0.4)	4.2 (0.6)	8.0 (4.0)

Figure : Mean *l*-Amphetamine Plasma Concentrations over Time After Seven Once-Daily Oral Doses of SPD465 to Healthy Subjects

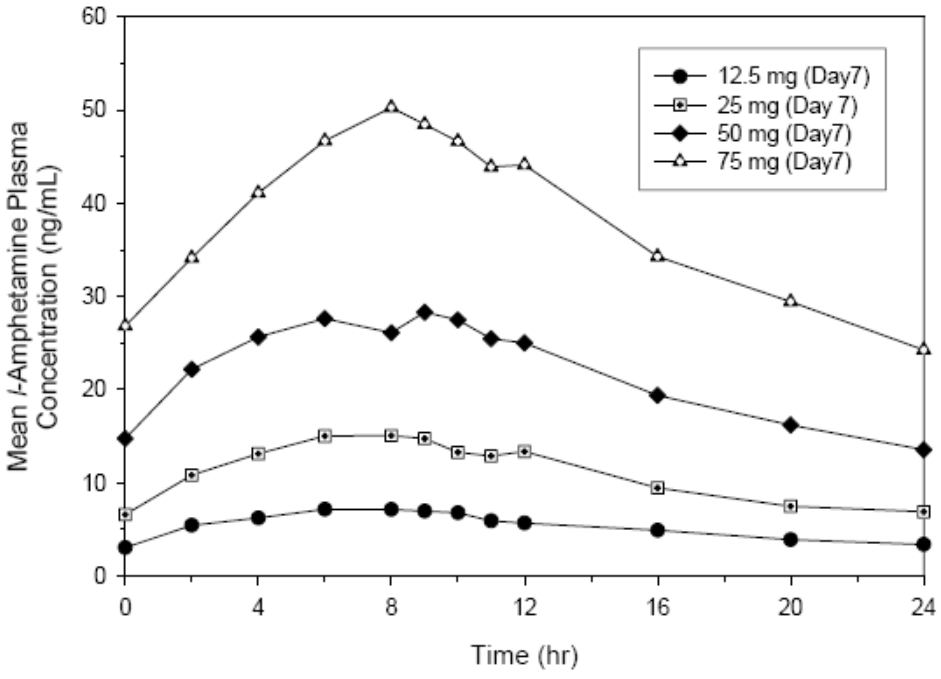


Table: *l*-Amphetamine Plasma Pharmacokinetic Parameters Following Single and Seven Once-Daily Oral SPD465 Doses to Healthy Subjects

Parameter	Statistic	Single Dose (Day 1)	Multiple Dose (Day 7)			
		12.5mg N=18*	12.5mg N=18*	25mg N=9	50mg N=8	75mg N=17*
C_{max} (ng/mL)	Mean (SD)	5.2 (0.9)	7.6 (1.8)	15.9 (1.6)	30.2 (8.7)	52.0 (9.6)
T_{max} (hr)	Median (Min, Max)	8.0 (6.0, 10.0)	8.0 (2.0, 10.1)	8.0 (4.0, 9.0)	9.0 (4.0, 12.1)	8.0 (6.0, 12.0)
AUC_{0-24} (hr*ng /mL)	Mean (SD)	81.3 (14.8)	126.4 (29.9)	261.5 (31.8)	514.7 (148.5)	899.3 (205.9)
C_{min} (ng/mL)	Mean (SD)	--	3.0 (1.0)	6.6 (2.1)	14.8 (4.3)	26.8 (10.1)
CL/F (L/hr)	Mean (SD)	39.7 (7.1)	26.8 (10.2)	24.2 (3.1)	26.6 (9.7)	21.6 (3.9)
CL/F/Wt (L/hr/kg)	Mean (SD)	0.52 (0.08)	0.36 (0.14)	0.34 (0.05)	0.36 (0.14)	0.30 (0.07)
R	Mean (SD)	--	1.6 (0.3)	--	--	--
AUC_{0-24}/AUC_{0-24} 12.5mg	Mean (SD)	--	--	2.2 (0.4)	4.1 (0.8)	7.8 (3.4)

Source: Section 12.1, Table 2.2
--: Not Determined

Table Results from determination of steady-state based upon a Duncan's multiple range test. was used and the results are summarized below.

Analyte	Dose (mg)	Day				p-value
		5	6	7	8	
d-amphetamine	12.5	A	A	A	A	0.69
	25	A	A	A	A	0.17
	50	A	A	A	A	0.31
	75	B	B A	A	B A	0.09
l-amphetamine	12.5	A	A	A	A	0.21
	25	A	A	A	A	0.32
	50	A	A	A	A	0.46
	75	A	A	A	A	0.13

Days with same letter indicate no significant difference from Duncan's Multiple Range Test

Statistical Analysis of Dose Proportionality of Cmax and AUC(0-24)
(PK Population)

Analyte	PK Parameter	Slope	90% Confidence Interval
d-Amphetamine	Cmax (ng/mL)	1.0777	[1.0152, 1.1402]
	AUC (0-24) (hr*ng/mL)	1.0999	[1.0361, 1.1636]
l-Amphetamine	Cmax (ng/mL)	1.0711	[1.0118, 1.1303]
	AUC (0-24) (hr*ng/mL)	1.0868	[1.0264, 1.1472]

Comment:

The exposure to *d*-amphetamine, as described by C_{max} and AUC_{0-24} was higher after the seventh daily 12.5 mg SPD465 dose when compared with the single dose exposure. The accumulation ratio (R) calculated as Day 7 AUC_{0-24} divided by Day 1 AUC_{0-24} was 1.4 which was consistent with the R from a previous study (R=1.5; SPD465-107). The statistical comparison between the Day 5-8 predose concentrations (Appendix 1.9.1) indicated that steady-state for *d*-amphetamine was achieved between Day 5 and 8 after once-daily doses of SPD465 12.5mg. The median time to maximum plasma concentrations, T_{max}, after a single 12.5mg SPD465 dose was 8 hours, which decreased to a median value of 6 hours following the once-daily dose on Day 7. However, the T_{max} following single and multiple 12.5 mg doses were contained entirely within the range of 2-10 hours. The mean CL/F values for single and multiple 12.5mg doses were 39.0 and 29.5L/hr, respectively, and the individual subject weight-adjusted mean values were 0.5 and 0.4L/hr/kg, respectively.

The exposure to *l*-amphetamine, as described by its C_{max} and AUC_{0-24} was higher after the seventh daily 12.5mg SPD465 dose when compared with the single dose exposure. The mean R was 1.6 which, as for *d*-amphetamine, was consistent with the R from a previous study (R=1.56; SPD465-107). The statistical comparison between the Day 5-8 predose concentrations (Appendix 1.9.1) indicated that steady-state for *l*-amphetamine was achieved between Day 5 and 8 after once-daily doses of SPD465 12.5mg. The median T_{max} after a single 12.5mg SPD465 dose and after seven once-daily doses on Day 7 was similar at 8 hours. The mean CL/F values for single and multiple 12.5mg doses were 39.7 and 26.8L/hr, respectively, and the individual subject weight-adjusted mean values were 0.5 and 0.4L/hr/kg, respectively.

Results from the steady-state p values indicates that steady-state had been achieved. The slopes were near 1 and all the 90% CI resulting from the power analysis had lower limits =1 which indicates that both d and l amphetamine are linear with respect to dose for Cmax and AUC(0-24hr)

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[i]

[ii]

[iii]

[iv] Mean values represent the average of n=6 samples

[v] Reference analysis report #AR03L002 for lot #B03044

[vi] Reference analysis report #AR03L003 for lot #B03045

[vii] Reference analysis report #3211 AR-24FEB2005 for lot #A08767

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