CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208147Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	208147
Generic Name:	Amphetamine Extended Release Oral Suspension
Strength:	2.5 mg amphetamine base per mL
Trade Name:	Dyanavel™ XR
Sponsor:	Tris Pharma
Indication:	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Submission Type:	New Formulation, 505(b)(2)
Classification:	Standard
Submission Dates:	12/18/14, 5/8/15
OCP Division:	DCP1
OND Division:	DPP
CP Review Team	Kofi Kumi, Ph.D., Li Zhang, Ph.D., Kevin Krudys, Ph.D., Hao Zhu, Ph.D.

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1 EXECUTIVE SUMMARY

The sponsor submitted 505(b)(2) application for a new formulation of Amphetamine for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Amphetamine Extended Release (ER) Oral Suspension is a once daily extended-release formulation developed to provide patients who cannot or will not swallow solid oral dosage forms with an ER amphetamine in liquid form for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).The reference listed product (RLD) for this application is Adderall® immediate release (IR) tablets (NDA 011522, Teva Womens). Adderall IR tablet is discontinued; therefore the sponsor used generic RLD, dextromaphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate and amphetamine sulfate 15 mg tablet (ANDA 040422, Teva Pharmaceuticals/Barr Labs.,) as the reference drug in the pivotal relative bioavailability study.

Amphetamine ER Oral Suspension is a formulation of (b) (4) Amphetamine ER oral suspension is designed to release drug and be effective for at least 12-hours and is intended to be taken once a day.

The clinical program included a pivotal efficacy and safety trial (TRI102-ADD-001) in pediatric patients 6 -12 years of age with ADHD, a study evaluating the pharmacokinetics in children (6 – 12 years), and a single-dose relative bioavailability and food effect trial in healthy adult subjects to support this application. The intended commercial formulation was used in all three clinical trials. In addition to the clinical trials, the application contains a modeling and simulation report to simulate the exposure and pharmacokinetic profile in adolescents, age 13 -17 years old based on those of children 6-12 years and adults, 18 years or older. Furthermore, a report on modeling to simulate the steady state pharmacokinetic profile of amphetamine based on available single-dose pharmacokinetic data was also included.

Office of Clinical Pharmacology (OCP) key findings are summarized as follows

- An adequate link has been established between the Amphetamine ER Oral Suspension and amphetamine IR tablet (i.e., the RLD). Between the Amphetamine ER Oral Suspension and Amphetamine IR tablet, the total exposure (AUC0-∞), AUC(0-t) and Cmax of both d- and l-amphetamine were equivalent; however, pAUC(0-4) and pAUC(0-5) of both d- and l-amphetamine were not equivalent.

- The similarity of PK profiles in adults, adolescents (13 – 17 years), and children (6 – 12 years) in combination with the prior knowledge of the Amphetamine IR tablet (i.e., RLD) and clinical practice supports the approval and dosing recommendations in adolescents and adults.
    - PK profile in adolescents was simulated based on the data in children (6-12 years) and adults (17 years above). Modeling and simulation indicated that the PK, adjusted for body weight, in children (6-12 years), adolescents (13 -17 years) and adults (17 years and above) were similar. Based on similar PK profiles in conjunction with the understanding of PK/PD relationship, the safety and efficacy observed in children (6-12 years) can be anticipated in adolescents and adults; hence supports the approval of this product in adolescents and adults.

    - The sponsor proposed a [redacted] (b) (4) .

- The pharmacokinetic profiles of Amphetamine ER Oral Suspension in patients of different age ranges are sufficient to support a once daily dosing.

- Food does not significantly affect the exposure and the shape of pharmacokinetic profiles of both d- and l-amphetamine after administration of Amphetamine ER Oral Suspension. Therefore, Amphetamine ER Oral Suspension can be given with or without food.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information submitted in NDA 208147 and supports a recommendation of approval for Amphetamine ER Oral Suspension for the treatment of ADHD provided an agreement on the label can be reached with the sponsor. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP	Recommendations and Comments
• Overall	☒ Yes ☐ No ☐ NA	• Pending labeling agreements with the sponsor.
• Evidence of Effectiveness	☒ Yes ☐ No ☐ NA	• Pivotal safety and efficacy trial
• Proposed dose for general population	☒ Yes ☐ No ☐ NA	In children 6 years of age and older, start with 2.5 mg or 5 mg once daily in the morning. The dose may be increased in increments of 2.5 mg to 10 mg per day every 4 to 7 days until an optimal response is obtained. Daily doses above 20 mg have not been studied and are not recommended.
• Proposed dosing in specific populations	☐ Yes ☐ No ☒ NA	• Similar to Reference Drug, Adderall IR Tablets
• Pivotal bioequivalence studies	☐ Yes ☐ No ☒ NA	• The To Be Marketed and Clinical Trial formulations are the same.
• Labeling	☐ Yes ☒ No ☐ NA	• Pending satisfactory agreement with the sponsor.

1.2 Post Marketing Studies

No post-marketing studies are recommended by OCP

1.3 Labeling Recommendations

Sponsor's recommended language for Clinical Pharmacology Sections is acceptable

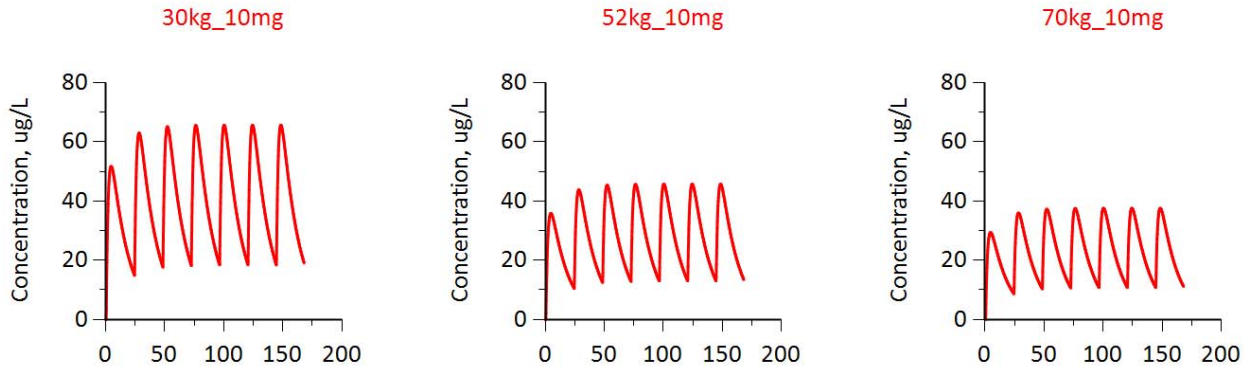
1.4 Summary of Clinical Pharmacology Findings

1.4.1 Population Pharmacokinetics (PopPK)

Modeling and simulation indicated that interpolation of the PK from the data in children (6-12 years) and adults (17 years above) supported the approval and dosing recommendations of amphetamine extended release (ER) oral suspension in adolescents (13 -17 years).

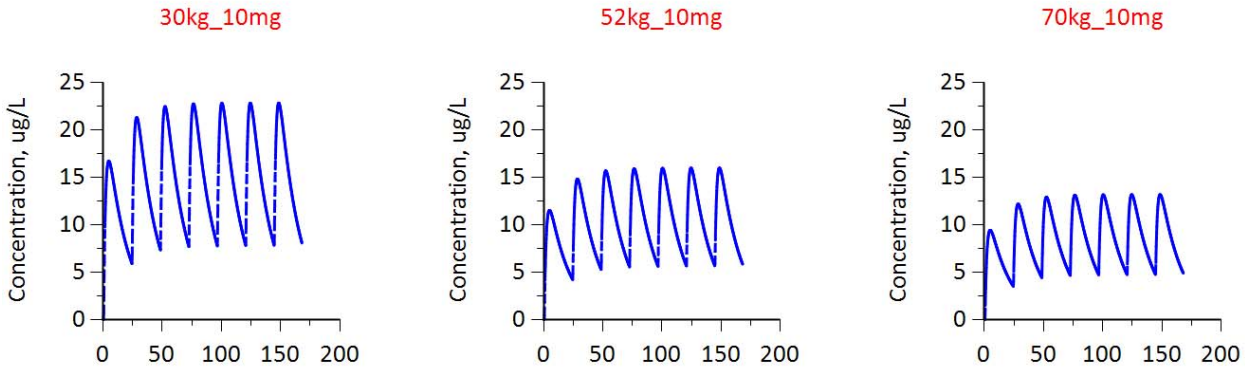
Modeling and simulation demonstrated that the projected PK profile of amphetamine in adolescents (13-17 years) matched closely to observed PK profiles in children (6-12 years). It also indicated that the PK, adjusted for body weight, in children (6-12 years), adolescents (13 -17 years) and adults (17 years and above) were similar. Body weight was the only prognostic factor that explained between subject variability of PK in children, adolescents and adults. The pharmacokinetic findings appear to support the extension of the indication from pediatric patients to adults. The similar PK in children, adolescents and adults and the individual dose titration scheme support the same dosing regimen of amphetamine ER oral suspension in children, adolescents and adults.

Figure 1: Simulated d-amphetamine pharmacokinetic profiles for a typical child (30 kg), adolescent (52 kg) and adult (70 kg) each receiving 10 mg of amphetamine ER oral suspension once daily**.**



Source: PM Review

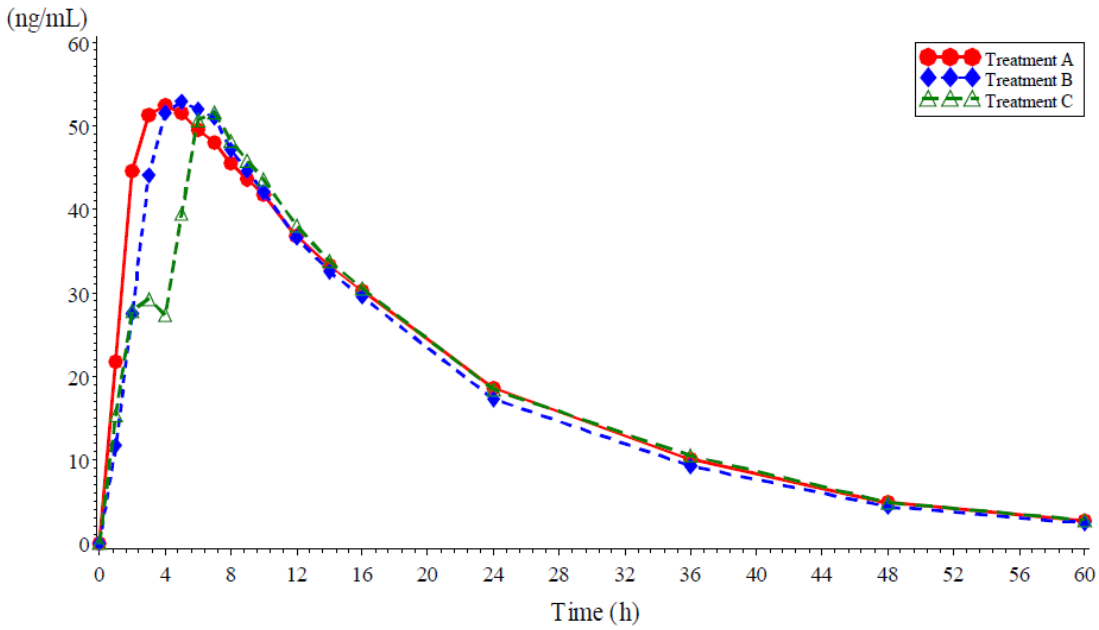
Figure 2: Simulated l-amphetamine pharmacokinetic profiles for a typical child (30 kg), adolescent (52 kg) and adult (70 kg) each receiving 10 mg of amphetamine ER oral suspension once daily.



Source: PM Review

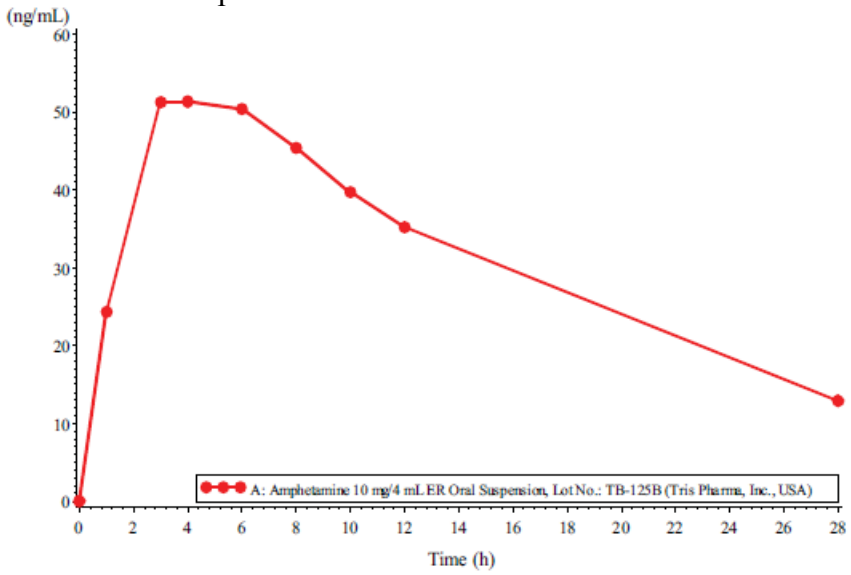
The shape of the plasma concentration-time profiles of d-amphetamine after administration of Amphetamine ER Oral Suspension in adults and pediatric children are similar. Similar observation was made for l-amphetamine plasma-concentration time profiles (Figures 3, 4)

Figure 3: Arithmetic Mean Plasma Concentration-Time Profiles of d-Amphetamine (red profile) in Adults (Study 2014-3401)



Treatment A (Test-1)	*FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment B (Test-2)	*FED:Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII) , Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment C (Ref)	*FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)*

Figure 4: Mean d-Amphetamine Plasma Concentration-Time Profile for Children (6 -12 years)



The profiles for l-amphetamine were also similar when children and adults were compared.

1.4.2 Pharmacokinetics

An adequate link has been established between the Amphetamine ER Oral Suspension and amphetamine IR tablet through a relative bioavailability study. The pharmacokinetic profile of amphetamine following the administration of Amphetamine ER Oral Suspension supports a once-daily dosing. Between the Amphetamine ER Oral Suspension and amphetamine IR tablet (i.e., RLD), total exposure (AUC0-∞), AUC(0-t) and Cmax of both d- and l-amphetamine were equivalent, however, partial(p) AUC(0-4) and pAUC(0-5) of both d- and l-amphetamine were not equivalent. Partial AUC(5-t) of amphetamine was equivalent.

Table 1: Test Product-Fasted (Treatment A) vs Reference Product-Fasted (Treatment C) Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI) Ln-Transformed *d*- and *l*-Amphetamine data (N=29)

Parameter	*d*-Amphetamine			90% Confidence Interval
	Geometric Mean [a]		%Ratio [b]	
	Test	Ref		
AUC_t (ng·h/mL)	1119.647	1053.113	106.32	102.03-110.78
AUC_{inf} (ng·h/mL)	1168.903	1103.036	105.97	101.45-110.70
C_{max} (ng/mL)	53.026	51.732	102.50	100.15-104.91
Parameter	***l*-Amphetamine**			**90% Confidence Interval**
	Geometric Mean [a]		**%Ratio [b]**	
	Test	**Ref**		
AUC_t (ng·h/mL)	414.681	372.403	111.35	106.22-116.73
AUC_{inf} (ng·h/mL)	448.439	405.169	110.68	104.97-116.70
C_{max} (ng/mL)	16.917	15.952	106.05	103.56-108.59

[a] *Geometric Mean for Test Formulation-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values*

[b] *Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)*

Source: Study 2014-3401

In the food effect comparison, administration with a high fat meal resulted in no significant change in the exposure and shape of pharmacokinetic profiles. Therefore, Amphetamine ER Oral Suspension can be given with or without food.

Table 2: Test Product- Fed (Treatment B) vs Test Product-Fasted (Treatment A) Geometric Means, Ratio of Means, and 90% Confidence (CI) Ln-Transformed *d*- and *l*-Amphetamine data (N=29)

Parameter	*d*-Amphetamine			90% Confidence Interval
	Geometric Mean [a]		%Ratio [b]	
	Test	Ref		
AUC_t (ng·h/mL)	1119.647	1059.438	94.62	91.17-98.21
AUC_{inf} (ng·h/mL)	1168.903	1102.66	94.33	90.68-98.12
C_{max} (ng/mL)	53.026	54.009	101.85	99.32-104.45
Parameter	***l*-Amphetamine**			**90% Confidence Interval**
	Geometric Mean [a]		**%Ratio [b]**	
	Test	**Ref**		
AUC_t (ng·h/mL)	414.681	386.833	93.28	89.64-97.08
AUC_{inf} (ng·h/mL)	448.439	415.443	92.64	88.57-96.90
C_{max} (ng/mL)	16.917	17.321	102.39	99.83-105.01

[a] *Geometric Mean for Test Formulation-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values*

[b] *Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)*

Source: Study 2014-3401

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 *What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?*

The sponsor submitted 505(b)(2) application for a new formulation of Amphetamine for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The reference listed product (RLD) for this application is Adderall® tablets (NDA 011522, Teva Womens). The sponsor stated that because the RLD is discontinued, the sponsor used generic RLD, dextromaphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate and amphetamine sulfate 15 mg tablet (ANDA 040422, Teva Pharmaceuticals/Barr Labs.,) as the reference drug in the relative bioavailability study. In a pre-NDA meeting, the sponsor was informed that in order to obtain the full label claim for the reference product (children 6 years and older) the development plan must include a pharmacokinetic study in this age group. The sponsor therefore submitted, after the original submission, a study report for a pharmacokinetic study in children 6- 12 years old with ADHD and a modeling and simulation report on the interpolation of available pediatric and adult data to the adolescent age group.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics?

Amphetamine ER Oral Suspension is a single product with once daily dosing frequency. Amphetamine ER Oral Suspension contains the equivalent of 2.5 mg amphetamine base per mL of suspension providing a daily dose concentration of amphetamine comparable to that of Adderall® tablets, the RLD. Amphetamine ER Oral Suspension is a formulation (b) (4) The sponsor states that the liquid drug product is designed to achieve at least 12-hour extended release. The sponsor states that the ratio of *d*- to *l*-amphetamine is approximately 3:1 in both, the Amphetamine ER Oral Suspension and the mixed amphetamine salts product line. The following table contains a comparison of the active ingredients composition of Amphetamine ER Oral Suspension and the RLD, Adderall Tablets, 30 mg

Table 3: Amphetamine ER Oral Suspension vs Adderall Tablets

	Amphetamine ER Oral Suspension, 8 mL		Adderall® Tablets, 30 mg	
	Salt	Base	Salt	Base
(b) (4)				
Total Amount				(b) (4)

Source: Sponsor's Quality Overall Summary: Drug Product

2.1.3 What are the proposed mechanism (s) of action and therapeutic indication(s)?

Amphetamine is a non-catecholamine sympathomimetic amine with central nervous system stimulant activity indicated for the treatment of ADHD. The mode of therapeutic action of amphetamines is unknown in ADHD; however, amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of the monoamines into the extra neuronal space. Two optically active forms of amphetamine, the dextro- (*d*) and levo- (*l*) isomers, are known to be clinically effective in the treatment of ADHD. Mixed amphetamine salts such as Amphetamine Oral ER Suspension and Adderall, RLD, consist of a ratio of approximately 3:1 *d*-amphetamine to *l*-amphetamine.

2.1.4 What are the proposed dosage and route of administration?

Amphetamine ER Oral Suspension should be orally administered once daily in the morning with or without food. The dose should be individualized according to the needs and responses of the patient. In children 6 years of age and older, start with 2.5 mg or 5 mg once daily in the morning. The dose may be increased in increments of 2.5 mg to 10 mg per day every 4 to 7 days until an optimal response is obtained. Daily doses above 20 mg have not been studied and are not recommended.

2.2 General Clinical Pharmacology

2.2.1 *What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

The clinical development program for Amphetamine ER Oral Suspension is comprised of 1 clinical safety and efficacy study, 1 relative bioavailability (BA) study in adults that included a food effect arm, 2 pilot pharmacokinetic studies in healthy adults to support early formulation development, a single dose pharmacokinetic study in children 6- 12 years old and modeling and simulation of PK profile in adolescent patients based on the clinical pharmacokinetic data available in pediatric and adult subjects with intent to interpolate pharmacokinetics in the adolescent population.

The relative BA study was a single-dose, open-label, randomized, three-period, three-treatment crossover study conducted in 30 healthy adults to evaluate the relative bioavailability of Amphetamine ER Oral Suspension (Test Formulation/Test Product) under fasted conditions against the reference product (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate and amphetamine sulfate tablet, Teva Pharmaceuticals USA /Barr Laboratories, Inc), and to evaluate the effect of administration of the ER oral suspension with a high fat meal.

The pivotal safety and efficacy trial was a multicenter, dose-optimized, double-blind, randomized, placebo-controlled study intended to evaluate efficacy of Amphetamine ER Oral Suspension (TRI102) in pediatric patients with ADHD in a laboratory school setting. The study was conducted in 108 pediatric patients, 6 to 12 years of age, with ADHD. After screening and baseline evaluations, eligible subjects were enrolled in the study and entered the open-label phase, dose-optimization phase. Subjects who achieved a stable dose during dose optimization of open-label TRI102 continued in the study and were randomized to double-blind treatment with the optimal dose of TRI102 that was established in the open-label, dose optimization phase, or placebo for one week.

The pharmacokinetic (PK) study in pediatric patients (6 -12 years old) with ADHD was a single center, single dose, randomized, open label study.

2.2.2 What was the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The sponsor stated that a specific etiology (or etiologies) of this disorder is unknown, and there is no single diagnostic test. Therefore, clinical diagnosis requires the use of medical tools and may also require use of special psychological, educational, and social assessment tools. Impairment from symptoms must be present in 2 or more settings. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV characteristics. The Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) is a recognized and accepted diagnostic tool for ADHD. The primary efficacy endpoint was the SKAMP-Combined score at 4 hours post-dose. The key secondary efficacy parameters were the onset and duration of clinical effect as determined by SKAMP Combined scores at each post-dose time point.

2.2.3 What were the design features of the pivotal efficacy and safety trial?

The pivotal safety and efficacy trial was a multicenter, dose-optimized, double-blind, randomized, placebo-controlled study intended to evaluate efficacy of Amphetamine ER Oral Suspension (TRI102) in pediatric patients with ADHD in a laboratory school setting. The study was conducted in 108 pediatric patients, 6-12 years of age, with ADHD. After screening and baseline evaluations, eligible subjects were enrolled in the study and entered the open-label, dose-optimization phase. Amphetamine ER Oral Suspension was taken once daily and subjects underwent dose optimization activities for 5 weeks. In the open-label dose optimization phase (5 weeks), the initial Amphetamine ER Oral Suspension dose was 2.5 or 5.0 mg once daily in the morning. The dose could be titrated twice a week in increments of 2.5 or 5.0 mg or once a week in increments of 5 or 10 mg until an optimal dose or maximum dose (20 mg/day) was reached. Subjects who could not tolerate a minimum dose of 10 mg/day were to be discontinued from the study.

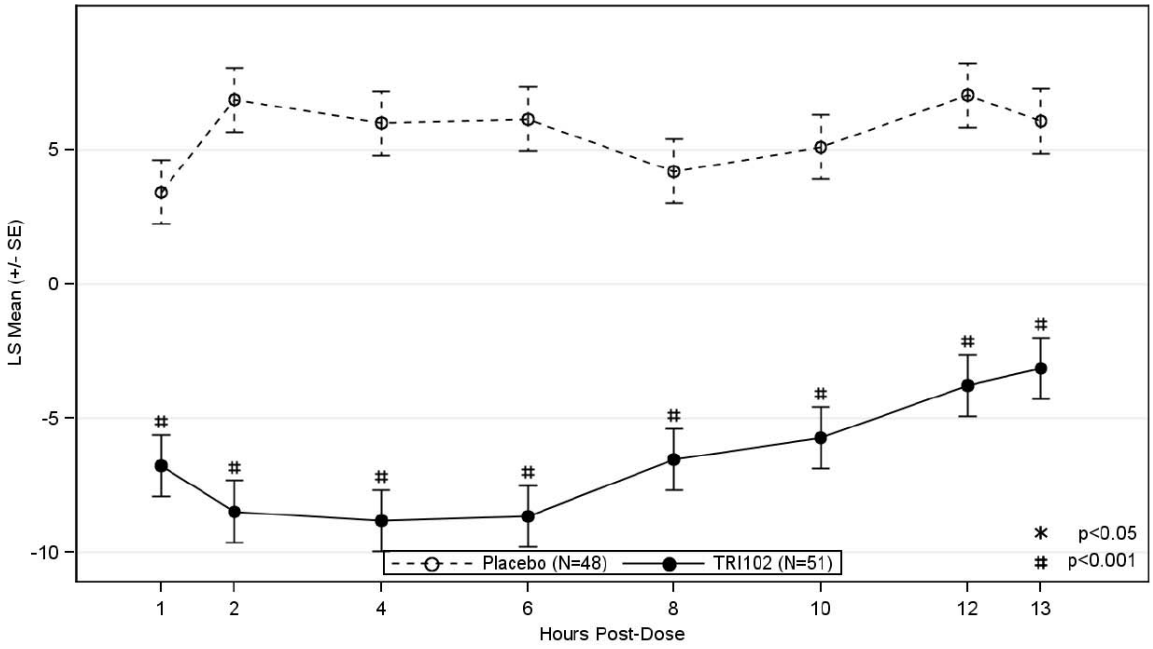
Subjects who achieved a stable dose during dose optimization of open-label TRI102 continued in the study and were randomized to double-blind treatment with the optimal dose of TRI102 that was established in the open-label, dose optimization phase, or placebo for one week. At the end of the week-long double-blind Treatment Period, subjects were evaluated for ADHD symptoms in a laboratory classroom setting utilizing the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale (SKAMP) and Permanent Product Measure of Performance (PERMP) assessments. There was a practice laboratory classroom session before the randomized, controlled phase. The primary efficacy endpoint was the SKAMP-Combined score at 4 hours post-dose. The key secondary efficacy parameters were the onset and duration of clinical effect as determined by SKAMP Combined scores at each post-dose time point.

2.2.4 What are the evidences of efficacy provided by the sponsor in support of the application?

The sponsor stated that the analysis of the SKAMP Attention and Deportment subscale scores (LS mean ± SE) over time by treatment group demonstrated significant response to TRI102 at all individual post dose time points (all p-values <0.001) and as an average across all time points (treatment difference LS mean [SE]: -2.2 [0.39] Attention, -3.3 [0.51] Deportment, all p-values <0.001). Refer to Medical review for Agency's conclusions on the pivotal safety and efficacy study.

The sponsor reported that in the pivotal safety and efficacy trial, the onset of treatment effect occurred at the earliest time point assessed, 1 hour post-dose (treatment difference LS mean [SE]: -10.2 [1.61], p <0.0001). The duration of efficacy persisted until the final time point at 13 hours post-dose (treatment difference LS mean [SE]: -9.2 [1.61], p <0.0001). The highest magnitude of effect relative to pre-dose in the TRI102 group occurred at the 4-hour post-dose time point (LS mean [SE]: -8.8 [1.14]), and the highest treatment difference relative to placebo occurred at 2 hours post-dose (treatment difference LS mean [SE]: -15.3 [1.61], p <0.0001).

Figure 5: Change From Pre-dose SKAMP-Combined Scores Over Time (LS Mean ± SE) by Treatment Group- ITT Population



ITT: Intent-to-Treat; LS: least squares; Max: maximum; Min: minimum; SE: standard error

Source: Sponsor's Clinical Overview Report

2.2.5 What are the evidences of safety provided by the sponsor in support of the application?

The sponsor reported that the safety of TRI102 was evaluated in four clinical studies of Amphetamine ER Oral Suspension (also referred to as Amphetamine ER Oral Suspension and TRI102): three single dose pharmacokinetic (PK) studies (Studies 2013-3144, 2013-3198, and 2014-3401) in healthy adult subjects and one multiple-dose phase 3 study (Study TRI102-ADD-001) in pediatric patients with ADHD (aged 6-12 years).

During the open-label treatment period of the Phase 3 study in children with ADHD (Study TRI102-ADD-001), the most frequently occurring TEAEs by system organ class (SOC) term were psychiatric disorders (33 subjects [30.8%]); metabolism and nutrition disorders (28 [26.2%]); gastrointestinal disorders (21 [19.6%]); injury, poisoning, and procedural complications (10 [9.3%]); nervous system disorders (10 [9.3%]); infections and infestations (8 [7.5%]); general disorders and administration site conditions (6 [5.6%]); and respiratory, thoracic, and mediastinal disorders (6 [5.6%]). All other SOC terms occurred in <5% of subjects. During the double-blind Treatment Period, the most frequently occurring TEAE by SOC term was respiratory, thoracic, and mediastinal disorders (3 TRI102 subjects [5.8%]). No AE (preferred term or combined SOC) occurred in more than 2 subjects in either the TRI102 or placebo group, with the exception of respiratory, thoracic and mediastinal disorders (comprised of epistaxis and allergic rhinitis), which occurred in 3 subjects on TRI102 and no subjects on placebo. Four subjects (3 placebo [6.3%], 1 TRI102 [1.9%]) had at least one treatment-related TEAE. No specific SOC term occurred in >5% of subjects. Three adverse events occurred in >2% of subjects on TRI102 and greater than placebo during the double-blind Treatment Period: Epistaxis, Rhinitis Allergic and Abdominal Pain Upper. Each of these occurred in 2 subjects (3.8%). The sponsor reported that adverse events reported in the trials were similar in quality, frequency and severity to the expected adverse events for amphetamines used for the treatment of ADHD. Refer to medical review for Agency's evaluation of the safety of Amphetamine ER Oral Suspension

The sponsor reported that in the bioavailability study, the most commonly reported AEs were headache (27.7% of subjects; 10.3% following Treatment A (TRI102 fasting), 10.0% following Treatment B (TRI102 fed) and 6.9% following Treatment C (Reference Product), Dizziness (10.0% of subjects; 3.4% following Treatment A (TRI102 fasting), 3.3% following Treatment B (TRI102 fed) and 3.4% following Treatment C (Reference Product), Dry Mouth (10.0% of subjects; 6.9% following Treatment A (TRI102 fasting), 6.7% following Treatment B (TRI102 fed) and 3.4% following Treatment C (Reference Product), and Tachycardia (10.0% of subjects; 6.9% following Treatment A (TRI102 fasting), 3 and 6.9% following Treatment C (Reference Product).

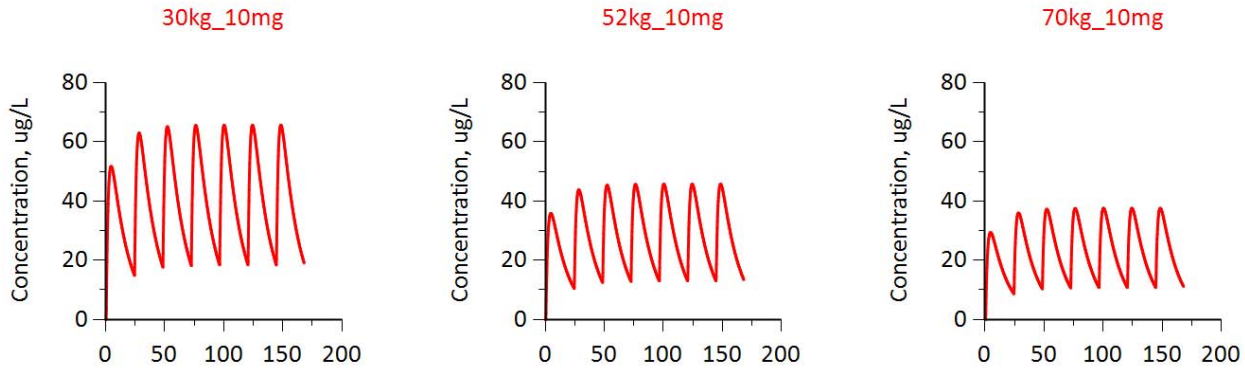
2.3 Exposure Response

2.3.1 Does the interpolation of the PK support the approval and dosing recommendations of amphetamine extended release (ER) oral suspension in adolescents?

Yes, the interpolation of the PK from the data in children (6-12 years) and adults (17 years above) supports the approval and dosing recommendations of amphetamine extended release (ER) oral suspension in adolescents. FDA's modeling and simulation demonstrated the projected PK profile of amphetamine in adolescents (13-17 years) matched closely to observed PK profiles

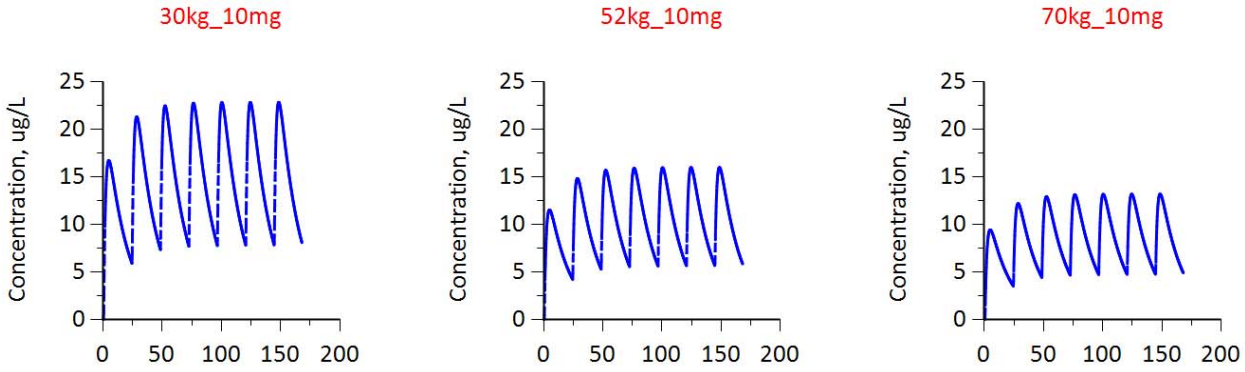
in children (6-12 years). Body weight was the only prognostic factor that explained between-subject variability of PK in children and adolescents. The similar PK in adolescents and individual dose titration scheme supported the same dosing regimen of amphetamine ER oral suspension in this population as in children (6-12 years).

Figure 6: Simulated d-amphetamine pharmacokinetic profiles for a typical child (30 kg), adolescent (52 kg) and adult (70 kg) each receiving 10 mg of amphetamine ER oral suspension once daily**.**



Source: Pharmacometric (PM) review

Figure 7: Simulated l-amphetamine pharmacokinetic profiles for a typical child (30 kg), adolescent (52 kg) and adult (70 kg) each receiving 10 mg of amphetamine ER oral suspension once daily.



Source: Pharmacometric (PM) review

2.3.2 Are the exposures to d- and l-amphetamine in pediatric children, 6 -12 years old, Adolescents (13-17 years old) similar to Adults (18 years and above)?

Yes, the exposures to d- and l-amphetamine in pediatric children, 6-12 years old, Adolescents (13 -17 years old), when adjusted for body weight, are similar to Adults (18 years and older) based on Figures 6 and 7.

Body weight was the only prognostic factor that explained between-subject variability of PK in children, adolescents and adults.

2.4 General Pharmacokinetics

2.4.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

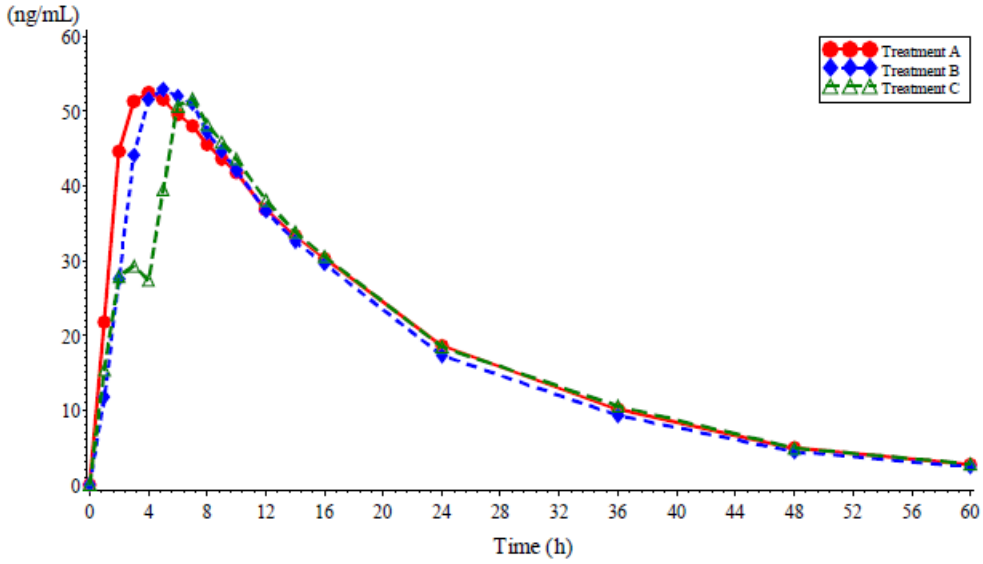
Yes. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay was used for the quantitation of d- and l-amphetamine in plasma. The method was adequately validated and is acceptable.

2.4.2 Is exposure to amphetamine similar after administration of Amphetamine ER Oral Suspension and the RLD, Mixed Amphetamine Salts Tablet (Teva Pharmaceuticals)?

Total exposure (AUC0-∞), AUCt and Cmax of both d- and l-amphetamine were equivalent, however, pAUC(0-4) and pAUC(0-5) of both d- and l-amphetamine were not equivalent. Partial AUC(5-t) of amphetamine was equivalent. The non-equivalence of pAUC(0-4) and pAUC(0-5) does not appear to be clinically significant since the drug was reported to be efficacious during the treatment duration in the pivotal safety and efficacy trial.

The median (range) Tmax of d-amphetamine after administration of the Amphetamine ER Oral Suspension was 4 (2 – 7) hours compared to 6 (6 -8) hours after administration of the RLD, Mixed Amphetamine Salts (Teva Pharmaceuticals) under fasting conditions. The mean ± SD of T ½ of d-amphetamine after administration of Amphetamine ER Oral Suspension was 12.36 ± 2.94 hours compared to 12.24 ± 2.50 hours after administration of the RLD. The median (range) Tmax of l-amphetamine after administration of the Amphetamine ER Oral Suspension was 4 (2 – 7) hours compared to 7 (6 -9) hours after administration of the RLD, Mixed Amphetamine Salts (Teva Pharmaceuticals) under fasting conditions. The mean ± SD of T ½ of d-amphetamine after administration of Amphetamine ER Oral Suspension was 15.12 ± 4.40 hours compared to 15.11 ± 3.71 hours after administration of the RLD.

Figure 9: Mean Plasma Concentration-Time Profiles of d-Amphetamine



Treatment A (Test-1)	*FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment B (Test-2)	*FED:Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII) , Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment C (Ref)	*FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)*

Source: Study 2014-3401

Table 4: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of d-Amphetamine Comparing Test Product – Fasted (Treatment A) to Reference Product- Fasted (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Intra-Sbj
	Test	Ref	(Test/Ref)	Lower	Upper	CV%
$\ln(C_{max})$ *(ng/mL)*	53.026	51.732	102.50	100.15	104.91	5
$\ln(AUC_t)$ *(ng·h/mL)*	1119.647	1053.113	106.32	102.03	110.78	9
$\ln(AUC_{0-\infty})$ *(ng·h/mL)*	1168.903	1103.036	105.97	101.45	110.70	9

[a] *Geometric Mean for Test Product-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values*
[b] *Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)*
[c] *90% Confidence Interval*

Source: Study 2014-3401

Table 5: Summary of Partial Pharmacokinetic Parameters and Statistical Results of d-Amphetamine

			Based on Raw Data					
Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_{0-4} *(ng·h/mL)*	A	29	143.813 (23)	139.463	A vs C	169.17	160.79 - 177.99	11
	B	29	109.242 (29)	104.037	B vs A	74.60	66.83 - 83.27	25
	C	29	86.036 (29)	82.438				
AUC_{4-t} *(ng·h/mL)*	A	29	1000.236 (21)	977.489	A vs C	100.86	96.52 - 105.40	10
	B	29	970.791 (21)	949.674	B vs A	97.15	93.16 - 101.32	9
	C	29	992.910 (22)	969.180				
AUC_{0-5} *(ng·h/mL)*	A	29	195.695 (21)	190.570	A vs C	165.37	158.70 - 172.31	9
	B	29	161.272 (24)	156.010	B vs A	81.87	75.40 - 88.88	19
	C	29	119.430 (26)	115.241				
AUC_{5-t} *(ng·h/mL)*	A	29	948.354 (22)	926.159	A vs C	98.92	94.54 - 103.50	10
	B	29	918.762 (22)	897.737	B vs A	96.93	92.77 - 101.28	10
	C	29	959.516 (23)	936.291				

Treatment A (Test-1)	*FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment B (Test-2)	*FED:Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment C (Ref)	*FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)*

Source: Study 2014-3401

Table 6: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of l-Amphetamine Comparing Test Product- Fasted (Treatment A) to Reference Product-Fasted (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Intra-Sbj
	Test	Ref	(Test/Ref)	Lower	Upper	CV%
$ln(C_{max})$ *(ng/mL)*	16.917	15.917	106.05	103.56	108.59	5
$ln(AUC_t)$ *(ng·h/mL)*	414.681	372.403	111.35	106.22	116.73	11
$ln(AUC_{0-\infty})$ *(ng·h/mL)*	448.439	405.169	110.68	104.97	116.70	12

[a] *Geometric Mean for Test Product-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values*
[b] *Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)*
[c] *90% Confidence Interval*
Source: Study 2014-3401

Table 7: Summary of Partial Pharmacokinetic Parameters and Statistical Results of l-Amphetamine

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_{0-4}	A	29	45.013 (23)	43.572	A vs C	177.40	168.46 - 186.82	12
(ng·h/mL)	B	29	34.356 (30)	32.646	B vs A	74.92	67.12 - 83.63	25
	C	29	25.693 (29)	24.561				
AUC_{4-t}	A	29	379.822 (21)	370.379	A vs C	106.60	101.47 - 112.00	11
(ng·h/mL)	B	29	361.438 (21)	352.405	B vs A	95.15	91.05 - 99.43	10
	C	29	357.427 (23)	347.436				
AUC_{0-5}	A	29	61.642 (22)	59.920	A vs C	173.59	166.42 - 181.08	9
(ng·h/mL)	B	29	50.963 (25)	49.196	B vs A	82.10	75.62 - 89.14	19
	C	29	35.862 (27)	34.517				
AUC_{5-t}	A	29	363.193 (22)	353.968	A vs C	104.90	99.73 - 110.33	11
(ng·h/mL)	B	29	344.831 (22)	335.871	B vs A	94.89	90.65 - 99.32	10
	C	29	347.257 (23)	337.446				

Source: Study 2014-3401

2.4.3 What is the pharmacokinetics of d- and l-amphetamine in pediatric children, 6 -12 years old with ADHD?

Table 8 and 9 contain the descriptive pharmacokinetics of d- and l- amphetamine, respectively after administration of Amphetamine ER Oral Suspension to children 6-12 years old with ADHD. The Tmax and T ½ were similar to that observed for Adults

Table 8: Descriptive Statistics for Plasma d-Amphetamine Pharmacokinetic Parameters

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	**A**	821.150	857.008	248.825	29.03	836.601	406.830	1250.222	10
AUC_{inf}	**A**	1012.702	1061.199	309.200	29.14	1064.757	466.290	1474.361	10
AUC_t/AUC_{inf}	**A**	81.09	81.28	5.83	7.17	81.65	71.27	87.97	10
C_{max}	**A**	52.596	54.870	15.221	27.74	51.950	24.300	78.700	10
T_{max}	**A**	3.85	4.04	1.37	33.84	3.43	2.92	5.93	10
$t_{½}$	**A**	10.43	10.59	2.01	19.01	9.93	8.43	14.19	10
k_{el}	**A**	0.0664	0.0674	0.0114	16.90	0.0699	0.0489	0.0822	10
RStart	**A**	8.66	8.93	1.92	21.55	9.92	3.98	9.92	10
REend	**A**	26.94	26.95	0.80	2.97	26.64	26.10	28.17	10
n	**A**	3	4	1	27.77	3	3	6	10
LQCT	**A**	26.94	26.95	0.80	2.97	26.64	26.10	28.17	10
Ct	**A**	12.088	12.936	4.339	33.54	14.200	4.890	18.200	10

RStart = start time for linear regression
REnd = end time for linear regression
n = number of data points used in the regression analysis
LQCT = time of the last quantifiable concentration
Ct = last measurable concentration value at LQCT. This value was used for the extrapolation to infinity
Source: Study TRI102-PK-200

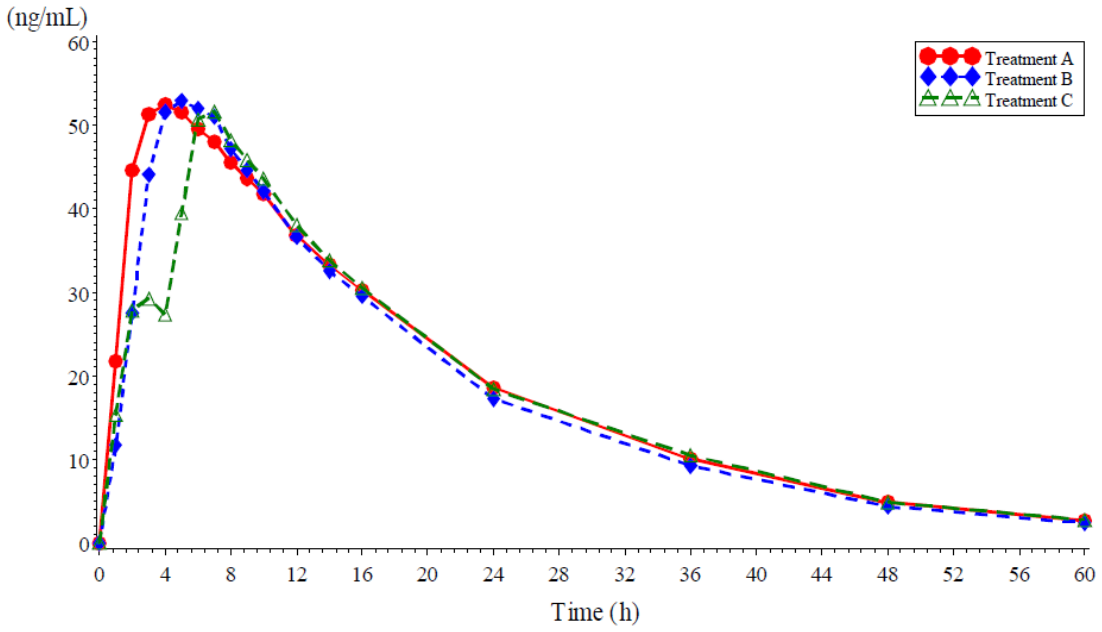
Table 9: Descriptive Statistics for Plasma l-Amphetamine Pharmacokinetic Parameters

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	**A**	274.103	286.078	83.541	29.20	279.955	132.330	440.294	11
AUC_{inf}	**A**	362.089	380.533	112.234	29.49	407.504	155.574	546.303	11
AUC_t/AUC_{inf}	**A**	75.70	76.11	7.99	10.50	75.85	60.68	85.06	11
C_{max}	**A**	16.345	17.148	5.206	30.36	16.300	7.430	26.800	11
T_{max}	**A**	4.50	4.85	1.96	40.52	4.05	2.92	7.93	11
$t_{½}$	**A**	12.14	12.46	3.15	25.31	11.94	9.05	18.67	11
k_{el}	**A**	0.0571	0.0585	0.0127	21.71	0.0580	0.0371	0.0766	11
RStart	**A**	9.33	9.38	0.93	9.89	9.92	7.92	9.93	11
REend	**A**	27.03	27.04	0.81	3.00	26.70	26.10	28.17	11
n	**A**	3	3	0	14.27	3	3	4	11
LQCT	**A**	27.03	27.04	0.81	3.00	26.70	26.10	28.17	11
Ct	**A**	4.712	5.036	1.644	32.63	5.560	1.780	6.650	11

RStart = start time for linear regression
REnd = end time for linear regression
n = number of data points used in the regression analysis
LQCT = time of the last quantifiable concentration
Ct = last measurable concentration value at LQCT. This value was used for the extrapolation to infinity
Source: Study TRI102-PK-200

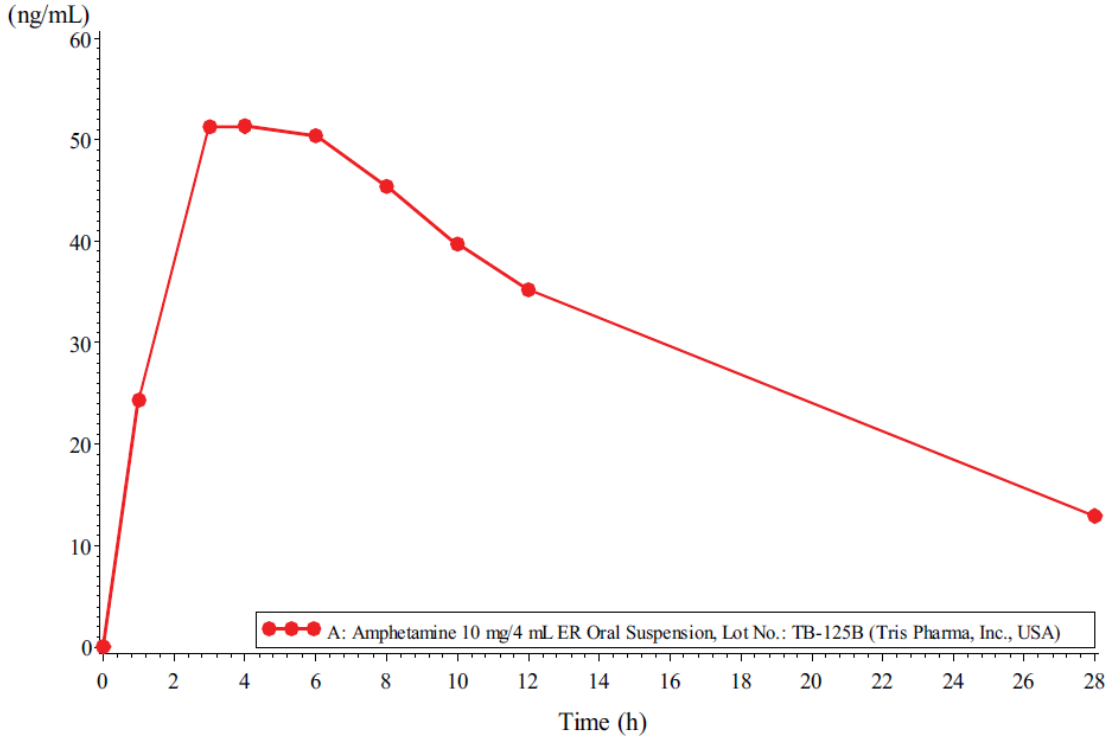
The shape of the plasma concentration time profiles of d-amphetamine after administration of Amphetamine ER Oral suspension to adults is similar to that observed after administration to pediatric patients (6-12 years) (Figures 10 and 11).Similar observation as made for l-amphetamine.

Figure 10: Arithmetic Mean Plasma Concentration-Time Profiles of d-Amphetamine (red curve) in Adults (Study 2014-3401)



Treatment A (Test-1)	*FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment B (Test-2)	*FED:Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII) , Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment C (Ref)	*FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)*

Figure 11: Mean d-Amphetamine Plasma Concentration-Time Profiles (6 – 12 years)



The descriptive pharmacokinetics for children (6-12 years) in Study TRI102-PPK-200 was similar to that of adults (Study 2014-3401) after administration of Amphetamine Oral Suspension (Tables 4, 5, 7, 8, 9).

2.4.3 Intrinsic Factors

2.4.4.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in subjects and how much of the variability is explained by the identified covariates?

Based on modeling and simulation, body weight was the only prognostic factor that explained between-subject variability of PK in children and adolescents.
No new evaluation of intrinsic factors (e.g. renal, hepatic impairment) was conducted for this application. Information on intrinsic factors in the RLD, Adderall IR is included in the proposed label.

2.4.4 Extrinsic Factors

2.4.5.1 Is the exposure different after administration of Amphetamine ER Oral Suspension under fed compared to fasting conditions?

Food does not affect AUC0-∞, AUCt, and Cmax of both d- and l-amphetamine after administration of Amphetamine ER Oral Suspension. However, pAUC(0-4), pAUC(0-5) are decreased after administration with food. pAUC(5-t) and pAUC(4-t) are not affected by administration with food. Median Tmax (range) for d- and l-amphetamine was 5 (3 – 8) hours after administration with food compared to 4 (2-7) hours, respectively under fasting conditions. We do not consider this level of change in pharmacokinetic profile is clinically meaningful. Amphetamine ER Oral suspension can be administered with or without food

Table 10: Statistical Analysis of Test Product- Fed (Treatment B) vs Test Product- Fasted (Treatment A)

Parameter	*d*-Amphetamine			90% Confidence Interval
	Geometric Mean [a]		%Ratio [b]	
	Test	Ref		
AUC_t (ng·h/mL)	1119.647	1059.438	94.62	91.17-98.21
AUC_{inf} (ng·h/mL)	1168.903	1102.66	94.33	90.68-98.12
C_{max} (ng/mL)	53.026	54.009	101.85	99.32-104.45
Parameter	***l*-Amphetamine**			**90% Confidence Interval**
	Geometric Mean [a]		**%Ratio [b]**	
	Test	**Ref**		
AUC_t (ng·h/mL)	414.681	386.833	93.28	89.64-97.08
AUC_{inf} (ng·h/mL)	448.439	415.443	92.64	88.57-96.90
C_{max} (ng/mL)	16.917	17.321	102.39	99.83-105.01

[a] *Geometric Mean for Test Formulation-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values*
[b] *Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)*
Source: Study 2014-3401

Table 11: Summary of Partial Pharmacokinetic Parameters and Statistical Results of d-Amphetamine

Based on Raw Data								
Parameter	***Trt***	***n***	***Arithmetic Mean (CV%)***	***Geometric Mean***	***Contrast***	***Ratio (%)***	***90% Confidence Interval***	***Intra-Sbj CV(%)***
AUC_{0-4}	**A**	29	143.813 (23)	139.463	**A vs C**	169.17	160.79 - 177.99	11
(ng·h/mL)	**B**	29	109.242 (29)	104.037	**B vs A**	74.60	66.83 - 83.27	25
	C	29	86.036 (29)	82.438				
AUC_{4-t}	**A**	29	1000.236 (21)	977.489	**A vs C**	100.86	96.52 - 105.40	10
(ng·h/mL)	**B**	29	970.791 (21)	949.674	**B vs A**	97.15	93.16 - 101.32	9
	C	29	992.910 (22)	969.180				
AUC_{0-5}	**A**	29	195.695 (21)	190.570	**A vs C**	165.37	158.70 - 172.31	9
(ng·h/mL)	**B**	29	161.272 (24)	156.010	**B vs A**	81.87	75.40 - 88.88	19
	C	29	119.430 (26)	115.241				
AUC_{5-t}	**A**	29	948.354 (22)	926.159	**A vs C**	98.92	94.54 - 103.50	10
(ng·h/mL)	**B**	29	918.762 (22)	897.737	**B vs A**	96.93	92.77 - 101.28	10
	C	29	959.516 (23)	936.291				

Treatment A (Test-1)	*FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment B (Test-2)	*FED:Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment C (Ref)	*FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)*

Table 12: Summary of Pharmacokinetic Parameters and Statistical Results of l-Amphetamine

Based on Raw Data								
Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_{0-4}	**A**	29	45.013 (23)	43.572	**A vs C**	177.40	168.46 - 186.82	12
(ng·h/mL)	**B**	29	34.356 (30)	32.646	**B vs A**	74.92	67.12 - 83.63	25
	C	29	25.693 (29)	24.561				
AUC_{4-t}	**A**	29	379.822 (21)	370.379	**A vs C**	106.60	101.47 - 112.00	11
(ng·h/mL)	**B**	29	361.438 (21)	352.405	**B vs A**	95.15	91.05 - 99.43	10
	C	29	357.427 (23)	347.436				
AUC_{0-5}	**A**	29	61.642 (22)	59.920	**A vs C**	173.59	166.42 - 181.08	9
(ng·h/mL)	**B**	29	50.963 (25)	49.196	**B vs A**	82.10	75.62 - 89.14	19
	C	29	35.862 (27)	34.517				
AUC_{5-t}	**A**	29	363.193 (22)	353.968	**A vs C**	104.90	99.73 - 110.33	11
(ng·h/mL)	**B**	29	344.831 (22)	335.871	**B vs A**	94.89	90.65 - 99.32	10
	C	29	347.257 (23)	337.446				

Treatment A (Test-1)	*FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment B (Test-2)	*FED:Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment C (Ref)	*FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)*

Source: Study 2014-3401

2.4.5.2 What are the drug-drug interactions?

No new drug-drug interactions were conducted for this application. Drug interaction studies that were conducted as part of the clinical pharmacology programs for Adderall IR are included in the proposed label.

2.5 General Biopharmaceutics

2.5.1 How is the proposed to be marketed (TBM) formulation linked to the clinical trial material?

The TBM formulation was used in the pivotal relative bioavailability trial, pediatric pharmacokinetic trial, and clinical trial.

2.5.2 What is the composition of the TBM formulation?

The composition of the TBM is illustrated in Table 13.

Table 13: Quantitative Composition of Amphetamine ER Oral Suspension

Ingredients	Quantity (mg/mL)	Function
(b) (4)	(b) (4)	(b) (4)
Amphetamine Base	2.5 [1]	Active
(b) (4)	(b) (4)	
Sodium Polystyrene Sulfonate, USP	(b) (4)	(b) (4)
Povidone, USP		
Triacetin, USP		
Polyvinyl Acetate Dispersion (b) (4)		Rate Controlling Polymer
(b) (4)		
Polysorbate 80, NF		(b) (4)
Anhydrous Citric Acid, USP		
Sucralose, NF		
(b) (4) (Food Starch Modified)		
Glycerin, USP		
Methylparaben, NF		
Propylparaben, NF		
Xanthan Gum, NF		
Bubblegum Flavor (b) (4)		Flavor
(b) (4)		
(b) (4)		(b) (4)

[1] Amphetamine Base calculated based on the following conversion factors:

[2] (b) (4)

Source: Quality Overall Summary: Drug Product

2.5.3 What is the Relative Bioavailability of Amphetamine ER Oral Suspension with an Immediate Release Mixed Amphetamine Salts Tablet as Reference?

The bioavailability of d-amphetamine after administration of Amphetamine ER Oral Suspension is about 106% relative to the RLD, Mixed Amphetamine Salts (Teva). The bioavailability of l-amphetamine after administration of Amphetamine ER Oral Suspension is about 111% relative to the RLD, Mixed Amphetamine Salts (Teva).

Table 14: Summary of Partial Pharmacokinetic Parameters and Statistical Results of d- and l-Amphetamine

Parameter	*d*-Amphetamine			90% Confidence Interval
	Geometric Mean [a]		%Ratio [b]	
	Test	Ref		
AUC_t (ng·h/mL)	1119.647	1053.113	106.32	102.03-110.78
AUC_{inf} (ng·h/mL)	1168.903	1103.036	105.97	101.45-110.70
C_{max} (ng/mL)	53.026	51.732	102.50	100.15-104.91
Parameter	***l*-Amphetamine**			**90% Confidence Interval**
	Geometric Mean [a]		**%Ratio [b]**	
	Test	**Ref**		
AUC_t (ng·h/mL)	414.681	372.403	111.35	106.22-116.73
AUC_{inf} (ng·h/mL)	448.439	405.169	110.68	104.97-116.70
C_{max} (ng/mL)	16.917	15.952	106.05	103.56-108.59

[a] *Geometric Mean for Test Formulation-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values*
[b] *Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)*
Source: Sponsor's Summary of Biopharmaceutics Studies

2.6 Analytical Methods

2.6.1 What bioanalytical methods are used to assess concentrations of d- and l-amphetamine and is the validation complete and acceptable?

Liquid chromatography-tandem mass spectrometry(LC-MS/MS) assays were used for the quantification of d- and l-amphetamine. The methods are validated and acceptable.

Table 15: Summary of Bioanalytical Methods

Analyte	Method Title	Sensitivity Range
d-Amphetamine	PMRI-1425-13; Liquid-liquid extraction; LC-MS-MS	0.200 to 80.0 ng/mL
l-Amphetamine	PMRI-1425-13; Liquid-liquid extraction; LC-MS-MS	0.200 to 80.0 ng/mL

Source: Sponsor's Summary of Biopharmaceutics Studies

Table 16: Bioanalytical Method Validation

Analyte	*d*-Amphetamine and *l*-Amphetamine
Internal standard (IS)	(±)-Amphetamine-D_{10}
Method description	Liquid-liquid extraction followed by derivatization and another liquid-liquid extraction.; liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) method
Limit of quantitation	0.200, ng/mL for each *d*-Amphetamine and *l*-Amphetamine
Average recovery of drug (%)	68.0 to 87.2 for *d*-Amphetamine 68.3 to 87.8 for *l*-Amphetamine
Average recovery of IS (%)	79.1 for internal standard for *d*-Amphetamine 79.2 for internal standard for *l*-Amphetamine
Standard curve concentrations (ng/mL)	0.200, 0.400, 1.00, 2.50, 5.00, 12.5, 25.0, 50.0 and 80.0 for each *d*-Amphetamine and *l*-Amphetamine
QC concentrations (ng/mL)	0.600, 40.0 and 65.0 for each *d*-Amphetamine and *l*-Amphetamine
QC Intraday precision range (%)	0.6 to 6.0 for *d*-Amphetamine 0.4 to 6.9 for *l*-Amphetamine
QC Intraday accuracy range (%)	96.5 to 108.2 for *d*-Amphetamine 97.1 to 108.8 for *l*-Amphetamine
QC Interday precision range (%)	1.5 to 4.9 for *d*-Amphetamine 1.5 to 5.2 for *l*-Amphetamine
QC Interday accuracy range (%)	99.4 to 100.8 for *d*-Amphetamine 99.1 to 101.0 for *l*-Amphetamine
Bench-top stability (hrs)	17.50 @ room temperature 17.50 @ on ice
Stock stability (days)	103 @ 5 ± 3°C for (±)-Amphetamine 140 @ 5 ± 3°C for (±)-Amphetamine-D_{10}
Processed stability (hrs)	75.75 @ approximately 5°C
Freeze-thaw stability (cycles)	3
Long-term storage stability (days)	119 @ -25 ± 10°C
Dilution integrity	Concentration diluted 2-fold and 5-fold
Selectivity	The selectivity test met SOP acceptance criteria as all (b) (4)

Source: Sponsor's Summary of Biopharmaceutics Studies

3 APPENDIX

3.1 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Does the interpolation of the PK support the approval and dosing recommendations of amphetamine extended release (ER) oral suspension in adolescents?

Yes, the interpolation of the PK from the data in children (6-12 years) and adults (17 years above) supports the approval and dosing recommendations of amphetamine extended release (ER) oral suspension in adolescents.

Based on section 505B(a)(2)(B)(ii) of the PREA: "A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group", sponsor conducted a population PK analysis for adolescents using interpolation of data from children (6-12 years) and adults. FDA's modeling and simulation demonstrated the projected PK profile of amphetamine in adolescents (13-17 years) matched closely to observed PK profiles in children (6-12 years). Body weight was the only prognostic factor that explained between-subject variability of PK in children and adolescents.

In the American Academy of Pediatric guidelines (2011) and the labeling of approved medications for the treatment of ADHD (e.g., Adderall), the effects of stimulants are the same for the age groups 6-12 and 13-17. Here, the safety and efficacy of amphetamine in children has been established in submitted pediatric (6-12 years) clinical studies (TRI102-ADD-001), which support the approval in adolescents.

Also, in the labeling of approved medications (e.g., Adderall) for the treatment of ADHD, the dosage is the same for the age groups 6-12 and 13-17. Here, the similar PK in adolescents and individual dose titration scheme supported the same dosing regimen of amphetamine ER oral suspension in this population as in children (6-12 years) : starting dose begins at 2.5 mg once daily in the morning. The dose may be increased in increments of 2.5 to 10 mg per day every 4 to 7 days until an optimal response is obtained.

1.2 Recommendations

Given the fact that the use of medications in treating ADHD is essentially the same for the age groups 6-12 and 13-17, the effects of stimulants in treating ADHD symptoms do not vary by age and sex, and the PK profile of amphetamine in adolescents (13-17 years) is similar to PK profile in children (6-12 years), we recommend the labeling of "Dosage and Administration" section :

In children 6 years of age and older, recommended starting dose is 2.5 mg once daily in the morning. Dosage may be increased in increments of 2.5 mg to 10 mg per day every 4-7 days until optimal response obtained.

2 PERTINENT REGULATORY BACKGROUND

Amphetamine is indicated for the treatment of attention deficit hyperactivity disorder (ADHD). It is a non-catecholamine sympathomimetic amine that has the ability to stimulate central nervous system (CNS) activity.

Tris Pharma has submitted this 505(b) (2) New Drug Application (NDA) for amphetamine ER oral suspension as a new NDA to the Food and Drug Administration (FDA) for treatment of patients with Attention-Deficit Hyperactivity Disorder (ADHD). It is recommended that starting dose begins at 2.5 mg once daily in the morning. The dose may be increased in increments of 2.5 to 10 mg per day every 4 to 7 days until an optimal response is obtained. Daily doses above 20 mg have not been studied and are not recommended.

In the NDA submitted on December 19, 2014, sponsor provided two PK studies (2014-3401 and TRI102-PPK-200) to describe PK of amphetamine ER oral suspension in adults (older than 17 years) and children (6-12 years). Also, sponsor requested a waiver from the requirement to conduct studies in children 13-17 years of age. In this review cycle (May 7, 2015), sponsor submitted a PK report to bridge different patient populations from children to adolescents.

3 RESULTS OF SPONSOR'S ANALYSIS

Sponsor used PK data from Study 2014-3401 (adults) and Study TRI102-PPK-200 (children) to study the PK of amphetamine ER oral suspension in adolescents. Sponsor developed a PK model with a delayed first-order absorption and first-order disposition that described the concentration-time profiles from children to adolescents and adults.

3.1 Data

Study 2014-3401 was an open-label, single-dose, randomized, three-period, three-treatment, six-sequence, cross-over, relative bioavailability and food-effect study in 30 healthy adult subjects (older than 17 years). Three treatments were amphetamine ER oral suspension (fasted), amphetamine ER oral suspension (fed) and the reference product (DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets). The daily dose is 18.8 mg amphetamine. Blood samples were collected pre-dose and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours after drug administration. 29 subjects were included in PK analysis.

Study TR102-PPK-200 was a Phase 1, open-label study in children (6-12 years) with ADHD following the administration of a single 10 mg dose of amphetamine ER oral suspension. 12 subjects were included (6 subjects aged 6 to 9 years and 6 subjects aged 10 to 12 years). Blood

samples were collected pre-dose and 1, 3, 4, 6, 8, 10, 12, and 26-30 hours post-dose after drug administration.

In total 1178 concentration-time points for d-amphetamine and l-amphetamine were included for the PK analysis. All children were dosed under fasted conditions. For Study 2014-3401, only data from the fasted state were used for the analysis. In both studies, the d- and l-amphetamine amounts were present in a 3:1 ratio (Table 1 Amphetamine dosing in Study 2014-3401 and Study TRI102-PPK-200. The d-amphetamine and l-amphetamine amounts are present in 3:1 ratio in each dose unit.Table 1 Amphetamine dosing in Study 2014-3401 and Study TRI102-PPK-200. The d-amphetamine and l-amphetamine amounts are present in 3:1 ratio in each dose unit.Table 1).

Table 1 Amphetamine dosing in Study 2014-3401 and Study TRI102-PPK-200. The d-amphetamine and l-amphetamine amounts are present in 3:1 ratio in each dose unit.

Study	Total Amphetamine Dose, mg	d-Amphetamine Dose, ug	l-Amphetamine Dose, ug
2014-3401	18.8	14323.810	4476.190
TRI102-PPK-200	10	7619.048	2380.952

Source: sponsor's population-pk-report.pdf, Table 1

3.2 Analytical Methodologies

Sponsor assumed no different PK characteristics between l- and d-amphetamine, therefore l-amphetamine concentrations were modelled using the following equation:

$$C_l = \frac{C_d}{3.2} + \varepsilon_{l,ij}$$

Where, C_l and C_d are the concentrations of l- and d-amphetamine; $\varepsilon_{l,ij}$ is the residual error of l-amphetamine concentrations for the ith subject and jth time point. The C_d are divided by the ratio of the two moieties.

Sponsor develop an one-compartment model with the apparent clearance (CL/F), apparent volume of distribution (V/F), first-order rate constant for absorption (k_a) and a time-lag for absorption (t_{lag}). Body weight was used to explain the between-subject variability, where t_{vCL} and t_{vV} are the typical values of CL/F and V/F in a 70 kg subject.

$$\frac{CL}{F} = tvCL \cdot \left[\frac{wt}{70}\right]^{\beta CL}$$

$$\frac{V}{F} = tvV \cdot \left[\frac{wt}{70}\right]^{\beta V}$$

3.3 Analytical Software

All estimations and simulations were conducted using Phoenix® 6.4.

3.4 PPK Model Parameters

The final parameter estimates and their precision are provided (Table 2). The confidence limits for CL/F and V/F are well within 60%-140% of the point estimates, which meets the FDA guidance for designing pediatrics pharmacokinetic studies. The mean apparent clearance (CL/F) in a typical child (30kg), adolescent (52kg) and adult (70kg) are: 7.1 L/hr, 10.1 L/hr and 12.3 L/hr, respectively. The mean apparent volume of distribution (V/F) in typical child (30kg), adolescent (52kg) and adult (70kg) are: 111.1 L, 160.9 L and 196.7 L, respectively. The between-subject variability in was 18.9% for CL/F and 11.2% for V/F.

Table 2 Final model parameter estimates

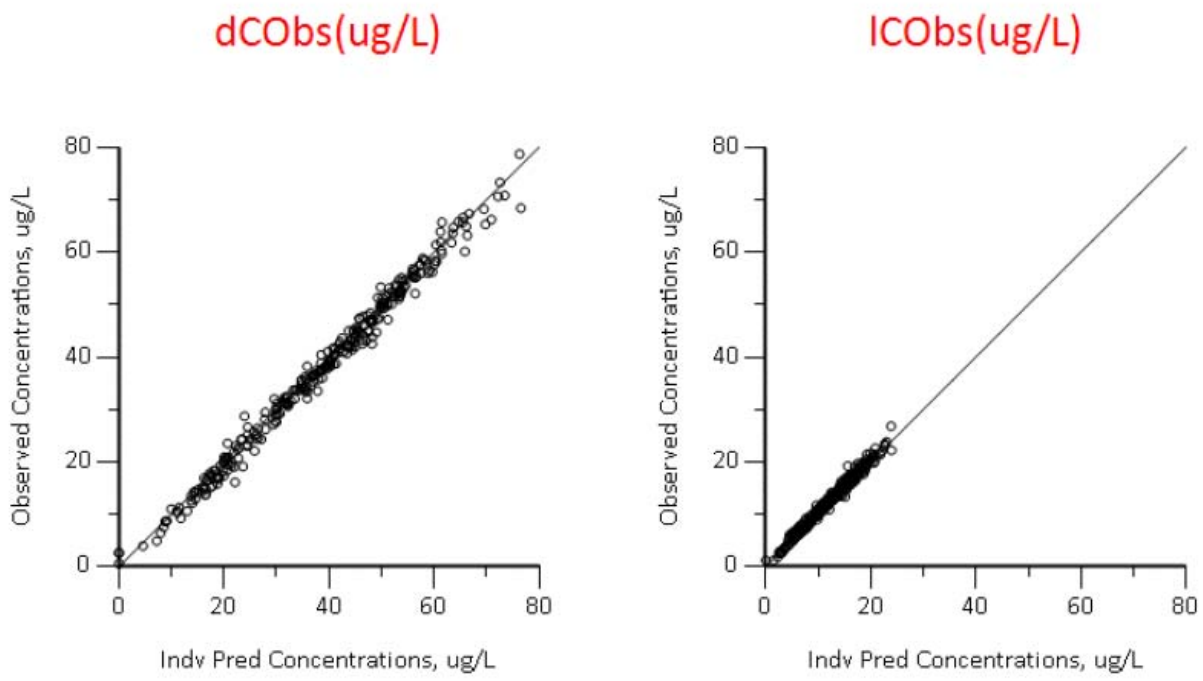
Parameter	Estimate (95% CI)
Mean Volume, L/70 kg	196.70 (188.95, 204.45)
Mean Clearance, L/hr/70 kg	12.29 (11.46, 13.13)
Mean absorption rate constant, 1/hr	0.597 (0.526, 0.669)
Mean absorption delay, hr	0.604 (0.469, 0.739)
Allometric exponent for Volume (βV)	0.674 (0.592, 0.756)
Allometric exponent for Clearance (βCL)	0.646 (0.530, 0.762)
Residual error (d-), ug/L	2.44 (2.21, 2.68)
Residual error (l-), ug/L	0.904 (0.809, 0.993)
	Estimate (%RSE)
BSV Volume	11.2% (23.5%)
BSV Clearance	18.9% (21.3%)
BSV absorption rate constant	34.8% (26.5%)
BSV absorption delay	65.4% (28.0%)

Source: sponsor's population-pk-report.pdf, Table 3

3.4.1 Model Evaluation

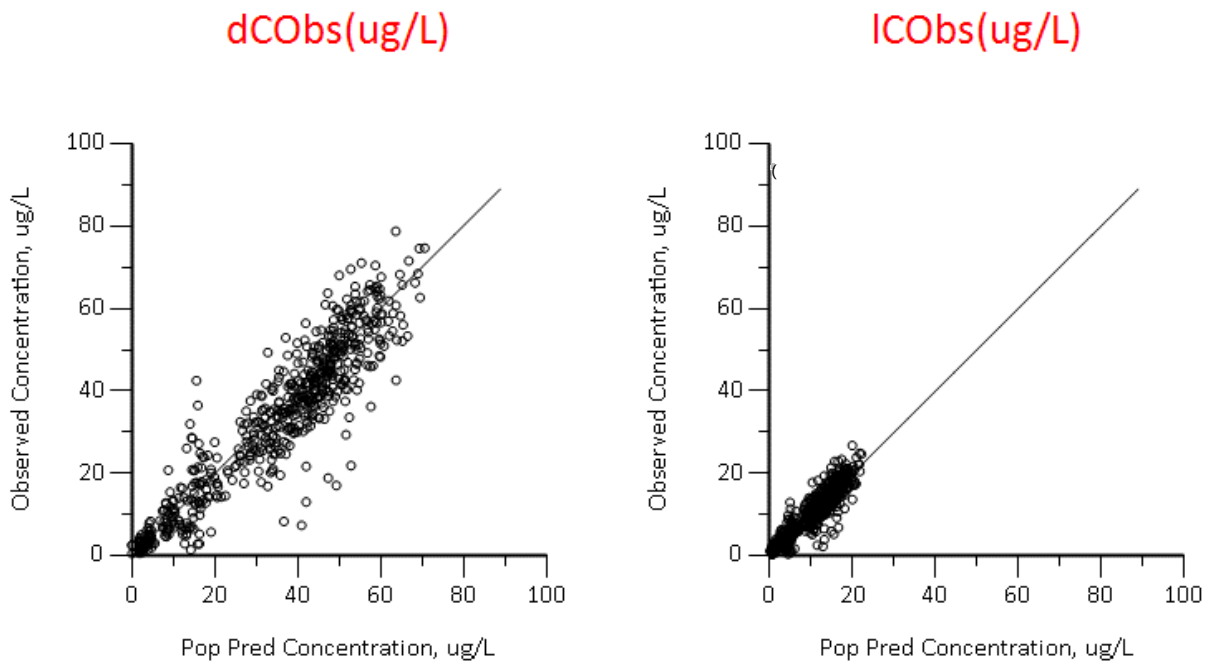
Both the individual prediction (Figure 1) and population prediction (Figure 2) describe the observed concentration data well.

Figure 1 The individual predicted and observed concentrations of d- and l-amphetamine (dCObs = d-amphetamine; lCObs=l-amphetamine)



Source: sponsor's population-pk-report.pdf, figure 3

Figure 2 The population predicted and observed concentrations of d- and l-amphetamine (dCObs = d-amphetamine; lCObs=l-amphetamine)

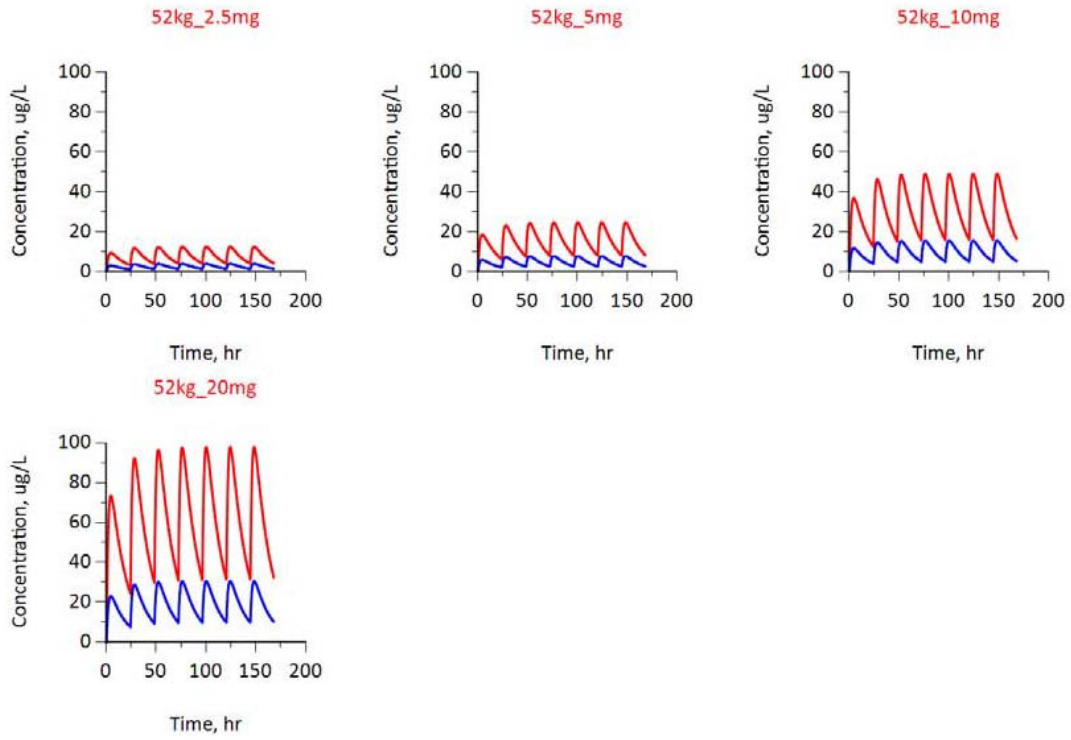


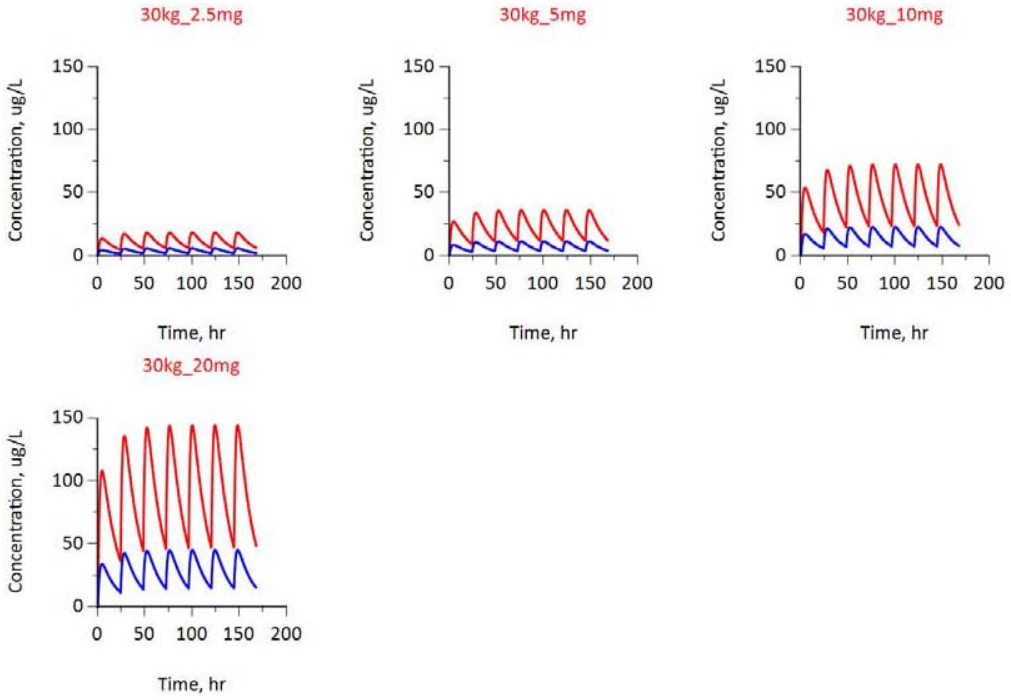
Source: sponsor's population-pk-report.pdf, figure 4

3.5 PK Simulations for Adolescents

Sponsor simulated the PK profiles in adolescents at 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg doses QD based on PK parameters estimated from the children and adult data (Figure 3 and Figure 4).

Figure 3 Simulated PK profiles for an adolescent weighing 52 kg and a child weighing 30 kg administered 2.5 mg, 5 mg, 10 mg and 20 mg QD amphetamine ER oral suspension (d-amphetamine concentrations represented in red; l-amphetamine concentrations represented in blue)

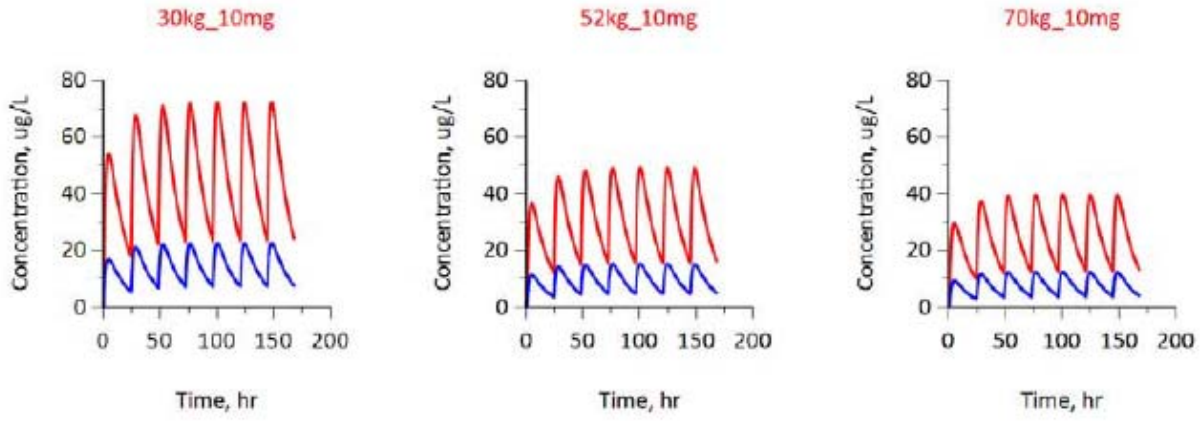




Source: sponsor's population-pk-report.pdf, figure 8

Sponsor also simulated the concentration-time profiles in a typical child (6-12 years), adolescent (13-17 years) and adult (17 years above) each receiving 10 mg once daily dosing (Figure 4). For the same dose, the concentrations in a child are greater than those in adults owing to body weight differences.

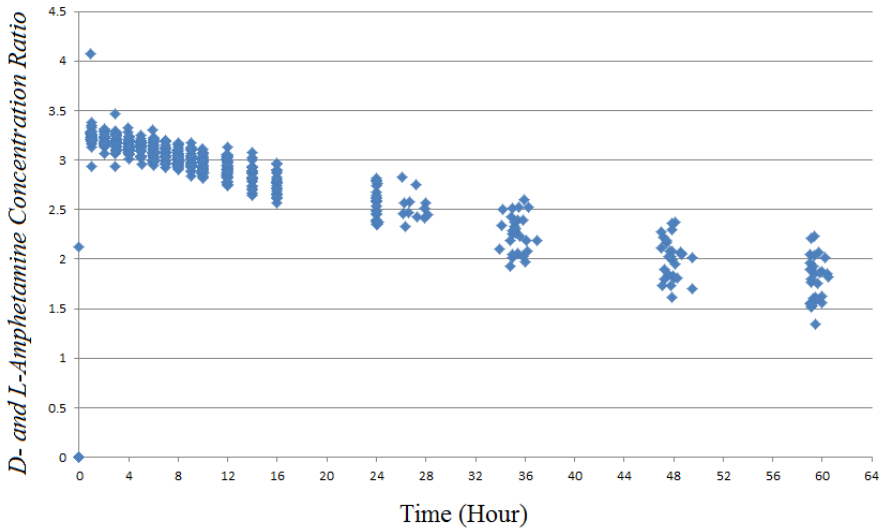
Figure 4 Simulated pharmacokinetic profiles for a typical child (30 kg), adolescent (52 kg) and adult (70 kg) each receiving 10 mg QD amphetamine ER oral suspension (d-amphetamine concentrations represented in red; l-amphetamine concentrations represented in blue)



Source: sponsor's population-pk-report.pdf, figure 9

Reviewer's comments: *The datasets of Study 2014-3401 and Study TR102-PPK-200 seems to include a sufficient number of subjects in children (6-12 years) and adult (17 years above) population with an adequate number of PK observations at informative time points. However, the assumption that a 3.2:1 ratio of d- and l-amphetamine concentrations is not supported by the data (Figure 5). In addition, following a single 10 mg oral dose of amphetamine ER oral suspension in 12 pediatric subjects with ADHD (aged 6-12 years) under fasting conditions, the mean plasma terminal elimination half-life of d-amphetamine was 10.43 (± 2.01 h) hours and the mean plasma terminal half-life for l-amphetamine was 12.14 (± 3.15 h) hours. Therefore, sponsor's hypothesis of same PK characterics between d- and l-amphetamine in the population PK model is not valid.*

Figure 5 D- and L-Amphetamine Concentration Ratio v.s Time



Source: reviewer's analysis

4 REVIEWER'S ANALYSIS

4.1 Objectives

To confirm whether the interpolation of the PK support the approval and dosing recommendations of amphetamine extended release (ER) oral suspension in adolescents.

4.2 Methods

4.2.1 Data Sets

Data sets used are summarized in Table 3.

Table 3 Analysis Data Sets

Study Number	**Name**	**Location in \\cdsnas\pharmacometrics**
Study 2014-3401 and Study TRI102-PPK-200	PPK.xls	\Reviews\ Ongoing PM Reviews\Amphetamine_NDA 208147_LZ\FDA Analysis\

4.2.2 Software

Population PK modeling and PK profile simulation were conducted using the Phoenix® 6.4.

4.2.3 Models

We used the sponsor's proposed one compartment model, which was parameterized in terms of the apparent clearance (CL/F), apparent volume of distribution (V/F), first-order rate constant for absorption (ka) and a time-lag for absorption (tlag). Without the assumption of 3.2:1 ratio of d- and l-amphetamine concentrations, we built two seperate population PK models for d- and l-amphetamine concentrations.

4.3 Results

The final parameter estimates and their precision are provided in Table 4. The Cl estimates of d- and l-amphetamine are different. The other parameter estimates are similar.

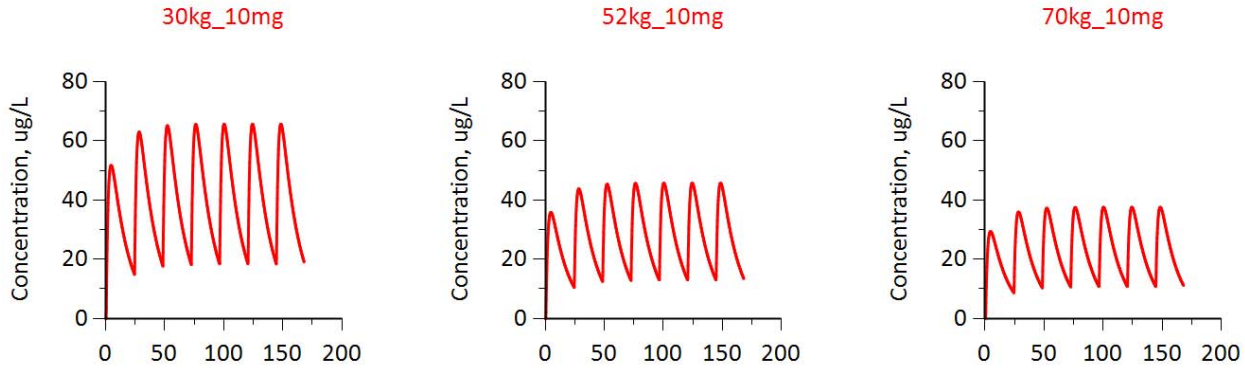
Table 4 Final model parameters based on the Population PK model for d- and l-amphetamine concentrations.

Parameter	Estimates (95% CI)	
	d-amphetamine	l-amphetamine
Mean Volume, L/70 kg	195.21 (187.56, 202.86)	198.37 (190.55, 206.17)
Mean Clearance, L/hr/70 kg	13.29 (12.42,14.16)	11.05 (10.26, 11.83)
Mean absorption rate constant, 1/hr	0.582 (0.521, 0.644)	0.598 (0.527, 0.668)
Mean absorption delay, hr	0.593 (0.464, 0.722)	0.620 (0.488, 0.751)
Allometric exponent for Volume (βV)	0.671 (0.594, 0.749)	0.686 (0.605, 0.766)
Allometric exponent for Clearance (βCL)	0.650 (0.544, 0.757)	0.630 (0.510, 0.750)
Residual error, ug/L	2.30 (1.99, 2.61)	0.763 (0.673, 0.853)

Source: reviewer's analysis

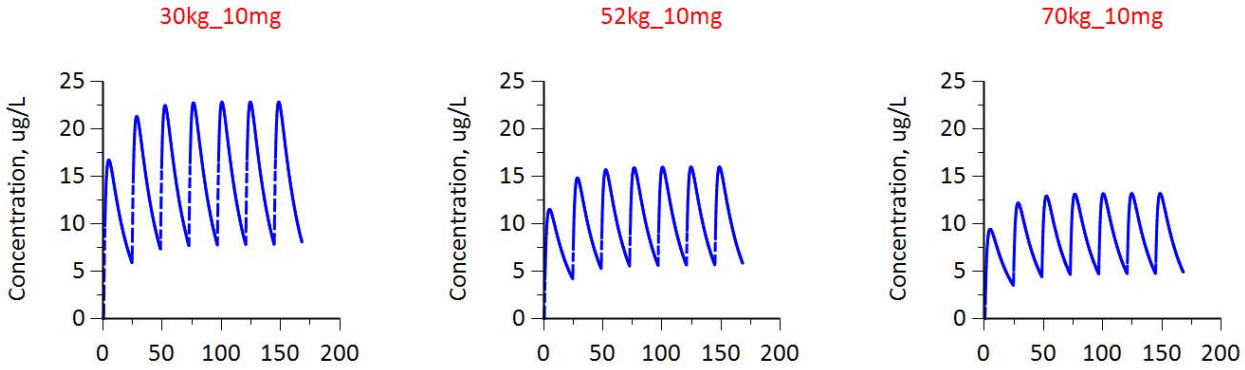
Figure 6 and Figure 7 demonstrate the d- and l-amphetamine concentration-time profiles in a typical child, adolescent and adult each receiving 10 mg once daily dosing. For the same dose, the concentrations in a child are greater than those in adolescents and adults due to body weight differences.

Figure 6 Simulated d-amphetamine pharmacokinetic profiles for a typical child (30 kg), adolescent (52 kg) and adult (70 kg) each receiving 10 mg of amphetamine ER oral suspension once daily.



Source: reviewer's analysis

Figure 7 Simulated l-amphetamine pharmacokinetic profiles for a typical child (30 kg), adolescent (52 kg) and adult (70 kg) each receiving 10 mg of amphetamine ER oral suspension once daily.



Source: reviewer's analysis

FDA's modeling and simulation demonstrated the projected PK profile of amphetamine in adolescents (13-17 years) matched closely to observed PK profiles in children (6-12 years). Body weight was the only prognostic factor that explained between-subject variability of PK in children and adolescents. The similar PK in adolescents and individual dose titration scheme supported the same dosing regimen of amphetamine ER oral suspension in this population as in children (6-12 years) : starting dose begins at 2.5 mg once daily in the morning. The dose may be increased in increments of 2.5 to 10 mg per day every 4 to 7 days until an optimal response is obtained.

Individual Studies Review

CLINICAL PHARMACOLOGY REVIEW
Biopharmaceutics – Bioavailability/ Bioequivalence

Report #: Study Number: 2014-3401 NDA 208147	**Study Period:** Study Initiation: February 22, 2014 Study Completion: March 10, 2014
Study Site: ! ! Pharma Medica Research Inc. 400 Fountain Lakes Boulevard St. Charles, Missouri, USA, 63301	**Investigator:** Hooman Hajian, MD
Link: \\cdsesub1\evsprod\nda208147\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\pivotal-pk-2014-3401\a-2014-3401-study-report.pdf	

Title	An Open-label, Randomized, Three-way Cross-over, Single-Dose Pivotal Study to Evaluate the Bioavailability of a Test Product Formulation of Amphetamine Extended-Release Oral Suspension under Fasted and Fed Conditions and to Evaluate the Relative Bioavailability of the Test Product Formulation to an Equivalent Dose of a Commercially Available Reference Product under Fasted Conditions in Healthy Adult Subjects
Objectives	Primary Objectives: • To compare the relative bioavailability of the test product (Amphetamine ER Oral Suspension) versus the reference product (DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets) at the same daily dose of 18.8 mg of amphetamine base. • To compare the relative bioavailability of the test product (Amphetamine ER Oral Suspension) under fed and fasted conditions after a single-dose in healthy subjects Secondary Objectives: • to ensure that the plasma concentration versus time profile established for the extended-release product meets the goal of once a day dosing, and • to demonstrate that there is no dose dumping after a single-dose in healthy subjects under fasting and fed conditions
Rationale	

Study Design

☑ Bioequivalence	☐ Absolute Bioavailability	☐ Relative Bioavailability

Subjects were randomly assigned to one treatment sequence according to a predetermined computer-generated randomization scheme

Sequence	Treatment		
	Period 1	Period 2	Period 3
ABC	A	B	C
ACB	A	C	B
BAC	B	A	C
BCA	B	C	A
CAB	C	A	B
CBA	C	B	A

The following drug products were used in this study:

Test Product:
Amphetamine ER Oral Suspension, 20 mg of amphetamine base per 8 mL (CII)
Tris Pharma Inc., USA
(Treatment A and B)

Potency: 99.1% of label claim
Lot No.: TB-125B
Expiry Date: 10/15

Reference:
DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets
15 mg mixed amphetamine salts (9.4 mg amphetamine base)
Teva Pharmaceuticals USA
(Treatment C)

Potency: 99.6% of label claim
Lot No.: 34016745A
Expiry Date: 08/16

The washout between drug administrations for each subject was at least 7 days (± 3 hours) from the first drug administration of the period.
Treatment A
Test Product:
One dose, 7.5 mL of oral suspension (containing 18.8 mg of amphetamine base), administered after an overnight fast of at least 10 hours
Treatment B
Test Product:
One dose, 7.5 mL of oral suspension (containing 18.8 mg of amphetamine base), administered 30 minutes after the start of a high-fat, high-calorie breakfast
Treatment C
Reference Product:
One 15 mg (eq to 9.4 mg amphetamine base) tablet administered at 0 and 4 hours under fasting conditions:

• For the 0-hour dose, subjects were required to fast for at least 10 hours prior to drug administration and 6 hours following drug administration. • For the 4-hour dose, subjects were required to fast for at least 4 hours prior to drug administration and 2 hours following drug administration.	
Sampling Times	Prior to dosing (0-hour) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours after drug administration
PK Analysis	PK analysis was performed on available data from subjects in the PK dataset. The actual post-dose sample collection times were used in the PK analysis. The following PK parameters were estimated for *d*-amphetamine and *l*-amphetamine using a non-compartmental approach in SAS®: AUC_t: The area under the analyte concentration versus time curve, from time zero (0) to the time of the last measurable analyte concentration (t), as calculated by the linear trapezoidal method. AUC_{0-4} The area under the analyte concentration versus time curve, from time zero (0) to 4 hours after dosing, as calculated by the linear trapezoidal method. *AUC_{0-4} was based on all measureable concentrations within the first 4 hours and presented as AUC_{0-4}.* AUC_{4-t} The area under the analyte concentration versus time curve, from 4 hours after dosing to the last measurable analyte concentration (t), as calculated by the linear trapezoidal method. AUC_{0-5} The area under the analyte concentration versus time curve, from time zero (0) to 5 hours after dosing, as calculated by the linear trapezoidal method. *AUC_{0-5} was based on all measureable concentrations within the first 5 hours and presented as AUC_{0-5}.* AUC_{5-t} The area under the analyte concentration versus time curve, from 5 hours after dosing to the last measurable analyte concentration (t), as calculated by the linear trapezoidal method. AUC_{inf}: The area under the analyte concentration versus time curve from time zero to infinity. $AUC_{inf} = AUC_t + C_t/K_{el}$, where C_t is the last measurable analyte concentration. *Note: AUC_t = The area under the analyte concentration versus time curve, from time zero (0) to the time of the last measurable analyte concentration (t), as calculated by the linear trapezoidal method.* C_{max}: Maximum measured analyte concentration over the entire sampling period. T_{max}: Time of the maximum measured analyte concentration over the entire sampling period. K_{el}: The apparent first-order elimination rate constant. T_{half}: The apparent elimination half-life. K_{el}, T_{half} and AUC_{inf} parameters were not estimated for concentration-time profiles where the terminal linear phase was not clearly defined.
Statistical Analysis	Descriptive statistics for the pharmacokinetic parameters of d-amphetamine and l-

	amphetamine are presented. Descriptive statistics include number of observations, arithmetic mean, standard deviation, geometric mean (where applicable), CV, median, minimum and maximum. Statistical analysis was performed on quality assured data from subjects in the statistical dataset. The PROC MIXED procedure from SAS□ version 9.3 was used. The statistical model used PROC MIXED to allow for the estimation of separate intrasubject variances for each contrast. Analysis of variance (ANOVA) was performed on log-transformed AUCt, AUCinf and Cmax parameters, as well as on AUC0-4, AUC4-t, AUC0-5, AUC5-t for information purposes only. The significance of the sequence, period, treatment and subject-within sequence effects were tested. Using the same statistical model, the least-squares-means, the differences between the treatments least-squares-means and the corresponding standard errors of these differences were estimated for log-transformed AUC0-4, AUC4-t, AUC0-5, AUC5-t, AUCinf and Cmax parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated.

Analytical Method

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	l-Amphetamine and d-Amphetamine were analyzed 0.200, 0.400, 1.00, 2.50, 5.00, 12.5, 25.0, 50.0 and 80.0 ng/mL.		

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes

▪ Accuracy and precision of the quality control samples acceptable	☐ No ☑ Yes
▪ Overall performance acceptable	☐ No ☑ Yes ☐ No

Notes:

Results

Study Population

Randomized Treated Completed Discontinued Due to AE PK Population/Safety Population	30 A-29 B-30 C29 A-29 B-29 C29 B-1-Headache, vomit
Age [Median (range)]	40(18-54)
Male/Female	15/14
Race (Caucasian/Black/Asian/Hispanic)	White 9 (30.0%)-A 8 (27.6%)-B 8 (27.6%)-C Black 20 (66.7%)-A 20 (69.0%)-B 20 (69.0%)-C Other 1 (3.3%)-A 1 (3.4%)-B 1 (3.4%)-C

Results See Appendix

Comments:

1. **Food decreases the PAUC and AUC values for d-amphetamine but does not impact Cmax**
2. **The suspension is not BE under fed conditions to the fasting state for d-amphetamine. The 90% CI lower limit was below 80% for PAUC0-4 and PAUC0-5.**
3. **Food decreases the PAUC and AUC values for l-amphetamine but does not impact Cmax**
4. **The suspension is not BE under fed conditions to the fasting state for l-amphetamine. The 90% CI lower limit was below 80% for PAUC0-4 and PAUC0-5.**

5. **The PAUC values of 0-4 and 0-5 for d and l amphetamine have very high intrasubject variability of ~ 25%.**
6. **The mean ±SD T ½ of d- and l- amphetamine under fasting conditions were 12.36 ± 2.94 and 15.12 ± 4.40 hours.**

Label: The drug can be given without regard to food. However the peak onset of action may be delayed by 1 hr.

APPENDIX
Figure 1 Arithmetic Mean Plasma Concentration-Time Profiles of d-Amphetamine
Study No.: 2014-3401
Mean Plasma d-Amphetamine Concentration-Time Profiles
(A: n = 29 / B: n = 29 / C: n = 29)

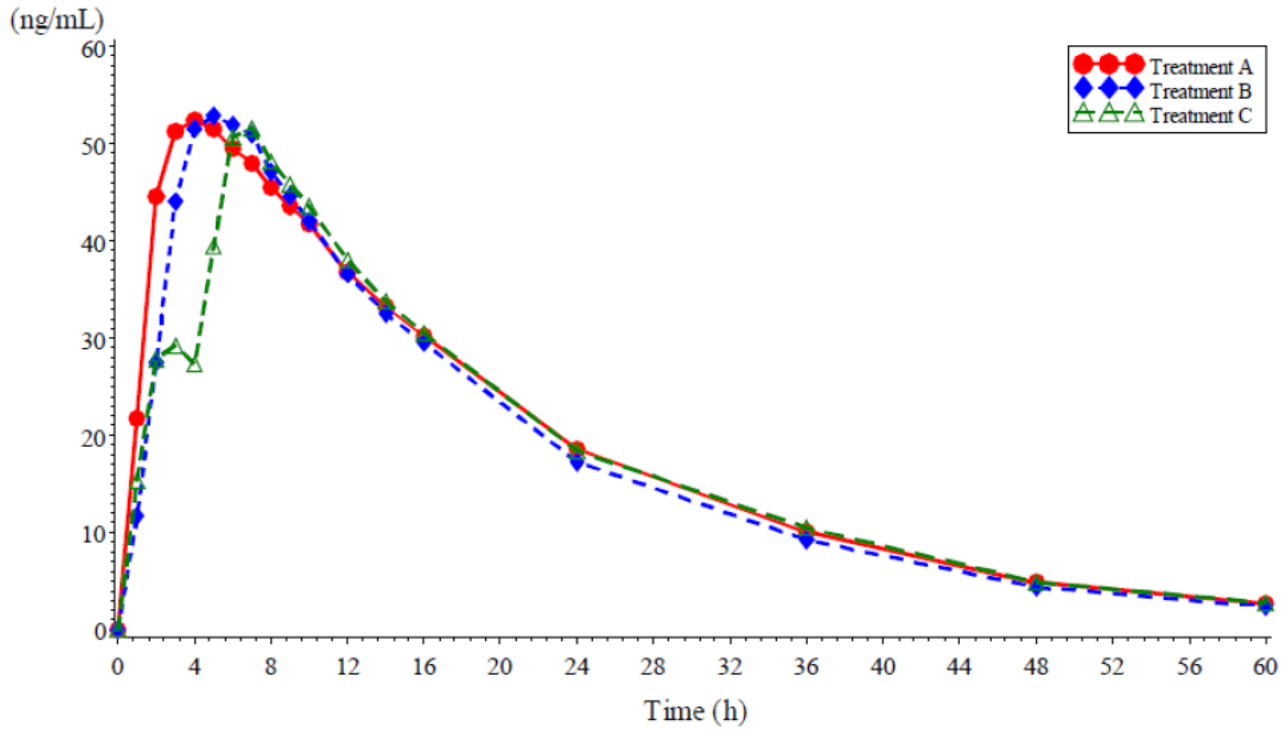


Table 1. Summary of Pharmacokinetic Parameters and Statistical Results of d-Amphetamine

Based on Raw Data								
Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
C_{max}	A	29	54.128 (19)	53.026	A vs C	102.50	100.15 - 104.91	5
(ng/mL)	B	29	55.031 (18)	54.009	B vs A	101.85	99.32 - 104.45	6
	C	29	52.714 (18)	51.732				
AUC_t	A	29	1144.050 (20)	1119.647	A vs C	106.32	102.03 - 110.78	9
(ng·h/mL)	B	29	1080.034 (19)	1059.438	B vs A	94.62	91.17 - 98.21	8
	C	29	1078.946 (22)	1053.113				
AUC_{inf}	A	29	1197.321 (22)	1168.903	A vs C	105.97	101.45 - 110.70	10
(ng·h/mL)	B	29	1125.248 (20)	1102.633	B vs A	94.33	90.68 - 98.12	9
	C	29	1133.257 (24)	1103.036				
		n	*Median*	*Range*				
T_{max}	A	29	4.00	2.00- 7.00				
(h)	B	29	5.00	3.00- 8.00				
	C	29	6.02	6.00- 8.00				

Treatment A (Test-1) *FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*

Treatment B (Test-2) *FED:Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII) , Lot No.: TB-125B (Tris Pharma, Inc., USA)*

Treatment C (Ref) *FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)*

Table 2. Summary of Partial Pharmacokinetic Parameters and Statistical Results of d-Amphetamine

Based on Raw Data								
Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_{0-4}	**A**	29	143.813 (23)	139.463	**A vs C**	169.17	160.79 - 177.99	11
(ng·h/mL)	**B**	29	109.242 (29)	104.037	**B vs A**	74.60	66.83 - 83.27	25
	C	29	86.036 (29)	82.438				
AUC_{4-t}	**A**	29	1000.236 (21)	977.489	**A vs C**	100.86	96.52 - 105.40	10
(ng·h/mL)	**B**	29	970.791 (21)	949.674	**B vs A**	97.15	93.16 - 101.32	9
	C	29	992.910 (22)	969.180				
AUC_{0-5}	**A**	29	195.695 (21)	190.570	**A vs C**	165.37	158.70 - 172.31	9
(ng·h/mL)	**B**	29	161.272 (24)	156.010	**B vs A**	81.87	75.40 - 88.88	19
	C	29	119.430 (26)	115.241				
AUC_{5-t}	**A**	29	948.354 (22)	926.159	**A vs C**	98.92	94.54 - 103.50	10
(ng·h/mL)	**B**	29	918.762 (22)	897.737	**B vs A**	96.93	92.77 - 101.28	10
	C	29	959.516 (23)	936.291				

Treatment A (Test-1)	*FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment B (Test-2)	*FED:Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment C (Ref)	*FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)*

Figure 2 Arithmetic Mean Plasma Concentration-Time Profiles of l-Amphetamine

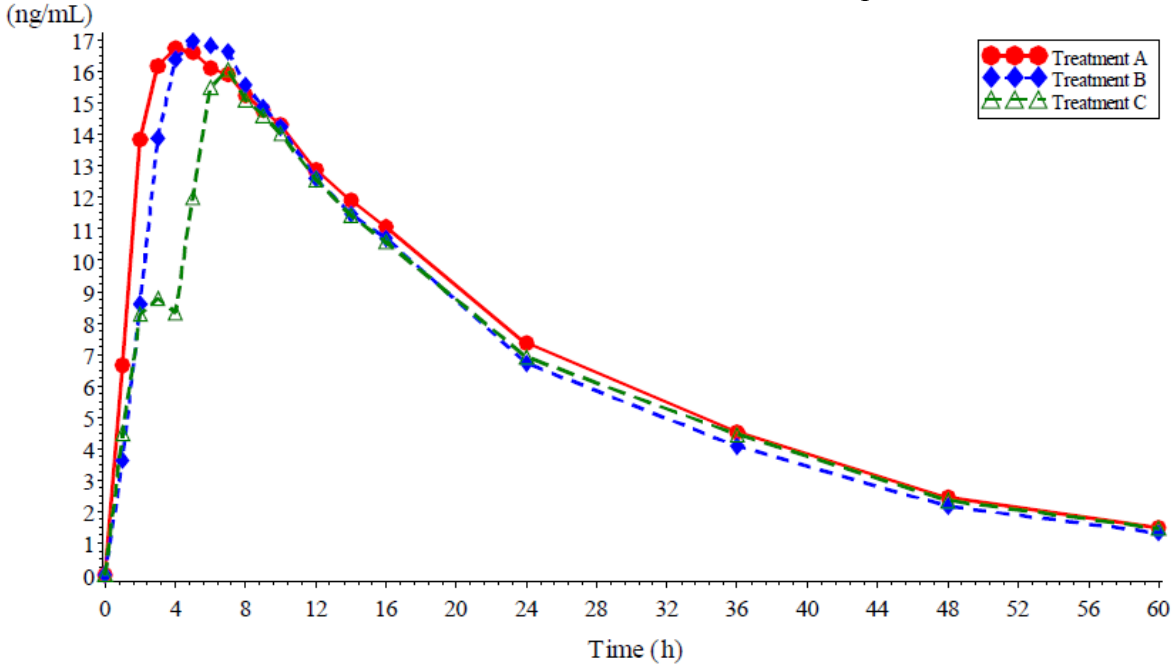


Table 3. Summary of Pharmacokinetic Parameters and Statistical Results of l-Amphetamine

Based on Raw Data

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
C_{max}	**A**	29	17.286 (19)	16.917	**A vs C**	106.05	103.56 - 108.59	5
(ng/mL)	**B**	29	17.683 (19)	17.321	**B vs A**	102.39	99.83 - 105.01	6
	C	29	16.290 (19)	15.952				
AUC_t	**A**	29	424.835 (20)	414.681	**A vs C**	111.35	106.22 - 116.73	11
(ng·h/mL)	**B**	29	395.794 (20)	386.833	**B vs A**	93.28	89.64 - 97.08	9
	C	29	383.120 (23)	372.403				
AUC_{inf}	**A**	29	461.544 (23)	448.439	**A vs C**	110.68	104.97 - 116.70	12
(ng·h/mL)	**B**	29	425.849 (21)	415.443	**B vs A**	92.64	88.57 - 96.90	10
	C	29	419.131 (26)	405.169				
		n	***Median***	***Range***				
T_{max}	**A**	29	4.00	2.00- 7.00				
(h)	**B**	29	5.00	3.00- 8.00				
	C	29	7.00	6.00- 9.00				

Treatment A (Test-1)	*FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment B (Test-2)	*FED:Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment C (Ref)	*FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)*

Table 4. Summary of Partial Pharmacokinetic Parameters and Statistical Results of l-Amphetamine

Based on Raw Data								
Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_{0-4}	**A**	29	45.013 (23)	43.572	**A vs C**	177.40	168.46 - 186.82	12
(ng·h/mL)	**B**	29	34.356 (30)	32.646	**B vs A**	74.92	67.12 - 83.63	25
	C	29	25.693 (29)	24.561				
AUC_{4-t}	**A**	29	379.822 (21)	370.379	**A vs C**	106.60	101.47 - 112.00	11
(ng·h/mL)	**B**	29	361.438 (21)	352.405	**B vs A**	95.15	91.05 - 99.43	10
	C	29	357.427 (23)	347.436				
AUC_{0-5}	**A**	29	61.642 (22)	59.920	**A vs C**	173.59	166.42 - 181.08	9
(ng·h/mL)	**B**	29	50.963 (25)	49.196	**B vs A**	82.10	75.62 - 89.14	19
	C	29	35.862 (27)	34.517				
AUC_{5-t}	**A**	29	363.193 (22)	353.968	**A vs C**	104.90	99.73 - 110.33	11
(ng·h/mL)	**B**	29	344.831 (22)	335.871	**B vs A**	94.89	90.65 - 99.32	10
	C	29	347.257 (23)	337.446				

Treatment A (Test-1)	*FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment B (Test-2)	*FED:Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)*
Treatment C (Ref)	*FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)*

Clinical Study Report Review

Study Report #: TRI102-PPK-200 Study Period: 4/11/12 – 4/12/15
Study Site: Center for Psychiatry and Behavior Medicine, Inc., 7351 Prairie Falcon Road, Las Vegas, Nevada, 89128
Principal Investigator: Ann C. Childress, MD
Link: \\cdsesub1\EVSPROD\nda208147\0010

Title: Evaluation of the Single Dose Pharmacokinetics of TRI102 in Children with ADHD

Objective: To evaluate the plasma amphetamine concentration/time profile of:
TRI102, Amphetamine Extended Release Oral Suspension (2.5 mg/mL) (Tris Pharma Inc.) after a single dose in children with ADHD

Study Design: Open-Label, single-dose, one-period, one-treatment study in 12 pediatric ADHD subjects who were otherwise healthy. Two age groups were included in the study: Six subjects between the ages of 6 to 9 years and 6 subjects between the ages of 10 to 12 years old. A "mid-range" amphetamine dose of 10 mg amphetamine base was evaluated. This, according to the sponsor, allowed the comparison of 10 mg amphetamine base to equivalents of other amphetamine products. Subjects abstained (wash out) from all pre-existing psychostimulant medication for 48 hours before dose administration. Therefore, per protocol, the last exposure to any stimulant medication was 72 hours prior to dosing with study medication. Subjects that were taking any daily medication aside from ADHD medication would not change the medications during the study.

Treatment: Test Product- TRI102, Amphetamine Extended Release Oral Suspension (2.5 mg/mL), Tris Pharma Inc. Lot No: TB-125B. Each subject received a single dose of TRI102, 10 mg amphetamine base on Day 1.

Pharmacokinetic Measurements: Blood samples for pharmacokinetic analysis were collected at pre-dose, and at the following times: Day 1: 1, 3, 4, 6, 8, 10, 12 and 28 hours post dose (Day 2). Plasma samples were assayed for d-amphetamine and l-amphetamine. PK parameters, AUCt, AUC∞, Cmax, Tmax, T ½ were estimated. Arithmetic mean, Geometric mean, standard deviation and percent coefficient of variation were determined

Safety Measurements: Safety was monitored through physical examinations, clinical laboratory evaluations, vital signs measurements, and ECGs.

Analytical Method:

Method	
Method Type	LC/MS/MS
Matrix	Plasma
Analytes	l-amphetamine and d-amphetamine
Calibration Range	0.2 to 80.0 ng/mL
Validation	
Method validated prior to use	Yes

Method validation acceptable	Yes
Study Sample Analysis	
Samples analyzed within the established stability period	Yes
Quality control samples range acceptable	Yes
Chromatograms provided	Yes
Accuracy and precision of the calibration curve acceptable	Yes
Accuracy and precision of the quality control samples acceptable	Yes
Overall performance acceptable	Yes

Results

Summary of Demographic Data

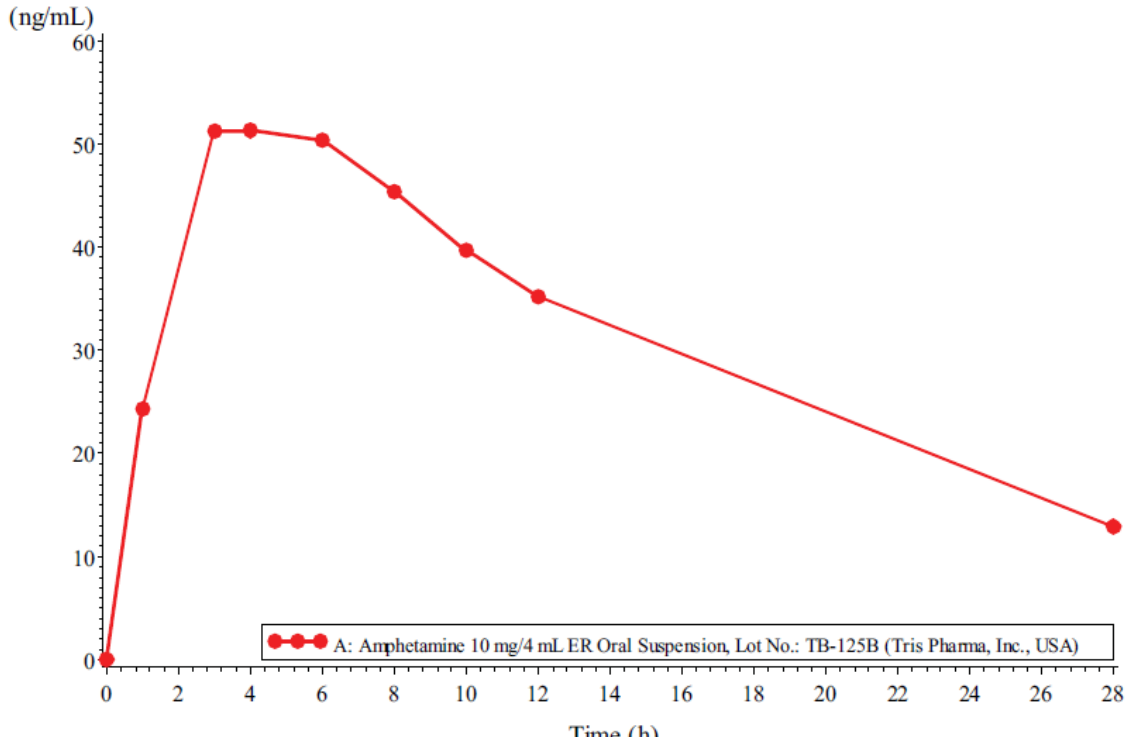
		Safety Dataset N = 12	**PK Dataset d-amphetamine N = 10**	**PK Dataset l-amphetamine N = 11**
Age (years)	Mean ± SD	9 ± 2	9 ± 2	9 ± 2
	Median	10	9	9
	Range	6 - 12	6 - 12	6 - 12
Height (in)	Mean ± SD	55.1 ± 6.5	53.7 ± 6.1	54.7 ± 6.7
	Median	53.7	51.9	52.5
	Range	46.0 - 65.0	46.0 - 63.5	46.0 - 65.0
Weight (LB)	Mean ± SD	80.3 ± 36.4	73.1 ± 34.9	75.5 ± 34.1
	Median	66.5	63.0	66.0
	Range	43.0 - 158.0	43.0 - 158.0	43.0 - 158.0
BMI (kg/m^2)	Mean ± SD	17.8 ± 4.7	17.0 ± 4.3	17.0 ± 4.1
	Median	16.2	15.6	15.7
	Range	12.9 - 28.4	12.9 - 28.4	12.9 - 28.4
Age	<6	0 (0%)	0 (0%)	0 (0%)

		Safety Dataset N = 12	PK Dataset d-amphetamine N = 10	PK Dataset l-amphetamine N = 11
Group (%)	6 - 9	6 (50.0%)	6 (60.0%)	6 (54.5%)
	10 - 12	6 (50.0%)	4 (40.0%)	5 (45.5%)
	>13	0 (0%)	0 (0%)	0 (0%)
Gender (%)	F	6 (50.0%)	5 (50.0%)	5 (45.5%)
	M	6 (50.0%)	5 (50.0%)	6 (54.5%)
Ethnicity (%)	Hispanic/Latino	3 (25.0%)	3 (30.0%)	3 (27.3%)
	Non-Hispanic/Latino	9 (75.0%)	7 (70.0%)	8 (72.7%)
Race (%)	American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)
	Black or African American	1 (8.3%)	1 (10.0%)	1 (9.1%)
	Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)
	Asian	0 (0%)	0 (0%)	0 (0%)
	White	8 (66.7%)	7 (70.0%)	7 (63.6%)
	Other	3 (25.0%)	2 (20.0%)	3 (27.3%)

d-Amphetamine

Mean Plasma concentration time profile is presented in the following figure

Mean d-Amphetamine Plasma Concentration – Time Profiles, Both Age Groups



Descriptive Statistics for Plasma d-Amphetamine Pharmacokinetic Parameters- Age Group: 6-9 years

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	**A**	963.095	981.728	208.013	21.19	970.298	714.812	1250.222	6
AUC_{inf}	**A**	1168.652	1191.422	248.614	20.87	1205.115	835.505	1474.361	6
AUC_t/AUC_{inf}	**A**	82.41	82.44	2.24	2.72	81.65	80.00	85.55	6
C_{max}	**A**	61.648	62.583	11.651	18.62	65.200	46.900	78.700	6
T_{max}	**A**	4.40	4.61	1.49	32.30	4.98	2.92	5.93	6
$t_{½}$	**A**	10.08	10.10	0.81	7.97	9.93	9.04	11.16	6
k_{el}	**A**	0.0688	0.0690	0.0055	7.93	0.0699	0.0621	0.0766	6
RStart	**A**	8.21	8.60	2.40	27.86	9.92	3.98	9.92	6
REend	**A**	26.86	26.87	0.91	3.40	26.43	26.10	28.17	6
n	**A**	4	4	1	33.03	3	3	6	6
LQCT	**A**	26.86	26.87	0.91	3.40	26.43	26.10	28.17	6
Ct	**A**	14.022	14.325	3.057	21.34	14.750	9.250	18.200	6

RStart = start time for linear regression
REnd = end time for linear regression
n = number of data points used in the regression analysis
LQCT = time of the last quantifiable concentration
Ct = last measurable concentration value at LQCT. This value was used for the extrapolation to infinity

Descriptive Statistics for Plasma d-Amphetamine Pharmacokinetic Parameters- Age Group: 10 - 12 years

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	**A**	646.477	669.927	189.341	28.26	707.493	406.830	857.890	4
AUC_{inf}	**A**	816.914	865.864	314.656	36.34	896.695	466.290	1203.775	4
AUC_t/AUC_{inf}	**A**	79.14	79.55	9.32	11.71	79.47	71.27	87.97	4
C_{max}	**A**	41.447	43.300	13.087	30.22	48.300	24.300	52.300	4
T_{max}	**A**	3.15	3.18	0.49	15.58	2.93	2.92	3.92	4
$t_{½}$	**A**	11.00	11.33	3.14	27.74	11.35	8.43	14.19	4
k_{el}	**A**	0.0630	0.0649	0.0181	27.80	0.0643	0.0489	0.0822	4
RStart	**A**	9.37	9.42	1.00	10.62	9.92	7.92	9.92	4
REend	**A**	27.06	27.07	0.71	2.61	26.97	26.37	27.98	4
n	**A**	3	3	1	15.38	3	3	4	4
LQCT	**A**	27.06	27.07	0.71	2.61	26.97	26.37	27.98	4
Ct	**A**	9.675	10.853	5.591	51.52	10.810	4.890	16.900	4

RStart = start time for linear regression
REnd = end time for linear regression
n = number of data points used in the regression analysis
LQCT = time of the last quantifiable concentration
Ct = last measurable concentration value at LQCT. This value was used for the extrapolation to infinity

Descriptive Statistics for Plasma d-Amphetamine Pharmacokinetic Parameters- Both Age Groups

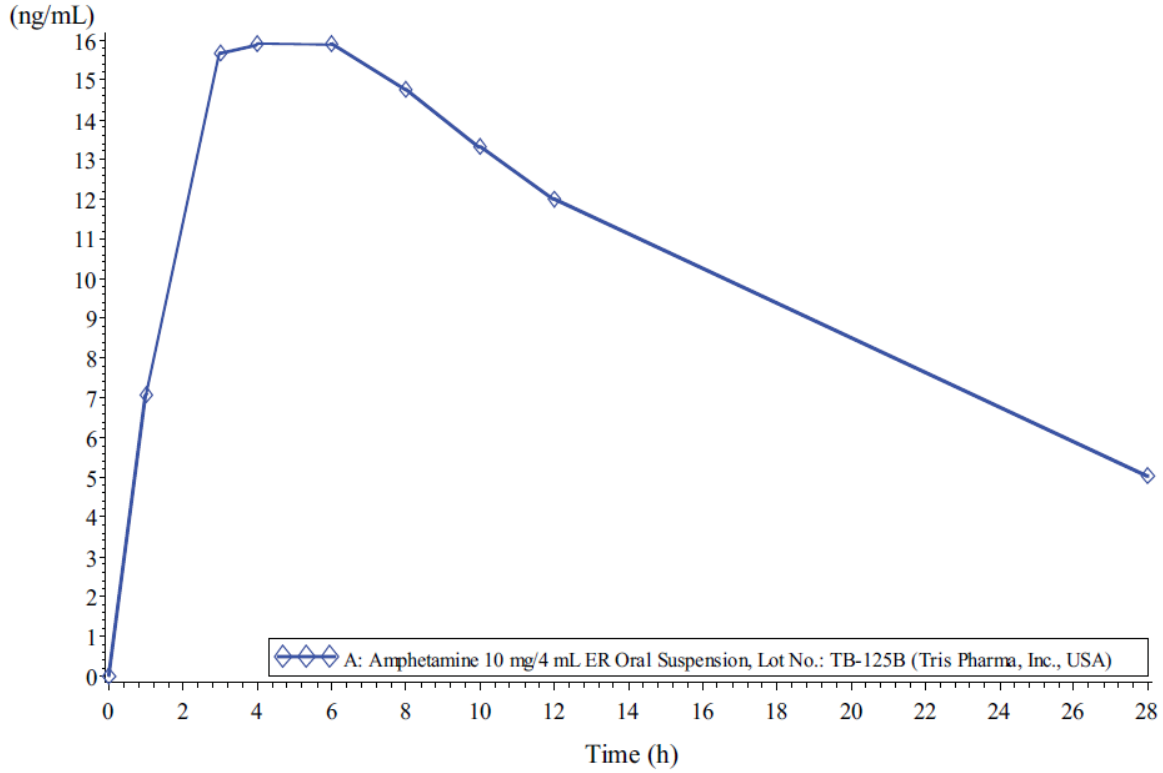
Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	**A**	821.150	857.008	248.825	29.03	836.601	406.830	1250.222	10
AUC_{inf}	**A**	1012.702	1061.199	309.200	29.14	1064.757	466.290	1474.361	10
AUC_t/AUC_{inf}	**A**	81.09	81.28	5.83	7.17	81.65	71.27	87.97	10
C_{max}	**A**	52.596	54.870	15.221	27.74	51.950	24.300	78.700	10
T_{max}	**A**	3.85	4.04	1.37	33.84	3.43	2.92	5.93	10
$t_{½}$	**A**	10.43	10.59	2.01	19.01	9.93	8.43	14.19	10
k_{el}	**A**	0.0664	0.0674	0.0114	16.90	0.0699	0.0489	0.0822	10
RStart	**A**	8.66	8.93	1.92	21.55	9.92	3.98	9.92	10
REend	**A**	26.94	26.95	0.80	2.97	26.64	26.10	28.17	10
n	**A**	3	4	1	27.77	3	3	6	10
LQCT	**A**	26.94	26.95	0.80	2.97	26.64	26.10	28.17	10
Ct	**A**	12.088	12.936	4.339	33.54	14.200	4.890	18.200	10

RStart = start time for linear regression
REnd = end time for linear regression
n = number of data points used in the regression analysis
LQCT = time of the last quantifiable concentration
Ct = last measurable concentration value at LQCT. This value was used for the extrapolation to infinity

l-Amphetamine

The mean plasma concentration-time profile for l-amphetamine is presented in the following figure

Mean l-Amphetamine Plasma Concentration-Time Profile- Both Groups



The mean pharmacokinetic parameters of l-amphetamine are presented in the following table.

Descriptive Statistics for Plasma l-Amphetamine Pharmacokinetic Parameters: 6 to 9 years

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	**A**	327.976	334.314	71.615	21.42	328.894	245.819	440.294	6
AUC_{inf}	**A**	421.442	429.190	87.258	20.33	441.026	301.567	546.303	6
AUC_t/AUC_{inf}	**A**	77.82	77.88	3.32	4.26	78.04	74.48	81.51	6
C_{max}	**A**	19.910	20.267	4.182	20.63	20.800	15.200	26.800	6
T_{max}	**A**	4.40	4.61	1.49	32.30	4.98	2.92	5.93	6
$t_{½}$	**A**	11.54	11.61	1.41	12.16	11.50	9.97	13.43	6
k_{el}	**A**	0.0601	0.0604	0.0073	12.08	0.0604	0.0516	0.0695	6
RStart	**A**	9.21	9.26	1.02	11.02	9.92	7.92	9.92	6
REend	**A**	26.86	26.87	0.91	3.40	26.43	26.10	28.17	6
n	**A**	3	3	1	15.49	3	3	4	6
LQCT	**A**	26.86	26.87	0.91	3.40	26.43	26.10	28.17	6
Ct	**A**	5.546	5.643	1.069	18.94	5.890	3.750	6.650	6

RStart = start time for linear regression
REnd = end time for linear regression
n = number of data points used in the regression analysis
LQCT = time of the last quantifiable concentration
Ct = last measurable concentration value at LQCT. This value was used for the extrapolation to infinity

Descriptive Statistics for Plasma l-Amphetamine Pharmacokinetic Parameters: 10 to 12 years

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	**A**	221.003	228.195	57.957	25.40	234.586	132.330	288.258	5
AUC_{inf}	**A**	301.793	322.145	119.000	36.94	308.246	155.574	455.892	5
AUC_t/AUC_{inf}	**A**	73.23	73.98	11.64	15.73	75.85	60.68	85.06	5
C_{max}	**A**	12.899	13.406	3.717	27.73	14.500	7.430	16.400	5
T_{max}	**A**	4.63	5.13	2.59	50.44	3.92	2.92	7.93	5
$t_{½}$	**A**	12.90	13.49	4.47	33.15	12.25	9.05	18.67	5
k_{el}	**A**	0.0537	0.0561	0.0180	32.06	0.0566	0.0371	0.0766	5
RStart	**A**	9.48	9.52	0.90	9.42	9.92	7.92	9.93	5
REend	**A**	27.23	27.24	0.71	2.62	27.23	26.37	27.98	5
n	**A**	3	3	0	13.98	3	3	4	5
LQCT	**A**	27.23	27.24	0.71	2.62	27.23	26.37	27.98	5
Ct	**A**	3.874	4.308	2.027	47.06	4.210	1.780	6.560	5

RStart = start time for linear regression
REnd = end time for linear regression
n = number of data points used in the regression analysis
LQCT = time of the last quantifiable concentration
Ct = last measurable concentration value at LQCT. This value was used for the extrapolation to infinity

Descriptive Statistics for Plasma l-Amphetamine Pharmacokinetic Parameters: Both Age Groups

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	**A**	274.103	286.078	83.541	29.20	279.955	132.330	440.294	11
AUC_{inf}	**A**	362.089	380.533	112.234	29.49	407.504	155.574	546.303	11
AUC_t/AUC_{inf}	**A**	75.70	76.11	7.99	10.50	75.85	60.68	85.06	11
C_{max}	**A**	16.345	17.148	5.206	30.36	16.300	7.430	26.800	11
T_{max}	**A**	4.50	4.85	1.96	40.52	4.05	2.92	7.93	11
$t_{½}$	**A**	12.14	12.46	3.15	25.31	11.94	9.05	18.67	11
k_{el}	**A**	0.0571	0.0585	0.0127	21.71	0.0580	0.0371	0.0766	11
RStart	**A**	9.33	9.38	0.93	9.89	9.92	7.92	9.93	11
REend	**A**	27.03	27.04	0.81	3.00	26.70	26.10	28.17	11
n	**A**	3	3	0	14.27	3	3	4	11
LQCT	**A**	27.03	27.04	0.81	3.00	26.70	26.10	28.17	11
Ct	**A**	4.712	5.036	1.644	32.63	5.560	1.780	6.650	11

RStart = start time for linear regression
REnd = end time for linear regression
n = number of data points used in the regression analysis
LQCT = time of the last quantifiable concentration
Ct = last measurable concentration value at LQCT. This value was used for the extrapolation to infinity

Pharmacokinetic Conclusions

The mean exposure (Cmax and AUC) to d- and l-amphetamine in pediatric patients 6 to 9 years old were higher than those 10 to 12 years old. For children between the ages of 6 to 9 years old, mean exposure to d-amphetamine was higher than to l-amphetamine. For children between 10 to 12 years old, exposure to d-amphetamine was higher than to l-amphetamine. The median time that the maximum d- and l-amphetamine concentrations were reached was around 3.43 and 4.5 hours pose-dose, respectively. The apparent elimination half-life was estimated to be 10.6 hours for d-amphetamine and 12.5 hours for l-amphetamine.

Safety Evaluation

Frequency of TEAEs and NTEAEs

Preferred Term	Reported Incidence by Treatment Group		
	Pre-dose N = 12	TRI102 N = 12	Total N = 12
Subjects with One or More Adverse Events	3 (25.0%)	1 (8.3%)	4 (33.3%)
Subjects with No Adverse Events	9 (75.0%)	11 (91.7%)	8 (66.7%)
Contusion	1 (8.3%)	0 (0%)	1 (8.3%)
Diarrhoea	0 (0%)	1 (8.3%)	1 (8.3%)
Pharyngitis	1 (8.3%)	0 (0%)	1 (8.3%)
Presyncope	1 (8.3%)	0 (0%)	1 (8.3%)
Rash	0 (0%)	1 (8.3%)	1 (8.3%)
Upper respiratory tract infection	1 (8.3%)	0 (0%)	1 (8.3%)

The sponsor reported that no serious adverse events or deaths occurred. The study medication was reported to be well tolerated.

CLINICAL PHARMACOLOGY REVIEW
Steady-state Simulation Study

NDA 208147	
Amphetamine Suspension	

Title	Simulation of Steady-State Pharmacokinetics of a Test Product Formulation of Amphetamine Extended-Release Oral Suspension and of the Immediate Release Amphetamine Tablets under Fasted Conditions in Healthy Adult Subjects
Objective	The objectives were: • to simulate the steady-state pharmacokinetics of the test and reference formulation starting from the measured concentrations of d- and l-amphetamine in a single-dose bioequivalence study 2014-3401. • To estimate the comparative bioavailability of the two drug-products at steady-state based on the AUCtau, Cmax and Ctrough pharmacokinetic parameters • To estimate the accumulation index of the test formulation

Study Design

☐ Bioequivalence	☐ Absolute Bioavailability	☐ Relative Bioavailability

Method:
Methodology:
The steady-state concentrations were obtained through the non-compartmental superposition.
The AUCtau, Cmax and Ctrough were estimated using a non-compartmental approach based on the simulated concentration in day 8.
The accumulation index was estimated as the ratio of the Cmax and Ctrough between the single-dose and the steady-state. The theoretical accumulation index as calculated based on the apparent elimination rate constant estimated in the single-dose study.

Statistical Methods:
Descriptive statistics were calculated on plasma concentrations and PK parameters. These descriptive statistics included number of observations, arithmetic mean, standard deviation, geometric mean (where applicable), CV, median, minimum and maximum.
Analysis of variance (ANOVA) was performed on log-transformed AUCtau, Cmax and Ctrough parameters. The significance of the sequence, period, treatment and subject-within-sequence effects were tested.
Using the same statistical model, the least-squares-means, the differences between the treatments least-squares-means and the corresponding standard errors of these differences were estimated for log-transformed AUCtau, Cmax and Ctrough parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated.
Criteria for Evaluation:
Based on the log-transformed parameters, the following criteria were used to evaluate the bioequivalence between the test and reference products:
• The 90% confidence intervals of the relative mean AUCtau, Cmax and Ctrough of the test to reference products should be between 80.00 and 125.00%.

Results

Table 1. Summary of Study Results Based on Plasma d-Amphetamine Levels at Steady-State

Based on Raw Data								
Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_{tau}	**A**	29	1191.638 (23)	1163.281	**A vs C**	105.74	101.29 - 110.39	10
(ng·h/mL)	**C**	29	1128.080 (23)	1100.108				
C_{max}	**A**	29	75.587 (20)	74.035	**A vs C**	106.16	102.54 - 109.90	8
(ng/mL)	**C**	29	71.156 (20)	69.741				
C_{trough}	**A**	29	26.490 (35)	25.221	**A vs C**	99.24	92.06 - 106.98	17
(ng/mL)	**C**	29	26.537 (32)	25.415				
		n	*Median*	*Range*				
Tmax	**A**	29	4.00	2.00- 5.00				
(h)	**C**	29	6.00	6.00- 8.00				

Treatment A (Test-1)	*Amphetamine ER Oral Suspension 20 mg/8 mL, 1 x 7.5 mL q24h*
Treatment C (Ref)	*Amphetamine 15 mg Tablets, 2 x 1 Tablet (0 and 4 hours) q24h*

Figure 1.Mean plasma d-amphetamine at steady-state

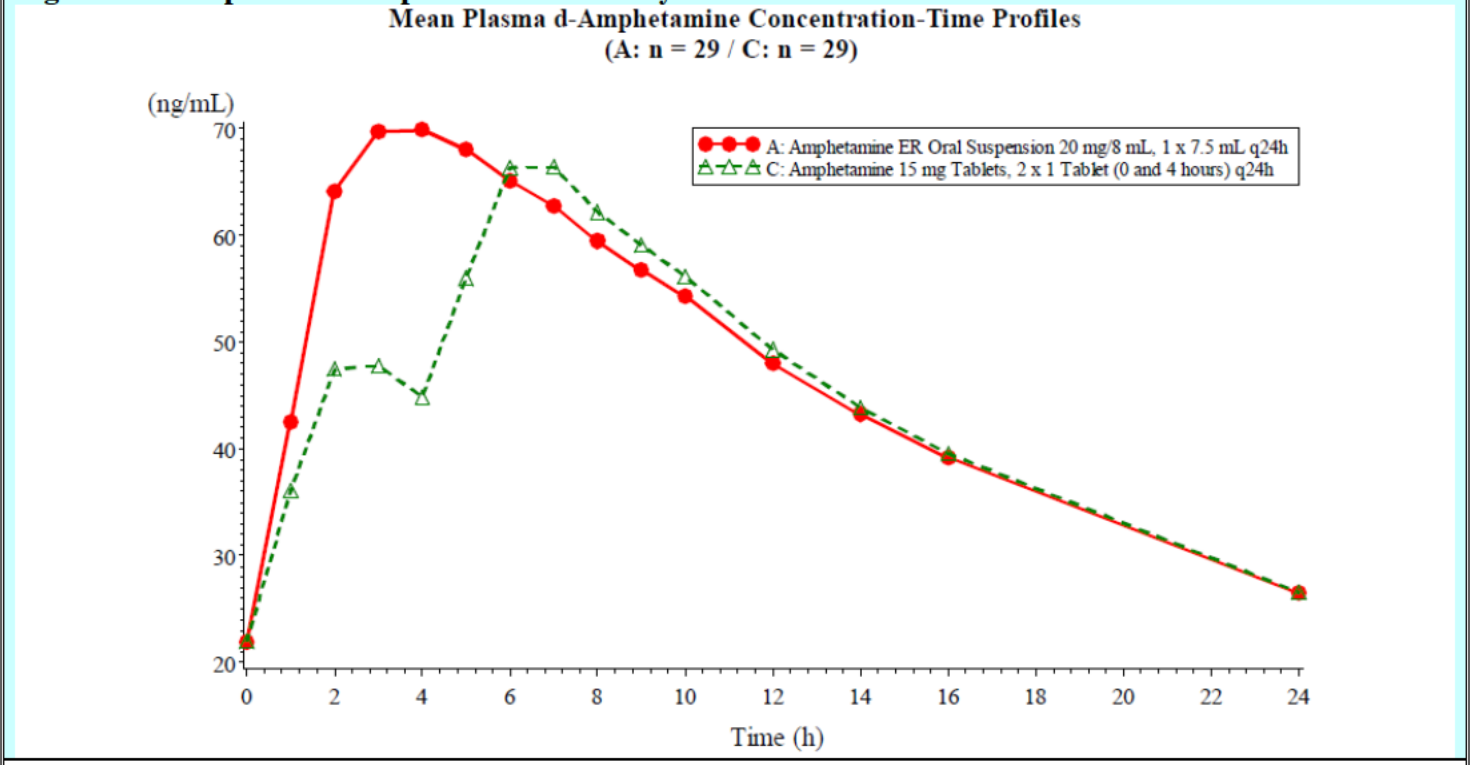
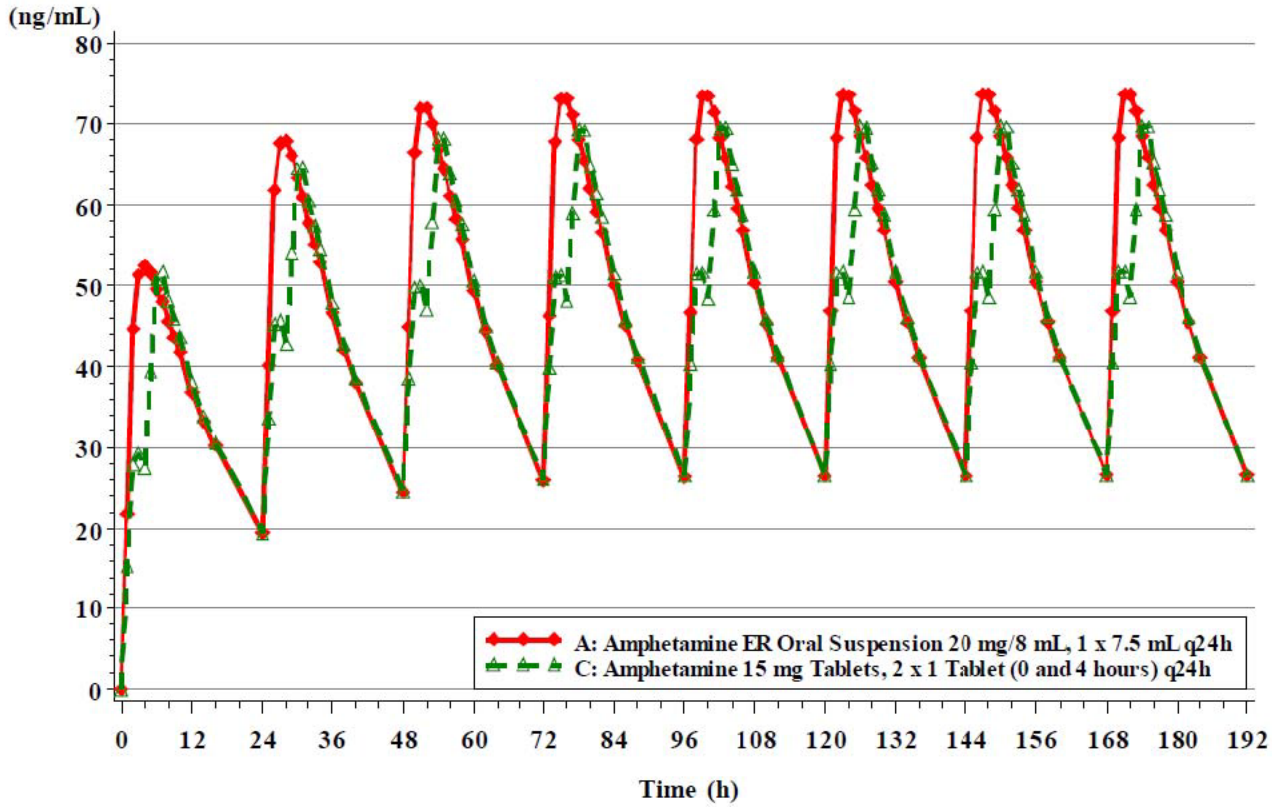


Figure 2. Mean simulated plasma d-amphetamine concentrations after multiple dosing q 24 h



Accumulation Index

PK Parameter	Mean	SD	Median	Min - Max
		d-Amphetamine		
Cmax	1.40	0.14	1.35	1.25 – 1.83
Ctrough	1.40	0.18	1.38	1.19 – 1.95
kel	1.36	0.16	1.33	1.16 – 1.98
		l-Amphetamine		
Cmax	1.57	0.19	1.53	1.36 – 2.11
Ctrough	1.57	0.27	1.52	1.21 – 2.47
kel	1.50	0.25	1.46	1.28 – 2.56

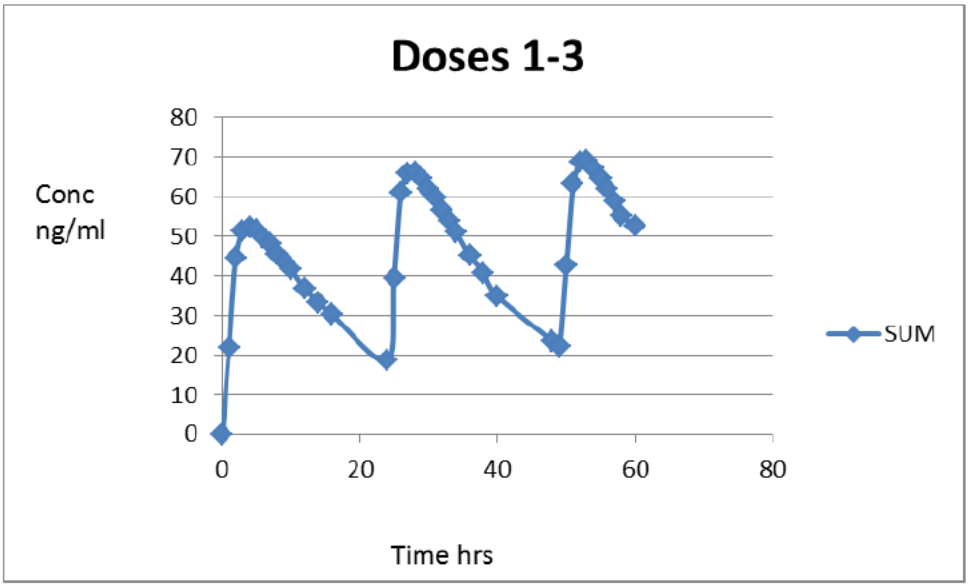
Conclusions:

1. **The steady-state is attained in the 4th day for both formulations.**
2. **Based on the simulated concentrations the test and the reference formulations are bioequivalent. The 90% confidence intervals for the ratio of the geometric means of AUCtau, Cmax and Ctrough are within the 80.00-125.00% range.**
3. **The accumulation of both d- and l-amphetamine is moderate under the once daily administration of the test formulation (ER oral suspension). The Cmax and the concentration at 24 hours post-dose increase with approximately 40% for d-ampletamine and approximately 57% for l-amphetamine.**

Comments:

The calculations done by FDA for the fasting treatment support the superposition simulations(see attached spreadsheet and graph)

Recommendations for Labeling



Raw calculations

TIME	DOSE 1 A Fast	Dose2	DOSE3	SUM SUM
0	0			0
1	21.77			21.77
2	44.56			44.56
3	51.23			51.23
4	52.4			52.4
5	51.51			51.51
6	49.72			49.72
7	47.96			47.96

8	45.49			45.49
9	43.56			43.56
10	41.77			41.77
12	36.77			36.77
14	33.22			33.22
16	30.18			30.18
24	18.56	0		18.56
25	17.5	21.77		39.27
26	16.53	44.56		61.09
27	14.73	51.23		65.96
28	13.9	52.4		66.3
29	13.12	51.51		64.63
30	12.39	49.72		62.11
31	11.69	47.96		59.65
32	11.04	45.49		56.53
33	10.42	43.56		53.98
34	9.28	41.77		51.05
36	8.27	36.77		45.04
38	7.37	33.22		40.59
40	4.64	30.18		34.82
48	4.9	18.56		23.46
49	4.62	17.5	0	22.12
50	4.36	16.53	21.77	42.66
51	3.89	14.73	44.56	63.18
52	3.67	13.9	51.23	68.8
53	3.46	13.12	52.4	68.98
54	3.27	12.39	51.51	67.17
55	3.08	11.69	49.72	64.49
56	2.91	11.04	47.96	61.91
57	2.75	10.42	45.49	58.66
58	2.45	9.28	43.56	55.29
60	2.67	8.27	41.77	52.71

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

/s/

KOFI A KUMI
09/21/2015

LI ZHANG
09/21/2015

HAO ZHU
09/21/2015
I sign this document also on behalf of Dr. Kevin Krudys.