Office of Clinical Pharmacology Review

NDA	204325
Link to EDR	\\CDSESUB1\evsprod\nda204325\0000
Submission Date	11/15/16
Submission Class	505(b)(2), Standard
Brand Name	Adzenys ER (b) (4)
Generic Name	Amphetamine Extended Release
Dosage Form and Strength	Extended Release Oral Suspension, 1.25 mg/mL
Route of Administration	Oral
Proposed Indication	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Applicant	Neos Therapeutics
Related IND	110281
OCP Review Team	Kofi A. Kumi, Ph.D., Hao Zhu, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

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1. Executive Summary

This New Drug Application (NDA) is for a new Amphetamine Extended Release (ER) oral suspension (OS). The sponsor submitted the NDA as 505(b)(2) application with Adderall XR (NDA 21303) as the Listed Drug (LD). Adderall XR is approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The sponsor is relying on the FDA's finding of safety and effectiveness for Adderall XR® Extended-Release Capsules and is seeking the same indication approved for Adderall XR.

The sponsor has developed Amphetamine ER-OS, a new extended release oral formulation of amphetamine, as an oral suspension 18.8 mg/15 mL (equivalent to 30 mg mixed amphetamine salts/15 mL). The Amphetamine ER-OS utilizes (b) (4)

The clinical development program included 5 Phase 1 studies. These 5 Phase 1 studies included a pivotal relative bioavailability study that compared Amphetamine ER-OS to Adderall XR, the

effect of a high fat meal on exposure (Cmax and AUC) and a pharmacokinetic study in pediatric subjects age 6 -12 years old. The sponsor included the pharmacokinetic study in pediatric subjects 6 -12 years in their development program. But it was not requested by the Office of Clinical Pharmacology (OCP). No new safety and efficacy study was included in the submission.

The key review issues are: 1) Are the exposure (Cmax and AUCs including partial AUCs) and pharmacokinetic profile after administration of Amphetamine ER-OS similar (i.e., meeting bioequivalent criteria) to those after administration of Adderall XR? 2) Is the proposed dosing regimen for Amphetamine ER-OS appropriate? 3) Should Amphetamine ER-OS be administered with or without food? 4) Are there dose adjustments for patients receiving a gastric pH modulator?

A consult was sent to the Office of Scientific Inspections and Surveillance (OSIS) requesting biopharmaceutical inspections for pivotal relative bioavailability studies NT0201-1008 and NT0201-1007. OSIS concluded that the data are acceptable based on the records of recent inspections of the study and bioanalytical sites.

1.1 Recommendations

The office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 204325 and supports the approval of Amphetamine ER-OS for the treatment of Attention Deficit Hyperactivity Disorder. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The exposures and pharmacokinetic profiles after administration of Amphetamine ER-OS and Adderall XR are similar; therefore, the efficacy and safety profiles following the treatment of Amphetamine ER-OS should be similar to those of the approved Adderall XR.
General dosing instructions	The dosing instructions are similar to that for Adderall XR and acceptable. Administer Amphetamine ER-OS orally once daily in the morning with or without food. The dose should be individualized according to the therapeutic needs and response of the patient. Pediatric Patients (6 to 17 years) The recommended starting dose is 6.3 mg (5 mL) once daily in the morning. Increase in increments of 3.1 mg (2.5 mL) or 6.3 mg (5 mL) at weekly intervals. The maximum dose is 18.8 mg (15 mL) daily for patients 6 to 12

	years, and 12.5 mg (10 mL) daily for patients 13 to 17 years Adults The recommended dose of Amphetamine ER-OS for adults is 12.5 mg (10 mL) daily.
Dosing in specific patients	Increased gastric pH due to concomitant use of a gastric pH modulator may change the exposure and pharmacokinetic profile of amphetamine. Concomitant use of the Amphetamine ER-OS with a gastric pH modulator is not recommended.
Bridge between the to be marketed and approved reference drug	D- and l-amphetamine exposures (AUC, Cmax) are similar (i.e. meeting BE criteria) and the pharmacokinetic profiles are also similar.

1.2 Post-Marketing Requirements and Commitments

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

This application does not trigger PREA since there is an approved Amphetamine Extended Release Oral Suspension (Dyanavel XR™) already approved and commercially available, according to PeRC. However, it is expected that this formulation would be used in children 4 to 5 years old; therefore, it is recommended that the safety and efficacy be evaluated. A Post Marketing Commitment (PMC) for a pharmacokinetic study in children 4 -5 years is recommended and requested to inform the dosing in these patients.

The Sponsor currently has an ongoing pediatric program for patients 4 to 5 years for the approved Amphetamine Orally Disintegrating (Adzenys XR-ODT™) product (NDA 204326). Adzenys-ODT and Amphetamine Extended Release Oral Suspension (Adenzys ER(b) (4)) have both been demonstrated to be similar (meets BE criteria) to Adderall XR, the Listed Drug. Therefore, the need for studies in pediatric patients 4 to 5 years for Adzenys-ER(b) (4) would be re-evaluated once the results of the pediatric studies for 4 to 5 years for Adzenys-ODT are submitted and reviewed. The PMC for Adzenys-ER(b) (4) would be considered satisfied if the results from the Adzenys XR-ODT are acceptable and can be extrapolated to Adzenys-ER(b) (4). Adzenys-ER(b) (4) and Adzenys XR-ODT belong to the same Sponsor.

2. Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

Amphetamine ER-OS is a new formulation of amphetamine, a stimulant used to treat ADHD. Amphetamine ER-OS is a once daily oral suspension of mixed amphetamine salt with an immediate release and a delayed release component. The formulation contains a drug-resin complex. (b) (4)

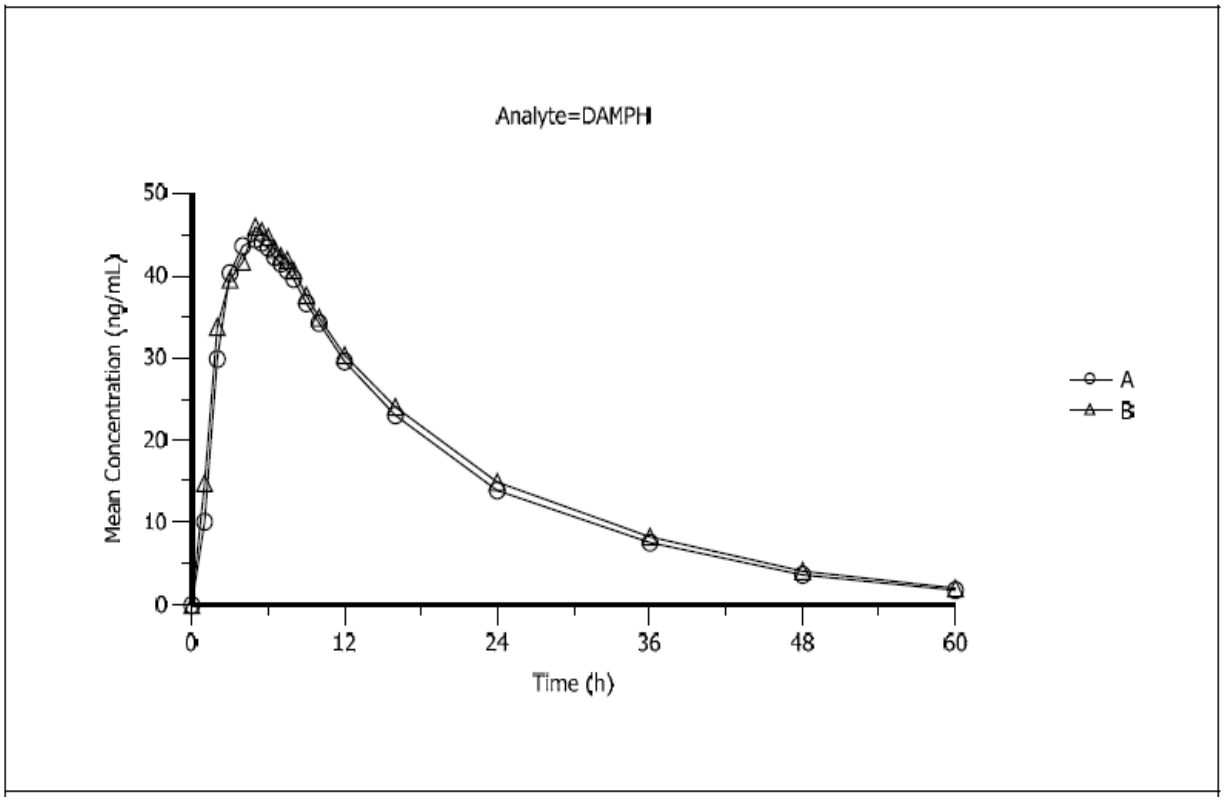
Amphetamine ER-OS provides a similar in vivo drug release and absorption profile to ADDERALL XR through the use of immediate-release and delayed release forms of amphetamine resinate loaded with a 3:1 ratio of the d- and l-isomers of amphetamine. The dose and dosing schedule for the Amphetamine ER-OS is the same as that of ADDERALL XR. Dosing for Amphetamine XR-OS can be accomplished by administration of different amounts of the oral suspension to achieve the equivalent Mixed Amphetamine Salt (MAS) dose of the ADDERALL XR. The comparison of the pharmacokinetic properties between Amphetamine ER-OS and Adderall XR were evaluated in single dose relative bioavailability studies in health adult subjects. The effect of food was also evaluated.

2.1.1 Pharmacokinetic Comparison between Amphetamine ER-OS and Adderall XR

Amphetamine ER-OS 30 mg (18.8 mg base) and Adderall XR 30 mg were similar (i.e. met BE criteria) with respect to Cmax and AUCs of d-and l-amphetamine. Partial AUC(0-5) and AUC(5-

t) were similar under fasting conditions. The mean pharmacokinetic profiles were also similar (Figures 1, 2 and Tables 1, 2 below). The mean time to maximum d- and l-amphetamine concentration (Tmax) was about 5 hours after administration of Amphetamine ER-OS and Adderall XR. The elimination half-lives of d- and l-amphetamine were about 11 and 14 hours, respectively after of both Amphetamine ER-OS and Adderall XR.

Figure 1: Mean d-amphetamine concentration time profiles after administration of Amphetamine ER-OS (Treatment A) and Adderall XR (Treatment B)



Source: Study NT0201-1008

Table 1: Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of *d*-amphetamine

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	46.5761	49.5015	94.09	92.32	95.90	1.0000	5.18
$\ln(AUC_{0-5})$	141.4171	144.7649	97.69	92.02	103.71	1.0000	16.39
$\ln(AUC_{5-last})$	727.0251	769.0353	94.54	91.27	97.92	1.0000	9.58
$\ln(AUC_{inf})$	904.1140	959.4967	94.23	91.50	97.04	1.0000	8.01

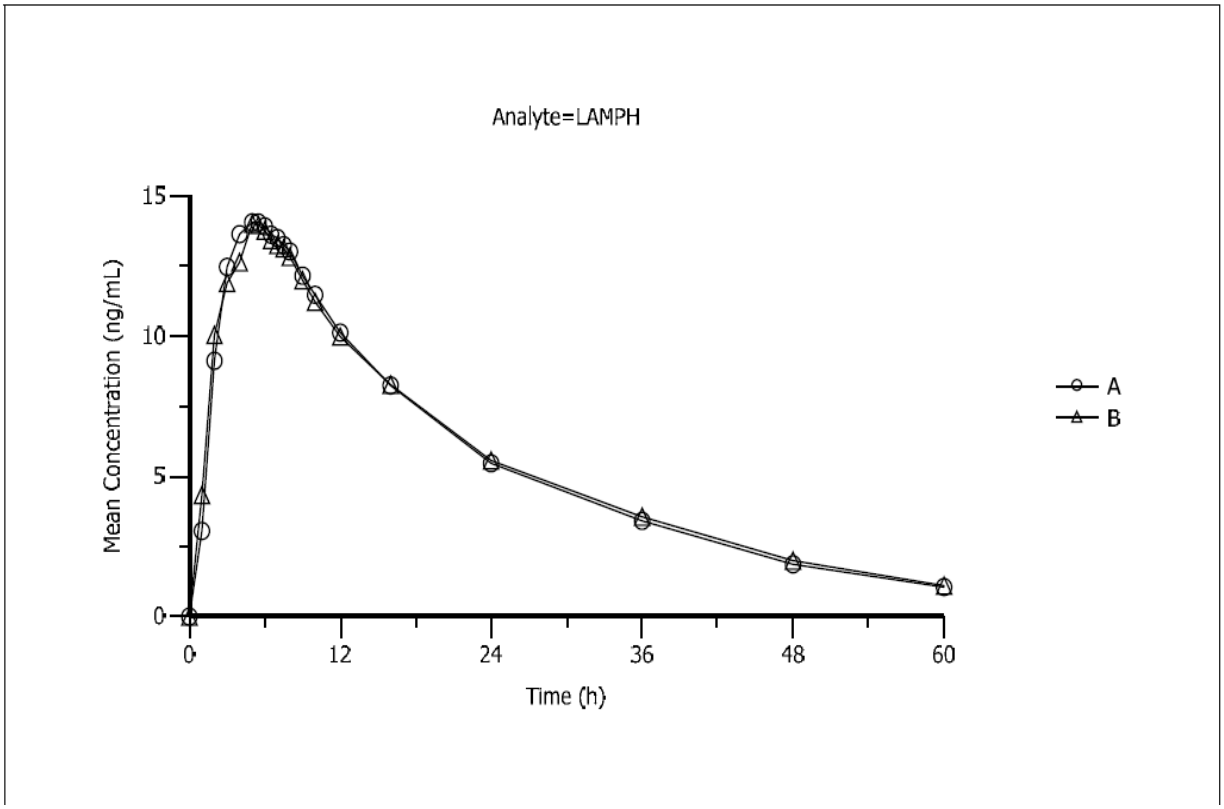
[a] Geometric Mean for AMP XR-OS (Test) and Adderall XR (Ref) based on Least Squares Mean of log-transformed parameter values

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

[c] 90% Confidence Interval

Source: NT0201-1008

Figure 2: Mean *l*-amphetamine Concentration-Time Profiles after Administration of Amphetamine ER-OS (Treatment A) and Adderall XR (Treatment B)



Source: Study NT0201-1008

Table 2: Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of *l*-amphetamine

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	14.7245	15.0694	97.71	95.91	99.55	1.0000	5.07
$\ln(AUC_{0-5})$	43.8159	43.4199	100.91	95.07	107.11	1.0000	16.33
$\ln(AUC_{5-last})$	272.9836	277.7308	98.29	94.83	101.87	1.0000	9.77
$\ln(AUC_{inf})$	340.2570	348.2751	97.70	94.54	100.96	1.0000	8.96

[a] Geometric Mean for AMP XR-OS (Test) and Adderall XR (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 NT0201-1008

2.1.2 Effect of Food on the Pharmacokinetics of Amphetamine ER-OS

Consumption of a high fat meal did not significantly affect pAUCs, Cmax or AUCs of d and l-amphetamine compared to administration of Amphetamine ER-OS under fasting conditions (i.e., meeting BE criteria). The Tmax was about 5 hours for taking Amphetamine ER-OS under both fed and fasting conditions. Amphetamine ER-OS can be taken with or without food.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The dosing regimen is similar to the approved dosing regimen for Adderall XR, the LD. Administer Amphetamine ER-OS orally once daily in the morning with or without food. The dose should be individualized according to the therapeutic needs and response of the patient. Do not add Amphetamine ER-OS to food or mix Amphetamine ER-OS with other liquids before consuming.

The recommended starting dose for pediatric patients 6 to 17 years is 6.3 mg (5 mL) once daily in the morning. Increase in increments of 3.1 mg (2.5 mL) or 6.3 mg (5 mL) at weekly intervals. The maximum dose is 18.8 mg (15 mL) daily for patients 6 to 12 years and 12.5 mg (10 mL) daily for patients 13 to 17 years

The recommended dose of Amphetamine ER-OS for adults is 12.5 mg (10 mL) daily.

The Sponsor demonstrated that exposure to d- and l-amphetamine after administration of Amphetamine ER-OS and Adderall XR, the RLD are equivalent (i.e. met the BE criteria).

Therefore, dosing regimen approved for Adderall XR can be applied to that for Amphetamine ER-OS. No clinical safety and efficacy trial was conducted.

2.2.2 Therapeutic Individualization

The dose should be individualized according to the therapeutic needs and response of the patient.

Since the DR/ER component of Amphetamine ER-OS is pH sensitive, it is not recommended to administer a pH modulator (e.g. proton pump inhibitor or H2 blocker) concomitantly with Amphetamine ER-OS.
Formal studies in patients with hepatic impairment were not conducted

Formal studies in patients with renal impairment were not conducted

2.3 Outstanding Issues

The current approved label for Adderall XR, the LD, is silent on dosing in renal impaired patients. (b) (4)

2.4 Summary of Labeling Recommendations

General dosing recommendations is acceptable. These recommendations are similar to that approved for Adderall XR.
It is not recommended to administer a pH modulator (e.g. proton pump inhibitor or H2 blocker) concomitantly with Amphetamine ER-OS.
Amphetamine ER-OS can be administered with or without food.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

The Sponsor (Neos Therapeutics, Inc) has developed an Extended Release (ER) oral suspension, 18.8 mg/15 mL and is seeking approval for use for the treatment of Attention Deficit Hyperactivity Disorder. The Sponsor is seeking approval via the 505(b)(2) route with Adderall XR, NDA 21303, as the reference drug. Therefore, the sponsor is relying on the efficacy and safety data that formed the basis of approval for the listed drug Adderall XR® Extended-Release Capsules. The Sponsor conducted 5 Phase 1 studies including a pharmacokinetic study in pediatric patients 6 – 12 years old. The pediatric pharmacokinetic study was part of the Sponsor's development program. OCP did not request the sponsor conduct the study.

Amphetamine ER-OS (oral suspension) utilizes (b) (4) [redacted].

The Sponsor states that the clinical trial and commercial scale formulations of Amphetamine XR-OS provide a similar in vivo drug release and absorption profile to ADDERALL XR through the use of immediate-release and delayed release forms of amphetamine resinate loaded with a 3:1 ratio of the d- and l-isomers of amphetamine.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	Amphetamine is non-catecholamine sympathomimetic amines. Exact mechanism of action in ADHD is not known
Active moieties	Mixed Amphetamine salts: Neutral sulfate salts of dextromamphetamine and amphetamine, amphetamine aspartate monohydrate
QT Prolongation	The potential of QT prolongation after administration of amphetamine products is not known
General Information	
Bioanalysis	LC/MS/MS Assay Linear Range: 0.5 to 80 ng/mL for d-amphetamine, 0.2 to 32 ng/mL for l-amphetamine
Drug exposure at steady state following the therapeutic dosing regimen	Steady state is expected to be reached by 5 of multiple dosing
Maximum tolerated dose or exposure	30 mg (18.8 mg base)
Linear Pharmacokinetics	Based on Adderall XR Label: 20 to 60 mg in adults; 10 to 40 mg in adolescents and 5 to 30 mg in pediatric 6 -12 years old
Accumulation	No unexpected accumulation based on Adderall XR
Absorption	Time to maximum concentration (Tmax) is approximately 5 hours. Effect of Food: Food did not significantly affect the exposure (Cmax, AUC) of d- and l-

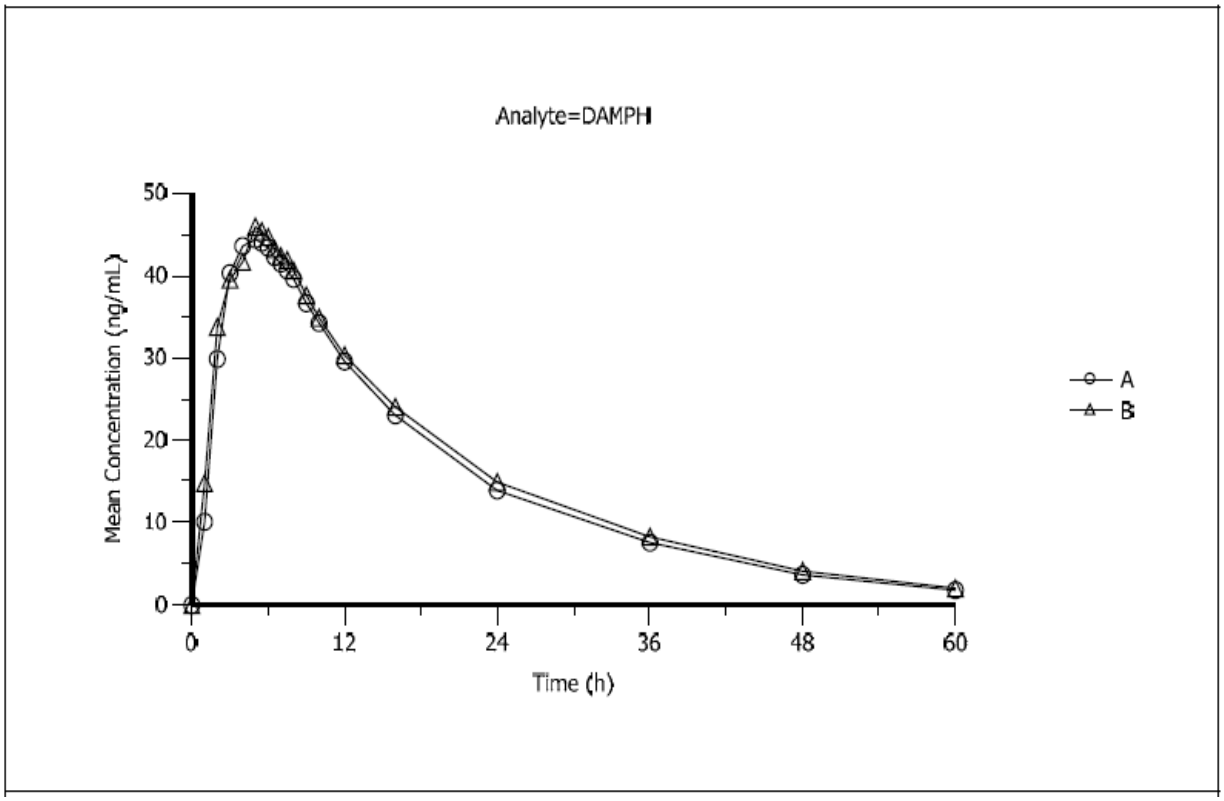
	amphetamine. Tmax was not significantly affected after administration with food compared to fasting conditions.
Distribution	Protein Binding about 40%
Elimination	T ½: Pediatric children 6 -12 years ranged from approximately 10 to 17 hours for d-amphetamine and 11 – 25 hours for l-amphetamine. Adult T ½ range from about 11 to 12 hours. Metabolism: CYP2D6, Flavin containing monooxygenase 3 (FMO) and dopamine β-hydroxylase Amphetamine is not inhibitor in vitro of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in human hepatic microsomal suspensions, nor was it an in vitro inducer of CYP1A2, CYP2B6 or CYP3A4/5 in cultured fresh human hepatocytes. Amphetamine is not an in vitro substrate for permeability glycoprotein (P-gp) in vitro inhibitor of P-gp. Excretion: Renal

3.3 Clinical Pharmacology Questions

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

This application is a 505(b)(2) application with Adderall XR as the listed drug (LD). Therefore, the application relies on the efficacy and safety data that formed the basis for approval of Adderall XR. The sponsor demonstrated in a relative bioavailability study that the d- and l-amphetamine exposures after administration 30 mg (18.8 mg base) of Amphetamine ER oral suspension is similar (i.e., meeting bioequivalence criteria) to those after administration of Adderall XR, The shape of the pharmacokinetic profiles were also similar. Therefore, the efficacy of Amphetamine ER oral suspension would be expected to be similar to that of Adderall XR. The following are the pharmacokinetic profile and results of the relative bioavailability study, `NT0201.1008

Figure 3: Mean *d*-amphetamine Concentration-Time Profiles after Administration of AMP XR-OS (Treatment A) and Adderall XR (Treatment B)



Source: Study NT0201.1008

Pharmacokinetic Parameters of d-amphetamine

Parameter	Treatment A, Test Formulation: AMP XR-OS				Treatment B, Reference Product: Adderall XR			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	42	5.00 (3.00, 7.50)			42	5.00 (2.00, 12.00)		
C_{max} (ng/mL)	42	47.2	7.68	16.26	42	50.3	8.93	17.74
AUC_{0-5} (h*ng/mL)	42	145.9	36.18	24.80	42	152.6	48.11	31.53
AUC_{5-last} (h*ng/mL)	42	745.7	175.8	23.58	42	783.5	152.7	19.49
AUC_{last} (h*ng/mL)	42	891.6	188.7	21.16	42	936.1	163.1	17.42
AUC_{inf} (h*ng/mL)	42	925.2	209.0	22.59	42	974.7	178.0	18.26
AUC_{Extrap} (%)	42	3.37	1.95	57.76	42	3.82	2.11	55.18
λ_z (h^{-1})	42	0.0632	0.0131	20.75	42	0.0608	0.0124	20.35
$T_{1/2}$ (h)	42	11.41	2.27	19.92	42	11.87	2.42	20.42
T_{last} (h)	42	59.15	3.13	5.29	42	59.16	4.10	6.94
C_{last} (ng/mL)	42	1.87	1.10	58.74	42	2.11	1.06	50.32

Note: T_{max} presented as Median (Min, Max)

Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of *d*-amphetamine

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	46.5761	49.5015	94.09	92.32	95.90	1.0000	5.18
$ln(AUC_{0-5})$	141.4171	144.7649	97.69	92.02	103.71	1.0000	16.39
$ln(AUC_{5-last})$	727.0251	769.0353	94.54	91.27	97.92	1.0000	9.58
$ln(AUC_{inf})$	904.1140	959.4967	94.23	91.50	97.04	1.0000	8.01

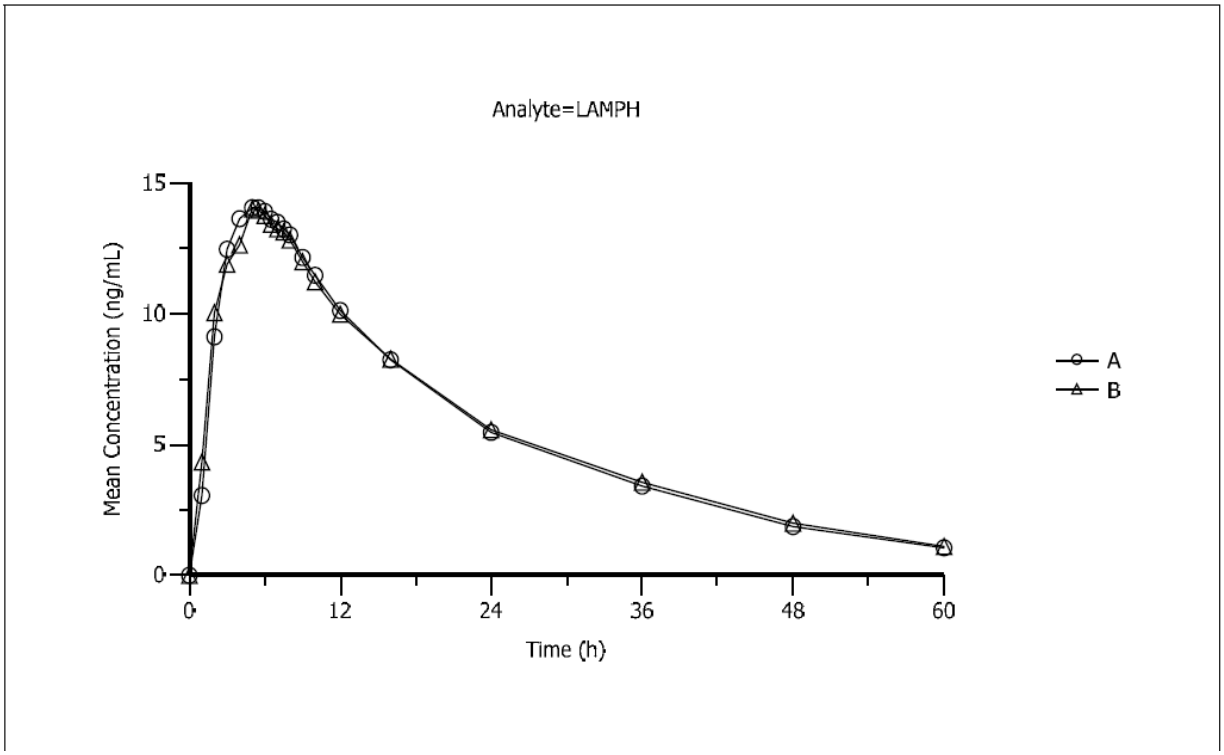
[a] Geometric Mean for AMP XR-OS (Test) and Adderall XR (Ref) based on Least Squares Mean of log-transformed parameter values

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

[c] 90% Confidence Interval

Source: Study NT0201.1008

Figure 4: Mean *l*-amphetamine Concentration-Time Profiles after Administration of AMP XR-OS (Treatment A) and Adderall XR (Treatment B)



Source: Study NT0201-1008

Table 5: Pharmacokinetic Parameters of l-amphetamine

Parameter	Treatment A, Test Formulation: AMP XR-OS				Treatment B, Reference Product: Adderall XR			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	42	5.00 (3.00, 8.00)			42	5.00 (2.00, 12.00)		
C_{max} (ng/mL)	42	14.9	2.40	16.09	42	15.3	2.66	17.39
AUC_{0-5} (h*ng/mL)	42	45.24	11.38	25.16	42	45.85	14.69	32.04
AUC_{5-last} (h*ng/mL)	42	280.6	67.60	24.09	42	282.9	54.23	19.17
AUC_{last} (h*ng/mL)	42	325.9	71.04	21.80	42	328.7	57.78	17.58
AUC_{inf} (h*ng/mL)	42	350.2	87.02	24.85	42	354.8	70.64	19.91
AUC_{Extrap} (%)	42	6.30	3.76	59.64	42	6.94	3.90	56.16
λ_z (h^{-1})	42	0.0522	0.0131	25.03	42	0.0505	0.0120	23.83
$T_{1/2}$ (h)	42	14.11	3.52	24.95	42	14.56	3.74	25.69
T_{last} (h)	42	59.72	1.85	3.10	42	59.16	4.10	6.94
C_{last} (ng/mL)	42	1.06	0.621	58.67	42	1.13	0.537	47.41

Note: T_{max} presented as Median (Min, Max)

Source: Study NT0201-1008

Table 6: Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of *l*-amphetamine

Dependent Variable	Geometric Mean[a]		Ratio (%)[b] (Test/Ref)	90% CI[c]		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
$ln(C_{max})$	14.7245	15.0694	97.71	95.91	99.55	1.0000	5.07
$ln(AUC_{0-5})$	43.8159	43.4199	100.91	95.07	107.11	1.0000	16.33
$ln(AUC_{5-last})$	272.9836	277.7308	98.29	94.83	101.87	1.0000	9.77
$ln(AUC_{inf})$	340.2570	348.2751	97.70	94.54	100.96	1.0000	8.96

[a] Geometric Mean for AMP XR-OS (Test) and Adderall XR (Ref) based on Least Squares Mean of log-transformed parameter values

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

[c] 90% Confidence Interval

Source: NT0201.1008

3.3.2 Is the proposed general dosing regimen appropriate?

Yes, the proposed dosing regime is acceptable. It is similar to the dosing regimen approved for the LD, Adderall XR.

The recommended starting dose for pediatric patients 6 -17 years is 6.3 mg (5 mL) once daily in the morning. Increase in increments of 3.1 mg (2.5 mL) or 6.3 mg (5 mL) at weekly intervals. The recommended dose of Amphetamine ER-OS for adults is 12.5 mg (10 mL) daily.

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

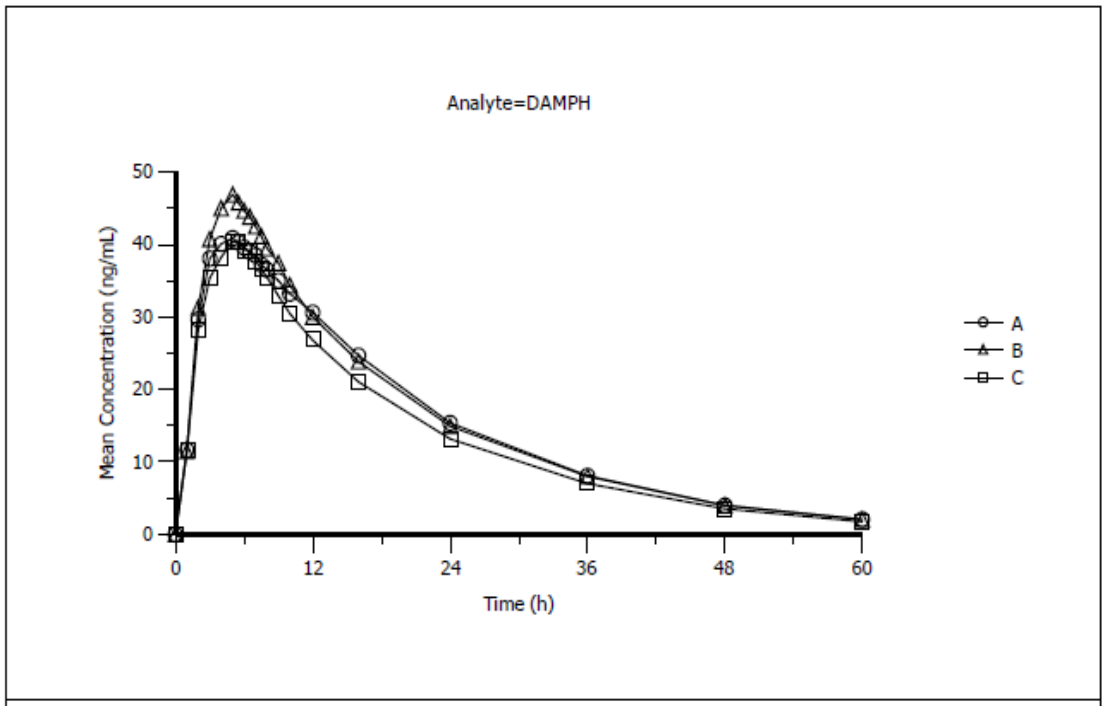
No. Based on the information currently in the label for the LD, dose adjustment is not required due to intrinsic factors. (b) (4)

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

There is no significant effect on exposure (Cmax and AUC) to d- and l-amphetamine and Tmax after administration of Amphetamine ER OS with a high fat meal. Therefore, Amphetamine ER-OS can be administered with or without food. The applicant evaluated the effect of a high fat meal on exposure to d- and l-amphetamine after administration of Amphetamine ER OS in Study NT0201-1007. Tmax was about 5 hours after administration of Amphetamine ER OS under fed and fasted conditions.

Figures 5 and 6 below depict the plasma concentration time profiles for d- and l-amphetamine, respectively, after administration of the commercial to be marketed formulation (TBM, Form1) under fed and fasting conditions. Included in the figure is also a plasma concentration time profile for the clinical trial formulation (Form 2) under fasting conditions. The shapes of the pharmacokinetic profiles are similar except Cmax is lower after administration of the TBM with food compared to under fasting conditions. This difference is not expected to be statistically and clinically significant (see Table 7). Incidentally, Cmax is similar when after administration of the clinical trial formulation under fasting conditions compared to the TBM under fed conditions, however, lower when compared to TBM under fasting conditions.

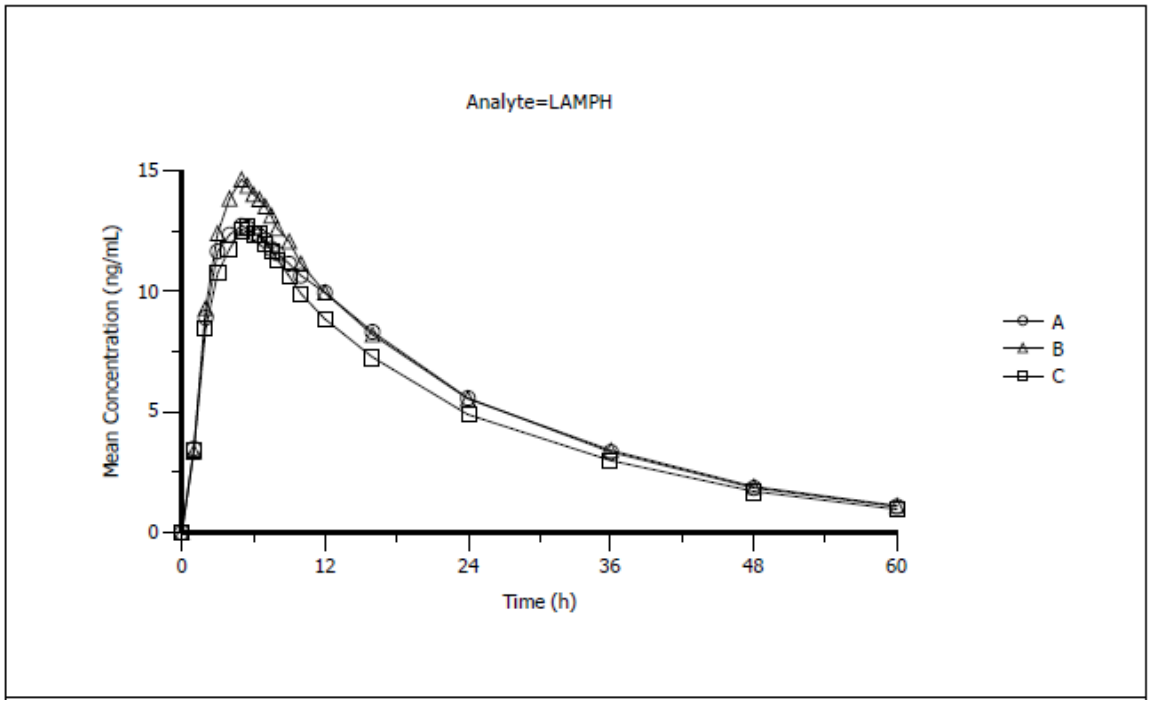
Figure 5: Mean *d*-amphetamine Concentration-Time Profiles after Administration of AMP XR OS under Fed Conditions (Treatment A, Formulation 1), AMP XR OS under Fasted Conditions (Treatment B, Formulation 1), and AMP XR OS under Fasted Conditions (Treatment C, Formulation 2)



Formulation 1: To Marketed Formulation (Treatments A and B). Formulation 2: Clinical Trial Formulation (Treatment C).

Source: Study NT0201-1007

Figure 6: Mean l-amphetamine Concentration-Time Profiles after Administration of AMP XR OS under Fed Conditions (Treatment A, Formulation 1), AMP XR OS under Fasted Conditions (Treatment B, Formulation 1), and AMP XR OS under Fasted Conditions (Treatment C, Formulation 2)



Formulation 1: To Marketed Formulation (Treatments A and B). Formulation 2: Clinical Trial Formulation (Treatment C).

Source: Study NT0201-1007

The statistical analyses are presented in the tables 7 and 8 below.

Table 7: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine comparing the Commercial Formulation of Amphetamine ER- OS under Fed Conditions (Treatment A) to the Commercial Formulation of Amphetamine ER- OS under Fasted Conditions (Treatment B)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	42.4585	47.8960	88.65	86.34	91.02	1.0000	7.71
$ln(AUC_{0-5})$	134.6968	148.3976	90.77	85.34	96.54	1.0000	18.13
$ln(AUC_{5-last})$	754.9487	765.2341	98.66	94.68	102.79	1.0000	12.02
$ln(AUC_{last})$	895.9045	917.3565	97.66	94.44	100.99	1.0000	9.80
$ln(AUC_{inf})$	931.5679	953.8341	97.67	94.30	101.15	1.0000	10.24

[a] Geometric Mean for AMP XR OS-Fed, Formulation 1 (Test) and AMP XR OS-Fasted, Formulation 1 (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 NT0201.1007

Table 8: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of l-amphetamine comparing the Commercial Formulation of Amphetamine ER- OS under Fed Conditions (Treatment A) to the Commercial Formulation of Amphetamine ER- OS under Fasted Conditions (Treatment B)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	15.0062	13.0520	114.97	111.79	118.24	1.0000	8.14
$\ln(AUC_{0-5})$	45.0998	39.3136	114.72	107.62	122.28	1.0000	18.71
$\ln(AUC_{5-last})$	276.1140	241.6469	114.26	109.45	119.29	1.0000	12.52
$\ln(AUC_{inf})$	346.1557	302.8299	114.31	109.87	118.92	1.0000	11.51

[a] Geometric Mean for AMP XR OS-Fasted, Formulation 1 (Test) and AMP XR OS-Fasted, Formulation 2 (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 NT0201-1007

No new drug interaction studies were conducted using Amphetamine ER OS. Drug interaction would be expected to be similar to that seen with Adderall XR.
CYP2D6 is known to be involved in the metabolism of Amphetamine to 4-ydroxyamphetamine. Since CYP2D6 is genetically polymorphic, population variations (different types of metabolizers) in amphetamine metabolism are a possibility. Potential pharmacokinetic drug interactions (DDI) involved in CYP2D6 cannot be excluded. Frequent monitoring is recommended.

3.3.5 What are the pharmacokinetic characteristics of d- and l-amphetamine after administration of Amphetamine ER OS to pediatric patients 6 -12 years, adolescents 13 -17 years and how do they compare to Adults?

The sponsor did not evaluate the pharmacokinetics of d-and l-amphetamine after administration of adolescents, 13 -17 years old. However, single dose pharmacokinetic studies were conducted in adults and pediatric patients 6 -12 years.

The PK profile after administration of the listed drug, ADDERALL XR, is well established in children, adolescents, and adults and described in the approved label for the RLD. According to the ADDERALL XR label, on a mg/kg basis, children have a higher clearance than adolescents or adults with a mean elimination half-life (t½) that is approximately 1 hour shorter for d-amphetamine and 2 hours shorter for l-amphetamine compared to adults. However, children have higher systemic exposure (based on AUC and Cmax) than adults for a given dose of ADDERALL XR, which can be attributed to the higher dose administered in children on a mg/kg basis compared to adults.

The sponsor conducted a pharmacokinetic study using Amphetamine ER-OS in pediatric subjects age 6 -12 years. An age-related trend in mean maximum and total *d*-amphetamine and *l*-amphetamine exposure was observed; as age increased, mean amphetamine exposure decreased. Mean weight-normalized CL/F values for *d*-amphetamine and *l*-amphetamine increased with an

increase in age while Vz/F values decreased. Mean T1/2 decreased as age increased, ranging from 9.65 hours in 10-12 years to 16.74 hours in 6-7 years for *d*-amphetamine and from 10.61 h 10-12 years to 24.61 hours in 6-7 years for *l*-amphetamine.

The following table contains pharmacokinetic parameters for d-and l-amphetamine after administration of Amphetamine ER-OS to pediatric children 6 -12 years old and adults in single dose pharmacokinetic studies

Table 9: Comparison of Mean (SD) Pharmacokinetic Parameters for d-Amphetamine from Clinical Studies of Amphetamine ER-OS

Study[a]	N	AUC_{last} (ng·hr/mL)	AUC_{last} /kg (ng·hr/mL/kg)	AUC_{inf} (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{½}$ (hr)
NT0201.1004							
Children (6-7 years old)	9	1238 (267.5)	49.13 (13.50)	2251 (1174)	76.8 (15.2)	5.67 (1.75)	16.74 (10.67)
Children (8-9 years old)	10	1088 (129.6)	35.68 (9.828)	1557 (310.9)	68.0 (8.11)	5.00 (1.83)	12.60 (2.47)
Children (10-12 years old)	10	873.6 (108.6)	22.80 (7.323)	1130 (172.7)	60.0 (7.07)	5.35 (1.25)	9.65 (1.02)
NT0201.1005							
Formulation #2	40	978.7 (207.0)	N/A	1022 (219.1)	51.0 (9.84)	5.28 (0.72)	12.44 (2.03)
ADDERALL XR	42	970.1 (213.4)	N/A	1017 (234.1)	50.6 (10.2)	4.55 (1.47)	12.55 (2.32)
NT0201.1006							
Amphetamine XR-OS	29	960.1 (180.8)	N/A	996.3(193.7)	51.9 (9.02)	4.95 (0.99)	11.82 (1.83)
Amphetamine XR-OS - Fed	29	923.1 (161.4)	N/A	961.5 (176.8)	45.9 (7.98)	5.47 (1.91)	12.12 (1.90)
ADDERALL XR - Fed	29	848.4 (146.4)	N/A	881.7 (157.5)	42.6 (9.48)	7.95 (2.50)	11.81 (1.54)
NT0201.1007							
Commercial Scale Formulation Amphetamine XR-OS - Fed	47	911.1 (157.0)	N/A	949.4 (174.3)	43.2 (7.16)	4.80 (1.80)	11.94 (1.88)
Commercial Scale Formulation Amphetamine XR-OS	47	930.1 (144.0)	N/A	969.4 (164.4)	48.6 (6.55)	4.86 (1.04)	12.09 (2.53)
Clinical Trial Formulation Amphetamine XR-OS	47	820.9 (162.0)	N/A	854.3 (179.6)	42.6 (7.59)	5.11 (1.55)	12.07 (2.14)
NT0201.1008							
Commercial Scale Formulation Amphetamine XR-OS	42	891.6 (188.7)	N/A	925.2 (209.0)	47.2 (7.68)	4.81 (1.16)	11.41 (2.27)
ADDERALL XR	42	936.1 (163.1)	N/A	974.7 (178.0)	50.3 (8.93)	4.88 (1.79)	11.87 (2.42)

[a] Unless indicated otherwise, PK studies were conducted under fasted conditions

N/A=Not applicable

Source: Sponsor's Clinical Pharmacology Summary-

Table 11: Comparison of Mean (SD) Pharmacokinetic Parameters for l-Amphetamine from Clinical Studies of Amphetamine ER-OS

Study[a]	N	AUC_{last} (ng·hr/mL)	AUC_{last} /kg (ng·hr/mL/kg)	AUC_{inf} (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{½}$ (hr)
NT0201.1004							
Children (6-7 years old)	9	448.2 (103.7)	17.75 (4.96)	1083 (986.4)	26.6 (4.69)	5.94 (1.91)	24.61 (25.93)
Children (8-9 years old)	10	393.3 (44.38)	12.88 (3.35)	547.9 (105.1)	23.9 (2.41)	6.30 (2.72)	13.07 (3.12)
Children (10-12 years old)	10	305.6 (36.72)	7.976 (2.56)	410.8 (59.26)	20.2 (2.20)	5.55 (1.07)	10.61 (1.03)
NT0201.1005							
Formulation #2	40	354.3 (85.92)	N/A	386.1 (100.1)	16.0 (3.29)	5.40 (0.85)	15.60 (3.13)
ADDERALL XR	42	339.3 (85.44)	N/A	372.2 (104.2)	15.3 (3.32)	4.84 (1.52)	15.63 (3.57)
NT0201.1006							
Amphetamine XR-OS	29	345.7 (71.42)	N/A	370.9 (83.23)	16.4 (2.97)	5.16 (1.02)	14.47 (2.80)
Amphetamine XR-OS - Fed	29	330.5 (63.16)	N/A	357.4 (76.22)	14.6 (2.61)	5.88 (2.16)	14.84 (3.07)
ADDERALL XR - Fed	29	286.6 (54.01)	N/A	308.2 (62.80)	12.8 (2.89)	8.16 (2.61)	14.45 (2.47)
NT0201.1007							
Commercial Scale Formulation Amphetamine XR-OS - Fed	47	316.5 (59.16)	N/A	340.3 (70.46)	13.5 (2.27)	5.60 (2.62)	14.36 (2.65)
Commercial Scale Formulation Amphetamine XR-OS	47	327.3 (54.33)	N/A	353.2 (69.13)	15.2 (2.07)	4.97 (1.11)	14.64 (3.57)
Clinical Trial Formulation Amphetamine XR-OS	47	289.2 (60.63)	N/A	311.6 (74.14)	13.3 (2.30)	5.32 (1.52)	14.72 (3.29)
NT0201.1008							
Commercial Scale Formulation Amphetamine XR-OS	42	325.9 (71.04)	N/A	350.2 (87.02)	14.9 (2.40)	5.13 (1.36)	14.11 (3.52)
ADDERALL XR	42	328.7 (57.78)	N/A	354.8 (70.64)	15.3 (2.66)	4.92 (1.83)	14.56 (3.74)

[a] Unless indicated otherwise, PK studies were conducted under fasted conditions

N/A=Not applicable

Source: Sponsor's Clinical Pharmacology Summary

4. Appendices

4.1 Summary of Bioanalytical Method Validation and Performance

Parameter	d-amphetamine	l-amphetamine
Standard Concentrations (ng/mL)	0.500, 1.00, 2.00, 6.00, 18.0, 40.0, 72.0, 80.0	0.200, 0.400, 0.800, 2.40, 7.20, 16.0, 28.8, 32.0
Linear Range (ng/mL)	0.500 to 80.0	0.200 to 32.0
Correlation Coefficient (r)	0.9945	0.9974
Accuracy Across Standard Curve Concentrations (% bias)	-8.8 – 9.2	-8.8 – 5.0
Recovery (%)	0.500 ng/mL: 97.95% 6.00 ng/mL: 80.97% 80.0 ng/mL: 101.02%	0.200 ng/mL: 90.60% 2.40 ng/mL: 77.12% 32.0 ng/mL: 93.52%
LLOQ (ng/mL)	0.500	0.200
Intra-Batch Precision (%CV) at LLOQ	2.7 – 4.7	6.3 – 9.0
Intra-Batch Accuracy (% bias) at LLOQ	-6.4 – 0.0	-7.0 – 7.0
Inter-Batch Precision (%CV) at LLOQ	4.5	9.2
Inter-Batch Accuracy (% bias) at LLOQ	-3.4	-1.5
QC Concentrations (ng/mL)	Low: 1.50 ng/mL Medium: 10.0 ng/mL High: 64.0 ng/mL	Low: 0.600 ng/mL Medium: 4.00 ng/mL High: 25.6 ng/mL
Intra-Batch Precision (%CV) of Quality Control Samples at Low, Medium, and High	Low: 1.4 - 3.0 Medium: 1.5 - 2.4 High: 0.8 – 1.7	Low: 1.9 – 2.7 Medium:1.5 – 2.9 High: 1.5 – 2.5

Source: Sponsor's Summary of Biopharmaceutics and Analytical methods

Summary of Bioanalytical Method Validation and Performance (contd)

Parameter	d-amphetamine	l-amphetamine
Intra-Batch Accuracy (% bias) of Quality Control Samples at Low, Medium, and High	Low: 2.0 – 6.7 Medium: 6.0 – 10.0 High: -3.8 - -2.5	Low: -0.2 – 3.7 Medium: 0.5 – 6.0 High: -1.2 – 1.2
Inter-Batch Precision (%CV) of Quality Control Samples at Low, Medium, and High	Low: 2.9 Medium: 2.6 High: 1.3	Low: 2.7 Medium: 3.1 High: 2.1
Inter-Batch Accuracy (% bias) of Quality Control Samples at Low, Medium, and High	Low: 4.7 Medium: 8.0 High: -3.0	Low: 1.5 Medium: 3.3 High: 0.0
Selectivity (% bias)	-10.6 - -4.6	-7.5 – 0.0
Stability		
Short-Term Stability	24 h (low and high) at 22°C	24 h (low and high QC) at 22°C
Freeze/Thaw Stability	5 cycles (low and high)	5 cycles (low and high)
Extract Stability	143 hr (low and high) at 4°C	143 hr (low and high) at 4°C
Long-Term Stability		
Dilution Integrity	Up to 400 ng/mL	Up to 160 ng/mL

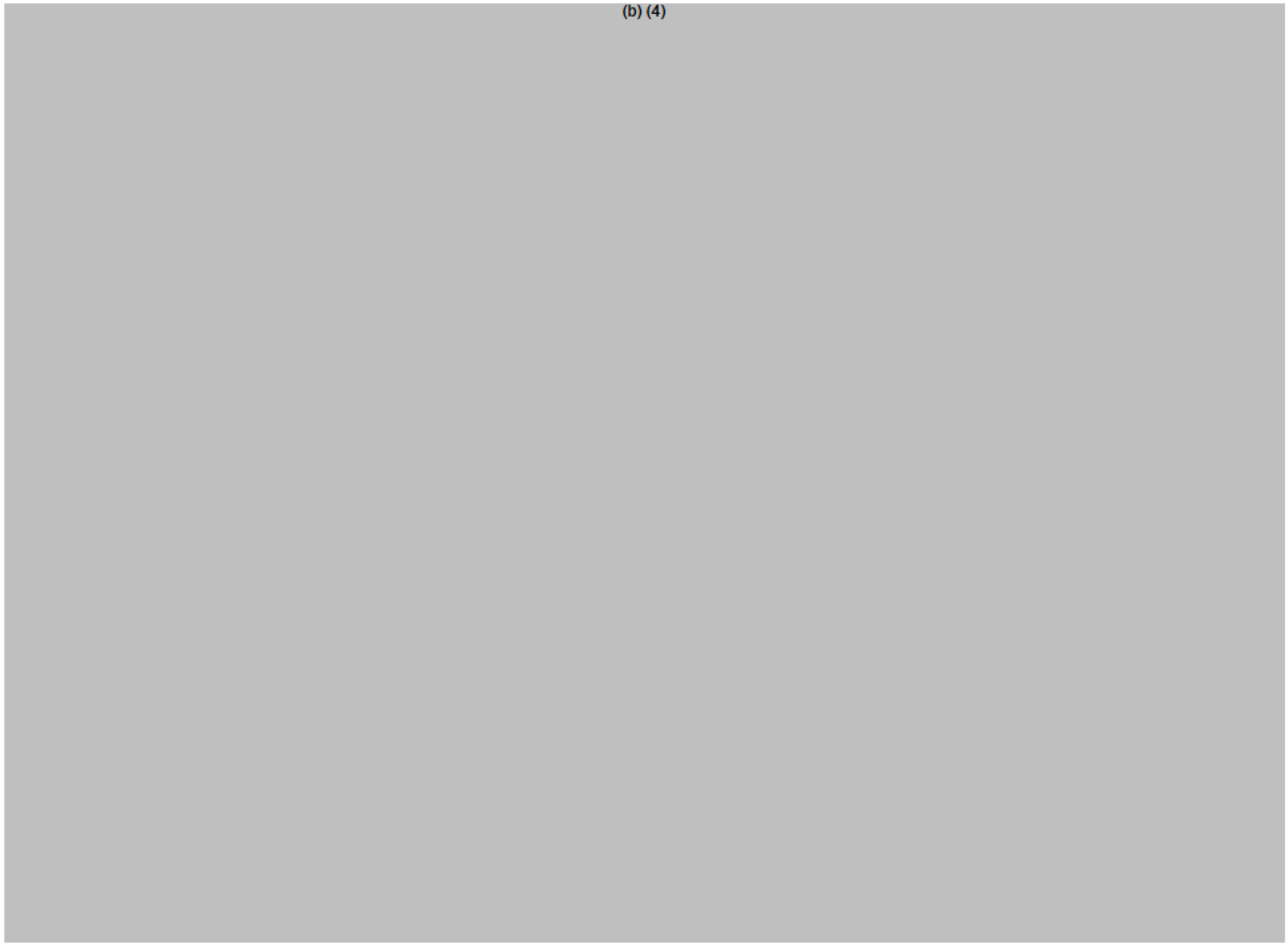
hr = hour(s); LLOQ = lower limit of quantitation; QC = quality control

Source: Sponsor's Summary of Biopharmaceutics and Associated Analytical methods

4.2 Composition of Amphetamine ER-OS Formulation

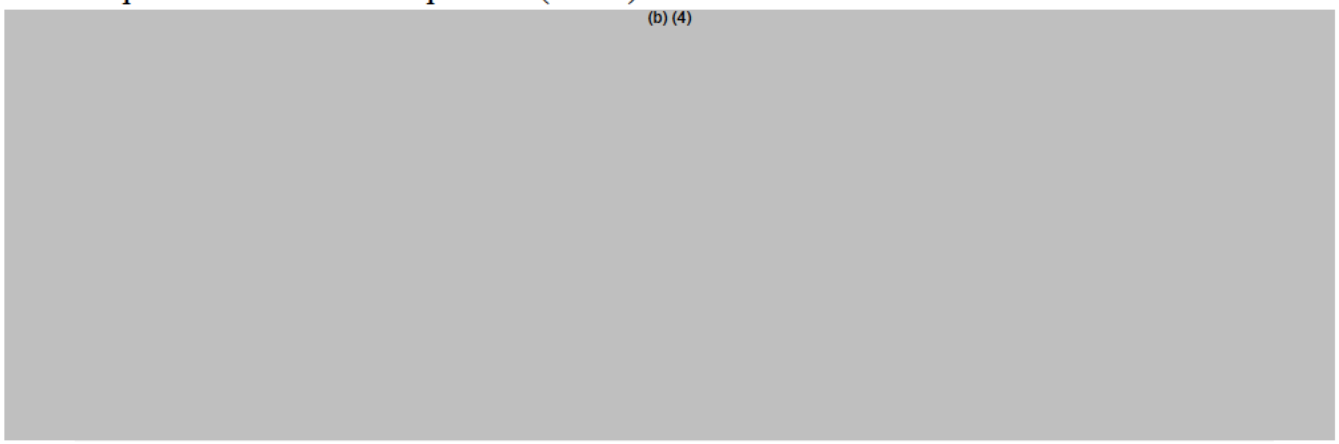
Amphetamine ER-OS Composition

(b) (4)



Amphetamine ER-OS Composition (contd.)

(b) (4)



Source: Summary of Biopharmaceutics Studies and Associated Analytical Methods

4.3 Clinical Pharmacokinetics

4.3.1 Individual Study Reports

Bioavailability Study Review

Report #: NT0201.1008 Study Period: 7/8/16 – 7/17/16

Study Sites: Worldwide Clinical Trials Early Phase Services, LLC

San Antonio, Texas

Analytical Site: (b) (4)

EDR Link: \\CDSESUB1\evsprod\NDA204325\0000

Title: A Single-Dose, Two-Period, Two-Treatment, Two-Way Crossover Bioequivalence Study of Amphetamine Extended-Release Oral Suspension (AMP XR-OS, equivalent to 30 mg Mixed Amphetamine Salts/15 mL) and Adderall Extended-Release 30 mg Capsules under Fasted Conditions

Objective: The objective of this study was to compare the rate of absorption and oral bioavailability of the commercial scale formulation of AMP XR-OS (equivalent to 30 mg mixed amphetamine salts/15 mL) manufactured by Neos Therapeutics, Inc. to an equivalent oral dose of the commercially available reference product, Adderall XR marketed by Shire US Inc., when administered under fasted conditions.

Study Design

Design: A single-dose, open-label, randomized, two-period, two-treatment crossover study in which 42 healthy adult subjects received a single dose of the commercial scale formulation of AMP XR-OS (equivalent to 30 mg mixed amphetamine salts/15 mL) in one period (Treatment A) and a single dose of Adderall XR 30 mg (Treatment B) in another period. Each dose was administered following an overnight fast of at least 10 hours.
Washout Period: at least 7 days
Randomization: AMP XR OS (Treatment A) or Adderall XR 30 mg (RLD, Treatment B)
Number of Subjects: 42 healthy adult subjects
Main Inclusion Criteria: Male or female subjects aged 18 years or older. Female not pregnant or breastfeeding. Body mass index (BMI) was between 18 and 30 kg/m2 (inclusive) and subject weighed a minimum of 50 kg (110 lbs). Vital signs (measured sitting after at least 3 minutes rest) at screening were within the following ranges: heart rate: 40–100 beats per minute [bpm]; systolic blood pressure (BP): 90–145 mmHg; diastolic BP: 50–95 mmHg. Out-of-range vital signs could be repeated once.
Main Exclusion Criteria: Had a clinically significant abnormal finding on the physical exam, medical history, electrocardiogram (ECG), or clinical laboratory results at screening had taken amphetamine or amphetamine-like medications as a treatment for ADHD, depression, etc. or received such medications in a clinical trial or used such medications recreationally, and was

not able to tolerate these medications. Used any over-the-counter (OTC) medication, nutritional or dietary supplements, herbal preparations, or vitamins within 7 days prior to the first dose of medication. Used any prescription medication (including methylxanthines or any known drugs that are moderate or strong inhibitors/inducers of cytochrome P450 [CYP] enzymes such as barbiturates, phenothiazines, cimetidine, carbamazepine, etc.), except hormonal contraceptive or hormonal replacement therapy, within 14 days prior to the first dose of study medication. Was unable to refrain from beverages and foods containing alcohol, grapefruit, or caffeine/xanthine from 48 hours prior to the first dose of study medication until the end-of-study visit.

Treatments

	Test (AMP OS XR)-Treatment A	Reference (Adderall XR)-Treatment B
Dosage Form	Oral Liquid Suspension	Extended Release Capsule
Dosage Strength	30 mg/15 mL	30 mg
Lot #	4E057B	AE9594A
Method of Administration	Oral Fasting	Oral Fasting

PK Sampling Times: Blood samples (1 x 4 mL) were collected at 0 (predose) and at 1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, and 60.0 hours after dosing.

Analytical method: LC/MS/MS

The method was validated for a range of 0.500 to 80.0 ng/mL for *d*-amphetamine and 0.200 to 32.0 ng/mL for *l*-amphetamine based on the analysis of 0.150 mL of plasma.

Linearity and Standard Curves

Analyte	Slope	Intercept	R^2
D-Amphetamine	0.169130619	0.013368062	0.9945
L-Amphetamine	0.218717293	0.001163350	0.9974

Precision and Accuracy

Analyte	CV		Bias	
	From	To	From	To
D-Amphetamine	0.5%	1.6%	-8.8%	9.2%
L-Amphetamine	0.5%	1.6%	-8.8%	5.0%

LLOQ Evaluation

Analyte	Intrarun				Inter-run	
	CV		Bias		CV	Bias
	From	To	From	To		
D-Amphetamine	2.7%	4.7%	-6.4%	0.0%	4.5%	-3.4%
L-Amphetamine	6.3%	9.0%	-7.0%	7.0%	9.2%	-1.5%

QC Evaluation

Analyte	Intrarun				Inter-run			
	CV		Bias		CV		Bias	
	From	To	From	To	From	To	From	To
D-Amphetamine	0.8%	3.0%	-3.8%	10.0%	1.3%	2.9%	-3.0%	8.0%
L-Amphetamine	1.5%	2.9%	-1.2%	6.0%	2.1%	3.1%	0.0%	3.3%

Recovery

Analyte	From	To	Internal Standard	From	To
D-Amphetamine	80.97%	101.02%	D-Amphetamine-D_5	73.28%	111.31%
L-Amphetamine	77.12%	93.52%	L-Amphetamine-D_5	68.44%	104.36%

The analytical method is acceptable

Moieties to be Measured: Blood samples were obtained to determine the pharmacokinetic profile and exposure of *d*-amphetamine and *l*-amphetamine after each treatment.
Protocol Deviations: The sponsor reported no significant protocol deviations during the conduct of the study.
Statistical Analysis: The concentration-time data for *d*-amphetamine and *l*-amphetamine were analyzed by noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3 or higher, Pharsight Corporation) WinNonlin.

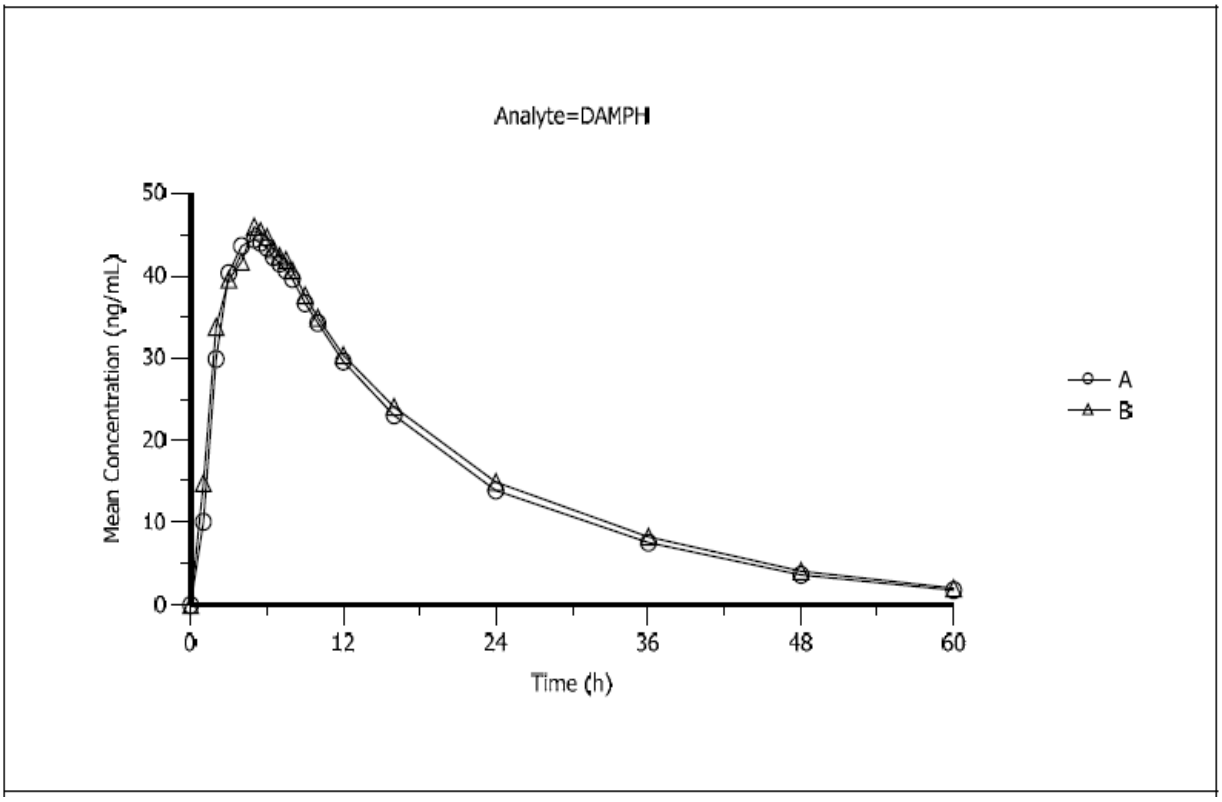
Results

Study Population

Randomized/Completed/Discontinued due to AE	42/42/0
Mean Age [Median (range)] years	43.7 [45(20,70)]
Male/Female	19/23
Race (Caucasian/Black/Other)	28/11/3
Mean weight (±SD) kg	76.44 (11.40)
BMI (±SD) kg/m^2	26.61 (2.44)

The mean plasma concentration-time profile for d-amphetamine is provided in the following figure. The pharmacokinetic parameters and statistical analysis are provided in the following tables

Mean *d*-amphetamine Concentration-Time Profiles after Administration of AMP XR-OS (Treatment A) and Adderall XR (Treatment B)



Pharmacokinetic Parameters of d-amphetamine

Parameter	Treatment A, Test Formulation: AMP XR-OS				Treatment B, Reference Product: Adderall XR			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	42	5.00 (3.00, 7.50)			42	5.00 (2.00, 12.00)		
C_{max} (ng/mL)	42	47.2	7.68	16.26	42	50.3	8.93	17.74
AUC_{0-5} (h*ng/mL)	42	145.9	36.18	24.80	42	152.6	48.11	31.53
AUC_{5-last} (h*ng/mL)	42	745.7	175.8	23.58	42	783.5	152.7	19.49
AUC_{last} (h*ng/mL)	42	891.6	188.7	21.16	42	936.1	163.1	17.42
AUC_{inf} (h*ng/mL)	42	925.2	209.0	22.59	42	974.7	178.0	18.26
AUC_{Extrap} (%)	42	3.37	1.95	57.76	42	3.82	2.11	55.18
λ_z (h^{-1})	42	0.0632	0.0131	20.75	42	0.0608	0.0124	20.35
$T_{1/2}$ (h)	42	11.41	2.27	19.92	42	11.87	2.42	20.42
T_{last} (h)	42	59.15	3.13	5.29	42	59.16	4.10	6.94
C_{last} (ng/mL)	42	1.87	1.10	58.74	42	2.11	1.06	50.32

Note: T_{max} presented as Median (Min, Max)

Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of *d*-amphetamine

Dependent Variable	Geometric Mean[a] Test	Ref	Ratio (%)[b] (Test/Ref)	90% CI[c] Lower	Upper	Power	ANOVA CV%
$\ln(C_{max})$	46.5761	49.5015	94.09	92.32	95.90	1.0000	5.18
$\ln(AUC_{0-5})$	141.4171	144.7649	97.69	92.02	103.71	1.0000	16.39
$\ln(AUC_{5-last})$	727.0251	769.0353	94.54	91.27	97.92	1.0000	9.58
$\ln(AUC_{inf})$	904.1140	959.4967	94.23	91.50	97.04	1.0000	8.01

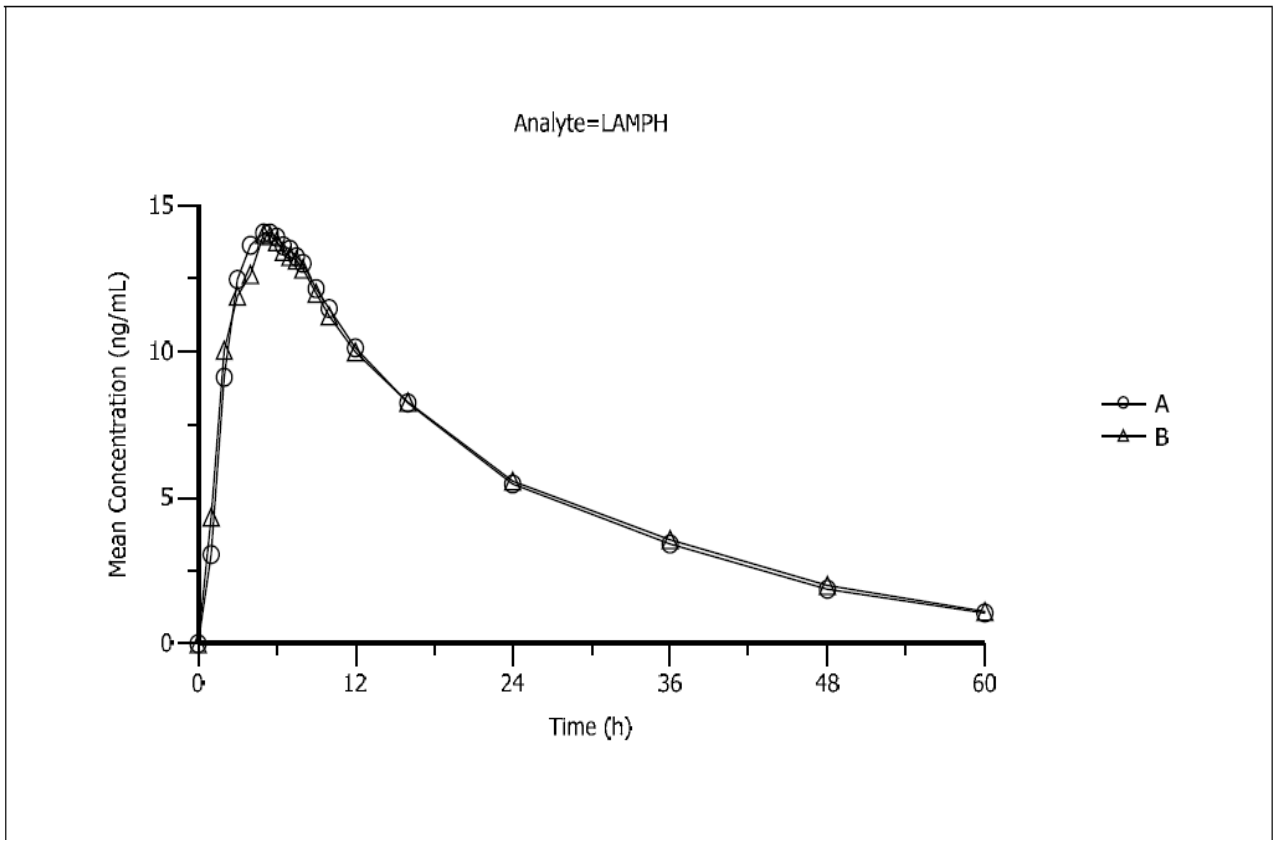
[a] Geometric Mean for AMP XR-OS (Test) and Adderall XR (Ref) based on Least Squares Mean of log-transformed parameter values

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

[c] 90% Confidence Interval

The mean plasma concentration-time profile for l-amphetamine is provided in the following figure. The pharmacokinetic parameters and statistical analysis are provided in the following tables

Mean *l*-amphetamine Concentration-Time Profiles after Administration of AMP XR-OS (Treatment A) and Adderall XR (Treatment B)



Pharmacokinetic Parameters of *l*-amphetamine

Parameter	Treatment A, Test Formulation: AMP XR-OS				Treatment B, Reference Product: Adderall XR			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	42	5.00 (3.00, 8.00)			42	5.00 (2.00, 12.00)		
C_{max} (ng/mL)	42	14.9	2.40	16.09	42	15.3	2.66	17.39
AUC_{0-5} (h*ng/mL)	42	45.24	11.38	25.16	42	45.85	14.69	32.04
AUC_{5-last} (h*ng/mL)	42	280.6	67.60	24.09	42	282.9	54.23	19.17
AUC_{last} (h*ng/mL)	42	325.9	71.04	21.80	42	328.7	57.78	17.58
AUC_{inf} (h*ng/mL)	42	350.2	87.02	24.85	42	354.8	70.64	19.91
AUC_{Extrap} (%)	42	6.30	3.76	59.64	42	6.94	3.90	56.16
λ_z (h^{-1})	42	0.0522	0.0131	25.03	42	0.0505	0.0120	23.83
$T_{1/2}$ (h)	42	14.11	3.52	24.95	42	14.56	3.74	25.69
T_{last} (h)	42	59.72	1.85	3.10	42	59.16	4.10	6.94
C_{last} (ng/mL)	42	1.06	0.621	58.67	42	1.13	0.537	47.41

Note: T_{max} presented as Median (Min, Max)

Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of *l*-amphetamine

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	14.7245	15.0694	97.71	95.91	99.55	1.0000	5.07
$\ln(AUC_{0-5})$	43.8159	43.4199	100.91	95.07	107.11	1.0000	16.33
$\ln(AUC_{5-last})$	272.9836	277.7308	98.29	94.83	101.87	1.0000	9.77
$\ln(AUC_{inf})$	340.2570	348.2751	97.70	94.54	100.96	1.0000	8.96

[a] Geometric Mean for AMP XR-OS (Test) and Adderall XR (Ref) based on Least Squares Mean of log-transformed parameter values

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

[c] 90% Confidence Interval

Pharmacokinetic Summary

For the comparison of the commercial scale formulation of AMP XR-OS (Treatment A) and the commercially available reference product, Adderall XR® (Treatment B), the 90% confidence intervals for the log-transformed Cmax, AUC(0-5), AUC(5-last), and AUC(0-inf) fell within the accepted 80%- 125% range for establishing bioequivalence for *d*- and *l*-amphetamine.

Safety Summary

The sponsor reported that a total of 12 AEs were reported by eight subjects over the course of the study. All AEs were mild in severity and occurred post dose. Six subjects (14.3%) reported an AE following Treatment A (AMP XR-OS) and five subjects (11.9%) reported an AE following Treatment B (Adderall XR). All AEs except one (muscle spasms unrelated to study treatment) resolved without intervention. The most commonly reported AEs were nausea (n=3; one subject following Treatment A and two subjects following Treatment B) and decreased appetite (n=3; two subjects following Treatment A and one subject following Treatment B). The sponsor reported that no clinically significant observations or changes in safety parameters were identified in the subject population during the study conduct.

Conclusion:

The 90% confidence intervals for the log-transformed Cmax, AUC(0-5), AUC(5-last), and AUCinf fell within the accepted 80%-125% range for establishing bioequivalence for *d*- and *l*-amphetamine. Therefore, the commercial scale formulation of AMP XR-OS (equivalent to 30 mg mixed amphetamine salts/15 mL) is bioequivalent to the reference product, Adderall XR® Capsule, 30 mg marketed by Shire US Inc., when administered under fasted conditions.

Reviewer Comments

1. *Study design: The study was conducted according to the protocol. The design of the study is consistent with recommendations in the Agency's draft guidance on Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs- General Considerations*

2. *Study conduct: No apparent protocol deviation that will affect the PK assessment has been identified.*
3. *Study analysis: All subjects completed the study and there were no discontinuations due to adverse events. Visual inspection of the pharmacokinetic profiles and pharmacokinetic data did not indicate there were outliers; all subjects were included in the pharmacokinetic analysis.*
4. *Study results: The reviewer agrees with the Sponsor's conclusion that Treatment A (30 mg AMP XR-OS) is bioequivalent to Treatment B (30 mg Adderall XR capsules). The 90% CIs of the mean ratios of AUC, Cmax and defined pAUCs are within the BE limits. In addition, the shape of the pharmacokinetic profiles for both d- and l- amphetamine are superimposable between the oral solution and the LD.*

Clinical Study Review- Food Effect

Report #: NT0201.1007	Study Period: 1/6/13 – 1/22/13
Study Sites:	Worldwide Clinical Trials Early Phase Services, LLC San Antonio, Texas
Principal Investigator:	Vanessa Smeberg, MD
Analytical Site:	(b) (4)
Bioanalytical Study Manager	(b) (4) BA

EDR Link: \\CDSESUB1\evsprod\NDA204325\0000

Title: A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Bioavailability Study of a Commercial Scale Formulation of Amphetamine Extended-Release Oral Suspension (AMP XR OS, equivalent to 30 mg Mixed Amphetamine Salts/15 mL) under Fed and Fasted Conditions and a Clinical Trial Formulation of AMP XR OS (equivalent to 30 mg Mixed Amphetamine Salts/15 mL) under Fasted Conditions

Objective: To compare the rate of absorption and oral bioavailability of the commercial scale formulation AMP XR OS (equivalent to 30 mg mixed amphetamine salts/15 mL) under fasted conditions to the previously studied clinical trial formulation AMP XR OS (equivalent to 30 mg mixed amphetamine salts/15 mL) under fasted conditions. Additionally, the rate of absorption and oral bioavailability of a commercial scale formulation of AMP XR OS (equivalent to 30 mg mixed amphetamine salts/15 mL) under fed and fasted conditions were compared to determine if a food effect was observed.

Study Design

Design: Single-dose, open-label, randomized, three-period, three-treatment crossover study in which 48 healthy adult subjects were scheduled to receive a single dose of the commercial scale formulation of AMP XR OS (formulation 1) under fed conditions in one period (Treatment A), a single dose of AMP XR OS (formulation 1) under fasted conditions in another period (Treatment B), and a single dose of the clinical trial formulation of AMP XR OS (formulation 2) under fasted conditions in a different period (Treatment C). Treatment A was administered after a 10-hour overnight fast followed by ingestion of FDA standard high-fat, high-calorie breakfast beginning 30 minutes before treatment administration. Treatments B and C were administered following an overnight fast of at least 10 hours.	
Screening:	Washout Period: 7 days
Randomization: Commercial scale formulation of AMP XR OS (formulation 1) under fed conditions (Treatment A) or AMP XR OS (formulation 1) under fasted conditions (Treatment B), or Clinical trial formulation of AMP XR OS (formulation 2) under fasted conditions (Treatment	

C).

Number of Subjects: 48; 46 completed study. Two subjects were withdrawn for non-safety related reasons

Treatments

	Treatment A: Commercial Scale Mixed Amphetamine Resins Oral Suspension (Form. 1) under fed conditions	Treatment B: Commercial Scale Mixed Amphetamine Resins Oral Suspension (Form 1) under fasting conditions	Treatment C: Clinical Trial Formulation of Mixed Amphetamine Resins Oral Suspension under (Form 2) fasting conditions
Dosage Form	Oral Liquid Suspension	Oral Liquid Suspension	Oral Liquid Suspension
Dosage Strength	30 mg/15 mL	30 mg/15 mL	30 mg/15 mL
Lot #:	4E057B	4E057B	2E083E2
Method of Administration	Oral	Oral	Oral
Manufacturer	Neos Therapeutics	Neos Therapeutics	Neos Therapeutics

PK Sampling Times: Blood samples (1 x 4 mL) were collected at 0 (predose) and at 1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, and 60.0 hours after dosing.

Analytical Method: The method was validated for a range of 0.500 to 80.0 ng/mL for *d*-amphetamine and 0.200 to 32.0 ng/mL for *l*-amphetamine based on the analysis of 0.150 mL of plasma.

Moieties to be Measured: Blood samples were obtained to determine the pharmacokinetic profile and exposure of *d*-amphetamine and *l*-amphetamine after each treatment.

Protocol Deviations: Two deviations occur for non-safety reasons. One subject was withdrawn for non-compliance and the 2nd subject for personal reasons.

Statistical Analysis: The concentration-time data for *d*-amphetamine and *l*-amphetamine were analyzed by noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3 or higher, Pharsight Corporation). Bioequivalence of the commercial scale formulation (fasted) [Test] vs. clinical trial formulation (fasted) [Reference] (Treatment B vs. Treatment C) was established if the 90% confidence intervals for log-transformed Cmax, AUC0-5, AUC5-last, and AUCinf fell within the accepted 80%-125% range. A lack of significant food effect of the Commercial Scale (fed) [Test] vs. Commercial Scale (fasted) [Reference] (Treatment A vs. Treatment B) was established if the log-transformed pharmacokinetic parameters Cmax, AUClast, and AUCinf fell within the accepted 80% to 125% range; the partial areas AUC0-5 and AUC5-last were included in the food effect assessment as exploratory endpoints.

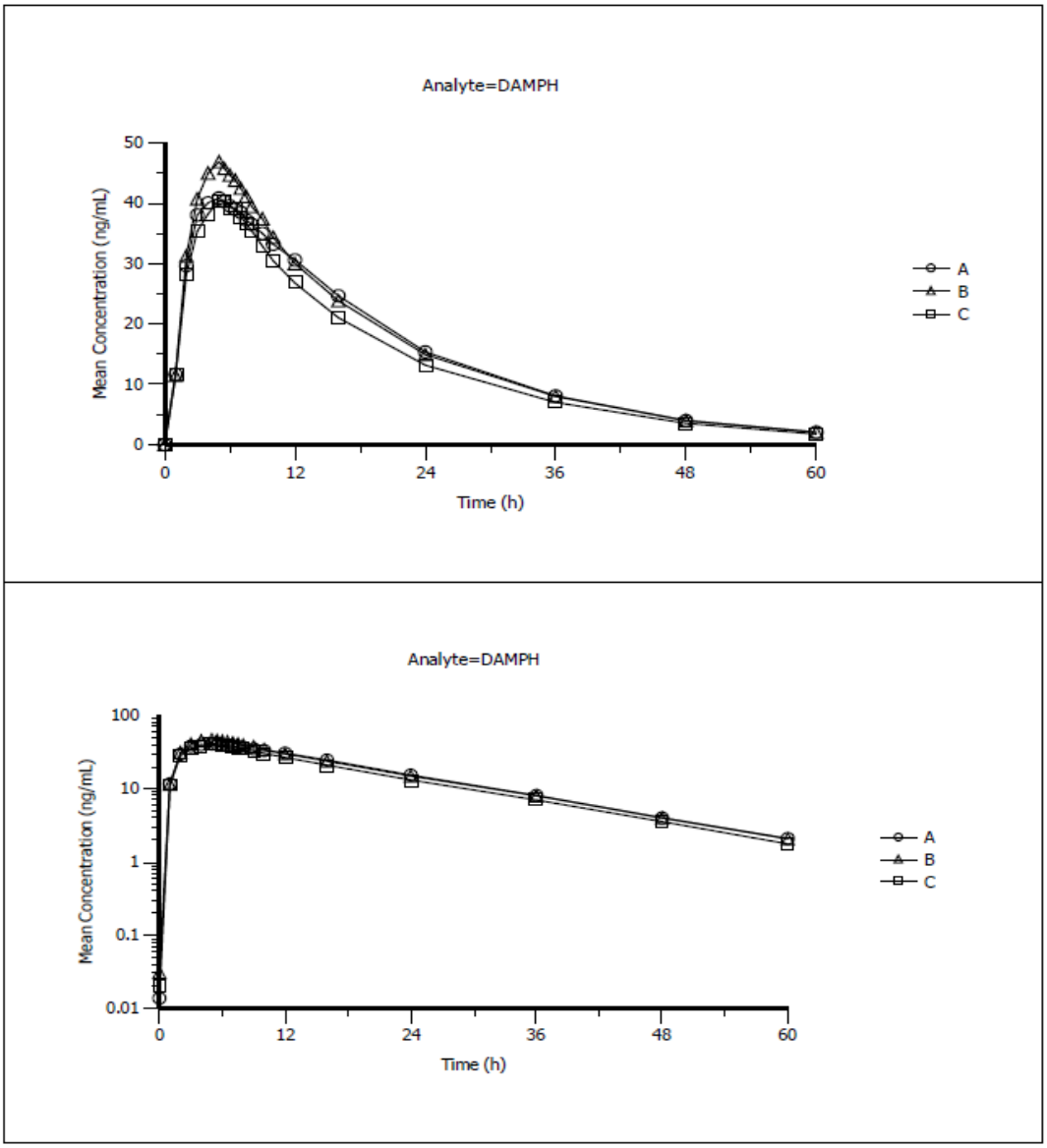
Results

Study Population

Randomized/Completed/Discontinued due to AE	48/46/0
Mean ±SD Age [Median (range)] years	46 ± 15.8 [48.5 (19, 73)]
Male/Female	21/27
Race (Caucasian/Black/Asian/Other)	31/13/2/2
Mean Weight (± SD) kg	72.3 ±10.75 [54.1, 97.5]
BMI (±SD) kg/m^2	25.76 ±2.76

D-amphetamine

Mean *d*-amphetamine Concentration-Time Profiles after Administration of AMP XR OS under Fed Conditions (Treatment A, Formulation 1), AMP XR OS under Fasted Conditions (Treatment B, Formulation 1), and AMP XR OS under Fasted Conditions (Treatment C, Formulation 2)



Pharmacokinetic Parameters of *d*-amphetamine

Parameter	Treatment A, Formulation 1: AMP XR OS Fed				Treatment B, Formulation 1: AMP XR OS Fasted				Treatment C, Formulation 2: AMP XR OS Fasted			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)*	47	5.00 (2.00, 12.00)			47	5.00 (3.00, 7.00)			47	5.08 (2.00, 12.00)		
C_{max} (ng/mL)	47	43.2	7.16	16.56	47	48.6	6.55	13.47	47	42.6	7.59	17.83
AUC_{0-5} (h*ng/mL)	47	139.7	35.20	25.20	47	151.8	30.25	19.93	47	133.4	32.25	24.18
AUC_{5-last} (h*ng/mL)	47	771.4	152.3	19.75	47	778.4	137.5	17.66	47	687.5	155.9	22.68
AUC_{last} (h*ng/mL)	47	911.1	157.0	17.23	47	930.1	144.0	15.48	47	820.9	162.0	19.73
AUC_{inf} (h*ng/mL)	47	949.4	174.3	18.36	47	969.4	164.4	16.96	47	854.3	179.6	21.02
AUC_{Extrap} (%)	47	3.81	1.76	46.26	47	3.80	2.13	55.94	47	3.66	1.87	51.04
λ_z (h^{-1})	47	0.0595	0.0097	16.22	47	0.0597	0.0119	19.97	47	0.0592	0.0103	17.41
$T_{1/2}$ (h)	47	11.94	1.88	15.72	47	12.09	2.53	20.92	47	12.07	2.14	17.74
T_{last} (h)	47	60.01	0.07	0.12	47	60.00	0.01	0.02	47	59.75	1.75	2.93
C_{last} (ng/mL)	47	2.09	0.988	47.18	47	2.07	1.04	50.01	47	1.79	0.918	51.32

*T_{max} presented as Median (Min, Max)

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine comparing the Commercial Formulation of AMP XR OS under Fed Conditions (Treatment A, Formulation 1) to the Commercial Formulation of AMP XR OS under Fasted Conditions (Treatment B, Formulation 1)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b] (Test/Ref)	90% CI[c]		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
$ln(C_{max})$	42.4585	47.8960	88.65	86.34	91.02	1.0000	7.71
$ln(AUC_{0-5})$	134.6968	148.3976	90.77	85.34	96.54	1.0000	18.13
$ln(AUC_{5-last})$	754.9487	765.2341	98.66	94.68	102.79	1.0000	12.02
$ln(AUC_{last})$	895.9045	917.3565	97.66	94.44	100.99	1.0000	9.80
$ln(AUC_{inf})$	931.5679	953.8341	97.67	94.30	101.15	1.0000	10.24

[a] Geometric Mean for AMP XR OS-Fed, Formulation 1 (Test) and AMP XR OS-Fasted, Formulation 1 (Ref) based on Least Squares Mean of log-transformed parameter values

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

[c] 90% Confidence Interval

For the comparison of the commercial scale formulation under fasted and fed conditions, the 90% confidence intervals for C_{max}, AUC_{0-5}, AUC_{5-last}, AUC_{last}, and AUC_{inf} fell within the accepted 80%-125% range for *d*--amphetamine. The presence of food did affect Tmax.

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine comparing the Commercial Formulation of AMP XR OS under Fasted Conditions (Treatment B, Formulation 1) to the Clinical Trail Formulation of AMP XR OS under Fasted Conditions (Treatment C, Formulation 2)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	47.8960	41.7602	114.69	111.69	117.78	1.0000	7.71
$\ln(AUC_{0-5})$	148.3976	129.5820	114.52	107.64	121.84	1.0000	18.13
$\ln(AUC_{5-last})$	765.2341	670.5131	114.13	109.51	118.94	1.0000	12.02
$\ln(AUC_{inf})$	953.8341	835.9408	114.10	110.15	118.20	1.0000	10.24

[a] Geometric Mean for AMP XR OS-Fasted, Formulation 1 (Test) and AMP XR OS-Fasted, Formulation 2 (Ref) based on Least Squares Mean of log-transformed parameter values

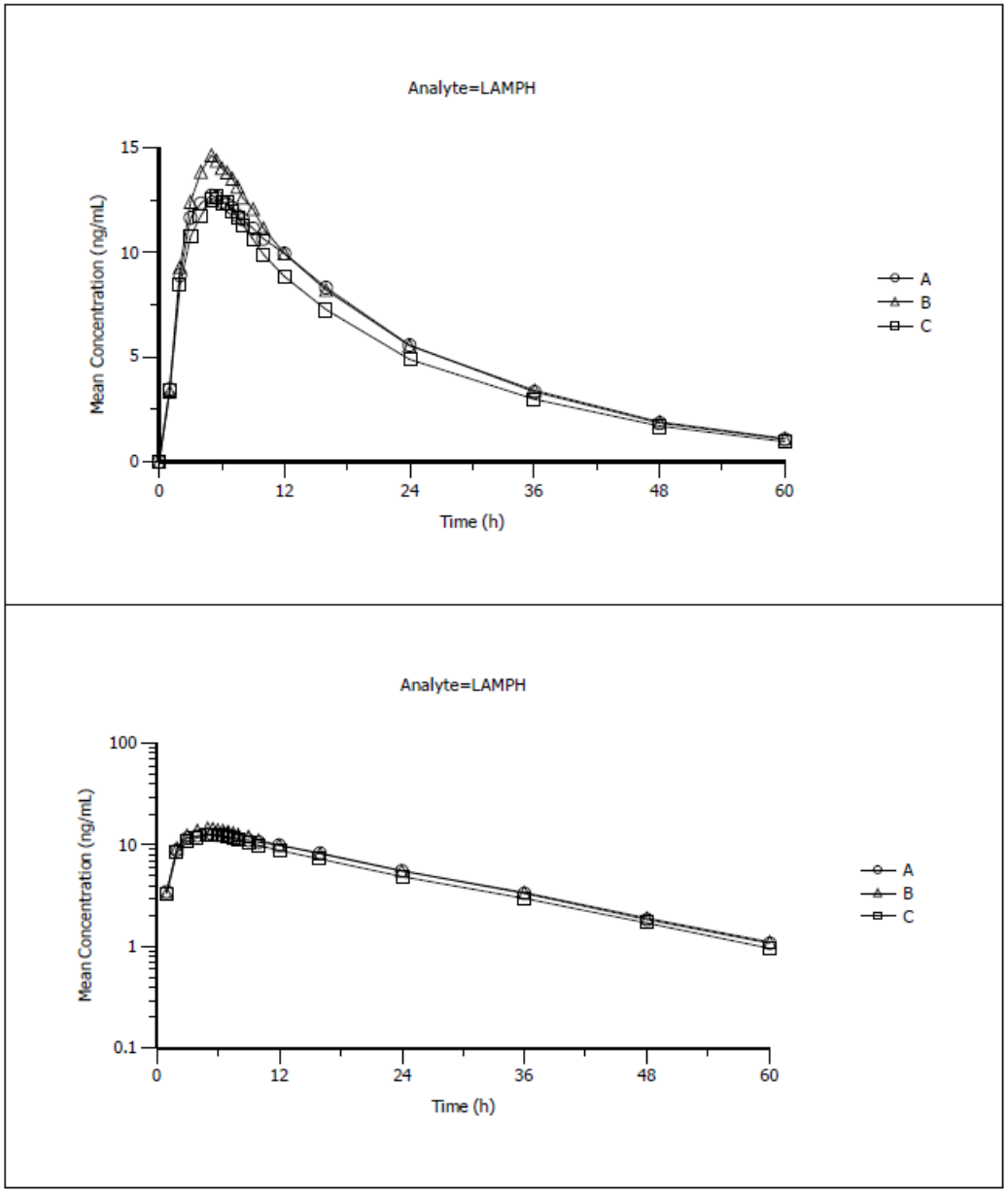
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

[c] 90% Confidence Interval

For the comparison of the commercial scale formulation (Treatment B) and the clinical trial formulation (Treatment C), the 90% confidence intervals for the log-transformed Cmax, AUC(0-5), AUC(5-last), and AUCinf fell within the accepted 80%-125% range for establishing bioequivalence for *d*-amphetamine.

L-amphetamine

Mean *l*-amphetamine Concentration-Time Profiles after Administration of AMP XR OS under Fed Conditions (Treatment A, Formulation 1), AMP XR OS under Fasted Conditions (Treatment B, Formulation 1), and AMP XR OS under Fasted Conditions (Treatment C, Formulation 2)



Pharmacokinetic Parameters of *l*-amphetamine

Parameter	Treatment A, Formulation 1: AMP XR OS Fed				Treatment B, Formulation 1: AMP XR OS Fasted				Treatment C, Formulation 2: AMP XR OS Fasted			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)*	47	5.03 (3.00, 16.00)			47	5.00 (3.00, 7.00)			47	5.50 (2.00, 12.00)		
C_{max} (ng/mL)	47	13.5	2.27	16.75	47	15.2	2.07	13.60	47	13.3	2.30	17.24
AUC_{0-5} (h*ng/mL)	47	42.68	11.00	25.77	47	46.17	9.306	20.16	47	40.53	9.960	24.57
AUC_{5-last} (h*ng/mL)	47	273.8	57.64	21.05	47	281.1	52.36	18.62	47	248.6	59.05	23.75
AUC_{last} (h*ng/mL)	47	316.5	59.16	18.69	47	327.3	54.33	16.60	47	289.2	60.63	20.97
AUC_{inf} (h*ng/mL)	47	340.3	70.46	20.70	47	353.2	69.13	19.58	47	311.6	74.14	23.80
AUC_{Extrap} (%)	47	6.59	3.00	45.54	47	6.77	3.82	56.44	47	6.59	3.45	52.25
λ_z (h^{-1})	47	0.0500	0.0095	19.04	47	0.0499	0.0116	23.27	47	0.0493	0.0104	21.10
$T_{1/2}$ (h)	47	14.36	2.65	18.45	47	14.64	3.57	24.36	47	14.72	3.29	22.33
T_{last} (h)	47	60.01	0.07	0.12	47	60.00	0.01	0.02	47	60.00	0.01	0.02
C_{last} (ng/mL)	47	1.08	0.501	46.47	47	1.11	0.549	49.52	47	0.961	0.497	51.72

*T_{max} presented as Median (Min, Max)

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *l*-amphetamine comparing Commercial Formulation of AMP XR OS under Fed Conditions (Treatment A, Formulation 1) to the Commercial Formulation of AMP XR OS under Fasted Conditions (Treatment B, Formulation 1)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	13.2876	15.0062	88.55	86.11	91.05	1.0000	8.14
$ln(AUC_{0-5})$	41.0935	45.0998	91.12	85.50	97.10	1.0000	18.71
$ln(AUC_{5-last})$	267.4489	276.1140	96.86	92.81	101.09	1.0000	12.52
$ln(AUC_{last})$	310.5830	322.4308	96.33	92.92	99.85	1.0000	10.51
$ln(AUC_{inf})$	332.6667	346.1557	96.10	92.39	99.96	1.0000	11.51

[a] Geometric Mean for AMP XR OS-Fed, Formulation 1 (Test) and AMP XR OS-Fasted, Formulation 1 (Ref) based on Least Squares Mean of log-transformed parameter values

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

[c] 90% Confidence Interval

For the comparison of the commercial scale formulation under fasted and fed conditions, the 90% confidence intervals for C_{max}, AUC_{0-5}, AUC_{5-last}, AUC_{last}, and AUC_{inf} fell within the accepted 80%-125% range for l--amphetamine. The presence of food did affect Tmax.

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *l*-amphetamine comparing the Commercial Formulation of AMP XR OS under Fasted Conditions (Treatment B, Formulation 1) to the Clinical Trail Formulation of AMP XR OS under Fasted Conditions (Treatment C, Formulation 2)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	15.0062	13.0520	114.97	111.79	118.24	1.0000	8.14
$\ln(AUC_{0-5})$	45.0998	39.3136	114.72	107.62	122.28	1.0000	18.71
$\ln(AUC_{5-last})$	276.1140	241.6469	114.26	109.45	119.29	1.0000	12.52
$\ln(AUC_{inf})$	346.1557	302.8299	114.31	109.87	118.92	1.0000	11.51

[a] Geometric Mean for AMP XR OS-Fasted, Formulation 1 (Test) and AMP XR OS-Fasted, Formulation 2 (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

For the comparison of the commercial scale formulation (Treatment B) and the clinical trial formulation (Treatment C), the 90% confidence intervals for the log-transformed Cmax, AUC(0-5), AUC(5-last), and AUCinf fell within the accepted 80%-125% range for establishing bioequivalence for l-amphetamine. The exposure after administration of the commercial formulation compared to the clinical trial formulation is not clinically significant.

Pharmacokinetic Summary
The 90% confidence intervals for Cmax, AUC(0-5), AUC(5-last), AUClast, and AUCinf fell within the accepted 80%-125% range for *d*- and *l*-amphetamine. Therefore, there is no significant food effect on the pharmacokinetic parameters of *d*- and *l*-amphetamine after administrations of commercial scale formulation of AMP XR OS (equivalent to 30 mg mixed amphetamine salts/15 mL, Formulation 1). The 90% confidence intervals for Cmax, AUC0-5, AUC5-last, and AUCinf fell within the accepted 80%-125% range for establishing bioequivalence for *d*- and *l*-amphetamine. Therefore, the commercial scale formulation (Treatment B, Formulation 1) of AMP XR OS (equivalent to 30 mg mixed amphetamine salts/15 mL) is bioequivalent to the clinical trial formulation (Treatment C, Formulation 2) of AMP XR OS (equivalent to 30 mg mixed amphetamine salts/15 mL) under fasted conditions.

Safety Summary

The sponsor reported that a total of 26 AEs were reported by 12 subjects following dose administration. Of these 26 treatment-emergent AEs (TEAEs), three were judged to be moderate in severity and the remainder was determined to be mild in severity. None of the TEAEs were considered serious or led to a subject discontinuation. Five subjects (10.6%) reported a TEAE following Treatment A (AMP XR OS 30 mg [Formulation 1], fed), four subjects (8.5%) following Treatment B (AMP XR OS 30 mg [Formulation 1], fasted), and eight subjects (17.0%) following Treatment C (AMP XR OS 30 mg [Formulation 2], fasted). The most commonly reported TEAEs were euphoric mood (n = 5; two following Treatment A, one following

Treatment B, and two following Treatment C) and headache (n=4; two following Treatment A and two following Treatment C). The sponsor reported that no deaths, serious AEs, or other significant AEs occurred during the conduct of the study.

Reviewer Comments

The reviewer agrees with the sponsor's conclusions. Food does not have significant effect on the pharmacokinetics of d- and l-amphetamine after administration of Amphetamine Oral Suspension. Tmax was similar when Amphetamine Oral Suspension was administered with food or under fasting conditions. Even though there was about a 10% decrease in Cmax when Amphetamine Oral Suspension is taken with food, this decrease is not expected to be significant. The clinical trial formulation was equivalent to the commercial formulation. The partial AUCs evaluated were acceptable and consistent with the amphetamine guidance.

1. *Study design: The design of the study was consistent with the recommendations in the food effect and the Adderall XR guidances. The type of food evaluated was the standard FDA high fat meal.*
2. *Study conduct: There is no protocol deviation that will compromise the study results.*
3. *Data analysis: There were no outliers in results and no one was dropped from the analysis.*
4. *Study results: The study results are acceptable.*

Clinical Study Review- Food Effect

Report #: NT0201.1006	Study Period: 1/6/13 – 1/22/13
Study Sites:	Worldwide Clinical Trials Early Phase Services, LLC San Antonio, Texas
Principal Investigator:	Nancy Hinitt, MD
Analytical Site:	(b) (4)
Bioanalytical Manager:	(b) (4), BA

EDR Link: \\CDSESUB1\evsprod\NDA204325\0000

Title: A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Food Effect Study of an Investigational Formulation of Amphetamine Polistirex Extended Release Oral Liquid Suspension (Equivalent to 30 mg Mixed Amphetamine Salts/15 mL) and Adderall XR® 30 mg Capsule

Objective: 1) To assess the effect of food on the rate of absorption and oral bioavailability of an investigational formulation of NT0201 Amphetamine Polistirex XR OLS (equivalent to 30 mg mixed amphetamine salts/15 mL) developed by Neos Therapeutics, Inc.; and
2) To compare the rate of absorption and oral bioavailability of NT0201 Amphetamine Polistirex XR OLS to an equivalent 30 mg oral dose of the commercially available reference product, Adderall XR (Shire US Inc.).

Study Design

Design: Single-dose, open-label, randomized, three-period, three-treatment crossover study in which subjects received one single-dose administration of NT0201 Amphetamine Polistirex XR OLS (equivalent to 30 mg mixed amphetamine salts/15 mL) under fasted conditions, one single-dose administration of NT0201 Amphetamine Polistirex XR OLS under fed conditions, and one single-dose administration of the RLD, Adderall XR, under fed conditions. Subjects who received the fasted treatment continued to fast up until the time that they were dosed.

Subjects in all three treatment conditions fasted overnight for at least 10 hours. Subjects who received either of the treatments under fed conditions were dosed 5 minutes after completing consumption of a Food and Drug Administration (FDA) standard high-calorie, high-fat breakfast meal; consumption of the high-fat breakfast began 30 minutes prior to dosing. Subjects who received the fasted treatment continued to fast up until the time that they were dosed. Each dose administration was separated by a washout period of at least 7 days.

Washout Period: 7 days
Randomization: Amphetamine XR OLS fasted, Amphetamine XR OLS fed, Adderall XR fed (1:1:1)
Number of Subjects: 30
Main Inclusion Criteria: Healthy adult male or non-pregnant, non-breastfeeding female volunteers, ≥18 years of age, with body mass index (BMI) between 18 and 30 kg/m2 (inclusive) and minimum weight of 50 kg (110 lbs).
Main Exclusion Criteria: History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results. History or presence of tics or Tourette's syndrome Had used any prescription medication (including methylxanthines or any known drugs that are moderate or strong inhibitors/inducers of CYP enzymes such as barbiturates, phenothiazines, cimetidine, carbamazepine, etc.), except hormonal contraceptive or hormonal replacement therapy, within 30 days prior to the first dose of study medication. Had smoked or used tobacco products within 60 days prior to the first dose of study medication;
Treatments Test Formulation: Treatment A/B NT0201 Amphetamine Polistirex Extended Release (XR) Oral Liquid Suspension (OLS) Equivalent to 30 mg/15 mL Mixed Amphetamine Salts Dose = 1 x 15 mL oral liquid suspension Neos Therapeutics, LP Lot: 2E083E2 Manufacture Date: 09/2012 Reference Product: Treatment C Adderall XR® (Mixed Salts of a Single-Entity Amphetamine Product) Extended-Release Capsules Dose = 1 x 30 mg capsule Shire US Inc. Lot: A90383A Expiration Date: 05/2016 Each dose of NT0201 Amphetamine Polistirex XR OLS was administered orally without water. Each dose of Adderall XR was administered orally with 60 mL (2 fl oz) of room temperature tap water.
PK Sampling: Blood samples (1 x 4 mL) were collected at 0 (predose) and at 1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, and 60.0 hours after dosing.
LC/MS/MS. Analytical Method: The method used in this study was validated for a range of 0.500 to 80.0 ng/mL for *d*-amphetamine and 0.200 to 32.0 ng/mL for *l*-amphetamine based on the analysis of 0.150 mL of plasma. Linearity and Standard Curve

Analyte	Slope	Intercept	R^2
D-Amphetamine	0.169130619	0.013368062	0.9945
L-Amphetamine	0.218717293	0.001163350	0.9974

Analyte	CV		Bias	
	From	To	From	To
D-Amphetamine	0.5%	1.6%	-8.8%	9.2%
L-Amphetamine	0.5%	1.6%	-8.8%	5.0%

LLOQ and QC Evaluation

Analyte	Intrarun				Inter-run	
	CV		Bias		CV	Bias
	From	To	From	To		
D-Amphetamine	2.7%	4.7%	-6.4%	0.0%	4.5%	-3.4%
L-Amphetamine	6.3%	9.0%	-7.0%	7.0%	9.2%	-1.5%

Analyte	Intrarun				Inter-run			
	CV		Bias		CV		Bias	
	From	To	From	To	From	To	From	To
D-Amphetamine	0.8%	3.0%	-3.8%	10.0%	1.3%	2.9%	-3.0%	8.0%
L-Amphetamine	1.5%	2.9%	-1.2%	6.0%	2.1%	3.1%	0.0%	3.3%

Recovery

Moieties to be Measured: d-amphetamine and l-amphetamine.

Protocol Deviations: The sponsor reported no protocol deviations during the conduct of the study

Statistical Analysis Plan: Data were analyzed by noncompartmental methods in WinNonlin. The natural logarithmic-transformed pharmacokinetic parameters were analyzed for differences between treatments using an ANOVA model with factors for sequence, subject within sequence, period, and treatment. The 90% confidence interval for the ratio of the geometric means of the test product and the reference listed drug was calculated for each parameter. Bioequivalence or lack of significant difference is demonstrated if the 90% confidence intervals for the log transformed exposure parameters are within the 80% to 125% interval. No significant food effect was demonstrated if the 90% confidence intervals were within the accepted limits of 80.00 to 125.00%.

Results

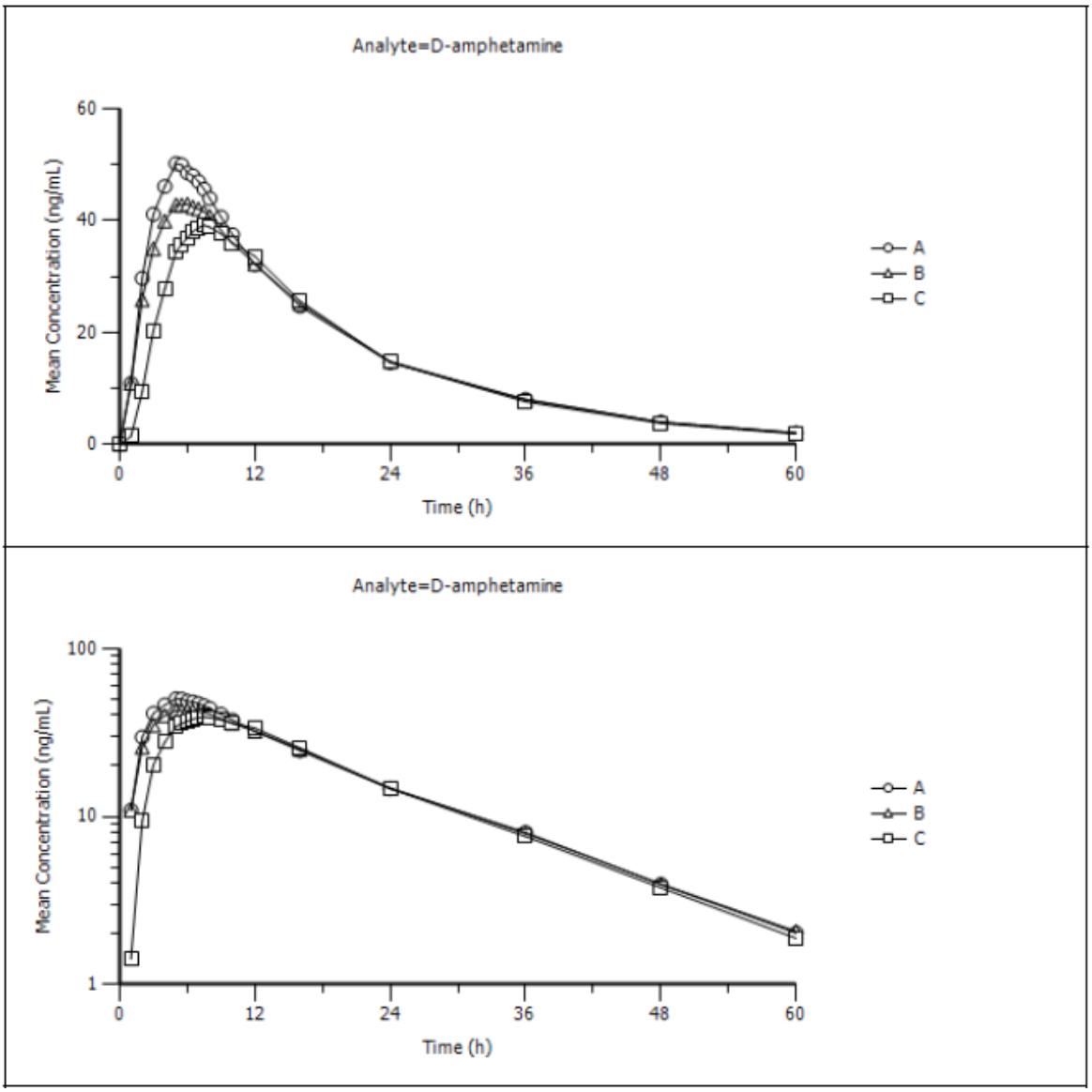
Study Population

Randomized/Completed/Discontinued due to AE	30/29/1
Mean ±SD Age [Median (range)] years	35.83 ± 13.96 [33 (20, 68)]
Male/Female	17/13
Race (Caucasian/Black/Asian/Other)	27/2/1/0
Mean Weight (± SD) kg	70.5 ±12.28
BMI (±SD) kg/m^2	25.36 ±2.75

One subject (#110) withdrew consent due to vomiting multiple times prior to Period 2 dosing

D-amphetamine
The mean plasma concentration time profile and mean pharmacokinetic parameters for d-amphetamine are provided in the following figure and tables

Mean *d*-amphetamine Concentration-Time Profiles after Administration of NT0201 Amphetamine Polistirex XR OLS under Fasted Conditions (Treatment A), NT0201 Amphetamine Polistirex XR OLS under Fed Conditions (Treatment B), and Adderall XR under Fed Conditions (Treatment C)


Analyte=D-amphetamine
Mean Concentration (ng/mL)
60
40
20
0
0
12
24
36
48
60
Time (h)
A
B
C
Analyte=D-amphetamine
Mean Concentration (ng/mL)
100
10
1
0
12
24
36
48
60
Time (h)
A
B
C

The pharmacokinetic parameters of d-amphetamine

Parameter	Treatment A: NT0201 Amphetamine Polistirex XR OLS Fasted				Treatment B: NT0201 Amphetamine Polistirex XR OLS Fed				Treatment C: Reference Product-Fed (Adderall XR)			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	29	4.95	0.99	20.04	29	5.47	1.91	34.92	29	7.95	2.50	31.42
C_{max} (ng/mL)	29	51.9	9.02	17.36	29	45.9	7.98	17.38	29	42.6	9.48	22.22
AUC_{0-5} (h*ng/mL)	29	152.7	40.30	26.38	29	132.9	45.00	33.85	29	75.85	23.69	31.23
AUC_{5-last} (h*ng/mL)	29	807.3	161.5	20.00	29	790.2	167.5	21.19	29	772.5	143.7	18.60
AUC_{last} (h*ng/mL)	29	960.1	180.8	18.83	29	923.1	161.4	17.49	29	848.4	146.4	17.25
AUC_{inf} (h*ng/mL)	29	996.3	193.7	19.44	29	961.5	176.8	18.39	29	881.7	157.5	17.86
AUC_{Extrap} (%)	29	3.51	1.62	46.09	29	3.81	1.95	51.05	29	3.66	1.54	42.11
λ_z (h^{-1})	29	0.0601	0.0095	15.79	29	0.0586	0.0098	16.77	29	0.0597	0.0078	13.08
$T_{1/2}$ (h)	29	11.82	1.83	15.51	29	12.12	1.90	15.69	29	11.81	1.54	13.05
T_{last} (h)	29	59.59	2.23	3.74	29	60.00	0.01	0.02	29	60.00	0.00	0.00
C_{last} (ng/mL)	29	2.01	0.876	43.54	29	2.07	1.02	49.35	29	1.88	0.783	41.67

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine Comparing NT0201 Amphetamine Polistirex XR OLS under Fed Conditions (Treatment B) to NT0201 Amphetamine Polistirex XR OLS under Fasted Conditions (Treatment A)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	45.3087	51.0913	88.68	85.41	92.08	1.0000	8.40
$ln(AUC_{last})$	909.6180	942.7716	96.48	93.20	99.89	1.0000	7.74
$ln(AUC_{inf})$	945.6631	977.1454	96.78	93.30	100.39	1.0000	8.19
Dependent Variable	**Geometric Mean[a]**		**Ratio (%)[b]**	**p-value[d]**			
	Test	**Ref**	**(Test/Ref)**				
$ln(AUC_{0-5})$	125.1175	147.3570	84.91	0.0888			

[a] Geometric Mean for NT0201 Amphetamine Polistirex XR OLS-Fed (Test) and NT0201 Amphetamine Polistirex XR OLS-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

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

[c] 90% Confidence Interval

[d] p-value for treatment in the ANOVA model

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine Comparing NT0201 Amphetamine Polistirex XR OLS under Fed Conditions (Treatment B) to Adderall XR under Fed Conditions (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	45.2535	41.6470	108.66	103.14	114.47	1.0000	11.66
$\ln(AUC_{0-5})$	125.0648	72.1095	173.44	145.51	206.73	0.6764	40.70
$\ln(AUC_{5-last})$	773.0222	757.8067	102.01	97.59	106.63	1.0000	9.90
$\ln(AUC_{inf})$	945.7804	866.6134	109.14	104.84	113.61	1.0000	8.97

[a] Geometric Mean for NT0201 Amphetamine Polistirex XR OLS-Fed (Test) and Adderall XR-Fed (Ref) based on Least Squares Mean of log-transformed parameter values

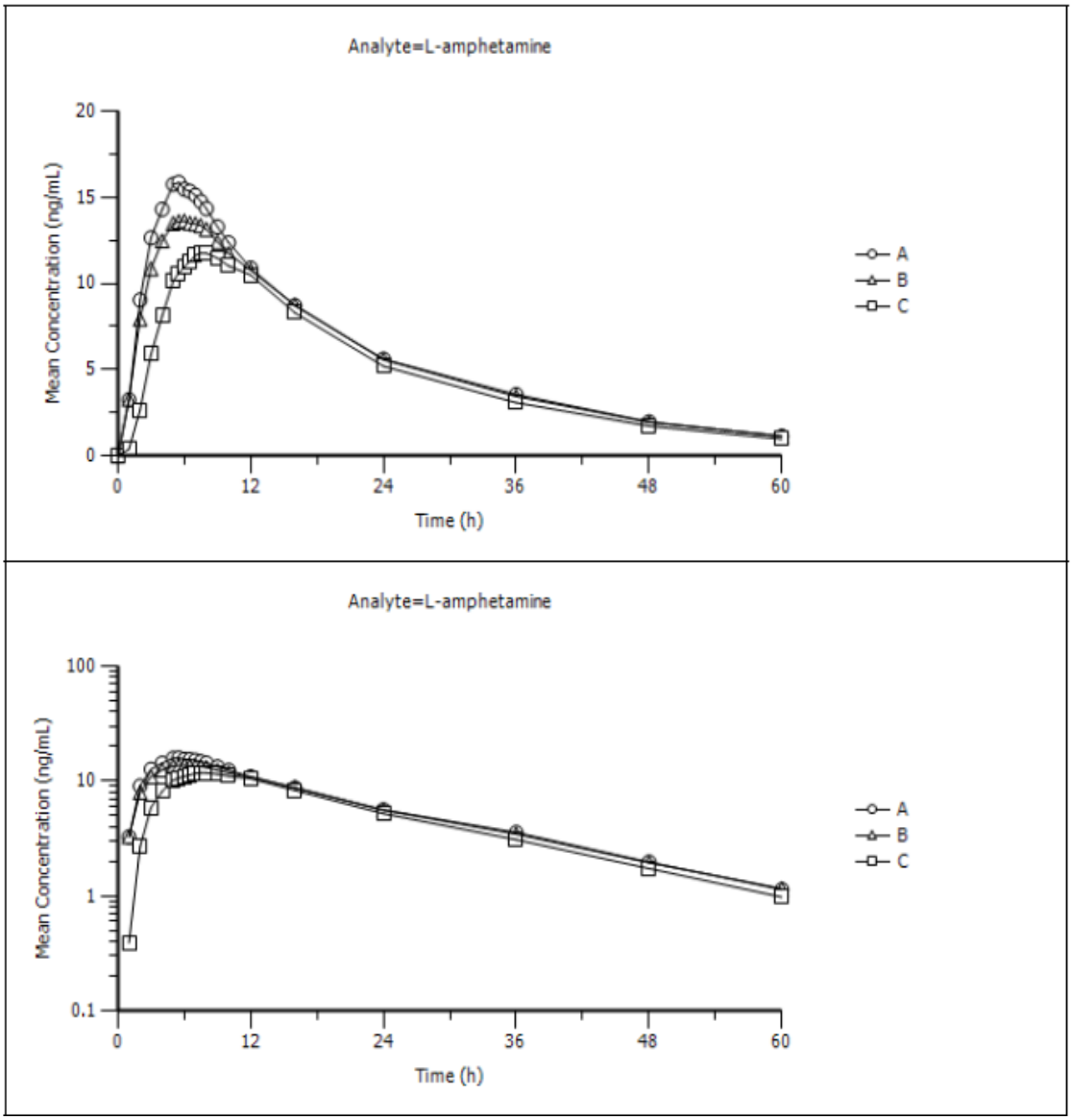
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

[c] 90% Confidence Interval

L-amphetamine

The mean plasma concentration time profile and mean pharmacokinetic parameters for l-amphetamine are provided in the following figure and tables

Mean *l*-amphetamine Concentration-Time Profiles after Administration of NT0201 Amphetamine Polistirex XR OLS under Fasted Conditions (Treatment A), NT0201 Amphetamine Polistirex XR OLS under Fed Conditions (Treatment B), and Adderall XR under Fed Conditions (Treatment C)



Pharmacokinetic Parameters of l-amphetamine

Parameter	Treatment A: NT0201 Amphetamine Polistirex XR OLS Fasted				Treatment B: NT0201 Amphetamine Polistirex XR OLS Fed				Treatment C: Reference Product-Fed (Adderall XR)			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	29	5.16	1.02	19.70	29	5.88	2.16	36.79	29	8.16	2.61	31.99
C_{max} (ng/mL)	29	16.4	2.97	18.16	29	14.6	2.61	17.88	29	12.8	2.89	22.55
AUC_{0-5} (h*ng/mL)	29	47.08	12.89	27.38	29	41.25	14.09	34.15	29	22.09	6.870	31.10
AUC_{5-last} (h*ng/mL)	29	298.6	65.04	21.78	29	289.3	66.17	22.87	29	264.5	53.32	20.15
AUC_{last} (h*ng/mL)	29	345.7	71.42	20.66	29	330.5	63.16	19.11	29	286.6	54.01	18.84
AUC_{inf} (h*ng/mL)	29	370.9	83.23	22.44	29	357.4	76.22	21.33	29	308.2	62.80	20.38
AUC_{Extrap} (%)	29	6.46	3.05	47.23	29	7.04	3.74	53.10	29	6.69	2.91	43.55
λ_z (h^{-1})	29	0.0496	0.0093	18.81	29	0.0488	0.0105	21.48	29	0.0493	0.0084	16.95
$T_{1/2}$ (h)	29	14.47	2.80	19.36	29	14.84	3.07	20.70	29	14.45	2.47	17.07
T_{last} (h)	29	59.59	2.23	3.74	29	60.00	0.01	0.02	29	60.00	0.00	0.00
C_{last} (ng/mL)	29	1.13	0.520	46.21	29	1.16	0.590	51.05	29	0.978	0.425	43.43

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *l*-amphetamine Comparing NT0201 Amphetamine Polistirex XR OLS under Fed Conditions (Treatment B) to NT0201 Amphetamine Polistirex XR OLS under Fasted Conditions (Treatment A)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	14.3990	16.0658	89.63	86.43	92.94	1.0000	8.11
$ln(AUC_{last})$	324.6557	338.2024	95.99	92.54	99.58	1.0000	8.19
$ln(AUC_{inf})$	349.3468	361.6533	96.60	92.75	100.61	1.0000	9.09
Dependent Variable	**Geometric Mean[a]**		**Ratio (%)[b]**	**p-value[d]**			
	Test	**Ref**	**(Test/Ref)**				
$ln(AUC_{0-5})$	38.7633	45.2749	85.62	0.1104			

[a] Geometric Mean for NT0201 Amphetamine Polistirex XR OLS-Fed (Test) and NT0201 Amphetamine Polistirex XR OLS-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
[d] p-value for treatment in the ANOVA model

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine Comparing NT0201 Amphetamine Polistirex XR OLS under Fed Conditions (Treatment B) to Adderall XR under Fed Conditions (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	14.3840	12.5275	114.82	109.16	120.78	1.0000	11.32
$ln(AUC_{0-5})$	38.7444	20.9999	184.50	154.35	220.53	0.6642	41.41
$ln(AUC_{5-last})$	281.9542	258.7635	108.96	103.88	114.29	1.0000	10.68
$ln(AUC_{inf})$	349.4520	301.4583	115.92	110.57	121.53	1.0000	10.56

[a] Geometric Mean for NT0201 Amphetamine Polistirex XR OLS-Fed (Test) and Adderall XR-Fed (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

Pharmacokinetic Summary

The 90% confidence intervals for the log-transformed exposure parameters Cmax, AUClast, and AUCinf for NT0201 Amphetamine Polistirex XR OLS under fed conditions relative to fasted conditions were within the accepted 80% to 125% range for *d*- and *l*-amphetamine. For the comparison of early systemic exposure to *d*-amphetamine and *l*-amphetamine, the AUC(0-5) of NT0201 Amphetamine Polistirex XR OLS was lower under fed conditions relative to fasted conditions. The median Tmax values of 5.00 h (fasted) and 5.50 h (fed) for *d*-amphetamine and 5.00 h (fasted) and 6.00 h (fed) for *l*-amphetamine were not significantly different, based on the p-values from the Wilcoxon Signed Rank test of 0.2836 and 0.2189, respectively.

The 90% confidence intervals for the log-transformed exposure parameters Cmax, AUC(5-t), and AUCinf of NT0201 Amphetamine Polistirex XR OLS relative to the RLD, Adderall XR under fed conditions, were within the accepted 80% to 125% range for establishing bioequivalence for *d*- and *l*-amphetamine. The 90% confidence intervals for the log-transformed early exposure parameter AUC(0-5) for NT0201 Amphetamine Polistirex XR OLS relative to Adderall XR under fed conditions were not within the accepted 80% to 125% range for establishing bioequivalence for *d*-and *l*-amphetamine. The Test/Reference ratios for AUC(0-5) for *d*-amphetamine and for *l*-amphetamine, indicating higher exposure after administration of NT0201 Amphetamine Polistirex XR OLS. The sponsor explained that the difference in early exposure between products is likely due to the prolongation in Tmax and decreased exposure for Adderall XR under fed conditions. The median Tmax values of 5.50 h (NT0201 Amphetamine Polistirex XR OLS) and 7.00 h (Adderall XR) for *d*-amphetamine and 6.00 h (NT0201 Amphetamine Polistirex XR OLS) and 7.50 h (Adderall XR) for *l*-amphetamine were significantly different, based on the p-values from the Wilcoxon Signed Rank test of <0.0001 and 0.0004, respectively.

Safety Evaluation
Thirty six (36) TEAEs reported, 31 were reported as mild and 5 were moderate. There were no serious TEAEs or deaths during the course of the study. The most commonly reported TEAEs, reported by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, were

nausea (n = 3; 1 following Treatment A and 2 following Treatment C; headache (n = 3; 1 following Treatment A and 2 following Treatment B); and anxiety (n = 3; all following Treatment A). In total, 20 AEs were reported following Treatment A, 9 AEs were reported following Treatment B, and 7 AEs were reported following administration of Treatment C. Clinically significant abnormalities in vital signs (tachycardia) were reported for Subject 105 and Subject 116. Subject 110 withdrew consent due to an AE of vomiting, multiple episodes prior to Period 2 dose.

In conclusion, based on Cmax, AUC(5-last), and AUCinf, NT0201 Amphetamine Polistirex XR OLS is bioequivalent to Adderall XR under fed conditions. However, for both *d*- and *l*-amphetamine, the AUC0-5 for NT0201 Amphetamine Polistirex XR OLS is significantly larger than that for Adderall XR and Tmax was observed earlier for NT0201 Amphetamine Polistirex XR OLS relative to Adderall XR, thus demonstrating less of a food effect than that reported for Adderall XR. Based on Cmax, AUClast, and AUCinf, food does not have a significant effect on the rate and extent of absorption for NT0201 Amphetamine Polistirex XR OLS. In addition, food has no significant effect on Tmax for *d*- and *l*-amphetamine after administration of Amphetamine Polistirex XR Oral LS. Based on Cmax, AUC5-last, and AUCinf, NT0201 Amphetamine Polistirex XR OLS is bioequivalent to Adderall XR under fed conditions. However, for both *d*- and *l*-amphetamine, the AUC0-5 for NT0201 Amphetamine Polistirex XR OLS is significantly larger than that for Adderall XR and Tmax was observed earlier for NT0201 Amphetamine Polistirex XR OLS relative to Adderall XR, thus demonstrating less of a food effect than that reported for Adderall XR.

Reviewer Comments

1. Study Design: *The study was conducted according to the protocol. The design of the study is consistent with recommendations in the Agency's draft guidance on Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs- General Considerations and the study is consistent with the recommendations in the food effect guidance and the type of food evaluated was the standard FDA high fat meal.*
2. *Study Conduct: No apparent protocol deviation that will affect the PK assessment has been identified.*
3. Study Analysis: *Visual inspection of the pharmacokinetic profiles and pharmacokinetic data did not indicate there were outliers; all subjects were included in the pharmacokinetic analysis. One subject (#110) was dropped from the study and pharmacokinetic analysis due to multiple vomiting.*
4. Study Results: *The reviewer agrees with the sponsor's conclusions that food does not have significant effect on d- and l- amphetamine AUC and Cmax after administration of Amphetamine Polistirex XR. Amphetamine Polistirex XR OLS is similar (i.e. meets BE criteria) to Adderall XR under fed conditions based on Cmax, AUC(5 –t) and AUC(0-inf). For both d-- and l-amphetamine, AUC(0-5) for Amphetamine Polistirex XR OLS was not equivalent to Adderall XR. Tmax was observed earlier for Amphetamine Polistirex XR OLS relative to Adderall XR. Since total exposure and early exposures (partial AUCs) are equivalent (i.e. meets BE criteria) under fasting conditions, Amphetamine Polistirex XR is equivalent to Adderall XR. The clinical significance of AUC(0-5) not being equivalent to Adderall XR under fed conditions is not clear since this It must be noted*

that this study used the clinical trial formulation (CTM) and another food effect study was conducted using the To Be Marketed formulation. The TBM formulation was demonstrated to be equivalent to the CTM. The study results are acceptable.

Clinical Study Review

Report #: NT0201.1005	Study Period:
Study Sites:	Worldwide Clinical Trials Early Phase Services San Antonio, Texas
Principal Investigator:	Cynthia A. Zamora, M.D
Analytical Site:	(b) (4)
Bioanalytical Investigator:	(b) (4) B.A.
EDR Link:	\\CDSESUB1\evsprod\NDA204325\0000

Title: A Single-Dose, Four-Period, Four-Treatment, Four-Way Crossover Bioequivalence Study of Three Formulations of NT0201 Amphetamine Polistirex Extended Release Oral Liquid Suspension (Equivalent to 30 mg Mixed Amphetamine Salts/15 mL) and Adderall XR® 30 mg Capsule under Fasted Conditions

Objectives: To compare the rate of absorption and oral bioavailability of three different formulations of NT0201 Amphetamine Polistirex Extended Release (XR) Oral Liquid Suspension (LS), equivalent to 30 mg mixed amphetamine salts/15 mL, developed by Neos Therapeutics, Inc. to an equivalent 30 mg oral dose of the commercially available reference product, Adderall XR® (Shire US Inc.) following an overnight fast of at least 10 hours.

Study Design

Design: Single-dose, open-label, randomized, four-period, four-treatment crossover study in which 44 healthy adult subjects were to receive a single separate dose of NT0201 Amphetamine Polistirex XR Oral LS (Test Formulation #1) in one period, a single separate dose of NT0201 Amphetamine Polistirex XR Oral LS (Test Formulation #2) in one period, a single separate dose of NT0201 Amphetamine Polistirex XR Oral LS (Test Formulation #3) in one period, and a single separate dose of Adderall XR 30 mg capsule in one period. Each dose was administered following an overnight fast of at least 10 hours.	
Washout Period	7 days
Randomization: NT0201 Amphetamine Polistirex XR Oral LS (Test Formulation #1) in one period, a single separate dose of NT0201 Amphetamine Polistirex XR Oral LS (Test Formulation #2) in one period, a single separate dose of NT0201 Amphetamine Polistirex XR Oral LS (Test Formulation #3) in one period, and a single separate dose of Adderall XR 30 mg capsule in one period.	
Main Inclusion Criteria: Male or non-pregnant, non-breastfeeding female; ≥18 years of age; Body mass index (BMI) between 18 and 30 kg/m2 (inclusive) and minimum weight of 50 kg (110 lbs). Vital signs measured sitting after 3 minutes rest within the following ranges: heart rate:	

40–90 bpm; systolic blood pressure (BP): 90–140 mmHg; diastolic BP: 50–90 mmHg.

Main Exclusion Criteria: History or presence of tics or Tourette's syndrome; Was currently receiving psychotropic medication for any reason; Had used any over-the-counter (OTC) medication, including nutritional supplements, within 7 days prior to the first dose of study medication; Had taken amphetamine or amphetamine-like medications as a treatment for ADHD, depression, etc., or received such medications in a clinical trial, or used such medications recreationally, and was not able to tolerate these medications. Had used any prescription medication (including methylxanthines or any known drugs that are moderate or strong inhibitors/inducers of CYP enzymes such as barbiturates, phenothiazines, cimetidine, carbamazepine, etc.), except hormonal contraceptive or hormonal replacement therapy, within 30 days prior to the first dose of study medication;

Treatments:

Test Formulation: Treatment A	NT0201 Amphetamine Polistirex Extended Release Oral Liquid Suspension Equivalent to 30 mg/15 mL Mixed Amphetamine Salts Dose = 1 x 15 mL oral liquid suspension Neos Therapeutics, Inc. Lot: 2E082E2 Manufacture Date: 09/12
Test Formulation: Treatment B	NT0201 Amphetamine Polistirex Extended Release Oral Liquid Suspension Equivalent to 30 mg/15 mL Mixed Amphetamine Salts Dose = 1 x 15 mL oral liquid suspension Neos Therapeutics, Inc. Lot: 2E083E2 Manufacture Date: 09/12
Test Formulation: Treatment C	NT0201 Amphetamine Polistirex Extended Release Oral Liquid Suspension Equivalent to 30 mg/15 mL Mixed Amphetamine Salts Dose = 1 x 15 mL oral liquid suspension Neos Therapeutics, Inc. Lot: 2E084E2 Manufacture Date: 09/12
Reference Product: Treatment D	Adderall XR® (Mixed Salts of a Single-Entity Amphetamine Product) Extended-Release Capsules Dose = 1 x 30 mg capsule Shire US Inc. Lot: A69231C Expiration Date: 01/2015

PK Sampling Times: Blood samples (1 x 4 mL) were collected at 0 (predose) and at 1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, and 60.0 hours after

dosing.

Analytical Methods: LC/MS/MS
Linear Range- 0.5 to 80 ng/mL for d-amphetamine and 0.2 to 32 ng/mL for l-amphetamine
Standard Curve

Analyte	CV		Bias	
	From	To	From	To
D-Amphetamine	0.5%	1.6%	-8.8%	9.2%
L-Amphetamine	0.5%	1.6%	-8.8%	5.0%

Precision and Accuracy

Analyte	Intrarun				Inter-run			
	CV		Bias		CV		Bias	
	From	To	From	To	From	To	From	To
D-Amphetamine	0.8%	3.0%	-3.8%	10.0%	1.3%	2.9%	-3.0%	8.0%
L-Amphetamine	1.5%	2.9%	-1.2%	6.0%	2.1%	3.1%	0.0%	3.3%

Recovery

Analyte	From	To	Internal Standard	From	To
D-Amphetamine	80.97%	101.02%	D-Amphetamine-D_5	73.28%	111.31%
L-Amphetamine	77.12%	93.52%	L-Amphetamine-D_5	68.44%	104.36%

Assay Selectivity

Analyte	Bias	
	From	To
D-Amphetamine	-10.6%	-4.6%
L-Amphetamine	-7.5%	0.0%

The analytical method is acceptable.

Moieties to be measured: d-amphetamine and l-amphetamine

Statistical Analysis: Noncompartmental methods

Protocol Deviations Leading to Discontinuation from Study

Safety Population

Subject ID	Timing	Treatment	Description
115	Period 2	C [NT0201 MAR CR LIQUID 3]	Subject was withdrawn for protocol non-compliance at Period 2 check-in (positive urine drug screen). End of study procedures were performed on 09/28/12
123	Period 4	D [NT0201 ADDERALL XR CAPSULE 30]	Subject was withdrawn from the study due to protocol non compliance at period 4 check-in (positive urine pregnancy). Early termination procedures were completed on 10/12/12. IRB notified on 10/15/12.

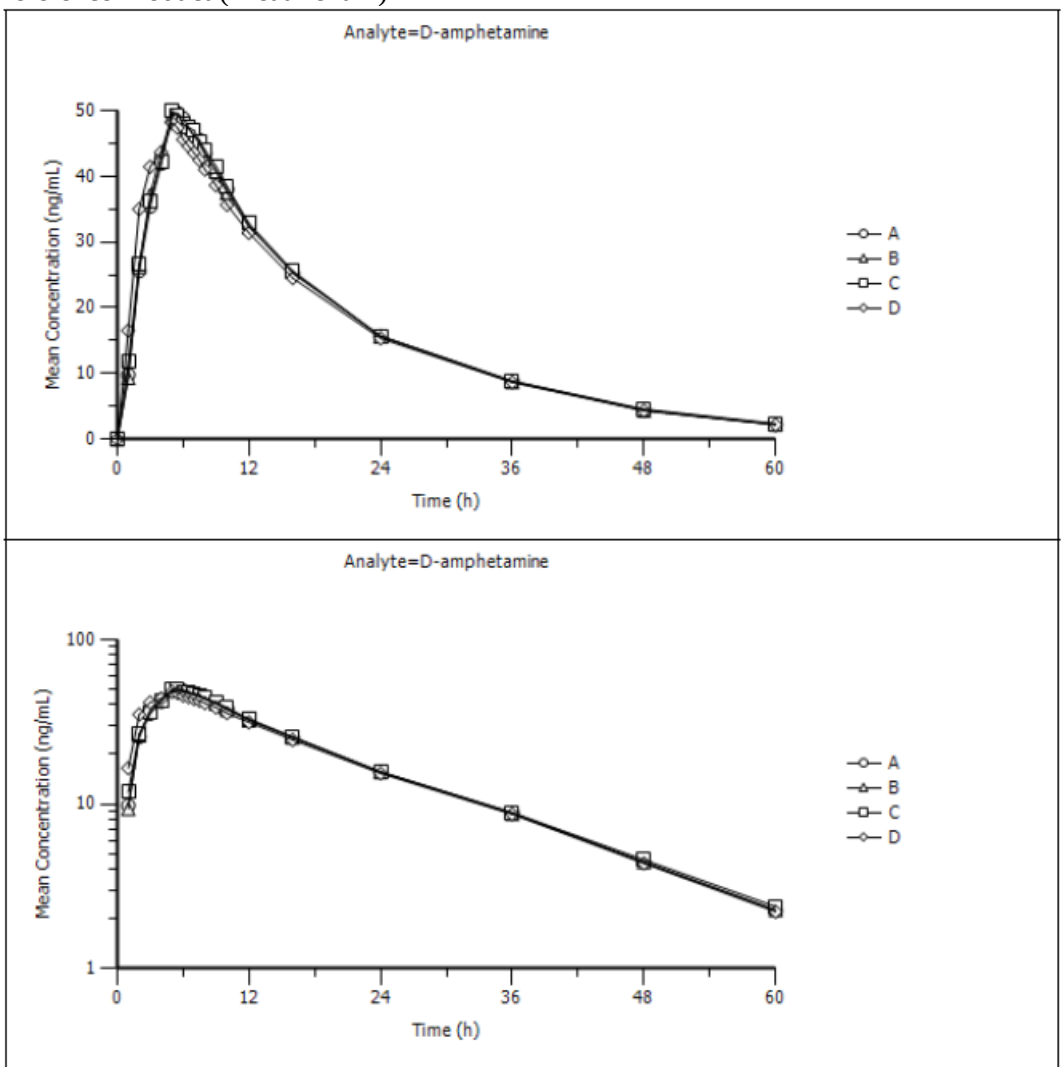
Results

Study Population

Randomized/Completed/Discontinued due to AE	44/39/1
Mean Age ±SD [Median (range)] years	42.8 ±16.2 [41.50 (18, 70)]
Male/Female	24/20
Race (Caucasian/Black/Other)	32/8/4
Mean Weight (± SD)	73..3 ± 12.1
BMI (± SD) kg/m^2	25.7 ± 2.6

The mean plasma concentration-time profile for d-amphetamine is provided in the following figure. The pharmacokinetic parameters and statistical analysis are provided in the following tables

Mean *d*-amphetamine Concentration-Time Profiles after Administration of Test Formulation #1 (Treatment A), Test Formulation #2 (Treatment B), Test Formulation #3 (Treatment C), and the Reference Product (Treatment D)



Pharmacokinetic Parameters of d-Amphetamine

Parameter	Treatment A: Test Formulation #1				Treatment B: Test Formulation #2			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	42	5.32	0.71	13.42	40	5.28	0.72	13.74
C_{max} (ng/mL)	42	51.4	11.2	21.77	40	51.0	9.84	19.29
AUC_{0-5} (h*ng/mL)	42	137.4	44.60	32.45	40	140.9	38.27	27.17
AUC_{5-12} (h*ng/mL)	42	293.9	61.49	20.92	40	291.7	56.93	19.52
AUC_{5-last}(h*ng/mL)	42	839.9	189.3	22.54	40	837.8	181.5	21.66
AUC_{last} (h*ng/mL)	42	977.3	214.1	21.90	40	978.7	207.0	21.15
AUC_{inf} (h*ng/mL)	42	1020	226.9	22.24	40	1022	219.1	21.45
AUC_{0-24} (h*ng/mL)	42	710.4	150.8	21.23	40	711.8	144.3	20.27
AUC_{Extrap} (%)	42	4.12	2.08	50.47	40	4.12	1.96	47.61
λ_z (h^{-1})	42	0.0576	0.0102	17.74	40	0.0572	0.0093	16.23
$T_{1/2}$ (h)	42	12.41	2.18	17.56	40	12.44	2.03	16.32
T_{last} (h)	42	59.80	1.61	2.70	40	60.00	0.01	0.01
C_{last} (ng/mL)	42	2.27	0.994	43.79	40	2.27	0.954	41.98
Parameter	**Treatment C: Test Formulation #3**				**Treatment D: Reference Product (Adderall XR)**			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	39	5.44	0.88	16.12	42	4.55	1.47	32.36
C_{max} (ng/mL)	39	52.0	11.1	21.33	42	50.6	10.2	20.25
AUC_{0-5} (h*ng/mL)	39	141.6	36.16	25.54	42	160.5	44.23	27.55
AUC_{5-12} (h*ng/mL)	39	295.7	60.65	20.51	42	277.9	59.53	21.42
AUC_{5-last}(h*ng/mL)	39	847.2	185.8	21.94	42	809.5	192.4	23.76
AUC_{last} (h*ng/mL)	39	988.7	203.5	20.58	42	970.1	213.4	21.99
AUC_{inf} (h*ng/mL)	39	1035	215.6	20.84	42	1017	234.1	23.02
AUC_{0-24} (h*ng/mL)	39	719.1	141.6	19.69	42	709.5	146.6	20.66
AUC_{Extrap} (%)	39	4.34	2.41	55.40	42	4.34	2.86	65.77
λ_z (h^{-1})	39	0.0562	0.0086	15.30	42	0.0570	0.0101	17.69
$T_{1/2}$ (h)	39	12.63	2.06	16.33	42	12.55	2.32	18.46
T_{last} (h)	39	60.00	0.01	0.01	42	59.72	1.85	3.10
C_{last} (ng/mL)	39	2.38	1.05	44.02	42	2.37	1.42	59.83

Note: Full precision data used in pharmacokinetic analysis

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine Comparing Test Formulation #1 (Treatment A) to the Reference Product (Treatment D)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	50.1580	49.5786	101.17	99.16	103.22	1.0000	5.43
$ln(AUC_{0-5})$	130.5315	153.2270	85.19	79.53	91.25	0.9997	18.76
$ln(AUC_{5-12})$	287.7548	272.5554	105.58	103.05	108.16	1.0000	6.56
$ln(AUC_{5-last})$	823.1422	791.9221	103.94	100.64	107.35	1.0000	8.75
$ln(AUC_{0-24})$	696.5164	696.4442	100.01	98.18	101.88	1.0000	5.01
$ln(AUC_{last})$	958.9738	951.6525	100.77	98.40	103.19	1.0000	6.45
$ln(AUC_{inf})$	1001.0534	995.6153	100.55	97.95	103.21	1.0000	7.10

[a] Geometric Mean for Test Formulation #1 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine Comparing Test Formulation #2 (Treatment B) to the Reference Product (Treatment D)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	50.0963	49.3574	101.50	99.82	103.20	1.0000	4.42
$\ln(AUC_{0-5})$	135.9603	152.6483	89.07	84.05	94.38	1.0000	15.45
$\ln(AUC_{5-12})$	286.6888	271.5835	105.56	103.52	107.64	1.0000	5.18
$\ln(AUC_{5-last})$	821.7640	789.8344	104.04	100.69	107.51	1.0000	8.71
$\ln(AUC_{0-24})$	699.0396	694.7072	100.62	98.59	102.70	1.0000	5.41
$\ln(AUC_{last})$	960.8482	949.2052	101.23	98.63	103.90	1.0000	6.91
$\ln(AUC_{inf})$	1003.0198	993.2407	100.98	98.07	103.99	1.0000	7.79

[a] Geometric Mean for Test Formulation #2 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine Comparing Test Formulation #3 (Treatment C) to the Reference Product (Treatment D)

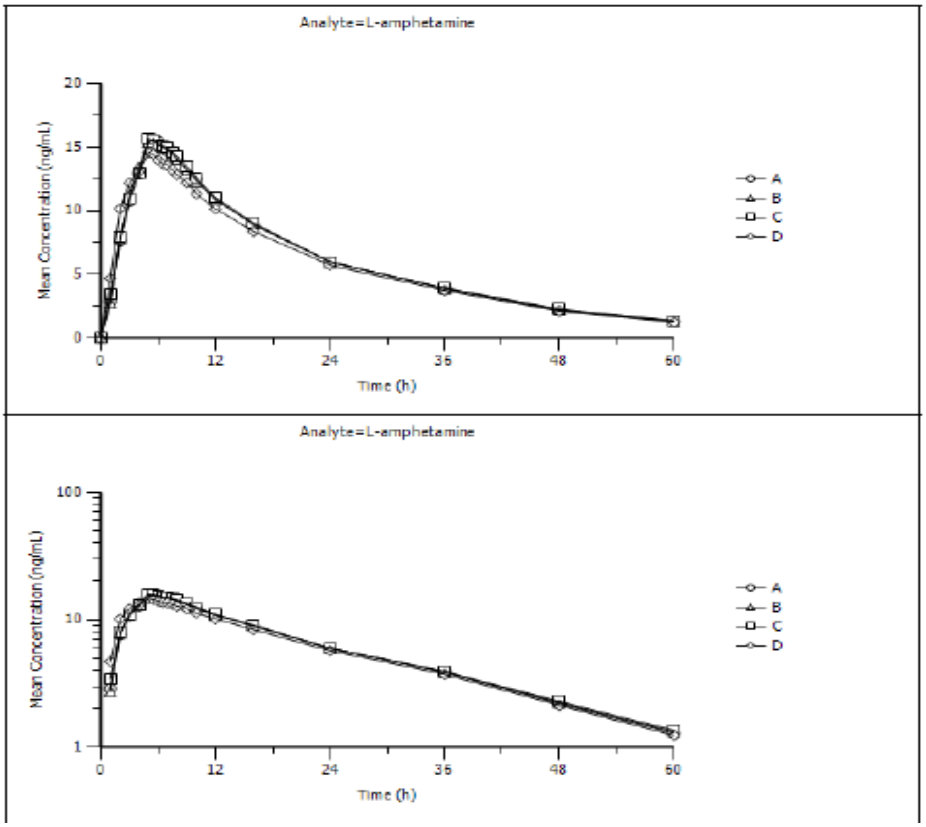
Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	50.7295	49.3066	102.89	100.35	105.49	1.0000	6.51
$\ln(AUC_{0-5})$	136.5321	152.7544	89.38	84.81	94.20	1.0000	13.75
$\ln(AUC_{5-12})$	289.7260	271.3370	106.78	105.26	108.31	1.0000	3.72
$\ln(AUC_{5-last})$	829.3721	787.7095	105.29	102.81	107.83	1.0000	6.22
$\ln(AUC_{0-24})$	705.8156	693.9269	101.71	99.85	103.61	1.0000	4.82
$\ln(AUC_{last})$	970.1670	947.3535	102.41	100.17	104.69	1.0000	5.76
$\ln(AUC_{inf})$	1015.0619	991.6597	102.36	99.66	105.13	1.0000	6.96

[a] Geometric Mean for Test Formulation #3 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

The shapes of d-amphetamine pharmacokinetic profiles for the test formulations were similar when compared to the reference, Adderall XR. The geometric mean ratio of Cmax and AUC, including partial AUCs, were within the 90% confidence interval except AUC(0-5) for formulation 1.

L-amphetamine

Mean *l*-amphetamine Concentration-Time Profiles after Administration of Test Formulation #1 (Treatment A), Test Formulation #2 (Treatment B), Test Formulation #3 (Treatment C), and the Reference Product (Treatment D)



Pharmacokinetic Parameters of l-amphetamine

Parameter	Treatment A: Test Formulation #1				Treatment B: Test Formulation #2			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	42	5.62	0.82	14.68	40	5.40	0.85	15.72
C_{max} (ng/mL)	42	16.1	3.79	23.47	40	16.0	3.29	20.55
AUC_{0-5} (h*ng/mL)	42	41.85	14.05	33.57	40	42.88	12.29	28.67
AUC_{5-12} (h*ng/mL)	42	94.95	21.32	22.45	40	94.29	19.87	21.07
AUC_{5-last}(h*ng/mL)	42	310.7	79.05	25.44	40	311.4	77.17	24.78
AUC_{last} (h*ng/mL)	42	352.5	87.18	24.73	40	354.3	85.92	24.25
AUC_{inf} (h*ng/mL)	42	384.0	101.6	26.47	40	386.1	100.1	25.92
AUC_{0-24} (h*ng/mL)	42	235.7	54.16	22.98	40	236.6	52.33	22.12
AUC_{Extrap} (%)	42	7.76	4.01	51.62	40	7.82	3.64	46.50
λ_z (h^{-1})	42	0.0467	0.0103	22.04	40	0.0463	0.0095	20.64
$T_{1/2}$ (h)	42	15.53	3.40	21.89	40	15.60	3.13	20.08
T_{last} (h)	42	59.80	1.61	2.70	40	60.00	0.01	0.01
C_{last} (ng/mL)	42	1.30	0.634	48.91	40	1.31	0.619	47.12
Parameter	Treatment C: Test Formulation #3				Treatment D: Reference Product (Adderall XR)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	39	5.60	0.93	16.55	42	4.84	1.52	31.36
C_{max} (ng/mL)	39	16.4	3.60	21.92	42	15.3	3.32	21.72
AUC_{0-5} (h*ng/mL)	39	43.03	11.33	26.34	42	47.34	13.54	28.60
AUC_{5-12} (h*ng/mL)	39	95.58	20.74	21.70	42	86.99	19.62	22.55
AUC_{5-last}(h*ng/mL)	39	314.2	77.13	24.55	42	291.9	78.59	26.92
AUC_{last} (h*ng/mL)	39	357.2	82.76	23.17	42	339.3	85.44	25.18
AUC_{inf} (h*ng/mL)	39	390.4	96.82	24.80	42	372.2	104.2	28.00
AUC_{0-24} (h*ng/mL)	39	238.7	50.30	21.08	42	227.7	51.06	22.42
AUC_{Extrap} (%)	39	8.07	4.26	52.76	42	8.08	4.87	60.32
λ_z (h^{-1})	39	0.0457	0.0086	18.80	42	0.0465	0.0101	21.66
$T_{1/2}$ (h)	39	15.77	3.38	21.45	42	15.63	3.57	22.82
T_{last} (h)	39	60.00	0.01	0.01	42	59.72	1.85	3.10
C_{last} (ng/mL)	39	1.35	0.641	47.43	42	1.32	0.806	61.27

Note: Full precision data used in pharmacokinetic analysis

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of l-amphetamine Comparing Test Formulation #1 (Treatment A) to the Reference Product (Treatment D)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	15.6903	14.9321	105.08	102.81	107.40	1.0000	5.92
$ln(AUC_{0-5})$	39.6019	45.0296	87.95	81.98	94.35	0.9996	19.20
$ln(AUC_{5-12})$	92.7020	85.1083	108.92	106.39	111.52	1.0000	6.39
$ln(AUC_{5-last})$	302.9169	283.7188	106.77	103.27	110.38	1.0000	9.03
$ln(AUC_{0-24})$	230.3610	222.7249	103.43	101.39	105.51	1.0000	5.40
$ln(AUC_{last})$	344.2092	330.7995	104.05	101.35	106.83	1.0000	7.14
$ln(AUC_{inf})$	373.9861	360.6700	103.69	100.39	107.10	1.0000	8.78

[a] Geometric Mean for Test Formulation #1 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values

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

[c] 90% Confidence Interval

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of l-amphetamine Comparing Test Formulation #2 (Treatment B) to the Reference Product (Treatment D)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	15.6747	14.8460	105.58	103.86	107.33	1.0000	4.36
$\ln(AUC_{0-5})$	41.2088	44.8276	91.93	86.65	97.52	1.0000	15.75
$\ln(AUC_{5-12})$	92.3827	84.8244	108.91	106.73	111.14	1.0000	5.37
$\ln(AUC_{5-last})$	303.6696	283.1073	107.26	103.43	111.24	1.0000	9.66
$\ln(AUC_{0-24})$	231.4482	222.2016	104.16	101.78	106.59	1.0000	6.12
$\ln(AUC_{last})$	345.8479	330.0470	104.79	101.67	108.00	1.0000	8.02
$\ln(AUC_{inf})$	375.9631	360.0332	104.42	100.75	108.23	1.0000	9.51

[a] Geometric Mean for Test Formulation #2 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *l*-amphetamine Comparing Test Formulation #3 (Treatment C) to the Reference Product (Treatment D)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	16.0082	14.8077	108.11	105.08	111.23	1.0000	7.42
$\ln(AUC_{0-5})$	41.4033	44.8626	92.29	87.52	97.32	1.0000	13.89
$\ln(AUC_{5-12})$	93.3817	84.7844	110.14	108.48	111.83	1.0000	3.97
$\ln(AUC_{5-last})$	305.8158	282.5814	108.22	105.23	111.30	1.0000	7.32
$\ln(AUC_{0-24})$	233.5886	222.0427	105.20	103.03	107.41	1.0000	5.42
$\ln(AUC_{last})$	348.6608	329.6149	105.78	103.04	108.59	1.0000	6.85
$\ln(AUC_{inf})$	380.0816	359.7935	105.64	101.93	109.48	1.0000	9.32

[a] Geometric Mean for Test Formulation #3 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

Pharmacokinetic Summary

The 90% confidence intervals for the log-transformed exposure parameters C_{max}, AUC_{last}, and AUC_{inf} were within the 90% CI 80% to 125% range for establishing bioequivalence across all treatment comparisons and analytes. With the exception of the log-transformed AUC_{0-5} Test Formulation #1 vs. reference comparison for *d*-amphetamine, all log-transformed partial AUC parameters were within the 90% CI of 80% to 125% range across all treatment comparisons and analytes.

For *d*-amphetamine, the p-value from the Wilcoxon signed rank test used to compare T_{max} across treatments (Test Formulation #1 vs. reference) was 0.0007; the p-value from the Wilcoxon signed rank test used to compare T_{max} across treatments (Test Formulation #2 vs. reference) was 0.0010; the p-value from the Wilcoxon signed rank test used to compare T_{max} across treatments (Test Formulation #3 vs. reference) was < 0.0001; the difference in T_{max} values between treatments were significant ($p < 0.05$). For *l*-amphetamine, the p-value from the Wilcoxon signed rank test used to compare T_{max} across treatments (Test Formulation #1 vs. reference) was 0.0025; the p-value from the Wilcoxon signed rank test used to compare T_{max} across treatments (Test Formulation #2 vs. reference) was 0.0378; the p-value from the Wilcoxon signed rank test used to compare T_{max} across treatments (Test Formulation #3 vs. reference) was 0.0002; the difference in T_{max} values between treatments were significant ($p < 0.05$).

Safety Summary

The sponsor reported that of the 125 TEAEs reported, 68 were mild and 57 were moderate. There were no serious TEAEs or deaths during the course of the study. There was one discontinuation due to a TEAE during the course of the study. A total of 116 of the TEAEs were related and the remaining 9 were not related to the study treatment. Activities (MedDRA) preferred term, were decreased appetite (n = 22 events reported by 9 [20.5%] subjects; 6 events following Treatment A, 5 following Treatment B, 6 following Treatment C, and 5 following Treatment D), headache (n = 13 events reported by 10 [22.7] subjects; 3 events following Treatment A, 1 following Treatment B, 6 following Treatment C, and 3 following Treatment D), abdominal pain (n = 11 events reported by 6 [13.6%] subjects; 3 following Treatment A, 3 following Treatment B, 2 following Treatment C, and 3 following Treatment D), and nausea (n = 11 events reported by 7 [15.9%] subjects; 2 events following Treatment A, 3 following Treatment B, 3 following Treatment C, and 3 following Treatment D). In addition, 3 TEAEs of vomiting were reported by 2 subjects (1 following Treatment A, 1 following Treatment C, and 1 following Treatment D).

Conclusions

Test Formulations #2 and #3 of NT0201 MAR CR Oral Liquid Suspension (equivalent to 30 mg mixed amphetamine salts/15 mL) developed by Neos Therapeutics, Inc. are bioequivalent to the reference listed drug product (RLD) Adderall XR by Shire US Inc. under fasted conditions. Test Formulation #2 was selected for further clinical development by the Sponsor.

Reviewer Comments

Study Design: The design of the study is consistent with recommendations in the Agency's draft guidance on Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs- General Considerations. This was a study to select a formulation for clinical development and not a pivotal trial.

1. *Study Conduct: The study was conducted according to the protocol. Forty-two subjects completed Treatments A and B and D. Thirty nine (39) completed all treatments. This was a study to select a formulation for clinical development and not a pivotal trial.*

2. *Data Analysis: There were no outliers in the results.*
3. *Study Results: The shape of the pharmacokinetic curves was similar to that observed after administration of the reference drug, Adderall XR 30 mg. Visual inspection of the pharmacokinetic profiles and pharmacokinetic data did not suggest there were outliers in the study. There were no serious adverse events or deaths reported. The reviewer agrees with the Sponsor's conclusion that Treatment B and C are bioequivalent to the Treatment D, the reference drug, Adderall XR 30 mg.*

Clinical Study Review- Pediatric PK

Report #: NT0201.1004	Study Period: 3/27/14 – 7/3/14
Study Sites:	Atlanta Center for Medical Research
	MRA Clinical Research , Florida
Principal Investigator:	Robert Riesenberg, MD; Americo Padilla, MD
Analytical Site:	(b) (4)
Bioanalytical Study Manager:	(b) (4), BA

EDR Link: \\CDSESUB1\evsprod\NDA204325\0000

Title: A single-dose, single-period, one-treatment, pharmacokinetic study of an extended release (XR) formulation of amphetamine oral suspension (equivalent to 30 mg mixed amphetamine salts/15 mL) under fasted conditions in children (ages 6-12) with attention-deficit hyperactivity disorder (ADHD)

Objectives: The primary objective of this study was to determine the pharmacokinetic (PK) profile of an extended release (XR) formulation of amphetamine oral suspension (equivalent to 30 mg mixed amphetamine salts [MAS]/15 mL) developed by Neos Therapeutics, Inc. in children, following an overnight fast of at least 10 hours.

Study Design:

Single-dose, open-label, single-period, one-treatment study. A total of 29 male and female children, aged 6 to 12 years (stratified into 3 groups of approximately 10 children: one group aged 6 to 7 years old, one group aged 8 to 9 years old, and one group aged 10 to 12 years old), were enrolled in this study. Children had a diagnosis of ADHD based on the DSM-IV-TR and were currently taking a stable dose of Adderall (XR or immediate release [IR]) or a comparable dose (in the opinion of the Investigator) of another amphetamine product (XR or IR) used to treat children with ADHD. Children were stabilized on a total daily dose of 20 mg or 30 mg Adderall XR or IR, or equivalent to this if another amphetamine product, for at least 1 month prior to the Screening Visit. After the Screening Visit (Visit 1), subjects discontinued their regular treatment regimen (Adderall [XR or IR, 20 mg or 30 mg], or a comparable dose [in the opinion of the Investigator] of another amphetamine product used to treat children with ADHD) and received a single dose of the investigational treatment.

Screening	Maximum of 3 weeks screening period
Washout Period	4 – day washout period for any previously prescribed amphetamine therapy

Treatment	Single dose of 15 mL (equivalent to 30 mg MAS/15 mL) NT0201 (amphetamine XR Oral Suspension) was administered after at least 10 hours overnight fast without water and swallowed. After dosing, no food was allowed until 4 hours post-dose. No water was allowed for 1 hour prior through 1 hour post-dose. Subjects did not resume their usual dose of amphetamines until after the last plasma sample was drawn (24 hours post-dose).
Number of Patients	A total of 29 male and female children, aged 6 to 12 years (stratified into 3 groups of approximately 10 children: one group aged 6 to 7 years old, one group aged 8 to 9 years old, and one group aged 10 to 12 years old).
Main Inclusion Criteria	Had a history of positive response to treatment (including tolerability, particularly a lack of significant atypical side effects) with a stable dose of Adderall XR or IR (20 or 30 mg), or a comparable dose (in the opinion of the PI) of another amphetamine product (XR or IR), including Vyvanse® 50 to 70 mg or Dexedrine® 20 to 40 mg, for at least 1 month prior to Screening (Visit 1). In addition, the patient must have been under treatment with this amphetamine product for a minimum of 3 months. Was willing to refrain from beverage and foods containing alcohol, grapefruit, or caffeine/xanthine from 48 hours prior to the dose of study medication until the end-of-study visit (Visit 3).
Main Exclusion Criteria	Was diagnosed with or had a history of a tic disorder or Tourette's syndrome, as well as any family history of Tourette's. Medication-induced tics were not exclusionary. Had a history of seizure disorder. Children with a single simple febrile seizure prior to age 5 years were not excluded as long as there was not more than 1 seizure. Had any history of suicidal ideation or suicidal behavior as assessed by the C-SSRS at the Screening Visit (Pediatric Baseline Version) or at the Baseline Visit (Pediatric Since Last Visit Version). Had used any OTC medications, including nutritional supplements, within 7 days prior to the first dose of study medication. Was unable to tolerate an interruption in current ADHD therapy. Had a known medical condition that would preclude the use of MAS. Had a recent history of inadequate response to Adderall XR or IR, or their current amphetamine treatment.

	Was currently taking antidepressants, psychotropic medication, or any medication with psychotropic properties (e.g., guanfacine, clonidine, gabapentin or other epilepsy drugs, hydroxyzine, diphenhydramine). Subjects took their usual dose of ADHD medication up until 4 days prior to dosing. Subjects were not allowed to take any other prescription medication (including methylxanthines or any known drugs that are moderate or strong inhibitors/inducers of cytochrome P450 (CYP) enzymes such as barbiturates, phenothiazines, cimetidine, carbamazepine, etc.), or recreational drugs, with the exception of female hormonal contraceptives or hormone replacement therapy, from 30 days prior to the dose of study medication until the end-of-study visit without evaluation and approval by the medical monitor. Subjects were not allowed to consume beverages and foods containing alcohol, grapefruit, or caffeine/xanthine from 48 hours prior to the dose of study medication until the end-of-study visit. However, one time incidental consumption could be allowed. Subjects were not allowed to use tobacco products from 60 days prior to the dose of study medication until the end-of-study visit.
PK Sampling Times	3-mL blood samples were obtained prior to dosing and at selected times through 24 hours post-dose. A total of 8 PK blood samples were collected from each patient. Samples were collected pre-dose at time 0, as well as at 0.75, 2, 3.5, 5.5, 8, 12, and 24 hours post-dose *Reviewer comment: The sampling time was short, less than 3-half-lives for d- and l-amphetamine*
Analytical Method	Validated LC/MS/MS method. The method was validated for a range of 0.500 to 80.0 ng/mL for *d*-amphetamine and 0.200 to 32.0 ng/mL for *l*-amphetamine. Appropriate PK parameters were calculated using non-compartmental methods. I
Moieties to be Measured	Dextro (d)-amphetamine and levo (l)-amphetamine
Statistical Analysis	Non-compartmental methods. The PK parameters for *d*-amphetamine and *l*-amphetamine were summarized using descriptive statistics, for all patients combined and for patients within each age-group stratum. The geometric means and 95% confidence intervals (CIs) were calculated for CL/F and Vz/F in each age group, to determine if the 95% CIs were within the target range of 60% to 140%. The sponsor stated that due to difficulty in defining the terminal elimination phase for some concentration-time profiles, AUCinf (and consequently CL/F and Vz/F) could not be calculated for a

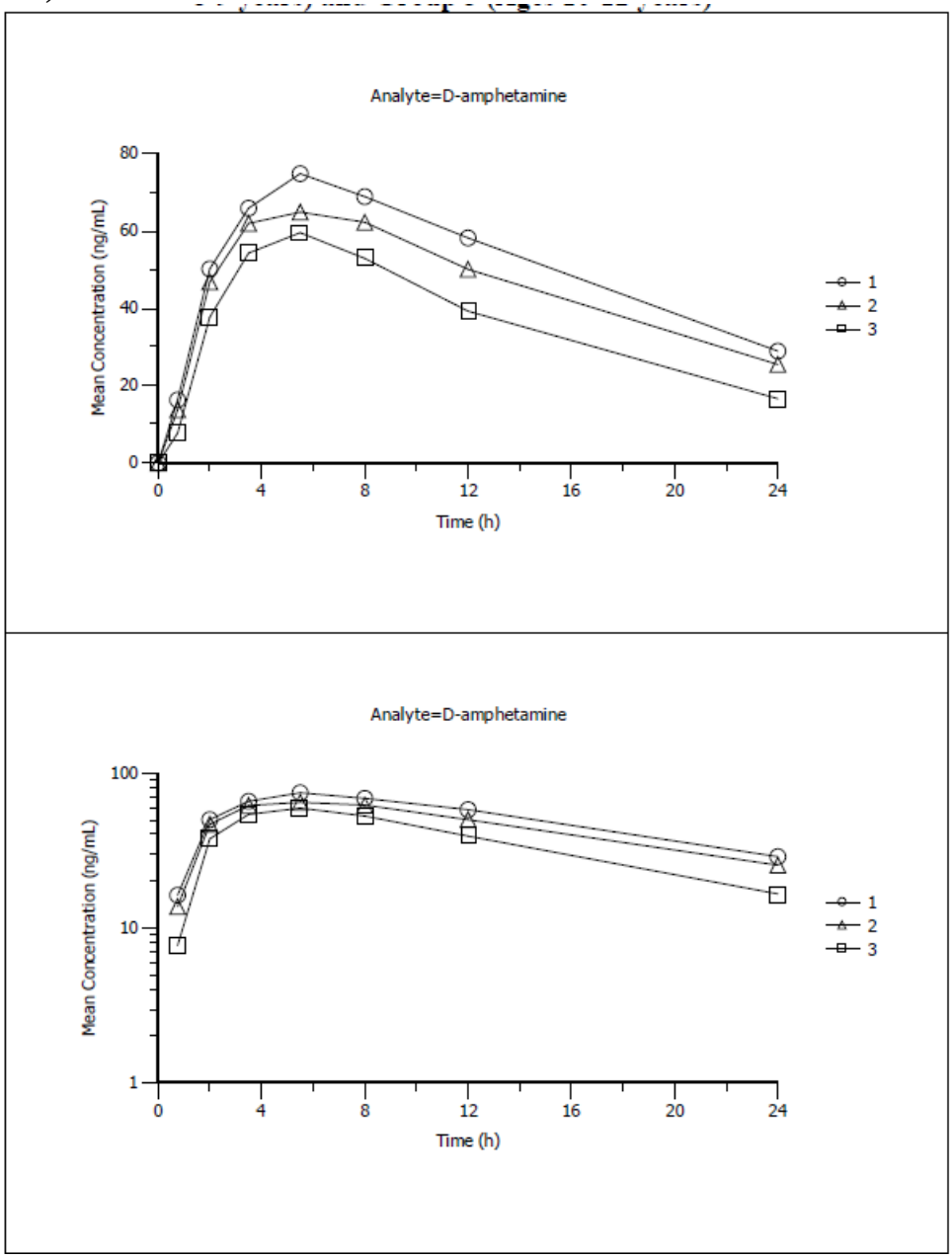
	few subjects. In order to provide a related comparison using data from all subjects, a secondary statistical analysis was performed using the 24-hour exposure (AUClast) following the same methodology as detailed in the protocol for weight-normalized CL/F and Vz/F.
Protocol Deviations	None reported.

Results

Study Population

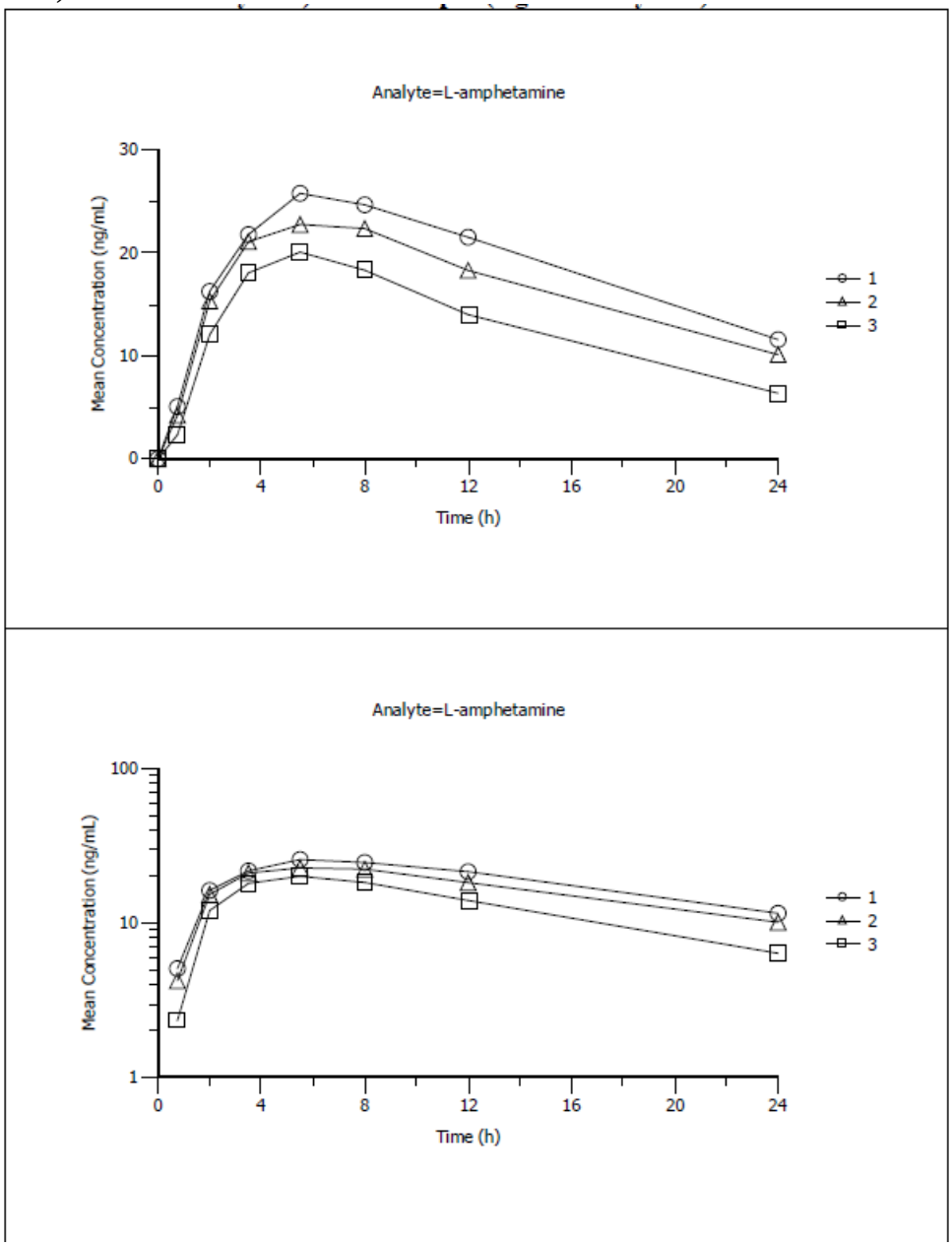
Randomized/Completed/Discontinued due to AE	29/29/0
Mean Age ±SD [Median (range)] years Age Group 6-7 years 8-10 years 11-12 years	8.8 ± 1.75 [9 (6,12)] 9 10 10
Male/Female	22/7
Race (Caucasian/Black/Other)	10/19/0
Mean weight (±SD) kg	
BMI (±SD) kg/m^2	17.36 ± 2.42

Mean *d*-amphetamine Concentration-Time Profiles after Administration of NT0201 (XR Oral Suspension) for Group 1 (Ages 6-7 years), Group 2 (Ages 8-9 years) and Group 3 (Ages 10-12 years)



Source: NT0201.1004 Study Report

Mean *l*-amphetamine Concentration-Time Profiles after Administration of NT0201 (XR Oral Suspension) for Group 1 (Ages 6-7 years), Group 2 (Ages 8-9 years) and Group 3 (Ages 10-12 years)



Source: NT0201.1004 Study Report

Descriptive Summary of Pharmacokinetic Parameters of d-amphetamine after administration of NT0201 XR Oral Suspension- All Subjects combined

Subject	Age Group	Age (year)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{last}/kg ((h*ng/mL)/kg)	AUC_{inf} (h*ng/mL)	AUC_{Extrap} (%)	λ_z (1/h)	$T_{1/2}$ (h)	T_{last} (h)	C_{last} (ng/mL)	CL/F (L/h)	Vz/F (L)	CL/F/kg ((L/h)/kg)	Vz/F/kg (L/kg)
		n	29	29	29	29	24	24	24	24	29	29	24	24	24	24
		Mean	5.33	68.0	1061	35.41	1599	27.64	0.0611	12.70	24.04	23.5	21.34	350.0	0.6559	11.04
		SD	1.59	12.3	229.2	14.75	784.4	11.27	0.0157	6.36	0.20	9.52	6.463	54.19	0.1749	2.370
		Min	2.00	46.8	694.7	12.87	847.2	15.97	0.0173	8.37	24.00	11.9	6.310	245.2	0.2475	6.231
		Median	5.50	66.2	1024	32.64	1379	23.32	0.0659	10.52	24.00	21.4	21.75	354.6	0.6487	11.04
		Max	8.00	106	1684	69.28	4754	68.24	0.0828	40.07	25.08	56.1	35.41	468.6	0.9986	16.96
		CV%	29.81	18.06	21.61	41.66	49.05	40.75	25.75	50.11	0.83	40.55	30.28	15.48	26.67	21.47
		Geometric Mean	.	.	.	32.56	.	.	.	.	.	.	20.21	345.8	0.6307	10.79
		CI 95% Lower GEO Mean	.	.	.	27.72	.	.	.	.	.	.	17.35	323.2	0.5553	9.833
		CI 95% Upper GEO Mean	.	.	.	38.25	.	.	.	.	.	.	23.55	370.0	0.7162	11.84

Pharmacokinetic Parameters for d-amphetamine by Age groups

Parameter	Age Group 1 (6-7 yrs): NT0201 (XR Oral Suspension) n	Mean	SD	CV%	Age Group 2 (8-9 yrs): NT0201 (XR Oral Suspension) n	Mean	SD	CV%
T_{max} (h)	9	5.67	1.75	30.88	10	5.00	1.83	36.51
C_{max} (ng/mL)	9	76.8	15.2	19.76	10	68.0	8.11	11.93
AUC_{last} (h*ng/mL)	9	1238	267.5	21.61	10	1088	129.6	11.91
AUC_{last}/kg (h*ng/mL/kg)	9	49.13	13.50	27.48	10	35.68	9.828	27.55
AUC_{inf} (h*ng/mL)	7	2251	1174	52.13	8	1557	310.9	19.97
AUC_{Extrap} (%)	7	34.73	16.64	47.89	8	29.08	7.25	24.92
λ_z (h^{-1})	7	0.0512	0.0201	39.22	8	0.0569	0.0108	19.02
$T_{1/2}$ (h)	7	16.74	10.67	63.71	8	12.60	2.47	19.61
T_{last} (h)	9	24.12	0.36	1.49	10	24.00	0.00	0.00
C_{last} (ng/mL)	9	28.9	12.8	44.38	10	25.5	5.98	23.51
CL/F (L/h)	7	15.54	5.291	34.04	8	19.91	3.680	18.49
Vz/F (L)	7	316.2	63.76	20.16	8	353.2	51.86	14.68
CL/F/kg (L/h/kg)	7	0.6183	0.2420	39.14	8	0.6345	0.1183	18.65
Vz/F/kg (L/kg)	7	12.43	2.582	20.78	8	11.35	1.995	17.58

Parameter	Age Group 3 (10-12 yrs): NT0201 (XR Oral Suspension) n	Mean	SD	CV%
T_{max} (h)	10	5.35	1.25	23.33
C_{max} (ng/mL)	10	60.0	7.07	11.78
AUC_{last} (h*ng/mL)	10	873.6	108.6	12.43
AUC_{last}/kg (h*ng/mL/kg)	10	22.80	7.323	32.12
AUC_{inf} (h*ng/mL)	9	1130	172.7	15.29
AUC_{Extrap} (%)	9	20.85	3.65	17.51
λ_z (h^{-1})	9	0.0725	0.0075	10.30
$T_{1/2}$ (h)	9	9.65	1.02	10.54
T_{last} (h)	10	24.00	0.00	0.00
C_{last} (ng/mL)	10	16.6	3.63	21.85
CL/F (L/h)	9	27.13	4.255	15.69
Vz/F (L)	9	373.4	37.57	10.06
CL/F/kg (L/h/kg)	9	0.7043	0.1658	23.54
Vz/F/kg (L/kg)	9	9.682	1.954	20.18

Abbreviations: CV=coefficient of variation, h=hour, NC=Not calculated, SD=standard deviation, XR=extended release.

Source NT0201.1004 Study Report

Descriptive Summary of Pharmacokinetic Parameters of l-amphetamine after administration of NT0201 XR Oral Suspension- All Subjects combined

Subject	Age Group	Age (year)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{last}/kg ((h*ng/mL)/kg)	AUC_{inf} (h*ng/mL)	AUC_{Extrap} (%)	λ_z (1/h)	$T_{1/2}$ (h)	T_{last} (h)	C_{last} (ng/mL)	CL/F (L/h)	Vz/F (L)	CL/F/kg ((L/h)/kg)	Vz/F/kg (L/kg)
		n	29	29	29	29	21	21	21	21	29	29	21	21	21	21
		Mean	5.93	23.5	380.1	12.70	642.1	30.54	0.0568	15.31	24.04	9.28	59.41	1049	1.802	32.71
		SD	1.97	4.10	87.60	5.376	576.7	13.59	0.0156	14.44	0.20	3.96	19.23	181.8	0.5300	7.534
		Min	2.00	16.6	240.1	4.447	303.1	18.81	0.0090	9.14	24.00	4.56	9.783	732.6	0.3837	18.16
		Median	5.50	22.9	356.4	11.72	494.8	26.23	0.0619	11.21	24.00	8.29	60.63	1035	1.840	32.98
		Max	12.00	34.6	624.3	25.69	3067	82.00	0.0758	77.08	25.08	22.6	98.98	1389	2.652	50.76
		CV%	33.24	17.46	23.05	42.33	89.81	44.49	27.42	94.27	0.83	42.69	32.37	17.33	29.42	23.03
		Geometric Mean	.	.	.	11.64	.	.	.	.	.	.	54.88	1033	1.693	31.88
		CI 95% Lower GEO Mean	.	.	.	9.868	.	.	.	.	.	.	44.16	952.7	1.403	28.64
		CI 95% Upper GEO Mean	.	.	.	13.72	.	.	.	.	.	.	68.21	1121	2.044	35.49

Pharmacokinetic Parameters of l-Amphetamine

Parameter	Age Group 1 (6-7 yrs): NT0201 (XR Oral Suspension)				Age Group 2 (8-9 yrs): NT0201 (XR Oral Suspension)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	9	5.94	1.91	32.15	10	6.30	2.72	43.16
C_{max} (ng/mL)	9	26.6	4.69	17.61	10	23.9	2.41	10.07
AUC_{last} (h*ng/mL)	9	448.2	103.7	23.13	10	393.3	44.38	11.28
AUC_{last}/kg (h*ng/mL/kg)	9	17.75	4.960	27.95	10	12.88	3.348	25.99
AUC_{inf} (h*ng/mL)	6	1083	986.4	91.04	6	547.9	105.1	19.19
AUC_{Extrap} (%)	6	40.51	21.69	53.54	6	30.12	7.43	24.68
λ_z (h^{-1})	6	0.0449	0.0215	47.98	6	0.0552	0.0109	19.83
$T_{1/2}$ (h)	6	24.61	25.93	105.38	6	13.07	3.12	23.86
T_{last} (h)	9	24.12	0.36	1.49	10	24.00	0.00	0.00
C_{last} (ng/mL)	9	11.6	5.38	46.46	10	10.1	2.49	24.63
CL/F (L/h)	6	40.04	17.82	44.52	6	56.19	9.062	16.13
Vz/F (L)	6	938.8	212.5	22.63	6	1037	182.2	17.58
CL/F/kg (L/h/kg)	6	1.624	0.8151	50.19	6	1.784	0.3044	17.06
Vz/F/kg (L/kg)	6	37.31	8.506	22.80	6	33.27	7.261	21.82

Parameter	Age Group 3 (10-12 yrs): NT0201 (XR Oral Suspension)			
	n	Mean	SD	CV%
T_{max} (h)	10	5.55	1.07	19.21
C_{max} (ng/mL)	10	20.2	2.20	10.89
AUC_{last} (h*ng/mL)	10	305.6	36.72	12.02
AUC_{last}/kg (h*ng/mL/kg)	10	7.976	2.555	32.03
AUC_{inf} (h*ng/mL)	9	410.8	59.26	14.43
AUC_{Extrap} (%)	9	24.16	3.51	14.54
λ_z (h^{-1})	9	0.0659	0.0064	9.74
$T_{1/2}$ (h)	9	10.61	1.03	9.74
T_{last} (h)	10	24.00	0.00	0.00
C_{last} (ng/mL)	10	6.37	1.20	18.87
CL/F (L/h)	9	74.47	11.40	15.31
Vz/F (L)	9	1130	130.3	11.53
CL/F/kg (L/h/kg)	9	1.932	0.4316	22.34
Vz/F/kg (L/kg)	9	29.28	5.862	20.02

Abbreviations: CV=coefficient of variation, h=hour, NC=Not calculated, SD=standard deviation, XR=extended release.
Source: NT0201-1004 Study Report

Pharmacokinetic Summary

An age-related trend in mean maximum and total *d*-amphetamine and *l*-amphetamine exposure was observed; as age increased, mean amphetamine exposure decreased. Mean weight-normalized CL/F values for *d*-amphetamine and *l*-amphetamine increased slightly with an increase in age while Vz/F values decreased. Mean T1/2 decreased as age increased, ranging from 9.65 h (Age Group 3; 10-12 yrs) to 16.74 h (Age Group 1; 6-7 yrs) for *d*-amphetamine and from 10.61 h (Age Group 3; 10-12 yrs) to 24.61 h (Age Group 1; 6-7 yrs) for *l*-amphetamine.

One subject in Age Group 1 exhibited an anomalous long T1/2 for both *d*-amphetamine and *l*-amphetamine; with this subject's data excluded from Age Group 1, *d*-amphetamine was within

the target range for both CL/F and Vz/F, but *l*-amphetamine was still out of the range for CL/F (95% upper bound: 2.719, target range: 1.075-2.507).

The geometric means and 95% CI calculated for *d*-amphetamine and *l*-amphetamine using weight-normalized 24-hour exposure data (AUClast), were within the target range of 60% to 140% for all age groups including data from Subject 2001. However the geometric means and 95% CI calculated for *d*-amphetamine and *l*-amphetamine CL/F and Vz/F were within the target range of 60% to 140% for Age Group 2 (8-9 yrs) and Age Group 3 (10-12 yrs) but not Age Group 1, 6 – 7 years old. One subject in Age Group 1 exhibited an anomalous long T1/2 for both *d*-amphetamine and *l*-amphetamine (T ½ for d- and l-amphetamine of about 40 and 77 hours, respectively). Once Subject 2001 was excluded from Age Group 1, *d*-amphetamine was within the target range for both CL/F and Vz/F but *l*-amphetamine was still out of the range for CL/F (95% upper bound: 2.719, target range: 1.075-2.507).

Since the geometric means and 95% CI calculated for amphetamine exposure over the 24 hour sampling schedule are within the target 60% to 140% range. The sponsor states that the variability observed in CL/F and Vz/F calculations was likely due to difficulty in extrapolating amphetamine exposure and elimination profiles past the final 24 hour sample for several subjects. Due to the high percent of extrapolation of AUCinf (≥20% in most subjects), the AUCinf data is inconclusive.

Safety Summary

Of the 29 enrolled subjects, 12 subjects (41.4%) experienced 14 TEAEs. All TEAEs were mild and included sinus tachycardia (10 subjects [34.5%], vomiting (3 subjects [10.3%], and nausea (1 subject [3.4%]). Most of these, with the exception of 1 incidence of sinus tachycardia and 1 instance of vomiting, were considered by the Investigator to be related to study drug. No subjects had clinically significant abnormal laboratory values, or end-of-study physical examinations or ECG results that were assessed by the investigator as clinically significant. Ten subjects had vital signs that were assessed by the Investigator as clinically significant and recorded as TEAEs of sinus tachycardia. All TEAEs were considered resolved by the end of the study. No deaths or non-fatal SAEs were reported, and there were no discontinuations due to TEAEs.

Reviewer's comments

1. *Study design: The study was conducted per protocol design and acceptable.*
2. *Study conduct: The sponsor reported no protocol deviations.*
3. *Data analysis: One subject had a very high AUCinf and T ½ data. The percentage of AUC extrapolated in the calculation of AUCinf was greater than 20% in most subject and therefore unreliable.*
4. *Conclusion: The reviewer agrees with the sponsor's conclusions that mean exposure (based on AUCt) decreased as age increased.*

4.4 OSIS Inspection

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/2/2017

TO: Division of Psychiatry Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 204325

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)
Clinical	Worldwide Clinical Trials Early Phase Services, LLC.	2455 NE Loop 410, Suite 150, San Antonio, TX.

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/s/

SHILA S NKAH
02/13/2017

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/s/

KOFI A KUMI
08/28/2017

HAO ZHU
08/28/2017

MEHUL U MEHTA
08/28/2017