

## Clinical Pharmacology Review

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NDA:	204326
Generic Name:	Amphetamine (b) (4) Extended-Release Orally Disintegrating Tablets
Trade Name:	ADZENYS-XR-ODT (proposed)
Strength and Dosage Form:	(b) (4)
Indication:	Attention Deficit Hyperactivity Disorder (ADHD) in Children (6-12 yr), Adolescents (13-17) and Adults
Sponsor:	NEOS Therapeutics
Submission Type:	Original NDA [505(b)(2)]
Priority Classification:	Standard
Submission Date:	Re-submission: 7/27/2015
PDUFA date:	1/27/2016 (6-month review cycle)
OCP Division:	DCP1
OND Division:	DPP
Reviewer:	Praveen V. Balimane, Ph.D.
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## Table of Contents

1. Executive Summary.....	3
1.1 Recommendation.....	3
1.2 Post-Marketing Studies .....	4
1.3 Summary of Clinical Pharmacology Findings.....	5
2. Question Based Review (QBR).....	8
2.1 General Attributes .....	8
2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug? .....	8
2.1.2 What are the highlights of the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics?.....	8
2.1.3. What are the proposed mechanism (s) of action and therapeutic indication(s)? .....	9
2.1.4. What are the proposed dosage and route of administration?.....	9

2.1.5. What is the reported adverse event profile from the bioequivalence studies?.....	9
2.2. General Clinical Pharmacology and Biopharmaceutics .....	10
2.2.1 What are the design features of the pivotal study used to support dosing or claims? ..	10
2.2.2. Is the Amphetamine Extended-Release Orally Disintegrating Tablets (XR-ODT) 30 mg under Fasted Conditions similar in PK profile and exposure to the reference listed drug, Adderall XR® Capsule 30 mg under Fasted Condition? .....	10
2.2.3 Is the exposure of amphetamine XR ODT significantly different based on administration with or without food? .....	12
2.2.4. What are the general PK Characteristics of Amphetamine XR ODT?.....	13
2.2.5. What is the composition of Amphetamine XR ODT formulation used in the relative BA study? .....	14
2.2.6. Is the formulation used in clinical study (NT0202.1005) identical to the to-be-marketed formulation?.....	15
3. Analytical Methods .....	16
3.1. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters? .....	16
3.2. What bioanalytical methods are used to assess concentrations of d and l-amphetamine and is the validation complete and acceptable? .....	16
4.1 Individual Study Report .....	19
4.2 OSI Inspection Report .....	33

## 1. Executive Summary

Neos Therapeutics, Inc (Neos) has submitted a New Drug Application (NDA) for Amphetamine (b)(4) Extended Release (XR) Orally Disintegrating Tablets (ODT) via the 505(b)(2) pathway. ADDERALL XR® is the reference listed product (RLD). In December 2012, Neos had submitted the original 505(b)(2) NDA for the Amphetamine XR ODT product to the U.S. Food and Drug Administration (FDA). During the review of the application in the 1<sup>st</sup> cycle, the Agency had identified significant CMC related issues (hardness, disintegration and friability) and issued a Complete Response letter dated September 24, 2013.

Neos re-submitted the NDA on July 27, 2015. The current development program is based on a single-dose bioequivalence (BE)/food effect clinical study (NT0202.1005) demonstrating similarity in pharmacokinetic profile and exposure between the amphetamine XR ODT product and ADDERALL XR® (RLD) and assessing the effect of food on PK of the amphetamine XR ODT product. No additional clinical safety and efficacy studies were submitted in this application. The efficacy and safety of the amphetamine XR ODT product is based on FDA's previous findings for the RLD-Adderall XR. The sponsor is seeking the indication for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) which is also the approved indication for ADDERALL XR®. Our findings are summarized as follows:

- The amphetamine XR ODT product demonstrated similar pharmacokinetic profile and exposure as compared to ADDERALL XR® and is anticipated to have similar efficacy and safety profiles to ADDERALL XR®.
- The amphetamine XR ODT product has no clinically meaningful food effect and thus can be administered with or without food.
- The amphetamine XR ODT product should be placed on the tongue. The tablet will disintegrate in saliva and should be swallowed without water or fluid.

### 1.1 Recommendation

The Office of Clinical Pharmacology (OCP) supports a recommendation for approval of Amphetamine (b)(4) Extended Release (XR) Orally Disintegrating Tablets (ODT) by Neos for the treatment of ADHD, provided no inspection issues are identified by the Office of Study Integrity and Surveillance (OSIS) on their inspection of the clinical site for Study NT0202.1005. The analytical site for the study was inspected by OSIS and the analytical portion of the BE/food effect study was found to be acceptable (OSIS review in DARRTS on 12/14/2015).

<b>Decision</b>	<b>Acceptable to OCP</b>	<b>Comment</b>
Overall	Yes	Pending labeling agreements with the sponsor.
Evidence of Effectiveness	Yes	Clinical efficacy and safety studies were not conducted and the information was borrowed from the RLD-Adderall XR
Proposed dose for general population	Yes	(b) (4)
Labeling	Yes	Pending satisfactory agreement with the sponsor.

## 1.2 Post-Marketing Studies

<b>PMC or PMR</b>	<b>Key Drug Development Question</b>	<b>Rationale</b>	<b>Design Summary (TBD)</b>
PMR	What are the PK properties of amphetamine XR ODT in male or female children (4 to less than 6 years of age) with ADHD?	Concentration time profile of amphetamine determines the onset and duration of the clinical response. It is valuable to assess the PK profile in ADHD patients 4-5 years old and ensure it is similar to that in older patients. This information can be used to support the clinical efficacy and safety trial design.	Study population: ADHD patients 4-5 years old Study design: single dose (b) (4), open label Sample size: prospectively powered to ensure a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution Dose(s): 10, 30 mg single dose (b) (4) Study length: one day Endpoints: AUC, Cmax

### 1.3 Summary of Clinical Pharmacology Findings

*Bioequivalent study to demonstrate similarity in pharmacokinetic profile and exposure of Amphetamine XR ODT vs. Adderall XR*

Neos performed an in vivo bridging study (NT0202.1005) at the 30 mg strength to demonstrate similarity in pharmacokinetic profile and exposure between the XR-ODT product and the listed drug, ADDERALL XR ®.

**Table 1: Bioequivalence data for *d*-amphetamine.**

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine Comparing amphetamine XR-ODT under Fasted Conditions (Treatment A) to the Reference Product under Fasted Conditions (Treatment C)

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	43.9361	45.3766	96.83	93.56	100.21	1.0000	8.99
ln(AUC <sub>0-5</sub> )	116.5182	140.8005	82.75	77.37	88.51	0.9998	17.72
ln(AUC <sub>5-last</sub> )	700.0723	676.8209	103.44	99.68	107.33	1.0000	9.68
ln(AUC <sub>inf</sub> )	822.2391	826.1451	99.53	96.73	102.41	1.0000	7.47
ln(AUC <sub>inf</sub> )	851.2894	856.4095	99.40	96.52	102.37	1.0000	7.70

<sup>a</sup> Geometric Mean for NT0202 XR-ODT-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

**Table 2: Bioequivalence data for *l*-amphetamine.**

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *l*-amphetamine Comparing amphetamine XR-ODT under Fasted Conditions (Treatment A) to the Reference Product under Fasted Conditions (Treatment C)

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	14.1535	14.0334	100.86	97.41	104.43	1.0000	9.11
ln(AUC <sub>0-5</sub> )	36.7157	43.1169	85.15	79.45	91.27	0.9997	18.27
ln(AUC <sub>5-last</sub> )	255.7442	240.5665	106.31	102.47	110.29	1.0000	9.64
ln(AUC <sub>inf</sub> )	294.2633	286.2231	102.81	99.83	105.88	1.0000	7.70
ln(AUC <sub>inf</sub> )	310.7037	303.0717	102.52	99.18	105.97	1.0000	8.67

<sup>a</sup> Geometric Mean for NT0202 XR-ODT-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

These results demonstrated that the amphetamine XR-ODT product has similar pharmacokinetic profiles and exposure to the RLD-Adderall XR.

- The 90% confidence intervals for the log-transformed exposure parameters C<sub>max</sub>, AUC<sub>last</sub>, AUC<sub>inf</sub>, and AUC<sub>5-last</sub> were within the 80% to 125% range for both *d*- and *l*-amphetamine
- Regarding early systemic exposure (AUC<sub>0-5</sub>), the geometric mean ratios (NT0202 XR-ODT/Adderall XR) were 82.75% for *d*-amphetamine and 85.15% for *l*-amphetamine and the lower 90% confidence intervals were just below the threshold value of 80% (77.37% for *d*-amphetamine and 79.45% for *l*-amphetamine). Variability in the rapidly changing concentrations during the first

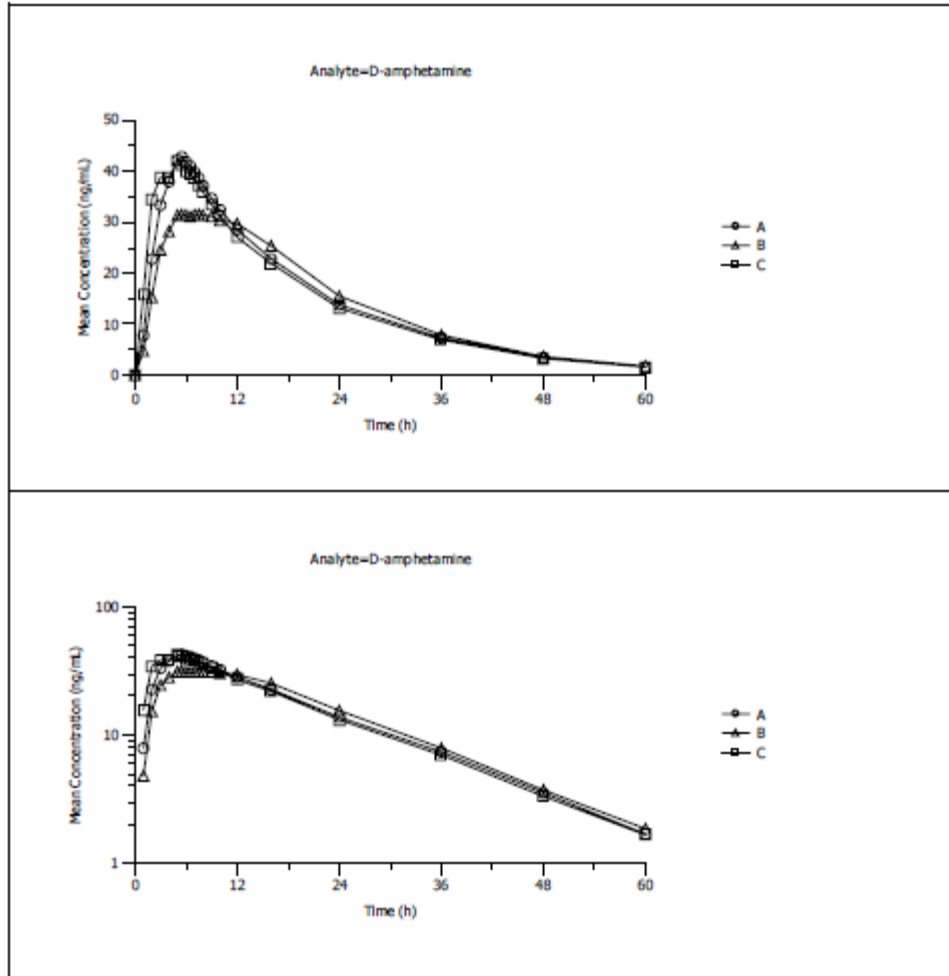
5 hours likely contributed to the width of the 90% confidence intervals of AUC<sub>0-5</sub>. In the study, though the lower bound of 90% CI of AUC<sub>0-5h</sub> was below 80%, the point estimate of the ratio of test/RLD for AUC<sub>0-5h</sub> was 83%. Additionally, it is known from published data (Current Medical Research and Opinion, Vol 18, 5, 311-316, 2002) that Adderall XR (RLD) is also known to have a 42% to 53% reduction in partial AUCs (0-to 6 h and 0-to 4 h, respectively) in presence of food. However, in spite of this reduction in early exposure of Adderall XR, its label recommends taking it without regards to food. Allowing Adderall XR being taken with or without food indicates that clinically meaningful changes following the treatment of Adderall XR is not anticipated in the presence or absence of food. Hence, it is also expected that a mean 17% reduction in AUC<sub>0-5h</sub> observed for amphetamine XR ODT product is also unlikely to cause any clinically meaningful changes.

- Visual inspection demonstrated that the shape of the mean pharmacokinetic profiles were similar between amphetamine XR ODT and Adderall XR (RLD).

#### *Food Effect Study for Amphetamine XR ODT*

In Study NT0202.1005, the effect of food on the rate of absorption and oral bioavailability for the Amphetamine XR-ODT was assessed.

**Figure 1: Mean *d*-amphetamine Concentration-Time Profiles after Administration of amphetamine XR-ODT under Fasted Conditions (Treatment A), amphetamine XR-ODT under Fed Conditions (Treatment B), and the Reference Product under Fasted Conditions (Treatment C)**



The presence of food decreased the rate of absorption of amphetamine XR-ODT, which resulted in a decrease in maximum exposure ( $C_{max}$ ) to *d*- and *l*-amphetamine by approximately 18% and a delay in the median  $T_{max}$  of approximately 2 hours (*d*-amphetamine) to 2.25 hours (*l*-amphetamine). However, no meaningful food effect was observed for overall systemic exposure, based on  $AUC_{last}$  and  $AUC_{inf}$ . This effect of food on the PK of amphetamine XR-ODT is very similar to the extent of food-effect observed for ADDERALL XR (the RLD) which is also known to have slight decrease in exposure (7% decrease in AUC and 14% decrease in  $C_{max}$ ) with a 2.5 hours increase in  $T_{max}$  in presence of food (Current Medical Research and Opinion, Vol 18, 5, 311-316, 2002). Similar to the RLD, this decrease in  $C_{max}$  and prolonged  $T_{max}$  is not considered to be clinically significant, and therefore amphetamine XR ODT could be taken without regards to meals.

*Clinical and Bioanalytical Site Inspections:*

The analytical site for the study was inspected by the Office of Study Integrity and Surveillance (OSIS) and the analytical portion of BE/food-effect study was found to be acceptable (OSIS review in DARRTS on 12/14/2015). The inspection report of the

clinical site for Study NT0202.1005 by OSIS is expected by Jan 13<sup>th</sup>, 2016 (Appendix 4.2).

## 2. Question Based Review (QBR)

### 2.1 General Attributes

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

Neos Therapeutics, Inc (Neos) has submitted a New Drug Application (NDA) for Amphetamine (b)(4) Extended Release (XR) Orally Disintegrating Tablets (ODT) via the 505(b)(2) pathway. ADDERALL XR® is the reference listed product (RLD). In December 2012, Neos had submitted the original 505(b)(2) NDA for the Amphetamine XR ODT product to the U.S. Food and Drug Administration (FDA). During the review of the application in the 1<sup>st</sup> cycle, the Agency had identified significant CMC related issues (hardness, disintegration and friability) and issued a Complete Response letter dated September 24, 2013.

Neos re-submitted the NDA on July 27, 2015. The current development program is based on a single-dose bioequivalence (BE) clinical study (NT0202.1005) demonstrating similarity in pharmacokinetic profile and exposure between the amphetamine XR ODT product and ADDERALL XR® (RLD) and assessing the effect of food on PK of the amphetamine XR ODT product. No additional clinical safety and efficacy studies were submitted in this application. The efficacy and safety of the amphetamine XR ODT product is based on FDA's previous findings for the RLD-Adderall XR. The sponsor is seeking the indication for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) which is also the approved indication for ADDERALL XR®.

#### 2.1.2 What are the highlights of the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics?

Amphetamine XR-ODT contains a Schedule II drug, amphetamine, in a 3:1 ratio of d- to l- isomer and is formulated in a new extended-release ODT dosage form. Amphetamine XR-ODT contains Amphetamine (b)(4) which contains a 3:1 ratio of d- to l- isomer, (b)(4) ODT along with other (b)(4) excipients. (b)(4) methacrylic acid copolymer type A and triethyl citrate.



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

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in ADHD is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extra-neuronal space.

### 2.1.4. What are the proposed dosage and route of administration?

The product is an XR-ODT tablet that is to be placed on the tongue where it disintegrates quickly followed by ingestion of the disintegrants with saliva. This is how the product is given in the clinical trial. Since this product will be taken without any water, no dedicated water-effect study was conducted to demonstrate lack of meaningful changes in pharmacokinetic profile and exposure of amphetamine when the product is taken with water. .

In children with ADHD who are 6-12 years of age and are either starting treatment for the first time or switching from another medication, start with (b) (4) mg once daily in the morning; daily dosage may be adjusted in increments of (b) (4)mg or (b) (4) mg at weekly intervals. The maximum recommended dose for children is (b) (4)mg/day.

The recommended starting dose for adolescents with ADHD who are 13-17 years of age and are either starting treatment for the first time or switching from another medication is (b) (4) mg/day. The dose may be increased to (b) (4) mg/day after one week if ADHD symptoms are not adequately controlled.

In adults with ADHD who are either starting treatment for the first time or switching from another medication, the recommended dose is amphetamine XR-ODT (b) (4) mg/day.

### 2.1.5. What is the reported adverse event profile from the bioequivalence studies?

The sponsor reported that in general, the clinical portion of the bioequivalence study (NT0202.1005) was completed with no serious adverse event (AE). The investigational drug was well tolerated by healthy subjects, as a single-dose administration. There were no deaths or serious adverse events reported in the study. The sponsor reported total of 46 treatment-emergent adverse events (TEAEs), which were reported by 17 subjects over the course of the study. Of these 46 TEAEs, 45 were mild and 1 was moderate; there were no serious TEAEs or deaths during the course of the study. In general, the nature of the TEAE's reported was consistent with the mechanism of action of the study medication.

The sponsor reported that there were no clinically significant findings in the vital signs assessment or the laboratory tests for any of the subjects. Refer to medical review for Agency's assessment of safety.

## **2.2. General Clinical Pharmacology and Biopharmaceutics**

### **2.2.1 What are the design features of the pivotal study used to support dosing or claims?**

The sponsor is seeking approval for the treatment of ADHD by Amphetamine (b) (4) Extended Release (XR) Orally Disintegrating Tablets (ODT). The current development program is based on a single-dose bioequivalence (BE)/food effect clinical study (NT0202.1005) demonstrating similarity in pharmacokinetic profile and exposure between amphetamine XR ODT product and ADDERALL XR<sup>®</sup> (RLD) and assessing the effect of food on PK of amphetamine XR ODT product. No additional clinical safety and efficacy studies were submitted in this application.

### **2.2.2. Is the Amphetamine Extended-Release Orally Disintegrating Tablets (XR-ODT) 30 mg under Fasted Conditions similar in PK profile and exposure to the reference listed drug, Adderall XR<sup>®</sup> Capsule 30 mg under Fasted Condition?**

Yes.

Sponsor's Amphetamine XR-ODT was found to be similar in PK profile and exposure to RLD- Adderall XR under Fasted Conditions.

The 90% confidence intervals for the log-transformed exposure parameters C<sub>max</sub>, AUC<sub>last</sub>, AUC<sub>inf</sub>, and AUC<sub>5-last</sub> were within the 80% to 125% range for both *d*- and *l*-amphetamine.

Regarding early systemic exposure (AUC<sub>0-5</sub>), the geometric mean ratios (amphetamine XR-ODT/Adderall XR) were 82.75% for *d*-amphetamine and 85.15% for *l*-amphetamine and the lower 90% confidence intervals were just below the threshold value of 80% (77.37% for *d*-amphetamine and 79.45% for *l*-amphetamine). Variability in the rapidly changing concentrations during the first 5 hours likely contributed to the width of the 90% confidence intervals about AUC<sub>0-5</sub>.

**Table 3: Bioequivalence data for *d*-amphetamine.** Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine Comparing amphetamine XR-ODT under Fasted Conditions (Treatment A) to the Reference Product under Fasted Conditions (Treatment C)

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	43.9361	45.3766	96.83	93.56	100.21	1.0000	8.99
ln(AUC <sub>0-2</sub> )	116.5182	140.8005	82.75	77.37	88.51	0.9998	17.72
ln(AUC <sub>0-12h</sub> )	700.0723	676.8209	103.44	99.68	107.33	1.0000	9.68
ln(AUC <sub>inf</sub> )	822.2391	826.1451	99.53	96.73	102.41	1.0000	7.47
ln(AUC <sub>inf</sub> )	851.2894	856.4095	99.40	96.52	102.37	1.0000	7.70

<sup>a</sup> Geometric Mean for NT0202 XR-ODT-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

**Table 4: Bioequivalence data for *l*-amphetamine.** Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *l*-amphetamine Comparing amphetamine XR-ODT under Fasted Conditions (Treatment A) to the Reference Product under Fasted Conditions (Treatment C)

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	14.1535	14.0334	100.86	97.41	104.43	1.0000	9.11
ln(AUC <sub>0-2</sub> )	36.7157	43.1169	85.15	79.45	91.27	0.9997	18.27
ln(AUC <sub>0-12h</sub> )	255.7442	240.5665	106.31	102.47	110.29	1.0000	9.64
ln(AUC <sub>inf</sub> )	294.2633	286.2231	102.81	99.83	105.88	1.0000	7.70
ln(AUC <sub>inf</sub> )	310.7037	303.0717	102.52	99.18	105.97	1.0000	8.67

<sup>a</sup> Geometric Mean for NT0202 XR-ODT-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

In addition to the comparison of the mean data, an assessment of intra-subject variability (XR-ODT vs. Adderall) for the key PK parameters was also performed. The Table below provides data on individual subjects and if there was any significant change in key PK parameters for individual subjects. None of the subjects had <50% decrease or >200% increase in ratio for any of the PK parameters. Majority of the subjects had ratio between 80% -125%

**Table 5: Number and Percentage of Subjects with Calculated Ratios that Meet the Indicated Conditions (>200%, >125%, <80%, <50%) for All Pharmacokinetic Parameters Applied for Bioequivalence Testing**

Analyte	Conditions	AUC <sub>0-5</sub>	AUC <sub>5-∞</sub>	C <sub>max</sub>	AUC <sub>0-∞</sub>	AUC <sub>0-inf</sub>
<i>d</i> -amphetamine (n=39)	>200%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>125%	3 (8%)	5 (13%)	0 (0%)	1 (3%)	1 (3%)
	<80%	21 (54%)	0 (0%)	2 (5%)	0 (0%)	0 (0%)
	<50%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<i>l</i> -amphetamine (n=39)	>200%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>125%	3 (8%)	4 (10%)	1 (3%)	4 (10%)	4 (10%)
	<80%	18 (46%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
	<50%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Abbreviations: AUC<sub>0-inf</sub> (AUC<sub>inf</sub>) = area under the plasma concentration–time curve at infinity; AUC<sub>0-t</sub> (AUC<sub>last</sub>) = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; AUC<sub>0-5</sub> = area under the plasma concentration versus time curve from time 0 to 5 hours; AUC<sub>5-t</sub> (AUC<sub>5-last</sub>) = area under the plasma concentration versus time curve from 5 hours to the last quantifiable concentration; C<sub>max</sub> = maximum plasma concentration

In the study, though the lower bound of 90% CI of pAUC0-5h was below 80%, the point estimate of the ratio of test/RLD for pAUC0-5h was 83%. Additionally, it is known from published data (Current Medical Research and Opinion, Vol 18, 5, 311-316, 2002) that Adderall XR (RLD) is also known to have a 42% to 53% reduction in pAUC (0-to 6hr and 0-to 4 hr, respectively) in presence of food. However, in spite of this reduction in early exposure of Adderall XR, its label recommends taking it without regards to food. Allowing Adderall XR being taken with or without food indicates that clinically meaningful changes following the treatment of Adderall XR is not anticipated in the presence or absence of food. Hence, it is also expected that a mean 17% reduction in pAUC0-5h observed for amphetamine XR ODT product is also unlikely to cause any clinically meaningful changes. Additionally, visual inspection demonstrated that the shape of the mean pharmacokinetic profiles were similar between amphetamine XR ODT and Adderall XR (RLD).

Therefore, considering all the data, we believe that amphetamine XR-ODT has similar PK profile and exposure to Adderall XR and thus is likely to have similar efficacy and safety profile to the RLD (ADDERALL-XR®).

### 2.2.3 Is the exposure of amphetamine XR ODT significantly different based on administration with or without food?

No.

Food effect study demonstrated that there was no meaningful effect of food on the overall systemic exposure (i.e. AUC<sub>last</sub> and AUC<sub>inf</sub>) for amphetamine XR ODT. However, the presence of food decreased the rate of absorption of amphetamine XR-ODT, which resulted in a decrease in maximum exposure (C<sub>max</sub>) to *d*- and *l*-amphetamine by approximately 18% and a delay in the median T<sub>max</sub> of approximately 2 hours (*d*-amphetamine) to 2.25 hours (*l*-amphetamine). This effect of food on the PK of amphetamine XR-ODT is very similar to the extent of food-effect observed for ADDERALL XR (the RLD) which is also known to have slight decrease in exposure (7% decrease in AUC and 14% decrease in C<sub>max</sub>) with a 2.5 hours increase in T<sub>max</sub> in presence of food (Current Medical Research and Opinion, Vol 18, 5, 311-316, 2002). This decrease in C<sub>max</sub> and prolonged T<sub>max</sub> is not clinically significant, and therefore amphetamine XR ODT could be taken without regards to meals, similar to the RLD.

Table 6: **Food-Effect data for *d*-amphetamine.** Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine Comparing amphetamine XR-ODT under Fed Conditions (Treatment B) to amphetamine XR-ODT under Fasted Conditions (Treatment A)

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	35.6699	43.9404	81.18	77.68	84.83	1.0000	11.54
ln(AUC <sub>0-∞</sub> )	84.0589	116.4805	72.17	64.73	80.46	0.9578	29.02
ln(AUC <sub>0-tmax</sub> )	719.3697	699.9546	102.77	99.51	106.15	1.0000	8.46
ln(AUC <sub>inf</sub> )	809.8683	821.9417	98.53	95.93	101.20	1.0000	6.99
ln(AUC <sub>inf</sub> )	840.3156	851.0481	98.74	95.98	101.58	1.0000	7.42

<sup>a</sup> Geometric Mean for NT0202 XR-ODT-Fed (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

Table 7: **Food-Effect data for *l*-amphetamine.** Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *l*-amphetamine Comparing amphetamine XR-ODT under Fed Conditions (Treatment B) to amphetamine XR-ODT under Fasted Conditions (Treatment A)

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	11.5346	14.1572	81.48	77.99	85.11	1.0000	11.46
ln(AUC <sub>0-∞</sub> )	26.5274	36.7053	72.27	64.69	80.74	0.9523	29.58
ln(AUC <sub>0-tmax</sub> )	258.2980	255.6891	101.02	97.72	104.43	1.0000	8.69
ln(AUC <sub>inf</sub> )	286.8474	294.1651	97.51	94.79	100.31	1.0000	7.41
ln(AUC <sub>inf</sub> )	304.3459	310.6676	97.97	94.86	101.18	1.0000	8.44

<sup>a</sup> Geometric Mean for NT0202 XR-ODT-Fed (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

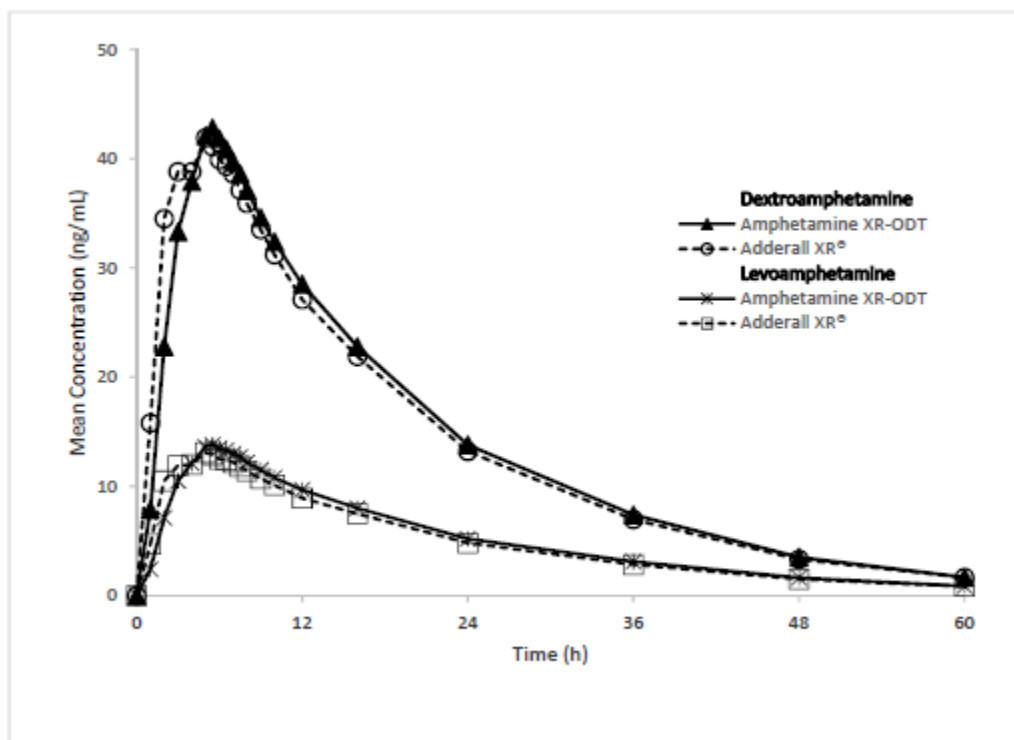
<sup>c</sup> 90% Confidence Interval

Therefore, food had no effect on overall AUC with only marginal effects on C<sub>max</sub> and T<sub>max</sub> and thus Amphetamine XR ODT can be taken without regards to food.

#### 2.2.4. What are the general PK Characteristics of Amphetamine XR ODT?

Following a single, 30 mg single oral dose of amphetamine XR-ODT in 40 healthy adult subjects in a crossover study under fasting conditions, *d*-amphetamine mean (+SD) peak plasma concentrations of 44.9 (+8.9) ng/mL occurred at a median time of 5.0 hours after dosing, and *l*-amphetamine mean (+SD) peak plasma concentrations of 14.5 (+ 3.0) ng/mL occurred at a median time of 5.25 hours after dosing.

Figure 2: Mean Concentration of D-Amphetamine (and L-Amphetamine) vs. Time for amphetamine XR-ODT and RLD- Adderall XR in the Fasted State



Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain  $\alpha$  or  $\beta$  carbons to form alpha-hydroxyamphetamine or norephedrine, respectively. Norephedrine and 4-hydroxyamphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxyamphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxyamphetamine.

### 2.2.5. What is the composition of Amphetamine XR ODT formulation used in the relative BA study?

Neos has developed Amphetamine Extended Release Orally Disintegrating Tablets (XR-ODT), an extended release oral formulation of Amphetamine, as an orally disintegrating tablet (ODT) intended for the treatment of attention deficit hyperactivity disorder (ADHD). The composition of the formulation used in the relative BA study is listed in Table 8.

**Table 8:** Amphetamine XR-ODT Composition

Ingredient	Application	(b) (4) mg ODT	(b) (4) ng ODT
(b) (4) Levoamphetamine <sup>a</sup>	Active	(b) (4)	
(b) (4) Dextroamphetamine <sup>b</sup>	Active		
(b) (4)			
(b) (4) Polystyrene Sulfonate <sup>c</sup>	(b) (4)		(b) (4)
(b) (4) Polyethylene Glycol <sup>(b) (4)</sup>			(b) (4)
Methacrylic Acid Copolymer type A			(b) (4)
Triethyl Citrate			(b) (4)
(b) (4)			(b) (4)
Crospovidone	(b) (4)		(b) (4)
Sucralose			(b) (4)
Citric Acid (b) (4)			(b) (4)
(b) (4) Orange Flavor (b) (4)			(b) (4)
Lake Blend Orange (b) (4)			(b) (4)
Magnesium Stearate			(b) (4)
(b) (4)			(b) (4)
<sup>a</sup> (b) (4) 3:1 (b) (4) ratio of dextroamphetamine to levoamphetamine			(b) (4)
<sup>b</sup> (b) (4)			(b) (4)
<sup>c</sup> Sodium polystyrene sulfonate (b) (4)			(b) (4)
<sup>d</sup> (b) (4) mannitol, fructose, microcrystalline cellulose, crospovidone, and colloidal silicon dioxide			(b) (4)

**2.2.6. Is the formulation used in clinical study (NT0202.1005) identical to the to-be-marketed formulation?**

The sponsor plans to use the same formulation which was used in the clinical study (NT0202.1005) as the commercial formulation (to-be-marketed) in the future. The detailed composition of the to-be-marketed formulation is provided in the response to Question 2.2.5.

### 3. Analytical Methods

#### **3.1. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?**

Yes, both d and l-amphetamine were appropriately measured in biological fluids.

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

The concentrations of *d* and *l*-amphetamine in human plasma were determined using a precise and accurate LC-MS/MS method. The method was adequately validated and acceptable.

Human plasma was analyzed for D-amphetamine and L-amphetamine according to (b) (4) procedure ATM-1784, Validation, effective 25 July 2011 and Original, effective 11 August 2011. 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. Human plasma containing D-amphetamine, L-amphetamine, and the ring pentadeuterated racemic internal standard, DL-amphetamine-D5, was extracted by liquid-liquid extraction. The organic phase was transferred and treated with a derivitization reagent. After evaporation and reconstitution, an aliquot was injected onto a Sciex 4000 LC-MS-MS equipped with an HPLC column. The peak area of m/z 329→91 amphetamine-TPC product ion was measured against the corresponding diastereomer peak area of the m/z 334→96 amphetamine-D5-TPC product ion of the internal standard. Quantitation was performed using separate weighted (1/x<sup>2</sup> for both analytes) linear least squares regression analyses generated from calibration standards prepared immediately prior to each run.

**Table 9: Bioanalytical Method Validation Summary for D-Amphetamine in Human K2-EDTA plasma**



Information Requested	Data
Analyte	D-Amphetamine
Internal standard (IS)	D-Amphetamine-D <sub>5</sub>
Method description	ATM-1784; Liquid-liquid extraction; Sciex API 4000 or 5000 LC-MS-MS; Masterfile 1004299
Limit of quantitation	0.500, ng/mL
Average recovery of drug (%)	93.31
Average recovery of IS (%)	87.77
Standard curve concentrations (ng/mL)	0.500 to 80.0 ng/mL
LLOQ Intra-Batch Precision (%CV)	2.7% to 4.7%
LLOQ Inter-Batch Precision (%CV)	4.5%
LLOQ Intra-Batch Accuracy (%bias)	-6.4% to 0.0%
LLOQ Inter-Batch Accuracy (%bias)	-3.4%
QC concentrations (ng/mL)	1.50, 10.0, 64.0
QC Intraday precision range (%)	0.9 to 3.0
QC Intraday accuracy range (%)	-3.1 to 3.0
QC Interday precision range (%)	1.3 to 2.9
QC Interday accuracy range (%)	-3.0 to 8.0
Bench-top stability (hrs)	24 hours @ room temperature
Stock stability (days)	75 days @ 4°C and 20 hours @ room temperature @ 50.0 µg/mL; 55 days @ 4°C and 17 hours @ room temperature @ approximately 3.75 ng/mL
Processed stability (hrs)	386 hours @ 4°C
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days)	226 days @ -20°C; 226 days @ -70°C
Dilution integrity	400 ng/mL diluted 10-fold
Selectivity	No interfering peaks noted in blank plasma samples

**Table 10: Bioanalytical Method Validation Summary for L-Amphetamine in Human K2-EDTA Plasma**

Information Requested	Data
Analyte	L-Amphetamine
Internal standard (IS)	L-Amphetamine-D <sub>5</sub>
Method description	ATM-1784; Liquid-liquid extraction; Sciex API 4000 or 5000 LC-MS-MS; Masterfile 1004299
Limit of quantitation	0.200, ng/mL
Average recovery of drug (%)	87.08
Average recovery of IS (%)	81.69
Standard curve concentrations (ng/mL)	0.200 to 32.0 ng/mL
LLOQ Intra-Batch Precision (%CV)	6.3% to 9.0%
LLOQ Inter-Batch Precision (%CV)	9.2%
LLOQ Intra-Batch Accuracy (%bias)	-7.0% to 7.0%
LLOQ Inter-Batch Accuracy (%bias)	-1.5%
QC concentrations (ng/mL)	0.600, 4.00, 25.6 ng/mL
QC Intraday precision range (%)	1.0 to 2.1
QC Intraday accuracy range (%)	-1.2 to 1.3
QC Interday precision range (%)	2.1 to 3.1
QC Interday accuracy range (%)	0.0 to 3.3
Bench-top stability (hrs)	24 hours @ room temperature
Stock stability (days)	75 days @ 4°C and 20 hours @ room temperature @ 50.0 µg/mL; 55 days @ 4°C and 17 hours @ room temperature @ 1.50 ng/mL
Processed stability (hrs)	386 hours @ 4°C
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days)	226 days @ -20°C; 226 days @ -70°C
Dilution integrity	160 ng/mL diluted 10-fold
Selectivity	No interfering peaks noted in blank plasma samples

## 4. Appendix

### ***4.1 Individual Study Report***

### Bioequivalence and Food-Effect Study

NDA 204326 (Amphetamine (b) (4) XR ODT Tablet)

<b>Report #</b> NT0202.1005	<b>Study Period:</b> 26 April 2014 to 12 May 2014	<b>EDR Link</b>
<b>Title</b>	<b>A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Bioavailability Study of an Investigational Formulation of NT0202 Amphetamine Extended-Release Orally Disintegrating Tablets (XR-ODT) 30 mg under Fed and Fasted Conditions and Adderall XR® Capsule 30 mg under Fasted Conditions</b>	
<b>Study Design &amp; Objective</b>		
<p><b>Objective:</b>                  The objectives of this single-dose, open-label, randomized, three-period, three-treatment crossover study were the following:</p> <p>1) To compare the rate of absorption and oral bioavailability of NT0202 Amphetamine XR-ODT (equivalent to 30 mg mixed amphetamine salts), developed by Neos Therapeutics, Inc., to an equivalent 30 mg oral dose of the commercially available reference product Adderall XR, manufactured for Shire US Inc., following an overnight fast of at least 10 hours.</p> <p>2) To assess the effect of food on the rate of absorption and oral bioavailability of NT0202 Amphetamine XR-ODT 30 mg.</p>		
<p><b>Study Design:</b>                  This was a single-dose, open-label, randomized, three-period, three-treatment crossover study in which 42 healthy adult subjects were to receive one single dose of NT0202 Amphetamine XR-ODT 30 mg under fasted conditions, one single dose of NT0202 Amphetamine XR-ODT 30 mg under fed conditions, and one single dose of Adderall XR 30 mg under fasted conditions. Subjects in all three treatment conditions fasted overnight for at least 10 hours. Subjects receiving the treatment under fed conditions were dosed 5 minutes after consuming a Food and Drug Administration (FDA) standard high-calorie, high-fat breakfast meal; consumption of the breakfast began 30 minutes prior to dosing. Subjects who received either of the fasted treatments continued to fast up until the time that they were dosed. All subjects fasted for 4 hours after dosing. Each dose administration was separated by a washout period of 7 days.</p>		
<input checked="" type="checkbox"/> Bioequivalence		<input checked="" type="checkbox"/> Bioavailability
Single-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy Volunteers		
<b>Screening:</b> ≤ NA		<b>Washout:</b> 7 days between treatments
<b>Period - 3</b>	Inpatient stay <input checked="" type="checkbox"/> Y <input type="checkbox"/> N:	

**Treatments:** (Active Ingredient: Amphetamine)

	<b>Treatment A: Test - Fasted</b>	<b>Treatment B: Test - Fed</b>	<b>Treatment C: Reference Adderall XR® - Fasted</b>
Dosage Form	XR-ODT Tablet	XR-ODT Tablet	XR- Tablet
Dosage Strength	1X30 mg	1X30 mg	1X30 mg
Fed or Fasted	Fasted	Fed	Fasted
Batch/Lot #	4E042E	4E042E	A90382A
Administration	Oral	Oral	Oral

Test Formulation (Treatments A and B), Dose and Mode of Administration, Lot Number:

NT0202 Amphetamine Extended-Release Orally Disintegrating Tablets (XR-ODT), Equivalent to 30 mg Mixed Amphetamine Salts

Dose = 1 x 30 mg ODT, orally administered

Lot: 4E042E

Treatment A was administered under fasted conditions. Treatment B was administered under fed conditions.

Duration of Treatment: Three single-dose treatments were administered with a 7-day washout period between doses.

Reference Product (Treatment C), Dose, and Mode of Administration, Lot Number:

Adderall® XR (Mixed Salts of A Single-Entity Amphetamine Product) Extended-Release Capsules, 30 mg CII

Dose = 1 x 30 mg Capsule, orally administered

Lot: A90382A

Treatment C was administered under fasted conditions.

**Sampling Times (PK, plasma):**

Blood samples (1 x 4 mL) were collected at 0 hours (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.

Samples were collected in appropriately labeled, 4 mL Vacutainer tubes containing K2-EDTA. Blood samples were centrifuged at approximately 3000 rpm for 10 minutes at approximately 4 °C, and the resulting plasma was harvested and transferred evenly into appropriately labeled polypropylene screw-cap tubes. Within 60 minutes of blood draw, samples were to be frozen at approximately -20 °C or lower pending transfer to (b) (4) for analysis.

**Analytical Method:**

The performance of the analytical method is acceptable. Yes  No

### LC/MS/MS:

Human plasma was analyzed for D-amphetamine and L-amphetamine using a 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 based on the analysis of 0.150 mL of plasma. Human plasma containing D-amphetamine, L-amphetamine, and the ring penta-deuterated racemic internal standard, DL-amphetamine-D5, was extracted by liquid-liquid extraction. The organic phase was transferred and treated with a derivitization reagent. After evaporation and reconstitution, an aliquot was injected onto a Sciex 4000 LC-MS-MS equipped with an HPLC column. The peak area of  $m/z$  329→91 amphetamine-TPC product ion was measured against the corresponding diastereomer peak area of the  $m/z$  334→96 amphetamine-D5-TPC product ion of the internal standard. Quantitation was performed using separate weighted ( $1/x^2$  for both analytes) linear least squares regression analyses generated from calibration standards prepared immediately prior to each run.

### Statistical Method:

The concentration-time data were transferred from Watson Laboratory Information Management System™ (LIMS, Version 7.2.0.03, Thermo Fisher Scientific) directly to Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin. Concentration-time data that were below the limit of quantification (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Full precision concentration data (not rounded to three significant figures) and actual sample times were used for all pharmacokinetic and statistical analyses.

The following pharmacokinetic parameters were calculated: peak concentration in plasma ( $C_{max}$ ), time to peak concentration ( $T_{max}$ ), elimination rate constant ( $\lambda_z$ ), terminal half-life ( $T_{1/2}$ ), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration ( $AUC_{last}$ ), area under the concentration-time curve from time-zero to 5 hours postdose ( $AUC_{0-5}$ ), area under the concentration-time curve from 5 hours postdose to the time of the last quantifiable concentration ( $AUC_{5-last}$ ), area under the plasma concentration time curve from time-zero extrapolated to infinity ( $AUC_{inf}$ ), apparent oral clearance ( $CL/F$ ), and weight-normalized apparent oral clearance ( $CL/F/kg$ ).

Analysis of variance (ANOVA) and the Schuirmann’s two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters,  $C_{max}$ ,  $AUC_{0-5}$ ,  $AUC_{5-last}$ ,  $AUC_{last}$ , and  $AUC_{inf}$ . The comparisons of interest were: Treatment B (NT0202-Fed) vs. Treatment A (NT0202-Fasted) and Treatment A (NT0202-Fasted) vs. Treatment C (Reference Product-Fasted). The ANOVA model included factors for sequence, subject within sequence, treatment, and period. The ratios of the geometric means (test to reference) and 90% confidence intervals were reported.

For the Treatment A (NT0202-Fasted) vs. Treatment C (Reference Product-Fasted) comparison, the Treatment A/Treatment C ratios of  $AUC_{0-5}$ ,  $AUC_{5-last}$ ,  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$  for individual subjects were calculated and summarized using descriptive statistics. The number and percentage of subjects with ratios >200%, >125%, <80%, and <50% were tabulated and also presented graphically.

### Study Population :

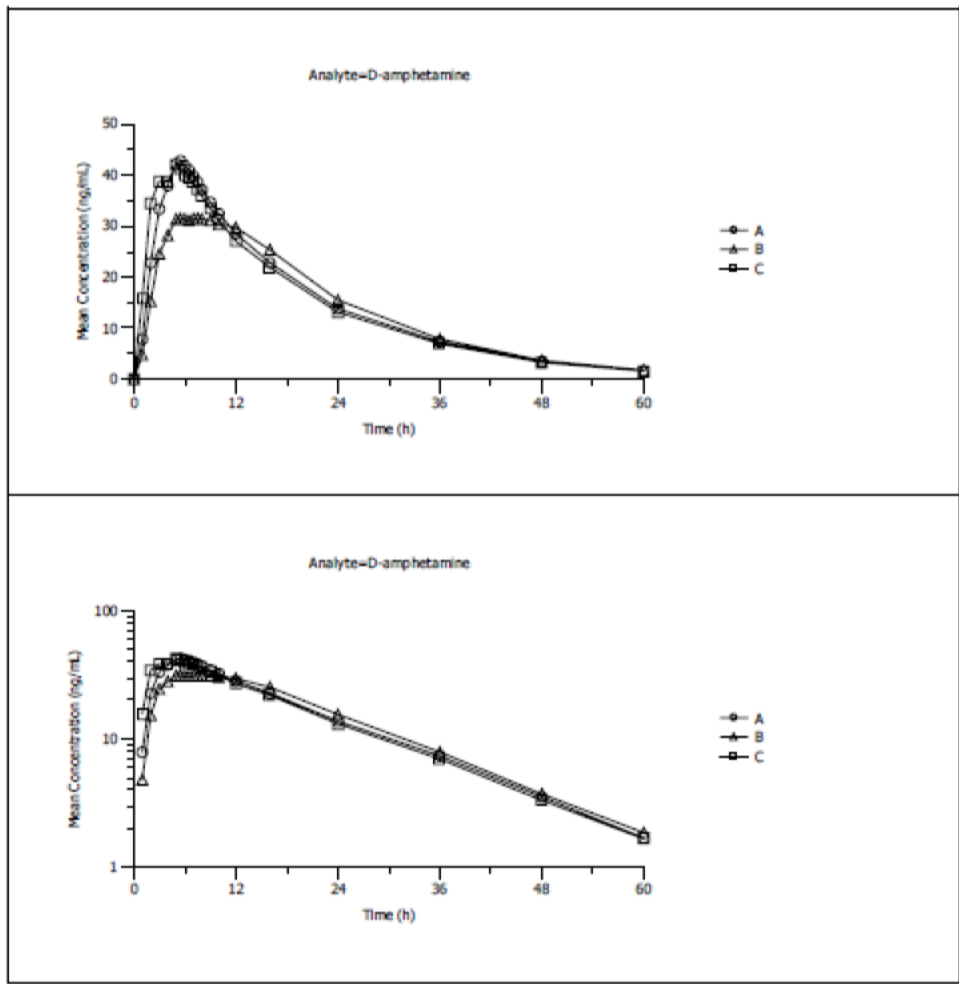
Randomized/Completed/ Discontinued	42/39/3 (1 withdrew due to personal reason, 1 withdrew due to family emergency, 1 withdrawn due to non-compliance- positive urine drug test)
Age [Median (range)]	32.5 (18-72) year
Male/Female	27/15

Race (Caucasian/Black/Asian/other)	25/14/0/3
------------------------------------	-----------

2 subjects withdrew due to personal and family reasons and were dosed only 1 treatment arm (out of 3 treatment arms). Thus, no data from these 2 subjects were included in any analysis. 3<sup>rd</sup> subject (who was found to be non-compliant due to positive urine drug test) was dosed for 2 treatment arms but did not have data for the 3<sup>rd</sup> treatment arm (fasted XR-ODT)

## Results

**Figure 1: Mean *d*-amphetamine Concentration–Time Profiles after Administration of NT0202 XR-ODT under Fasted Conditions (Treatment A), NT0202 XR-ODT under Fed Conditions (Treatment B), and the Reference Product under Fasted Conditions (Treatment C)**

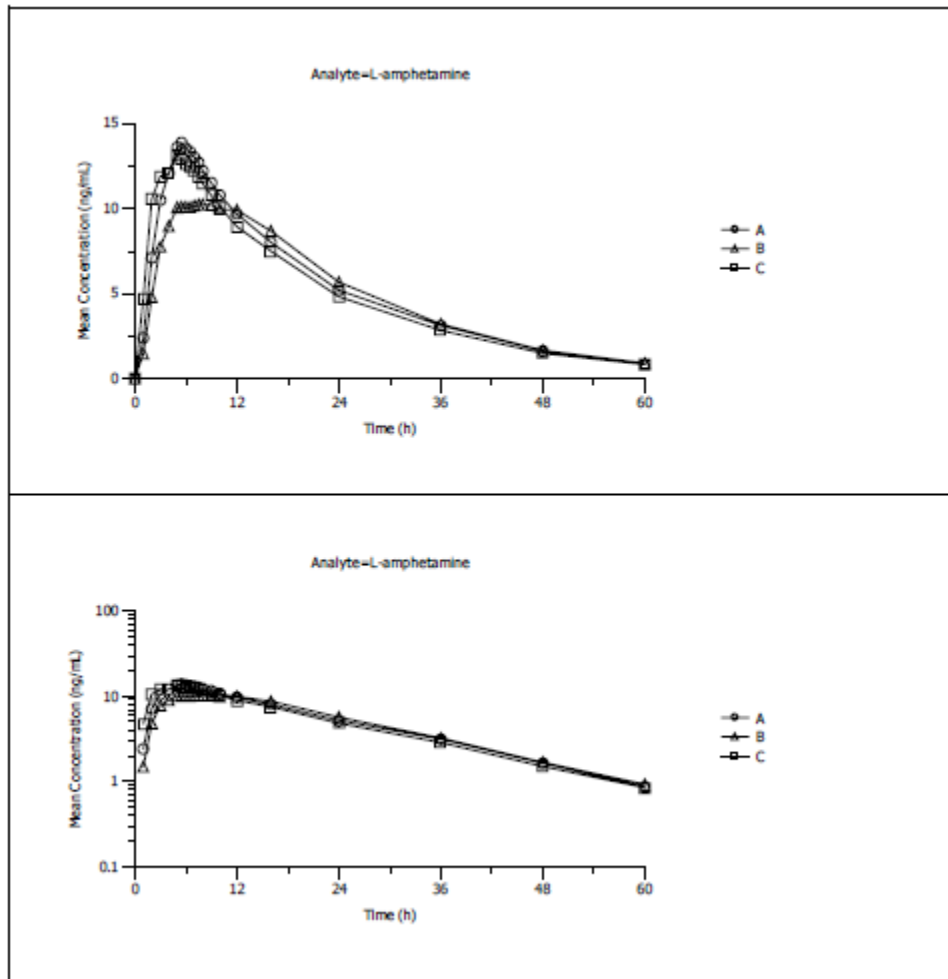


**Table 1: Pharmacokinetic Parameters of *d*-amphetamine**

Parameter	Treatment A: NT0202 XR-ODT Fasted			Treatment B: NT0202 XR-ODT Fed			Treatment C: Reference Product-Fasted (Adderall XR)				
	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
$T_{max}$ (h)*	5.00 (3.00, 12.00)			40	7.00 (3.00, 16.00)			40	5.00 (2.00, 12.00)		
$C_{max}$ (ng/mL)	44.9	8.94	19.94	40	36.3	6.85	18.88	40	46.4	10.2	21.98
$AUC_{0-5}$ (h*ng/mL)	122.8	40.04	32.60	40	88.48	31.00	35.03	40	148.7	49.62	33.37
$AUC_{0-t_{last}}$ (h*ng/mL)	723.8	155.5	21.49	40	735.1	151.6	20.62	40	692.9	144.6	20.88
$AUC_{inf}$ (h*ng/mL)	846.6	172.5	20.38	40	823.6	153.3	18.62	40	841.5	155.7	18.51
$AUC_{inf}$ (h*ng/mL)	876.9	182.4	20.81	40	856.3	166.1	19.40	40	873.6	167.6	19.18
$AUC_{extrap}$ (%)	3.36	1.86	55.43	40	3.66	1.96	53.61	40	3.54	1.79	50.46
$\lambda_z$ (h <sup>-1</sup> )	0.0637	0.0120	18.84	40	0.0630	0.0112	17.71	40	0.0609	0.0099	16.23
$T_{1/2}$ (h)	11.25	2.02	17.95	40	11.33	2.00	17.61	40	11.69	1.99	17.00
$T_{last}$ (h)	59.40	3.79	6.39	40	59.70	1.89	3.17	40	58.81	4.55	7.74
$C_{last}$ (ng/mL)	1.76	0.919	52.10	40	1.88	0.947	50.36	40	1.80	0.844	46.78
CLF (L/h)	35.63	7.183	20.16	40	36.31	6.865	18.91	40	35.60	6.925	19.45
CLF/kg (L/h/kg)	0.4853	0.1014	20.89	40	0.4937	0.1099	22.26	40	0.4842	0.1092	22.56

N=39 for Fasted XR-ODT; N=40 for other 2 treatment arms  
Tmax presented as Median (Min, Max)

**Figure 2: Mean l-amphetamine Concentration-Time Profiles after Administration of NT0202 XR-ODT under Fasted Conditions (Treatment A), NT0202 XR-ODT under Fed Conditions (Treatment B), and the Reference Product under Fasted Conditions (Treatment C)**





**Table 2: Pharmacokinetic Parameters of *l*-amphetamine**

Parameter	Treatment A: NT0202 XR-ODT Fasted			Treatment B: NT0202 XR-ODT Fed				Treatment C: Reference Product-Fasted (Adderall XR)			
	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T <sub>max</sub> (h)*	5.25 (3.00, 12.00)			40	7.50 (3.05, 16.00)			40	5.00 (2.00, 12.00)		
C <sub>max</sub> (ng/mL)	14.5	3.00	20.74	40	11.7	2.27	19.32	40	14.4	3.23	22.46
AUC <sub>0-5</sub> (h*ng/mL)	38.80	12.99	33.47	40	27.97	9.928	35.50	40	45.63	15.62	34.24
AUC <sub>5-12h</sub> (h*ng/mL)	264.4	56.77	21.48	40	263.8	53.45	20.26	40	246.0	51.25	20.83
AUC <sub>inf</sub> (h*ng/mL)	303.2	62.58	20.64	40	291.8	54.43	18.66	40	291.7	55.69	19.10
AUC <sub>inf</sub> (h*ng/mL)	320.7	69.96	21.81	40	310.7	62.11	19.99	40	310.0	64.29	20.74
AUC <sub>extrap</sub> (%)	5.21	3.03	58.10	40	5.80	3.12	53.79	40	5.57	3.22	57.79
λ <sub>1</sub> (h <sup>-1</sup> )	0.0558	0.0116	20.70	40	0.0546	0.0108	19.73	40	0.0537	0.0119	22.19
T <sub>1/2</sub> (h)	12.94	2.72	20.99	40	13.18	2.67	20.23	40	13.52	3.01	22.26
T <sub>1/2</sub> (h)	60.00	0.00	0.00	40	60.00	0.01	0.01	40	59.71	1.90	3.18
C <sub>last</sub> (ng/mL)	0.868	0.456	52.60	40	0.926	0.441	47.63	40	0.859	0.437	50.86
CL/F (L/h)	97.83	20.89	21.35	40	100.3	19.85	19.79	40	100.9	21.02	20.83
CL/F/kg (L/h/kg)	1.333	0.2916	21.88	40	1.366	0.3213	23.51	40	1.373	0.3273	23.84

N=39 for Fasted XR-ODT; N=40 for other 2 treatment arms

T<sub>max</sub> presented as Median (Min, Max)

**Table 3: Bioequivalence data for *d*-amphetamine. Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine Comparing NT0202 XR-ODT under Fasted Conditions (Treatment A) to the Reference Product under Fasted Conditions (Treatment C)**

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	43.9361	45.3766	96.83	93.56	100.21	1.0000	8.99
ln(AUC <sub>0-5</sub> )	116.5182	140.8005	82.75	77.37	88.51	0.9998	17.72
ln(AUC <sub>5-12h</sub> )	700.0723	676.8209	103.44	99.68	107.33	1.0000	9.68
ln(AUC <sub>inf</sub> )	822.2391	826.1451	99.53	96.73	102.41	1.0000	7.47
ln(AUC <sub>inf</sub> )	851.2894	856.4095	99.40	96.52	102.37	1.0000	7.70

<sup>a</sup> Geometric Mean for NT0202 XR-ODT-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

**Table 4: Bioequivalence data for *l*-amphetamine. Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *l*-amphetamine Comparing NT0202 XR-ODT under Fasted Conditions (Treatment A) to the Reference Product under Fasted Conditions (Treatment C)**

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	14.1535	14.0334	100.86	97.41	104.43	1.0000	9.11
ln(AUC <sub>0-5</sub> )	36.7157	43.1169	85.15	79.45	91.27	0.9997	18.27
ln(AUC <sub>5-12h</sub> )	255.7442	240.5665	106.31	102.47	110.29	1.0000	9.64
ln(AUC <sub>inf</sub> )	294.2633	286.2231	102.81	99.83	105.88	1.0000	7.70
ln(AUC <sub>inf</sub> )	310.7037	303.0717	102.52	99.18	105.97	1.0000	8.67

<sup>a</sup> Geometric Mean for NT0202 XR-ODT-Fasted (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

**Table 5: Food-Effect data for *d*-amphetamine. Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-amphetamine Comparing NT0202 XR-ODT under Fed Conditions**

(Treatment B) to NT0202 XR-ODT under Fasted Conditions (Treatment A)

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	35.6699	43.9404	81.18	77.68	84.83	1.0000	11.54
ln(AUC <sub>0-∞</sub> )	84.0589	116.4805	72.17	64.73	80.46	0.9578	29.02
ln(AUC <sub>5-∞</sub> )	719.3697	699.9546	102.77	99.51	106.15	1.0000	8.46
ln(AUC <sub>inf</sub> )	809.8683	821.9417	98.53	95.93	101.20	1.0000	6.99
ln(AUC <sub>inf</sub> )	840.3156	851.0481	98.74	95.98	101.58	1.0000	7.42

<sup>a</sup> Geometric Mean for NT0202 XR-ODT-Fed (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

<sup>c</sup> 90% Confidence Interval

**Table 6: Food-Effect data for *l*-amphetamine. Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *l*-amphetamine Comparing NT0202 XR-ODT under Fed Conditions (Treatment B) to NT0202 XR-ODT under Fasted Conditions (Treatment A)**

Dependent Variable	Geometric Mean <sup>a</sup>		Ratio (%) <sup>b</sup> (Test/Ref)	90% CI <sup>c</sup>		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C <sub>max</sub> )	11.5346	14.1572	81.48	77.99	85.11	1.0000	11.46
ln(AUC <sub>0-∞</sub> )	26.5274	36.7053	72.27	64.69	80.74	0.9523	29.58
ln(AUC <sub>5-∞</sub> )	258.2980	255.6891	101.02	97.72	104.43	1.0000	8.69
ln(AUC <sub>inf</sub> )	286.8474	294.1651	97.51	94.79	100.31	1.0000	7.41
ln(AUC <sub>inf</sub> )	304.3459	310.6676	97.97	94.86	101.18	1.0000	8.44

<sup>a</sup> Geometric Mean for NT0202 XR-ODT-Fed (Test) and Reference Product-Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

<sup>b</sup> Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

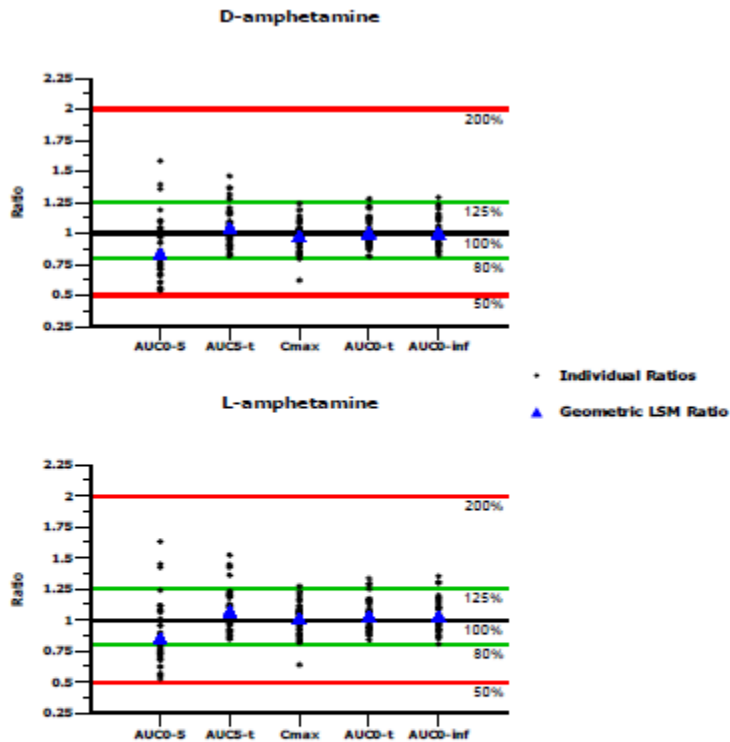
<sup>c</sup> 90% Confidence Interval

**Table 7: Number and Percentage of Subjects with Calculated Ratios that Meet the Indicated Conditions (>200%, >125%, <80%, <50%) for All Pharmacokinetic Parameters Applied for Bioequivalence Testing**

Analyte	Conditions	AUC <sub>0-5</sub>	AUC <sub>5-∞</sub>	C <sub>max</sub>	AUC <sub>0-∞</sub>	AUC <sub>0-inf</sub>
<i>d</i> -amphetamine (n=39)	>200%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>125%	3 (8%)	5 (13%)	0 (0%)	1 (3%)	1 (3%)
	<80%	21 (54%)	0 (0%)	2 (5%)	0 (0%)	0 (0%)
	<50%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<i>l</i> -amphetamine (n=39)	>200%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>125%	3 (8%)	4 (10%)	1 (3%)	4 (10%)	4 (10%)
	<80%	18 (46%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
	<50%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Abbreviations: AUC<sub>0-inf</sub> (AUC<sub>inf</sub>) = area under the plasma concentration–time curve at infinity; AUC<sub>0-∞</sub> (AUC<sub>inf</sub>) = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; AUC<sub>0-5</sub> = area under the plasma concentration versus time curve from time 0 to 5 hours; AUC<sub>5-∞</sub> (AUC<sub>5-inf</sub>) = area under the plasma concentration versus time curve from 5 hours to the last quantifiable concentration; C<sub>max</sub> = maximum plasma concentration

**Figure 3: Scatter Plot of Individual Ratios and Geometric Least Square Mean (LSM) Ratio for All Pharmacokinetic Parameters Applied for Bioequivalence Testing**



Note: Reference lines drawn at 200%, 125%, 100%, 80%, and 50%.

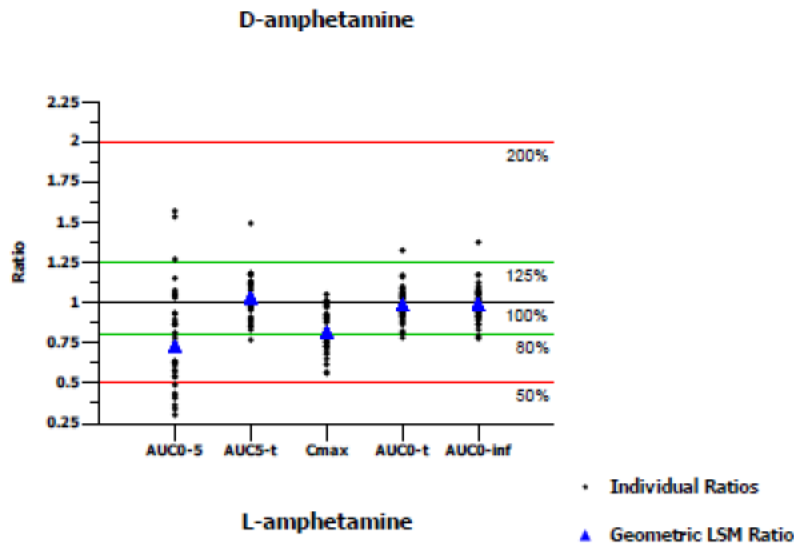
Abbreviations:  $AUC_{0-inf}$  ( $AUC_{inf}$ ) = area under the plasma concentration–time curve at infinity;  $AUC_{0-t}$  ( $AUC_{last}$ ) = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration;  $AUC_{0-5}$  = area under the plasma concentration versus time curve from time 0 to 5 hours;  $AUC_{5-t}$  ( $AUC_{5-last}$ ) = area under the plasma concentration versus time curve from 5 hours to the last quantifiable concentration;  $C_{max}$  = maximum plasma concentration

**Table 8: Number and Percentage of Subjects with Calculated Ratios that Meet the Indicated Conditions (>200%, >125%, <80%, <50%) for All Pharmacokinetic Parameters Applied for Food Effect Testing**

Analyte	Conditions	$AUC_{0-5}$	$AUC_{5-t}$	$C_{max}$	$AUC_{0-t}$	$AUC_{0-inf}$
<i>d</i> -amphetamine (n=39)	>200%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>125%	3 (8%)	1 (3%)	0 (0%)	1 (3%)	1 (3%)
	<80%	22 (56%)	1 (3%)	16 (41%)	1 (3%)	2 (5%)
	<50%	7 (18%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<i>l</i> -amphetamine (n=39)	>200%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>125%	3 (8%)	1 (3%)	0 (0%)	1 (3%)	1 (3%)
	<80%	22 (56%)	1 (3%)	17 (44%)	3 (8%)	2 (5%)
	<50%	7 (18%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Abbreviations:  $AUC_{0-inf}$  ( $AUC_{inf}$ ) = area under the plasma concentration–time curve at infinity;  $AUC_{0-t}$  ( $AUC_{last}$ ) = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration;  $AUC_{0-5}$  = area under the plasma concentration versus time curve from time 0 to 5 hours;  $AUC_{5-t}$  ( $AUC_{5-last}$ ) = area under the plasma concentration versus time curve from 5 hours to the last quantifiable concentration;  $C_{max}$  = maximum plasma concentration

**Figure 4: Scatter Plot of Individual Ratios and Geometric Least Square Mean (LSM) Ratio for All Pharmacokinetic Parameters Applied for Food Effect Testing**



Note: Reference lines drawn at 200%, 125%, 100%, 80%, and 50%.

Abbreviations:  $AUC_{0-inf}$  ( $AUC_{inf}$ ) = area under the plasma concentration–time curve at infinity;  $AUC_{0-t}$  ( $AUC_{last}$ ) = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration;  $AUC_{0-5}$  = area under the plasma concentration versus time curve from time 0 to 5 hours;  $AUC_{5-t}$  ( $AUC_{5-last}$ ) = area under the plasma concentration versus time curve from 5 hours to the last quantifiable concentration;  $C_{max}$  = maximum plasma concentration

### Site Inspected

**Requested:** Yes  No

**Performed:** Yes  No - Inspection report for clinical site will be available Jan 13<sup>th</sup>, 2016

### Safety

Was there any death or serious adverse events?  Yes  No  NA

#### SAFETY RESULTS:

A total of 46 treatment-emergent adverse events (TEAEs) were reported by 17 subjects over the course of the study. Of these 46 TEAEs, 45 were mild and 1 was moderate; there were no serious TEAEs or deaths during the course of the study. In general, the nature of the TEAE's reported were consistent with the mechanism of action of the study medication.

Category	Number of Subjects (%)	
	Any adverse events	17
Mild adverse events	17	(40.5)
Moderate adverse events	1	(2.4)
Severe adverse events	0	(0.0)
Serious adverse events	0	(0.0)
Withdrawals	0	(0.0)
Deaths	0	(0.0)

Source: Listing 16.2.7.1

The most commonly reported TEAEs, reported by Medical Dictionary for Regulatory Activities (MedDRA) preferred term, were nausea (n = 5; 3 following Treatment A and 2 following Treatment C) and dry mouth (n = 5; 1 following Treatment A, 1 following Treatment B, and 3 following Treatment C). In total, 16 TEAEs were reported following Treatment A, 9 following Treatment B, and 21 following Treatment C (Table 14.3.4).

Treatment A = Test - Fasted

Treatment B = Test - Fed

Treatment C = Reference (Adderall XR) - Fasted

### Sponsor's Conclusion

#### **NT0202 XR-ODT was found to be bioequivalent to RLD- Adderall XR under Fasted Conditions**

- The 90% confidence intervals for the log-transformed exposure parameters C<sub>max</sub>, AUC<sub>last</sub>, AUC<sub>inf</sub>, and AUC<sub>5-last</sub> were within the accepted 80% to 125% range for both *d*- and *l*-amphetamine
- Regarding early systemic exposure (AUC<sub>0-5</sub>), the geometric mean ratios (NT0202 XR-ODT/Adderall XR) were 82.75% for *d*-amphetamine and 85.15% for *l*-amphetamine and the lower 90% confidence intervals were just below the threshold value of 80% (77.37% for *d*-amphetamine and 79.45% for *l*-amphetamine). Variability in the rapidly changing concentrations during the first 5 hours likely contributed to the width of the 90% confidence intervals about AUC<sub>0-5</sub>.

#### **Food Effect for NT0202 XR-ODT**

- No significant food effect was observed for overall systemic exposure, based on AUC<sub>last</sub> and AUC<sub>inf</sub>. However, the presence of food decreased the rate of absorption of NT0202 XR-ODT, which resulted in a decrease in maximum exposure (C<sub>max</sub>) to *d*- and *l*-amphetamine by approximately 18% and a delay in the median T<sub>max</sub> of approximately 2 hours (*d*-amphetamine) to 2.25 hours (*l*-amphetamine). This decrease in maximum concentration (C<sub>max</sub>) and prolonged T<sub>max</sub> is not clinically significant, and therefore NT0202 could be taken without regards to meals.

### Reviewer Comments

1. Though 42 subjects were enrolled in the study, relative BA and food-effect was analyzed

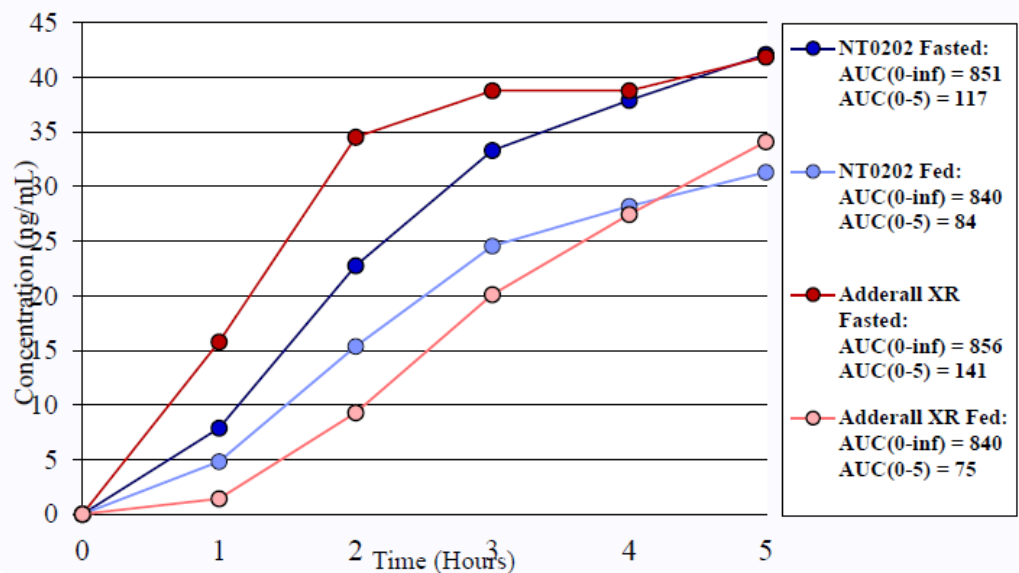
using only 39 subjects. Two subjects withdrew due to personal and family reasons and were dosed only 1 treatment arm (out of 3 treatment arms). Third subject was found to be non-compliant due to positive urine drug test and did not have data for the 3<sup>rd</sup> treatment arm (fasted XR-ODT). Thus, statistical analysis for relative BA data was performed for 39 subjects for whom the complete data set existed. This is acceptable.

2. The sponsor is planning to use the same formulation used in the clinical study (NT0202.1005) as their to-be-marketed (commercial) formulation. Thus, no additional bridging PK studies are required.
3. **Regarding the relative bioavailability (BA) of NT0202 XR-ODT to the RLD (Adderall XR) under Fasted Condition:**

The sponsor has performed appropriate statistical analysis with key pharmacokinetic parameters (C<sub>max</sub>, AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, AUC<sub>0-5</sub> and AUC<sub>5-t</sub>) to assess the bioequivalence of their product. All the BE criteria were met for all parameters except pAUC<sub>0-5h</sub>. Though this lower bound of the 90% CI for pAUC<sub>0-5h</sub> was below 80% , we have the following rationale for accepting the overall findings of product:

In the study, though the lower bound of 90%CI of pAUC<sub>0-5h</sub> was below 80%, the point estimate of the ratio of test/RLD for pAUC<sub>0-5h</sub> was 83%. Additionally, it is known from published data (Current Medical Research and Opinion, Vol 18, 5, 311-316, 2002) that Adderall XR (RLD) is also known to have a 42% to 53% reduction in pAUC (0-to 6hr and 0-to 4 hr, respectively) in presence of food. However, in spite of this significant reduction in early exposure of Adderall XR, its label recommends taking it without regards to food. Allowing Adderall XR being taken with or without food indicates that clinically meaningful changes following the treatment of Adderall XR is not anticipated in the presence or absence of food. Since no clinically meaningful changes are expected even when the early pAUC is reduced up to 50% for Adderall XR, it is also expected that a mean 17% reduction in pAUC<sub>0-5h</sub> observed for amphetamine XR ODT product is also unlikely to cause any clinically meaningful changes. Additionally, sponsors internal data (figure below) is also consistent with published literature and demonstrates that the AUC profiles in the fed and fasted state from zero to five hours for Amphetamine XR-ODT lie between those for ADDERALL XR (with and without food).

**Figure:** Early partial AUC<sub>0-5hr</sub> comparison: Amphetamine XR ODT (fed and fasted) and Adderall XR (fed and fasted)



Source: Amphetamine XR-ODT Fasted and Fed – Study NT0202.1005  
 Adderall XR Fasted– Study NT0202.1005  
 Adderall XR Fed – Study NT0201.1006

Therefore, considering all the data, we agree with the sponsor’s conclusion that Neos Therapeutics Inc.’s Amphetamine XR-ODT is likely to have similar efficacy and safety profile to the RLD (ADDERALL-XR®).

#### 4. Regarding the Food Effect for NT0202 XR-ODT

Food effect study demonstrated that there was no significant effect of food on the overall systemic exposure (i.e. AUC<sub>last</sub> and AUC<sub>inf</sub>). However, the presence of food decreased the C<sub>max</sub> for *d*- and *l*-amphetamine by approximately 18%. This effect of food on the PK of NT0202 XR-ODT is very similar to the extent of food-effect observed for ADDERALL XR (the RLD) which is also known to have slight decrease in exposure (7% decrease in AUC and 14% decrease in C<sub>max</sub>) in presence of food (Current Medical Research and Opinion, Vol 18, 5, 311-316, 2002).

In addition, it was observed that the early exposure pAUC<sub>0-5h</sub> was significantly reduced in presence of food. The pAUC<sub>0-5h</sub> was reduced up to 25% at the mean level and several individual subjects are demonstrated to have reduction of greater than 50% (up to 70%) in their AUC<sub>0-5h</sub>. However, similar dramatic reductions in early AUC<sub>0-5h</sub> have also been reported for the RLD, Adderall XR. A controlled food effect study (Current Medical Research and Opinion, Vol 18, 5, 311-316, 2002) lists 53% reduction in mean AUC<sub>0-4h</sub> and 42% reduction in mean AUC<sub>0-6h</sub>. This reduction in mean early partial AUC for Adderall XR in presence of food is generally similar to the levels of reduction for the test product NT0202 XR-ODT.

Thus, the food effect is not considered clinically meaningful and we recommend that amphetamine XR-ODT can be taken without regards to meals, similar to the RLD, Adderall XR.



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

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DATE: December 14, 2015

TO: Mitchell Mathis, M.D.,  
Director, Division of Psychiatry Products

Ann Farrell, M.D.,  
Director, Division of Hematology Products

Dale Conner, Pharm.D.  
Director (Acting)  
Office of Bioequivalence  
Office of Generic Drugs

FROM: Himanshu Gupta, Ph.D.  
Division of Generic Drug Bioequivalence Evaluation  
(DGDBE)  
Office of Study Integrity and Surveillance (OSIS)

Sam H. Haidar, Ph.D., R.Ph.  
Acting Director, Division of Generic Drug  
Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of Establishment Inspection Report (EIR)  
covering  
**NDA 204326**, Amphetamine Extended-Release Orally  
disintegrating Tablets (XR-ODT) 30mg sponsored by Neos  
Therapeutics Inc.,

(b) (4)



(b) (4)

**Summary: No Form FDA 483 was issued. The data can be accepted for further agency review.**

The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection at [REDACTED] from [REDACTED]

[REDACTED] The inspection was conducted in support of review of NDA 204326, [REDACTED]

[REDACTED] Specifically, the analytical portions of the following bioequivalence studies were audited during the inspection:

**NDA 204326**

**Amphetamine Extended-Release Orally disintegrating Tablets (XR-ODT) 30mg**

**Study #:**

**3007227 (Protocol #NT0202.1005)**

**Study Title:**

"A Single-Dose, Three-Period, Three Treatment, Three-Way Crossover Bioavailability Study of an Investigational Formulation of NT0202 Amphetamine Extended-Release Orally disintegrating Tablets (XR-ODT) 30mg under Fed and Fasted Conditions and Adderall XR Capsule 30mg under Fasted Conditions."

**Sample analysis:**

05/20/2014-06/10/2014

(b) (4)



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This inspection was conducted by Himanshu Gupta, Ph.D., and Sam H. Haidar, R.Ph., Ph.D. The audit included a thorough review of the method validation and the study records, examination of facilities and equipment, and interviews and discussions with the firm's management and staff.

At the conclusion of the inspection, no deficiencies were observed, and no Form FDA-483 was issued.

**Conclusion:**

Following review of the inspectional findings, these reviewers recommend that results from the bioanalytical portions of the following studies be accepted for further Agency review:

NDA 204326

Study #: 3007227 (Protocol # NT0202.1005)

(b) (4)

Himanshu Gupta, Ph.D.

Sam H. Haidar, Ph.D., R.Ph.

(b) (4)

**Final Classification:**

**NAI-**

(b) (4)

CC:

OTS/OSIS/Taylor/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Cho

OTS/OSIS/DGDBE/Haidar/Skelly/Choi/Gupta

Draft: HG 12/11/2015

Edit: SHH 12/14/2015

OSI File #:

NDA 204326 - BE#6970

(b) (4)

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Inspections/BE Program/Analytical  
sites/

(b) (4)

(b) (4) Surv Inspection

FACTS:

(b) (4)

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/s/  
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HIMANSHU GUPTA  
12/14/2015

SAM H HAIDAR  
12/14/2015

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PRAVEEN BALIMANE  
12/23/2015

HAO ZHU  
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MEHUL U MEHTA  
12/29/2015