Office of Clinical Pharmacology Review

NDA	209905
Link to EDR	\\CDSESUB1\evsprod\NDA209905\0000
Submission Dates	3/30/18
Submission Type	505(b)(2) NDA
Brand Name	Evekeo ODT
Generic Name	Amphetamine Sulfate
Dosage Form and Strength	Immediate Release Orally Disintegrating Tablets 5, 10, 15, 20, (b) (4) mg tablets
Route of Administration	Oral
Proposed Indication	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant	Arbor Pharmaceuticals
Associated IND	124019
OCP Review Team	Kofi Kumi, Ph.D., Luning (Ada) Zhuang, Ph.D.
OCP Final Signatory	Luning (Ada) Zhuang, Ph.D.

Table of Contents

1. Executive Summary

In this 505(b)(2) application, the sponsor has developed a racemic (d, l-) amphetamine sulfate immediate release (IR) orally disintegrating tablet (ODT) as a line extension to the sponsor's amphetamine sulfate immediate release 5 and 10 mg conventional tablets (Evekeo) (ANDA 200166). The application relies on the findings of safety and effectiveness for the listed drug Amphetamine Sulfate tablets via cross reference to NDA 83901 sponsored by Lannett, which is discontinued. Evekeo 10 mg is cited as reference standard drug in the orange book, therefore, the sponsor is using it as the reference drug for this application since the listed drug, NDA 83901 is discontinued. NDA 883901 was approved as part of the Drug Efficacy Study Implementation (DESI) program. The sponsor developed Evekeo IR ODT to provide a dosage form (b) (4) rapidly disintegrates on contact with saliva in the buccal cavity to facilitate treatment of patients who cannot swallow or have difficulty swallowing conventional tablets.

The Evekeo ODT development program consisted of a comparative bioavailability study to demonstrate bioequivalence to the reference standard, Evekeo IR conventional tablet (ANDA 200166). And a comparative bioavailability study to evaluate the effect of food on the absorption of amphetamine after administration of Evekeo ODT under fed and fasting conditions. No clinical efficacy and safety study was conducted with Evekeo ODT. However, the sponsor included a safety and efficacy study conducted with Evekeo IR conventional tablets and argues that since that trial evaluated the efficacy of Evekeo IR conventional tablets in 6 -12 year old children with ADHD, and comparative bioavailability demonstrated bioequivalence between IR tablets and Evekeo ODTs, the results should be included in the Evekeo ODT label. Please refer to medical review for details of the efficacy and safety in children 6 – 12 years using conventional Evekeo tablets.

The proposed dose for Evekeo ODT is as follows:
(b) (4)
increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day"

An Office of Study Integrity and Surveillance (OSIS) inspection was requested. OSIS declined to inspect the sites and recommended the data should be accepted because OSIS recently inspected the sites and the outcome was classified as No Action Indicated (NAI).

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information in NDA 209905 and supports the approval Evekeo ODT for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Key review issues with specific recommendations and comments are summaries below

Review Issues	Recommendation and Comments
Supportive evidence of effectiveness	This is a 505(b)(2) application. Evekeo ODT is bioequivalent to Evekeo IR conventional tablet. the reference standard. Therefore, Evekeo ODT should be effective as the listed drug which is approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)
General dosing instructions	The following dosing instructions approved for Evekeo IR conventional tablet is appropriate for Evekeo ODT: For children 6 years and older with ADHD, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed the total of 40 mg per day.
Should Evekeo ODT be administered under fed or fasting conditions	High fat meal did not significantly affect the d,l-amphetamine exposures (Cmax and AUC). Therefore, Evekeo can be administered under fed and fasting conditions

The Clinical Pharmacology findings are summarized below:

1. d,l-amphetamine concentrations after administration Evekeo ODT with or without water is equivalent to that after administration Evekeo IR conventional tablet
2. Food does not have significant effect on the exposures (Cmax, AUC) to d,-amphetamine after administration of Evekeo ODT under fed and fasting conditions. Evekeo ODT can be administered with or without food
3. The dosing regimen of Evekeo IR conventional tablet is acceptable to be used for Evekeo ODT

1.2 Post Marketing Requirements and Commitments

None

2. Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical Pharmacokinetics

Evekeo ODT is a 50:50 racemic mixture of *d*- and *l*-amphetamine. Racemic amphetamine sulfate is a central nervous system stimulant which is used to treat Attention Deficit Hyperactivity Disorder (ADHD) in children, adolescents and adults. D-amphetamine is reported to be 3 to 7-fold more potent that l-amphetamine. Racemic amphetamine is reported to demonstrate linear pharmacokinetics over the proposed therapeutic dosage range, which, for children ages 6 to (b) (4) years with ADHD is 5 mg/day to 40 mg/day as stated in DESI-based Evekeo RS labeling

Absorption

Evekeo ODT 20 mg administered without or with water was demonstrated to be bioequivalent to 20 mg Evekeo IR conventional tablet administered with water. Following single-dose oral administration of Evekeo ODT (20 mg) disintegrated/dissolved in the oral cavity (without water) in healthy adults under fasted conditions, the median (range) Tmax of *d*- and *l*-amphetamine were 3.5 (2, 5) and 3.5 (2, 8) hours, respectively. High fat meal did not have significant effect on the exposure (AUC and Cmax) to d- and l- amphetamine. Median Tmax for Evekeo ODT in the fed and fasted condition was 4.5 (2.5, 8) and 2.5 (1.5, 6) hours for *d*-amphetamine, respectively, and 4.5 (2.5, 8) and 2.5 (1.5, 6) hours for *l*-amphetamine, respectively

Distribution

Amphetamine isomers are reported to be approximately 16% to 20% bound to plasma proteins.

Elimination

Amphetamine is subject to both hepatic and renal elimination. The mean elimination T½ for *d*-amphetamine and *l*-amphetamine in healthy adults after administration of Evekeo ODT was 10.0 and 11.6 hours, respectively.

Metabolism

In-vitro and in-vivo metabolism and excretion studies have not been performed on Evekeo ODT or Evekeo RS tablets. However, based on the approved label for Adderall (mixed salt of single entity amphetamine), amphetamine is reported to be oxidized at the 4-postion of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. CYP2D6 is reported to be involved with formation of 4-hydroxy-amphetamine. Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various CYP450 isozymes have not been elucidated

Excretion

Renal elimination of amphetamine after clinical administration of Evekeo ODT or Evekeo RS tablets has not been studied. Amphetamine is subject to both hepatic and renal elimination. Amphetamine is reported to be renally eliminated in a pH-dependent manner. The renal

excretion rate of unchanged amphetamine at a urine pH of 6.6 averages 70% versus 17%-43% at urine pH of >6.7

2.2 Dosing and therapeutic Individualization

Amphetamine sulfate tablets (NDA 83901, Lannett) were approved based in part of FDA's Drug Efficacy Study Implementation (DESI) program. The DESI program used published safety and efficacy data from the literature to support the DESI. NDA 83901 was the reference listed drug for Evekeo IR conventional tablets (ANDA 21066). Therefore, the dosing regimen for Evekeo IR conventional tablet is proposed for Evekeo ODT and is acceptable. The proposed dosing regimen is for children 6 years and older with ADHD, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed the total of 40 mg per day.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The following is recommended to be added to Section 12.3

Following a single-dose oral administration of Evekeo ODT 20 mg disintegrated/dissolved in the oral cavity in healthy subjects in a crossover study, exposure (Cmax and AUC) to d- and l-amphetamine were comparable to that after administration of equal dose of Evekeo tablets swallowed intact with water. Median (range) T_{max} of *d*- and *l*-amphetamine was reached at approximately 3.5 (2, 8) hours and 3.0 (1,6) hours after administration without water and with water, respectively.

Administration of food (a high fat meal) does not affect the observed AUC and C_{max} of *d*- and *l*-amphetamine after single-dose oral administration of EVEKEO ODT (20 mg) in healthy adults who allowed the tablet to be disintegrated/dissolved in their oral cavity prior to swallowing without water. Median (range) Tmax increased from 2.5 (1.5 – 6) hours to 4.5 (2.5 – 8.0) hours when administration without compared to with food.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

The applicant submitted a 505(b)(2) application for racemic amphetamine sulfate orally disintegration tablet (ODT). The applicant is relying on the Agency's finding of safety and effectiveness for Amphetamine sulfate tablets under NDA 83901, the listed drug. Amphetamine sulfate tablet approved under NDA 83901 has been discontinued, therefore, the sponsor is bridging Evekeo ODT to their conventional amphetamine sulfate tablet (ANDA 200166), Evekeo tablets. Evekeo 10 mg is listed as a reference standard in the orange book.
NDA 83901 (Amphetamine Sulfate tablets) was held by Lannett was the reference drug for ANDA21066. Lannett's NDA 83901 was approved as part of the Agency Drug Efficacy Study Implementation Program (DESI).

The clinical program consisted of two biopharmaceutics studies, a comparative bioavailability study of single dose amphetamine sulfate ODT swallowed intact with water, versus single dose ODT tablets disintegrated/dissolved in the oral cavity swallowed without water, versus amphetamine sulfate immediate release (IR) reference tablets administered to fasting healthy subjects. And a single dose 2-period, 2-sequence, 2-way crossover bioavailability study of amphetamine sulfate ODT 20 mg administered to healthy adult subjects under fed and fasted conditions. The applicant is seeking biowaiver for the strengths not used in the bridging study.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	CNS Stimulant
Active moiety	D, l-Amphetamine sulfate
QT Prolongation	Not available
General Information	
Bioanalysis	Validated LC/MS/MS; range 0.5 to 80 ng/mL for d-amphetamine and 0.2 to 32 ng/mL for l-amphetamine
Maximum tolerated dose or exposure	40 mg
Dose Proportionality	5 to 40 mg
Accumulation	Not available
Absorption	Median Tmax of *d*- and *l*-amphetamine were approximately 3.5 hours, respectively following administration without water.
Distribution	Amphetamine isomers are reported to be approximately 16% to 20% bound to plasma proteins.
Metabolism	CYP2D6 is involved with formation of 4-hydroxy-amphetamine metabolite.
Elimination	Amphetamine is subject to both hepatic and renal elimination. The mean elimination T½ for *d*-amphetamine and *l*-amphetamine after administration of Evekeo ODT was 10.0 and 11.6 hours, respectively.

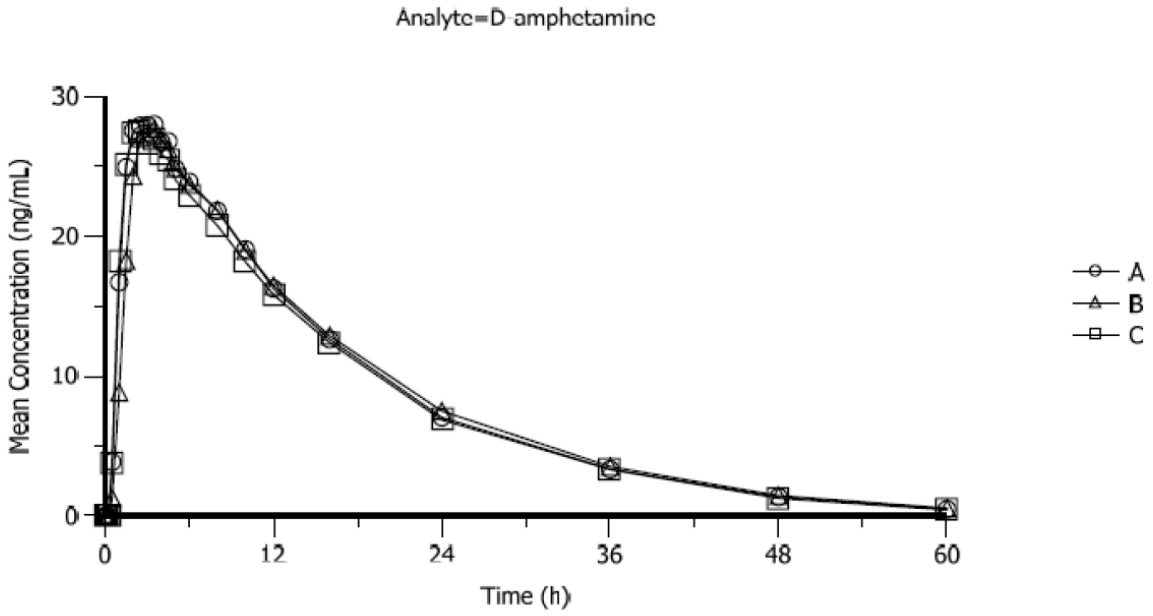
3.3 Clinical Pharmacology Questions

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

The applicant demonstrated that the exposures (AUC and Cmax) after administration of Evekeo ODT with or without water and Evekeo conventional tablets, with water are bioequivalent. Therefore, Evekeo ODT should be as effective in treating ADHD as the approved Evekeo IR conventional tablet.

The applicant conducted a comparative bioavailability study of a single dose Evekeo ODT swallowed intact with water, versus single dose ODT tablets disintegrated/dissolved in the oral cavity swallowed without water versus amphetamine sulfate, reference tablets in healthy fasting healthy volunteers. The mean plasma concentration time profile for d-amphetamine and the statistical analysis are provided in the following figure and table below

Figure 1 Mean *d*-amphetamine Concentration-Time Profile after Single-Dose Administration of Evekeo ODT 20 mg with Water (Treatment A), Evekeo ODT without Water (Treatment B), and Evekeo 2 x 10 mg Tablets (RS) with Water (Treatment C)



Source: Study AR17.001

The statistical comparisons of d-amphetamine after administration Evekeo ODT with or without water vs Evekeo IR conventional tablets

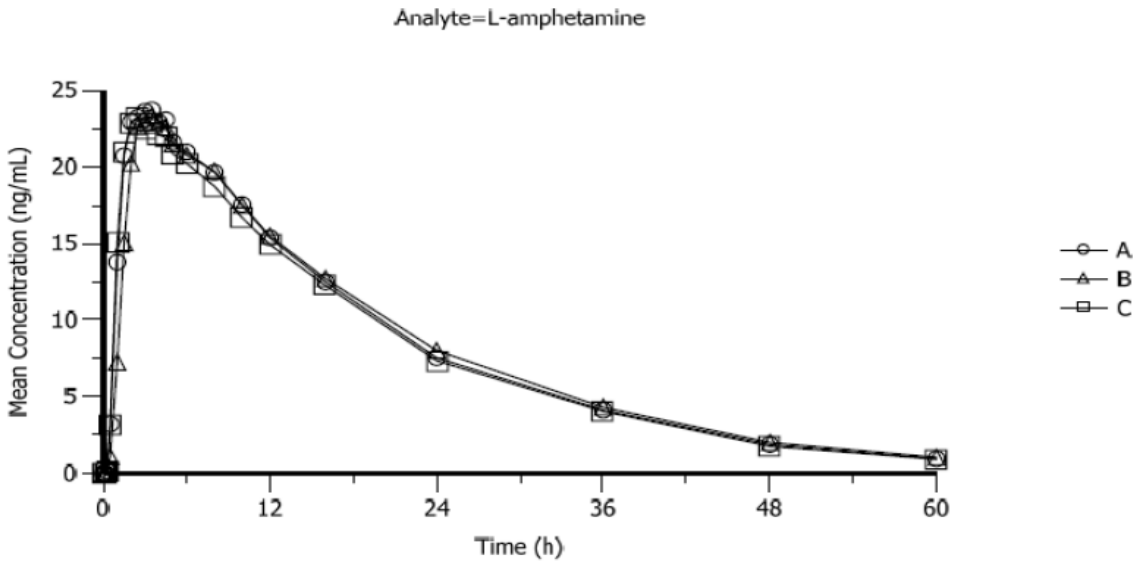
Table 1 Statistical Comparison, Pharmacokinetic Parameters for *d*-amphetamine

Parameter	Geometric Mean[a]		Ratio(%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	lower	upper
Treatment A (Evekeo ODT 20 mg with water; Test) vs Treatment C (Evekeo RS 2x 10 mg tablets with water; Ref)					
$ln(C_{max})^c$	29.0	29.1	99.46	96.68	102.32
$ln(AUC_{last})^c$	483	473	102.22	98.80	105.76
$ln(AUC_{inf})^c$	496	487	101.82	98.46	105.30
Treatment B (Evekeo ODT 20 mg without water; Test) vs Treatment C (Evekeo RS 2x 10 mg tablets with water; Ref)					
$ln(C_{max})^d$	28.9	29.1	99.28	96.53	102.10
$ln(AUC_{last})^d$	479	473	101.28	97.93	104.74
$ln(AUC_{inf})^d$	492	487	101.13	97.83	104.54
Treatment A (Evekeo ODT 20 mg with water; Test) vs Treatment B (Evekeo ODT 20 mg without water; Ref)					
$ln(C_{max})^e$	29.0	28.9	100.18	97.38	103.06
$ln(AUC_{last})^e$	483	479	100.93	97.56	104.42
$ln(AUC_{inf})^e$	496	492	100.68	97.37	104.11

a- Geometric Mean for Test and Ref based on Least Squares Mean of log-transformed parameter values.
b- Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref).

Source: Study AR17.001

Figure 2 Mean *l*-amphetamine Concentration-Time Profile after Single-Dose Administration of Evekeo ODT 20 mg with Water (Treatment A), Evekeo ODT without Water (Treatment B), and Evekeo 2 x 10 mg Tablets (RS) with Water (Treatment C)



Source: Study AR17.001

Table 2 Statistical Comparison, Pharmacokinetic Parameters for *l*-amphetamine

Dependent Variable	Geometric Mean[a]		Ratio(%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	lower	upper
Treatment A (Evekeo ODT 20 mg with water; Test) vs Treatment C (Evekeo RS 2x 10 mg tablets with water; Ref)					
$ln(C_{max})$[c]	24.4	24.6	99.19	96.56	101.89
$ln(AUC_{last})$[c]	475	467	101.70	98.24	105.28
$ln(AUC_{inf})$[c]	492	483	101.86	98.20	105.65
Treatment B (Evekeo ODT 20 mg without water; Test) vs Treatment C (Evekeo RS 2x 10 mg tablets with water; Ref)					
$ln(C_{max})$[d]	24.4	24.6	99.29	96.69	101.96
$ln(AUC_{last})$[d]	472	467	101.08	97.68	104.60
$ln(AUC_{inf})$[d]	490	483	101.38	97.78	105.11
Treatment A (Evekeo ODT 20 mg with water; Test) vs Treatment B (Evekeo ODT 20 mg without water; Ref)					
$ln(C_{max})$[e]	24.4	24.4	99.90	97.25	102.61
$ln(AUC_{last})$[e]	475	472	100.62	97.20	104.15
$ln(AUC_{inf})$[e]	492	490	100.47	96.87	104.20

a- Geometric Mean for Test and Ref based on Least Squares Mean of log-transformed parameter values.
b- Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref).

The 90% confidence interval (CI) around the mean ratio for Cmax and AUC of *d*- and *l*-amphetamine after administration Evekeo ODT versus Evekeo IR conventional tablet was contained within the 80% to 125% regulatory criteria for bioequivalence. This indicates that exposures to d- and l-amphetamine are bioequivalent after administration of Evekeo ODT with or without water and Evekeo conventional tablet with water. Swallowing Evekeo ODT intact with water does not significantly change exposures to *d,l*-amphetamine when it is compared to disintegrating/dissolving first Evekeo ODT in buccal cavity, then swallow.

3.3.2. Is the proposed general dosing regimen appropriate for the general population for which the indication is being sought?

Yes. The approved doses for Evekeo IR conventional tablet is appropriate to be used for Evekeo ODT in the general population. The approved dose for children 6 years and older with ADHD is to start at 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day

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

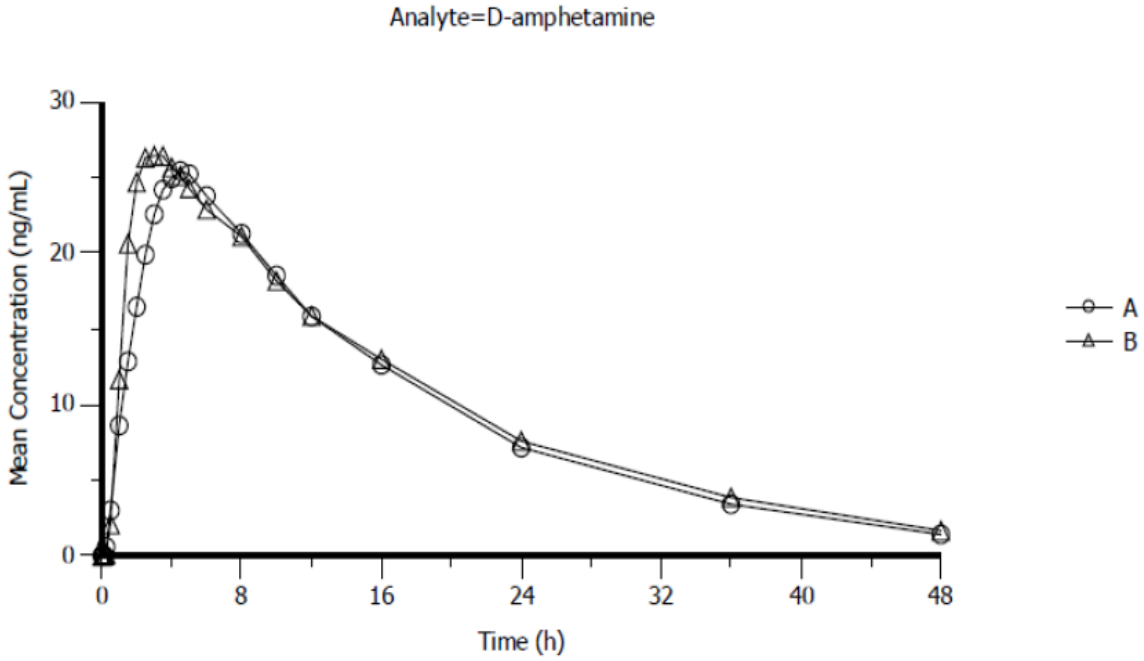
No. No studies in renal and hepatic patients were included in this 505(b)(2) application.

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

No, there was no significant food-drug interaction. Evekeo ODT can be administered under fed or fasted conditions. Time to maximum concentration (Tmax) for d- and l-amphetamine was increased by about 1 and 2 hours, respectively. No new drug interaction studies were submitted with this application. The drug interaction information in Evekeo IR conventional tablets is appropriate for Evekeo ODT.

The applicant conducted a study to evaluate the effect of a high fat meal on the exposures (AUC and Cmax) of d-amphetamine after administration Evekeo ODT. The following is a plasma concentration time profile after administration of Evekeo ODT with or without food.

Figure 3 Mean *d*-amphetamine Concentration-Time Profiles after Administration of Amphetamine Sulfate ODT-IR (Evekeo ODT) 20 mg under Fed (A) and Fasted (B) Conditions



Source: Study AR17.002

The statistical comparison for d-amphetamine after administration of Evekeo ODT with or without food is provided in the following table.

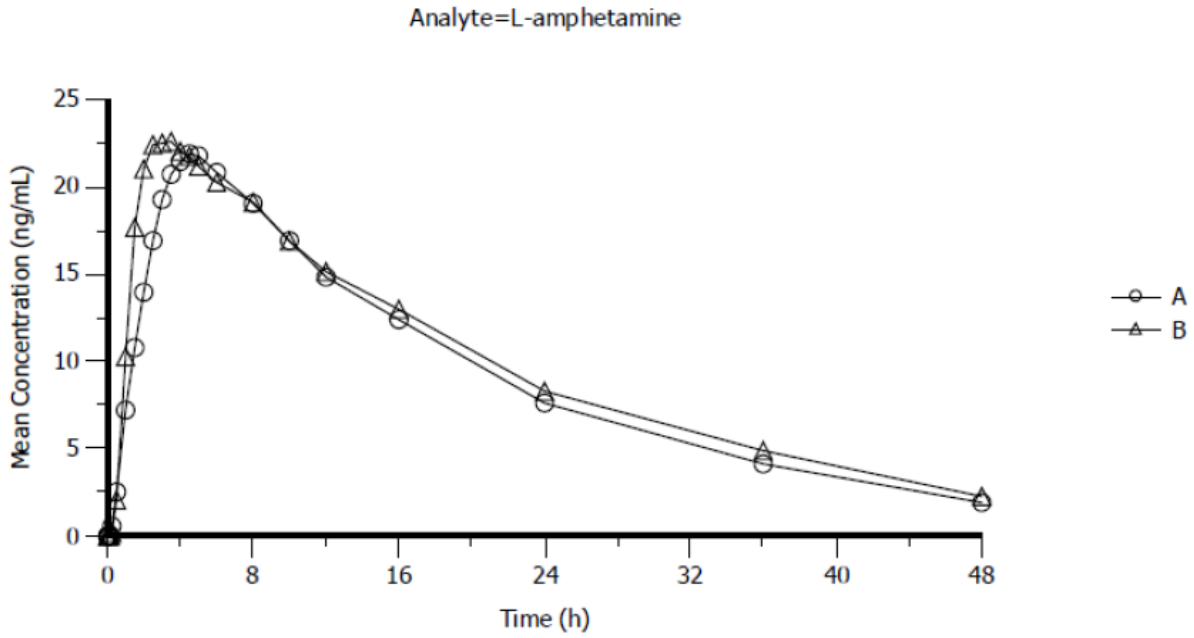
Table 3 Statistical Comparison, Food Effect, Pharmacokinetic Parameters for *d*-amphetamine

Parameter	Geometric Mean[a]		Ratio(%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	lower	upper
Treatment A (Evekeo ODT fed; Test) vs Treatment B (Evekeo ODT fasted; Ref)					
$\ln(C_{max})$	26.4	27.4	96.13	93.07	99.29
$\ln(AUC_{last})$	447	474	94.33	91.35	97.40
$\ln(AUC_{inf})$	468	500	93.62	90.44	96.90

a- Geometric Mean for Amphetamine Sulfate ODT-IR 20 mg, fed (Test) and Amphetamine Sulfate ODT-IR 20 mg, fasted (Ref) based on Least Squares Mean of log-transformed parameter values.
b- Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref).
c- Confidence interval.

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

Figure 4 Mean *l*-amphetamine Concentration-Time Profiles after Administration of Amphetamine Sulfate ODT-IR (Evekeo ODT) 20 mg under Fed (A) and Fasted (B) Conditions



Source: Study AR17.002

The statistical comparisons for l-amphetamine is provided in the following table

Table 4 Statistical Comparison, Food Effect, Pharmacokinetic Parameters for *l*-amphetamine

Parameter	Geometric Mean[a]		Ratio(%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	lower	upper
Treatment A (Evekeo ODT fed; Test) vs Treatment B (Evekeo ODT fasted; Ref)					
ln(C_{max})	22.9	23.6	96.89	93.85	100.03
ln(AUC_{last})	435	467	93.09	90.06	96.24
ln(AUC_{inf})	473	517	91.50	88.07	95.05

a- Geometric Mean for Amphetamine Sulfate ODT-IR 20 mg, fed (Test) and Amphetamine Sulfate ODT-IR 20 mg, fasted (Ref) based on Least Squares Mean of log-transformed parameter values.
b- Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref).
c- Confidence interval.

Source: Study AR17.002

The 90% CI around the mean ratio for d-and l-amphetamine after administration of Evekeo ODT under fed and fasting conditions were contained within 80% to 125% regulatory criteria indicating there is no significant effect of food on the exposures of d- and l-amphetamine.

4. APPENDIX

4.1 Individual Study Reports

Clinical Study Report

Report No.: AR17-0001	Study Period: 8/25/2016 – 9/8/2016
Study Center:	Worldwide Clinical Trials San Antonio, Texas
Principal Investigator:	Vanessa Smeberg, MD
Bioanalytical Facility:	(b) (4)
Principal Scientist:	

EDR: \\CDSESUB1\evsprod\NDA209905\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5352-stud-rep-uncontr\ar17.001

Title
Comparative Bioavailability Study of Single-Dose Amphetamine Sulfate Oral Disintegrating Immediate Release Tablets (ODT-IR) Swallowed Intact with Water, versus Single-Dose ODT-IR Tablets Disintegrated/Dissolved in the Oral Cavity Swallowed without Water, versus Amphetamine Sulfate Immediate Release (IR) Reference Tablets (Evekeo™) Administered to Fasting, Healthy Adult Volunteers

Objectives
Primary: To compare the bioavailability of amphetamine from: (1) Amphetamine Sulfate ODT-IR 20 mg test tablets given as a single intact 20 mg tablet swallowed with water, (2) Amphetamine Sulfate ODT-IR 20 mg test tablets given as a single 20 mg tablet disintegrated/dissolved in the oral cavity and then swallowed without water, and (3) Amphetamine Sulfate IR RLD (Evekeo™) given as two intact 10 mg tablets swallowed with water, all under fasting condition. Each treatment was compared with each other.
Secondary: To evaluate the safety of: (1) ODT-IR 20 mg tablets given as a single 20 mg dose swallowed intact with water, and (2) ODT-IR 20 mg tablets given as a single 20 mg dose disintegrated/dissolved in the oral cavity and then swallowed without water, each given to healthy and fasting adult volunteers.

Study Design

Design: Single-dose, open-label, randomized, three-period, three-treatment, six-sequence, crossover study in which 42 adult subjects received a single dose of Amphetamine Sulfate ODT-IR 20 mg swallowed intact with water in one period, a separate single dose of Amphetamine Sulfate ODT-IR 20 mg disintegrated/dissolved in the oral cavity and then swallowed without water in another period, and a separate single dose of Evekeo™ 10 mg x 2 (20 mg) swallowed intact with water in another period. Each drug administration followed an overnight fast of at least 10 hours. There was a washout period of at least 6 days between each dose. The study design allowed each subject to serve as his/her own control, precluding the need for a separate control group.
Reviewer comment: The study design is appropriate and acceptable

Screening:	**Washout**: 6 days
Randomized: 42	**Completed**: Treatment A: 39 Treatment B: 40, Treatment C: 39

Number of Subjects: 42

Main Inclusion Criteria: Male and Female subjects ages 18 to 45 years. Females subjects agreed to use an acceptable form of birth control as defined in protocol from screening until 14 days after completion of study. Subject's vital signs (measured sitting after 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: 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 have jeopardized the safety of the subject or the validity of the study results. History or presence of tics or Tourette's syndrome. Had 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. Required treatment with furazolidone or monoamine oxidase inhibitors (MAOIs) within 14 days of the first dose of study medication and throughout the duration of the study. Had been treated with any known drugs that are moderate or strong inhibitors/inducers of CYP enzymes such as barbiturates, phenothiazines, cimetidine, carbamazepine, etc., within 30 days prior to the first dose of study medication and that, in the Investigator's judgment, may have impacted subject safety or the validity of the study results.
Consumed beverages and foods containing grapefruit or caffeine/xanthine from 48 hours prior to the first dose of study medication until the end-of-study visit. Subjects were instructed not to consume any of the above products; however, allowance for an isolated single incidental consumption may have been evaluated and approved by the Investigator based on the potential for interaction with the study drug.
Subjects were required to abstain from alcohol for 24 hours before each study period until after the last pharmacokinetic blood sample was collected in each study period.

Treatments
Treatment A (Test): Amphetamine Sulfate ODT-IR Dose = 1 x 20 mg tablet
Lot:PF59310001. Swallowed intact with *water*
Treatment B (Test): Amphetamine Sulfate ODT-IR Dose = 1 x 20 mg tablet
Lot:PF59310001. Disintegrated/dissolved in the oral cavity and then swallowed *without water*

Treatment C (Reference): Evekeo™ (amphetamine sulfate) Dose = 2 x 10 mg tablets. Lot: G150512A. Swallowed intact with *water* Subjects were given a single, oral dose at a prespecified time in each period after an overnight fast of at least 10 hours. The subjects fasted for 4 hours thereafter. Standard meals were provided at approximately 4 and 10 hours after drug administration and at appropriate times thereafter. Except for the 240 mL of room temperature water provided with Treatments A and C, no water was consumed from 1 hour prior through 1 hour after each dose.
Pharmacokinetic Sampling: Blood samples (1 × 6 mL) were collected at 0 (predose), at 2, 5, 10, 15, and 30 minutes post dose, and then at 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, and 60.0 hours after dosing. *Reviewer comment: The blood sampling times covered about 5 half-lives for d- and l-amphetamine and are acceptable*
Statistical Analysis: Pharmacokinetic parameters for (1) *d*-amphetamine and *l*-amphetamine [primary analysis] and (2) racemic amphetamine (*d*-amphetamine + *l*-amphetamine) [secondary analysis] was calculated using noncompartmental analysis. Concentrations that were below the limit of quantification (BLQ) was treated as zero in the data summarization and descriptive statistics. The pharmacokinetic parameters Cmax, AUClast, and AUCinf will be analyzed using an ANOVA model with sequence, period and treatment as fixed effects, and subject within sequence as a random effect using natural log-transformed values. Comparative bioavailability among the three treatments will be assessed using the least squares geometric mean ratios and associated 90% confidence intervals. Comparable bioavailability will be concluded if the 90% confidence intervals of the least squares geometric mean ratio for absolute Cmax, AUClast, and AUCinf lie within the range of 80.00% to 125.00%.

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. The assay procedure was found to be linear over the range of 0.500 to 80.0 ng/mL for D-amphetamine and 0.200 to 32.0 ng/mL for L-amphetamine.

Calibration standards were prepared to yield 0.500, 1.00, 2.00, 6.00, 18.0, 40.0, 72.0, and 80.0 ng/mL for D-amphetamine and 0.200, 0.400, 0.800, 2.40, 7.20, 16.0, 28.8, and 32.0 ng/mL for L-amphetamine. All standards in the final calibration curve must be within ±15.0% of their theoretical values, except the LLOQ standard, which must be within ±20.0%.

High, medium, and low QC samples were prepared at 64.0, 10.0, and 1.50 ng/mL for D-amphetamine and 25.6, 4.00, and 0.600 ng/mL for L-amphetamine from the QC Very High pool.

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 and QC Evaluation

Intrarun and inter-run precision and accuracy must be ≤20.0%.

Precision and Accuracy

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 Pool (high, medium and low)

Intrarun and inter-run precision and accuracy must be ≤15.0%.

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%

Incurred Sample Reproducibility (ISR)

d-amphetamine

Number of Samples Analyzed	Evaluable Results	Number of Samples within 20.0%	Number of Samples Not within 20.0%	Percent Acceptable
286	286	279	7	97.55%

l-amphetamine

Number of Samples Analyzed	Evaluable Results	Number of Samples within 20.0%	Number of Samples Not within 20.0%	Percent Acceptable
286	284	276	8	97.18%

Reviewer comment: The analytical method was adequately validated and is acceptable

Pharmacokinetic Evaluation

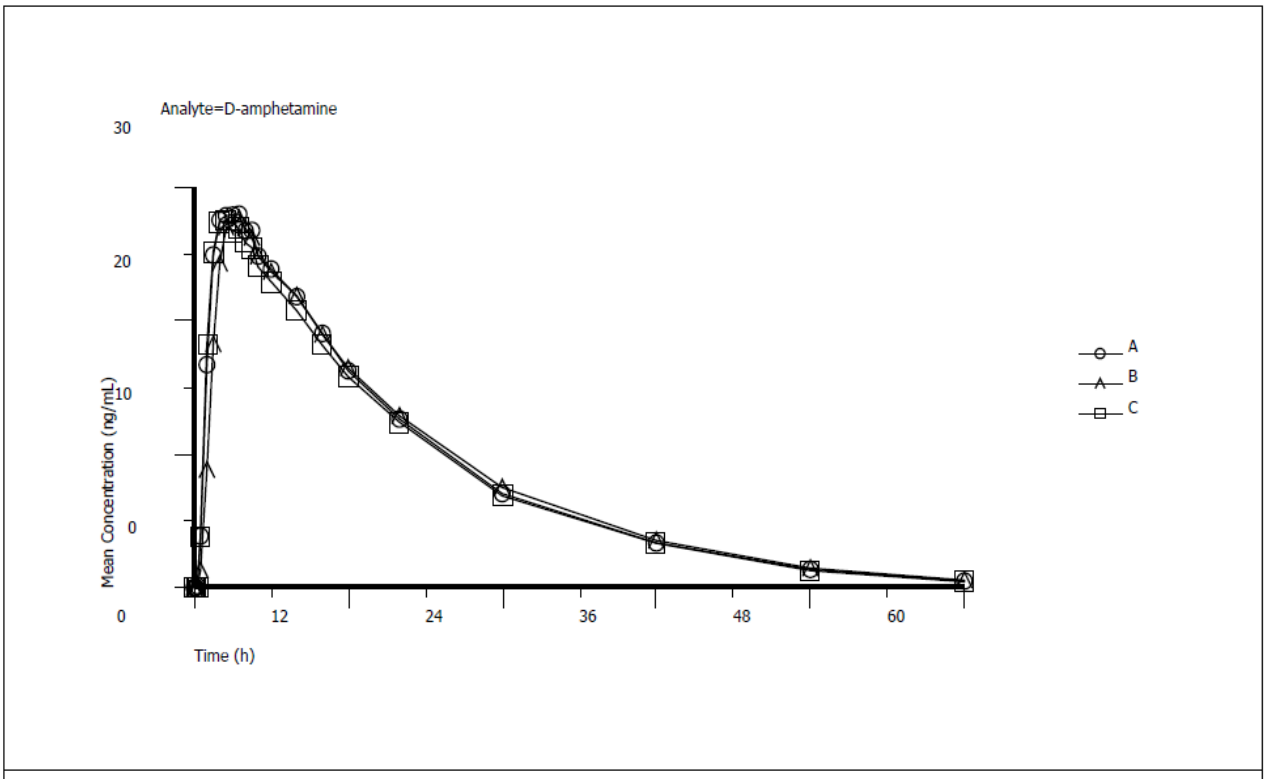
Study Disposition

Randomized/Completed/Discontinued due to AE	42/37/0
Mean Overall Age [Median (range)] years	31.6 [32.5(19 -41)]
Male/Female	20/22
Race (Caucasian/Black/Other	32/8/2
Overall Weight (±SD), kg	71.89 (10.9)

d-amphetamine

Summary of pharmacokinetic evaluation for d-amphetamine

Mean *d*-amphetamine Concentration-Time Profiles after Administration of Amphetamine Sulfate ODT-IR 20 mg with Water (Treatment A), Amphetamine Sulfate ODT-IR 20 mg without Water (Treatment B), and Evekeo 2 x 10 mg Tablets with Water (Treatment C)



Summary of Pharmacokinetic Parameters for d-amphetamine

Pharmacokinetic Parameters of *d*-amphetamine after Administration of Amphetamine Sulfate ODT-IR 20 mg with Water (Treatment A), Amphetamine Sulfate ODT-IR 20 mg without Water (Treatment B), and Evekeo 2 x 10 mg Tablets with Water (Treatment C)

Parameter	Treatment A: Amphetamine Sulfate ODT-IR 20 mg with Water				Treatment B: Amphetamine Sulfate ODT-IR 20 mg without Water			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{lag} (h)	39	0.244	0.0557	22.79	40	0.322	0.156	48.43
T_{max} (h)	39	2.74	0.909	33.23	40	3.28	0.698	21.30
C_{max} (ng/mL)	39	29.9	5.28	17.70	40	29.4	5.94	20.19
AUC_{last} (h*ng/mL)	39	494	96.1	19.46	40	493	105	21.31
AUC_{inf} (h*ng/mL)	39	506	98.6	19.48	40	506	107	21.19
AUC_{Extrap} (%)	39	2.45	0.789	32.17	40	2.66	0.952	35.79
λ_z (h^{-1})	39	0.0706	0.00992	14.05	40	0.0705	0.0104	14.72
$T_{1/2}$ (h)	39	10.0	1.38	13.81	40	10.0	1.41	14.05
T_{last} (h)	39	55.1	6.57	11.93	40	55.2	6.56	11.87
C_{last} (ng/mL)	39	0.854	0.278	32.57	40	0.898	0.253	28.13

Parameter	Treatment C: Evekeo 2 x 10 mg Tablets with Water			
	n	Mean	SD	CV%
T_{lag} (h)	39	0.266	0.0854	32.06
T_{max} (h)	39	2.51	0.936	37.22
C_{max} (ng/mL)	39	29.4	4.93	16.76
AUC_{last} (h*ng/mL)	39	479	86.3	18.00
AUC_{inf} (h*ng/mL)	39	493	85.8	17.42
AUC_{Extrap} (%)	39	2.83	1.24	43.69
λ_z (h^{-1})	39	0.0702	0.0111	15.81
$T_{1/2}$ (h)	39	10.1	1.55	15.34
T_{last} (h)	39	53.8	7.21	13.40
C_{last} (ng/mL)	39	0.916	0.263	28.72

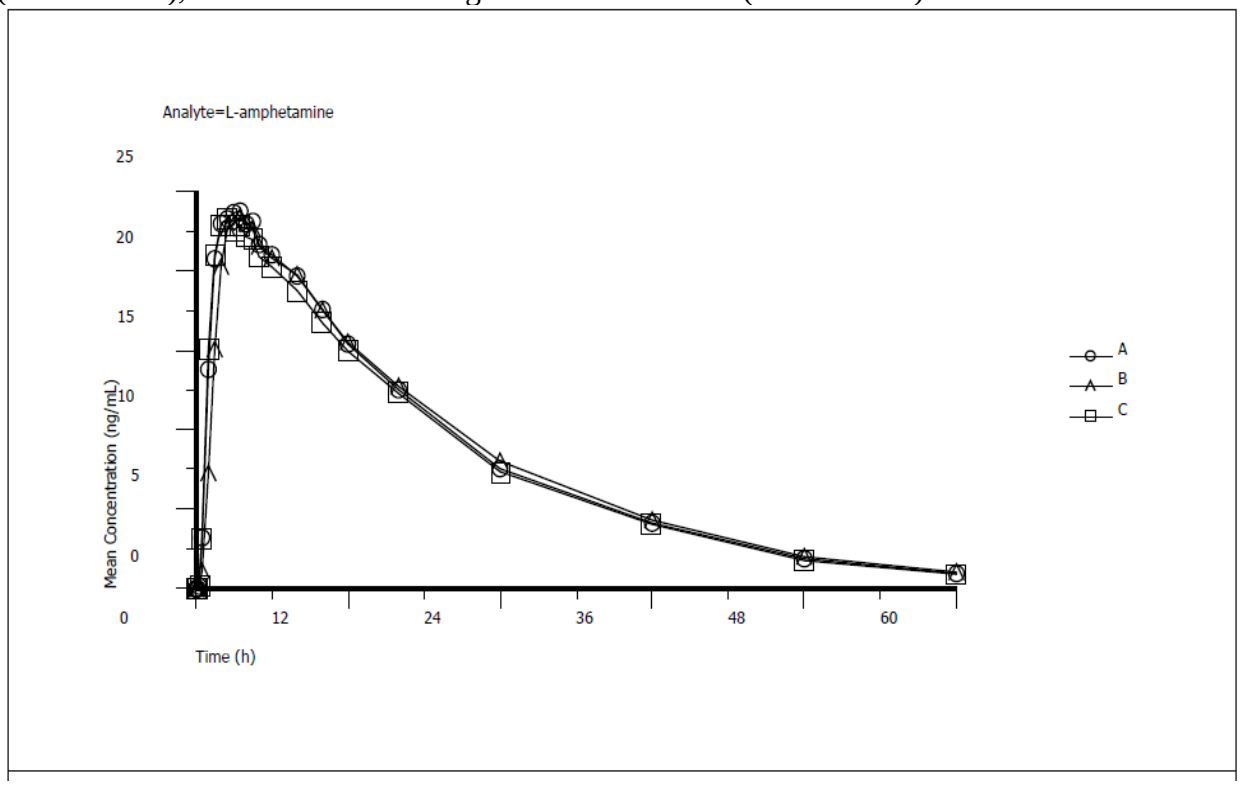
Parameter	Geometric Mean[a]		Ratio(%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	lower	upper
Treatment A (Evekeo ODT 20 mg with water; Test) vs Treatment C (Evekeo RS 2x 10 mg tablets with water; Ref)					
$ln(C_{max})$[c]	29.0	29.1	99.46	96.68	102.32
$ln(AUC_{last})$[c]	483	473	102.22	98.80	105.76
$ln(AUC_{inf})$[c]	496	487	101.82	98.46	105.30
Treatment B (Evekeo ODT 20 mg without water; Test) vs Treatment C (Evekeo RS 2x 10 mg tablets with water; Ref)					
$ln(C_{max})$[d]	28.9	29.1	99.28	96.53	102.10
$ln(AUC_{last})$[d]	479	473	101.28	97.93	104.74
$ln(AUC_{inf})$[d]	492	487	101.13	97.83	104.54
Treatment A (Evekeo ODT 20 mg with water; Test) vs Treatment B (Evekeo ODT 20 mg without water; Ref)					
$ln(C_{max})$[e]	29.0	28.9	100.18	97.38	103.06
$ln(AUC_{last})$[e]	483	479	100.93	97.56	104.42
$ln(AUC_{inf})$[e]	496	492	100.68	97.37	104.11

a- Geometric Mean for Test and Ref based on Least Squares Mean of log-transformed parameter values.
b- Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref).

Treatment A (Test): Amphetamine Sulfate ODT-IR 20 mg with water
Treatment B (Test): Amphetamine Sulfate ODT-IR 20 mg without water
Treatment C (Ref): Evekeo 2 x 10 mg Tablets with water

l-amphetamine

Mean *l*-amphetamine Concentration-Time Profiles after Administration of Amphetamine Sulfate ODT-IR 20 mg with Water (Treatment A), Amphetamine Sulfate ODT-IR 20 mg without Water (Treatment B), and Evekeo 2 x 10 mg Tablets with Water (Treatment C)



Pharmacokinetic Parameters of *l*-amphetamine after Administration of Amphetamine Sulfate ODT-IR 20 mg with Water (Treatment A), Amphetamine Sulfate ODT-IR 20 mg without Water (Treatment B), and Evekeo 2 x 10 mg Tablets with Water (Treatment C)

Parameter	Treatment A: Amphetamine Sulfate ODT-IR 20 mg with Water				Treatment B: Amphetamine Sulfate ODT-IR 20 mg without Water			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{lag} (h)	39	0.230	0.0618	26.88	40	0.262	0.101	38.53
T_{max} (h)	39	3.03	1.14	37.59	40	3.45	1.02	29.68
C_{max} (ng/mL)	39	25.1	4.29	17.13	40	24.8	4.92	19.83
AUC_{last} (h*ng/mL)	39	485	96.1	19.82	40	486	105	21.57
AUC_{inf} (h*ng/mL)	39	502	104	20.64	40	505	114	22.54
AUC_{Extrap} (%)	39	3.27	1.61	49.34	40	3.62	1.94	53.56
λ_z (h^{-1})	39	0.0611	0.00943	15.43	40	0.0610	0.0112	18.39
$T_{1/2}$ (h)	39	11.6	1.80	15.52	40	11.8	2.25	19.16
T_{last} (h)	39	60.0	0.0100	0.02	40	60.0	0.124	0.21
C_{last} (ng/mL)	39	0.969	0.485	50.12	40	1.05	0.533	50.53

Parameter	Treatment C: Evekeo 2 x 10 mg Tablets with Water			
	n	Mean	SD	CV%
T_{lag} (h)	39	0.235	0.0411	17.51
T_{max} (h)	39	2.72	1.13	41.64
C_{max} (ng/mL)	39	24.8	4.28	17.26
AUC_{last} (h*ng/mL)	39	471	79.4	16.85
AUC_{inf} (h*ng/mL)	39	488	84.5	17.31
AUC_{Extrap} (%)	39	3.31	1.78	53.92
λ_z (h^{-1})	39	0.0612	0.00978	15.98
$T_{1/2}$ (h)	39	11.6	2.04	17.56
T_{last} (h)	39	60.0	0.00267	0.00
C_{last} (ng/mL)	39	0.932	0.410	44.01

Dependent Variable	Geometric Mean[a]		Ratio(%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	lower	upper
Treatment A (Evekeo ODT 20 mg with water; Test) vs Treatment C (Evekeo RS 2x 10 mg tablets with water; Ref)					
$ln(C_{max})$[c]	24.4	24.6	99.19	96.56	101.89
$ln(AUC_{last})$[c]	475	467	101.70	98.24	105.28
$ln(AUC_{inf})$[c]	492	483	101.86	98.20	105.65
Treatment B (Evekeo ODT 20 mg without water; Test) vs Treatment C (Evekeo RS 2x 10 mg tablets with water; Ref)					
$ln(C_{max})$[d]	24.4	24.6	99.29	96.69	101.96
$ln(AUC_{last})$[d]	472	467	101.08	97.68	104.60
$ln(AUC_{inf})$[d]	490	483	101.38	97.78	105.11
Treatment A (Evekeo ODT 20 mg with water; Test) vs Treatment B (Evekeo ODT 20 mg without water; Ref)					
$ln(C_{max})$[e]	24.4	24.4	99.90	97.25	102.61
$ln(AUC_{last})$[e]	475	472	100.62	97.20	104.15
$ln(AUC_{inf})$[e]	492	490	100.47	96.87	104.20

a- Geometric Mean for Test and Ref based on Least Squares Mean of log-transformed parameter values.
b- Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref).

Pharmacokinetic Summary

When Amphetamine sulfate ODT-IR 20 mg administered with water was compared with Evekeo 20 mg (2 x 10 mg) tablets taken with water, the ratio of the exposures (Cmax and AUCs) of d- and l-amphetamine were contained within the 90% confidence interval (CI) criteria of 80% to 125%; therefore, the exposures were equivalent.
When Amphetamine ODT-IR 20 mg IR administered without water was compared to Evekeo 20 (2 x 10) mg tablets taken with water, the ratio of the exposures (Cmax and AUCs) to d-and l-amphetamine were contained within the 90% CI criteria of 80% to 125%; therefore, the exposures were equivalent.
When Amphetamine ODT-IR 20 mg IR administered with water was compared to Amphetamine ODT-IR administered without water, the ratio of the exposures (Cmax and AUCs) to d- and l-amphetamine were contained within the 90% confidence interval criteria of 80% to 125%; therefore, the exposures were equivalent

The racemic amphetamine was also equivalent when the various treatments are compared.

Safety Evaluation

The sponsor reported that the most common adverse events (AE) was headache, reported three times by two different subjects (one subject [2.4%] following Treatment B and two subjects [4.8%] following Treatment C). One AE was moderate in severity (dermatitis contact following Treatment B, judged not related to study treatment) and the rest were mild. No serious AE was reported according to the sponsor.

Reviewer comment

The reviewer agrees with the sponsor conclusion that the exposure (Cmax and AUC) to d- and l-amphetamine and racemic amphetamine are equivalent when Amphetamine ODT IR taken with water and without water are compared to Evekeo tablets taken with water. Also, when Amphetamine ODT taken with water is compared to that taken without water, the exposures are equivalent.

Clinical Study Report

Report No.: AR17-0002	Study Period: 11/10/16 – 11/18/16
Study Center:	Worldwide Clinical Trials Early Phase Services, San Antonio, TX
Principal Investigator:	Vanessa Sanberg, MD
Bioanalytical Facility:	(b) (4)
Principal Scientist:	

EDR: \\CDSESUB1\evsprod\nda209905\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5352-stud-rep-uncontr\ar17.002

Title: A Single-Dose, Two-Period, Two-Treatment, Two-Way Crossover Bioavailability Study of Amphetamine Sulfate Oral Disintegrating Immediate Release Tablets (ODT-IR) 20 mg Administered to Healthy Adult Volunteers under Fed and Fasted Conditions

Objectives: To compare the rate of absorption and oral bioavailability of a test formulation of Amphetamine Sulfate ODT-IR 20 mg manufactured by (b) (4) when administered under fed and fasted conditions.

Study Design

Design: Single-dose, open-label, randomized, two-period, two-treatment crossover study in which 32 healthy adult subjects were scheduled to receive a single dose of Amphetamine Sulfate ODT-IR 20 mg in one period under fed conditions, and a separate single dose of Amphetamine Sulfate ODT-IR 20 mg in another period under fasted conditions. *Reviewer comment: The study design is appropriate and reasonable*	
Screening:	**Washout**: 6 days
Randomized: 32	**Completed**: 32

Number of subjects: 32

Main Inclusion Criteria

Subjects were healthy males and females, 18-45 years of age (inclusive), with a body mass index between 18 and 30 kg/m2 (inclusive), and a minimum weight of 50 kg (110 lbs). Female subjects were not pregnant or breastfeeding. Female subjects agreed to use an acceptable form of birth control from Screening until 14 days after completion of the study as stated in protocol. Had vital signs (measured sitting after a minimum 3 minutes rest) at Screening 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. Predose vital signs were assessed by the Principal Investigator or designee (e.g., a medically qualified Sub-Investigator) prior to study drug administration. The Principal Investigator or designee verified the eligibility of each subject with out-of-range vital signs and documented approval prior to dosing.

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 have jeopardized the safety of the subject or the validity of the study results. History or presence of allergic or adverse response to amphetamine sulfate, sympathomimetic amines, or related drugs. 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, except hormonal contraceptive or hormonal replacement therapy, within 14 days prior to the first dose of study medication. Required treatment with furazolidone or monoamine oxidase inhibitors (MAOIs) within 14 days of the first dose of study medication and throughout the duration of the study. Had been treated with any known drugs that are moderate or strong inhibitors/inducers of CYP enzymes such as barbiturates, phenothiazines, cimetidine, carbamazepine, etc., within 30 days prior to the first dose of study medication, and that, in the Investigator's judgment, may have impacted subject safety or the validity of the study results. Smoked or used tobacco products within 60 days prior to the first dose of study medication. History of substance abuse or treatment (including alcohol) within the past 2 years.

Restrictions

Subjects were not permitted to consume beverages and foods containing grapefruit or caffeine/xanthine from 48 hours prior to the first dose of study medication until the end-of-study visit. Subjects were instructed not to consume any of the above products; however, allowance for an isolated single incidental consumption may have been evaluated and approved by the Investigator based on the potential for interaction with the study drug.

Treatments A and B

Amphetamine Sulfate Oral Disintegrating Immediate-Release Tablets (ODT-IR) 20 mg
Lot No.: PF59310001. Manufactured by: Adare Pharmaceuticals for Arbor Pharmaceuticals
Treatment A was administered under fed and Treatment B under fasting conditions.

Subjects were given a single oral dose of Amphetamine Sulfate ODT-IR 20 mg at a prespecified time in each period, after a 10-hour overnight fast (Treatment B) or after a

10-hour overnight fast followed by the ingestion an FDA standard meal (Treatment A). The subjects fasted for 4 hours thereafter. Water was allowed ad libitum during the study except for 1 hour prior through 1 hour post dose. Standard meals were provided at approximately 4 and 10 hours after drug administration and at appropriate times thereafter.
Pharmacokinetic analysis During each study period, 6 mL blood samples were obtained prior to each dose and following each dose at selected times through 48 hours post dose. Blood (plasma) pharmacokinetic characteristics were assessed after each dose of investigational product. Blood samples (1 x 6 mL) were collected at 0 (predose), at 2, 5, 10, 15, and 30 minutes post dose, and then at 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, and 48.0 hours after each dose. *Reviewer comment: The blood sampling period for pharmacokinetic analysis is adequate and acceptable*
Statistical Analysis Pharmacokinetic parameters were determined using non-compartmental methods. It is estimated that a sample size of 28 subjects will provide greater than or equal to 80% power at $\alpha = 0.05$ to obtain 90% confidence intervals for the least squares geometric mean ratios for maximum concentration (Cmax), area under the curve from time 0 hours to last quantifiable concentration (AUClast), and AUCinf between 80% and 125%, assuming a true difference of less than or equal to 5%. The absence of food effect will be concluded if the 90% confidence intervals of the least squares geometric mean ratio for absolute Cmax, AUClast, and AUCinf lie within the range of 80.00% to 125.00%.

Analytical Method

Plasma concentrations were determined by 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 human EDTA plasma.

Linearity and Standard Curves

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 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

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 Sensitivity

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

Incurred Sample Reanalysis (ISR)

d-amphetamine

Number of Samples Analyzed	Evaluable Results	Number of Samples within 20.0%	Number of Samples Not within 20.0%	Percent Acceptable
145	145	145	0	100.00%

l-amphetamine

Number of Samples Analyzed	Evaluable Results	Number of Samples within 20.0%	Number of Samples Not within 20.0%	Percent Acceptable
145	145	145	0	100.00%

Reviewer comment: The analytical method is adequately validated and acceptable

Pharmacokinetic Evaluation

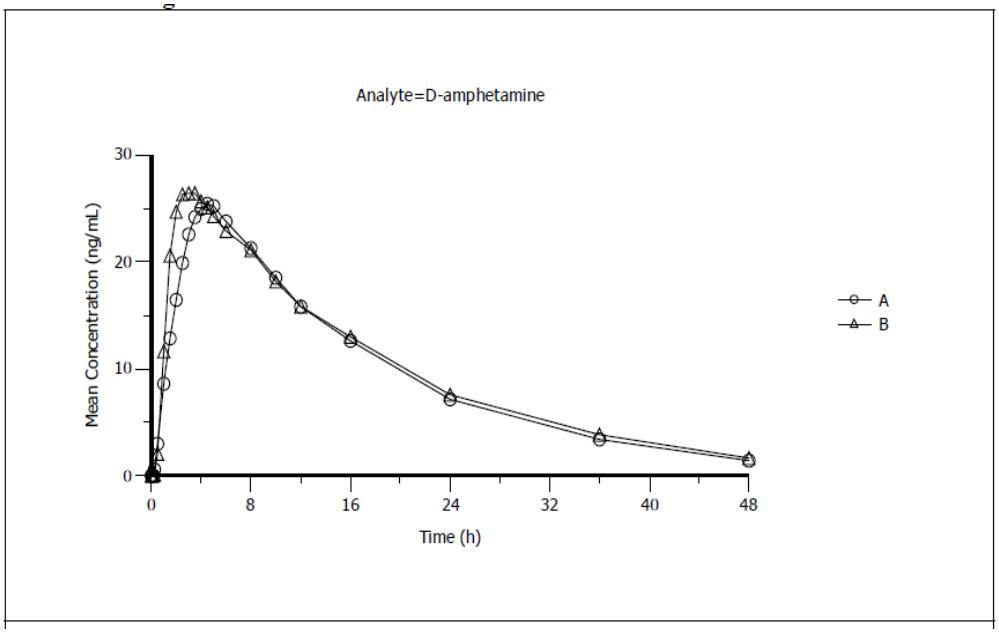
Study Disposition

Randomized/Completed/Discontinued due to AE	32/31/0
Mean Overall Age [Median (range)] years	30.9 [30.0 (22, 40)]
Male/Female	23/9
Race (Caucasian/Black/Other)	20/10/2
Overall Weight (± SD), Kg	76.48 (± 10.49)

d-Amphetamine

Summary of pharmacokinetic evaluation for d-amphetamine

Mean d-Amphetamine Concentration-Time Profiles after Administration of Amphetamine Sulfate-ODT IR 20 mg under Fed (A) and Fasted (B) Conditions



Pharmacokinetic parameters with descriptive statistics for d-amphetamine is provided in the following table

Pharmacokinetic Parameters of *d*-Amphetamine after Administration of Amphetamine Sulfate ODT-IR 20 mg under Fed and Fasted conditions

Parameter	Treatment A: Amphetamine Sulfate ODT-IR 20 mg, Fed				Treatment B: Amphetamine Sulfate ODT-IR 20 mg, Fasted			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	31	4.47	1.22	27.40	31	3.05	1.08	35.52
C_{max} (ng/mL)	31	26.7	4.62	17.27	31	28.0	5.99	21.42
AUC_{last} (h*ng/mL)	31	457	98.5	21.57	31	483	103	21.34
AUC_{inf} (h*ng/mL)	31	479	108	22.50	31	511	118	23.11
AUC_{Extrap} (%)	31	4.43	1.81	40.91	31	5.13	2.74	53.49
λ_z (h^{-1})	31	0.0701	0.0103	14.64	31	0.0658	0.0109	16.53
$T_{1/2}$ (h)	31	10.1	1.49	14.79	31	10.8	1.95	17.95
T_{last} (h)	31	47.6	2.16	4.54	31	48.1	0.461	0.96
C_{last} (ng/mL)	31	1.45	0.645	44.52	31	1.64	0.873	53.09

Statistical Analysis of *d*-Amphetamine after Administration of Amphetamine Sulfate ODT-IR 20 mg under Fed and Fasted Conditions

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	26.3760	27.4378	96.13	93.07	99.29	1.0000	7.49
$\ln(AUC_{last})$	447.2323	474.1251	94.33	91.35	97.40	1.0000	7.44
$\ln(AUC_{inf})$	468.0301	499.9467	93.62	90.44	96.90	1.0000	8.01

[a] Geometric Mean for Amphetamine Sulfate ODT-IR 20 mg, fed (Test) and Amphetamine Sulfate ODT-IR 20 mg, fasted (Ref) based on Least Squares Mean of log-transformed parameter values

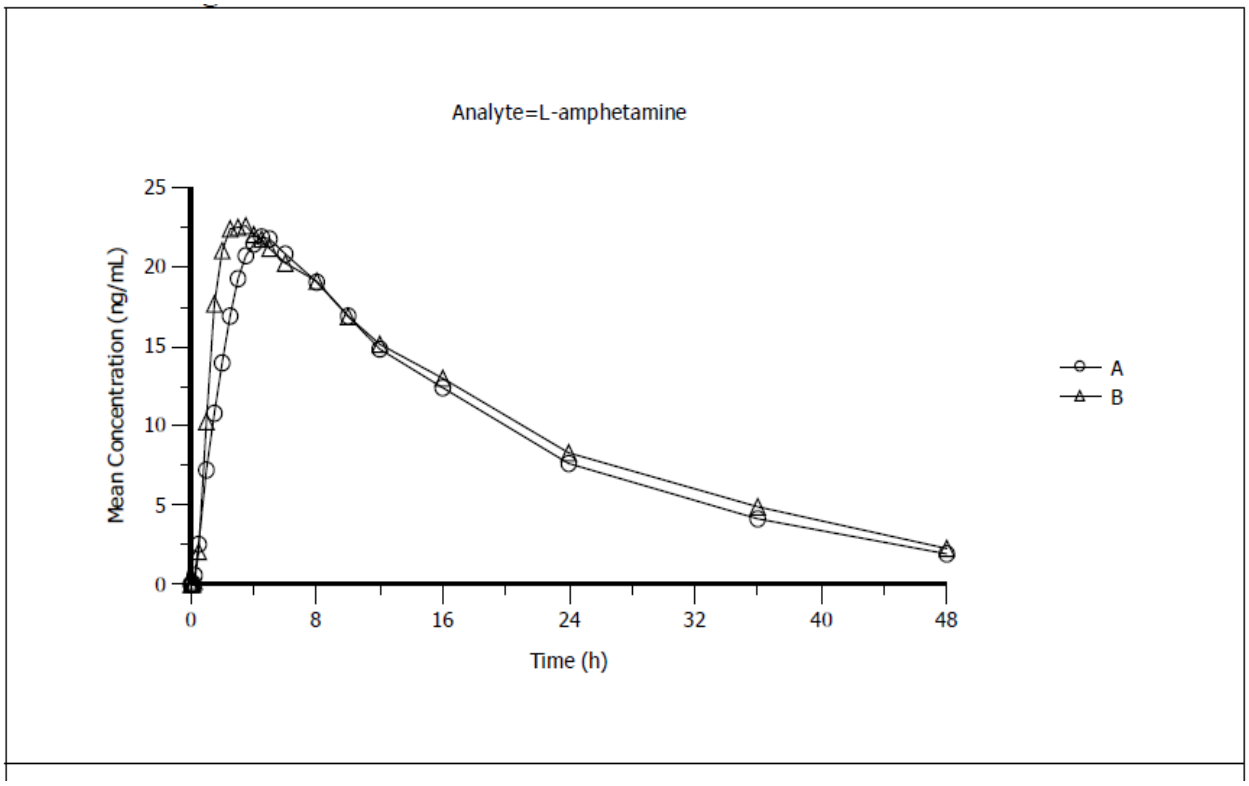
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

[c] 90% Confidence Interval

The 90% confidence interval (CI) around the ratio of the exposure parameters (Cmax and AUC) for d-amphetamine were contained within the prespecified criteria of 80% - 125%, indicating there is no significant effect of food. However, administration of Amphetamine ODT with food delayed the time maximum concentration (Tmax) of d-amphetamine. The median (range) Tmax was 4.5 (2.5 – 8.0) under fed conditions and 2.5 (1.5 – 6.0). The elimination half-life was similar after administration of Amphetamine ODT IR under fed or fasting conditions.

l-Amphetamine

Mean l-Amphetamine Concentration-Time Profiles after Administration of Amphetamine Sulfate-ODT IR 20 mg under Fed (A) and Fasted (B) Conditions



Pharmacokinetic Parameters of l-Amphetamine after Administration of Amphetamine Sulfate ODT-IR 20 mg under Fed and Fasted conditions

Parameter	Treatment A: Amphetamine Sulfate ODT-IR 20 mg, Fed				Treatment B: Amphetamine Sulfate ODT-IR 20 mg, Fasted			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	31	4.82	1.28	26.44	32	3.00	1.09	36.42
C_{max} (ng/mL)	31	23.1	4.09	17.74	32	24.1	5.10	21.21
AUC_{last} (h*ng/mL)	31	443	95.5	21.58	32	476	98.1	20.61
AUC_{inf} (h*ng/mL)	31	478	110	23.00	32	531	135	25.37
AUC_{Extrap} (%)	31	7.00	2.85	40.76	32	9.27	6.54	70.54
λ_z (h^{-1})	31	0.0594	0.00964	16.24	32	0.0543	0.0116	21.36
$T_{1/2}$ (h)	31	12.0	1.94	16.19	32	13.4	3.40	25.28
T_{last} (h)	31	48.0	0.126	0.26	32	47.7	2.17	4.54
C_{last} (ng/mL)	31	1.92	0.833	43.44	32	2.47	1.59	64.33

Statistical Analysis of l-Amphetamine after Administration of Amphetamine Sulfate ODT-IR 20 mg under Fed and Fasted Conditions

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$ln(C_{max})$	22.8580	23.5916	96.89	93.85	100.03	1.0000	7.40
$ln(AUC_{last})$	435.1159	467.3909	93.09	90.06	96.24	1.0000	7.71
$ln(AUC_{inf})$	472.6964	516.6233	91.50	88.07	95.05	1.0000	8.86

[a] Geometric Mean for Amphetamine Sulfate ODT-IR 20 mg, fed (Test) and Amphetamine Sulfate ODT-IR 20 mg, fasted (Ref) based on Least Squares Mean of log-transformed parameter values

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

[c] 90% Confidence Interval

The 90% CI around the exposures (Cmax, AUC) for l-amphetamine were within the prespecified criteria of 80% to 125%, indicating food does not have a significant effect on the exposures of l-amphetamine. However, Median Tmax was delayed by about 1.5 hours after administration of amphetamine ODT-IR with food. The median (range) Tmax was 4.5 (2.5 – 8.0) under fed and 2.5 (1.5 – 6) under fasting conditions.

Statistical Analysis of Racemic Amphetamine Comparing Sulfate ODT-IR 20 mg Fed (A) vs. Amphetamine Sulfate ODT-IR 20 mg Fasted (B)

Dependent Variable	Geometric Mean		Ratio (%)	90% CI	
	Test	Ref	(Test/Ref)	Lower	Upper
Ln Cmax	49.07	50.87	96.46	93.41	99.60
Ln AUClast	881.09	939.51	93.78	90.78	96.88
Ln AUCinf	933.34	1007.24	92.66	89.36	96.09

The median (range) Tmax for racemic amphetamine was 4.5 (2.5 -8.0) hours after fed and 2.5 (1.5 – 6) hours after fasting conditions.

Pharmacokinetic Summary
The 90% confidence intervals for the log-transformed exposure parameters Cmax, AUClast, and AUCinf, were within the pre-specified 80% to 125% range for both *d*- and *l*-amphetamine. Additionally, the 90% confidence intervals for the log-transformed exposure parameters Cmax, AUClast, and AUCinf, were within the accepted 80% to 125% range for racemic amphetamine. Median *d*- and *l*-amphetamine T_{max} was delayed by approximately 2 h and 1.5 h, respectively, under fed conditions compared to that under fasted conditions

Safety Evaluation
Four AEs were reported by three subjects (3/31, 9.7%) following Treatment A, and seven AEs were reported by five subjects (5/32, 15.6%) following Treatment B. All AEs were mild in severity and resolved by the end of the study without intervention. The most common AEs were palpitations (n=2, reported by two subjects following Treatment B) and change in sustained attention (n=2, reported once after Treatment A and once following Treatment B by the same subject). All 11 AEs during the study were mild in severity and resolved by the end of the study

without intervention. Following Treatment A, four AEs were reported, three of which were judged related to treatment. Following Treatment B, seven AEs were reported, six of which were judged related to treatment.

Reviewer Comments

The reviewer agrees with the sponsor conclusions. High fat meal does not have significant effect on the exposures (Cmax and AUC) to d- and l-amphetamine. However, high fat meal delays median Tmax by about 2 and 1.5 hours for d- amphetamine and l-amphetamine, respectively.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KOFI A KUMI
12/20/2018 03:24:32 PM

LUNING ZHUANG
12/21/2018 09:42:16 PM