Comparative Bioavailability of Amphetamine Extended-Release Oral Suspension (AMPH EROS, Dyanavel XR®) and Extended-Release Mixed Amphetamine Salts (ER MAS)

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AP, JCK, AE, LD, and TRK are employees of Tris Pharma, Inc., the developer and manufacturer of AMPH ER TAB and AMPH EROS. PMR, Inc. is a contracted service provider of Tris Pharma, Inc.

Abstract

PURPOSE:
This open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study evaluated the comparative bioavailability between amphetamine extended-release oral suspension (Treatment A: AMPH EROS, Dyanavel XR 2.5 mg/mL, 18.8 mg amphetamine base per 7.5 mL) and extended-release mixed amphetamine salts (Treatment B: ER MAS 30 mg capsules, equivalent to 18.8 mg amphetamine base per capsule) after a single dose in healthy adult subjects, under fasted conditions.
METHODS:
The crossover design allowed for intra-subject PK comparisons. Relative comparable bioavailability was determined by a statistical comparison of the AUC and C_{max} parameters for both *d*- and *l*-amphetamine, where the geometric mean ratios for AUC and C_{max} were within the 90% confidence limits (80.0%-125.0%) to determine comparable bioavailability between test products. Subjects in sequence 1 received treatment A followed by B; subjects in sequence 2 received treatment B followed by treatment A. PK samples were obtained at 0 (pre-dose) through 60 hours post-dose. The safety assessment was based on reported frequency and severity of adverse events.
RESULTS:
Thirty (30) subjects were enrolled and 28 completed. The mean age of subjects was 35 years, with a mean BMI of 25.9 kg/m2. Most subjects were Male (63.3%) and Black (56.7%). The geometric mean ratios for C_{max} and all AUC measurements were within the 80-125% bound indicating comparable bioavailability between both test products. Both test products were generally well-tolerated with no serious AEs reported.
CONCLUSIONS:
The bioavailability of a single 7.5 mL dose of AMPH EROS 2.5 mg/mL was comparable to a single 30 mg capsule dose of ER MAS. AMPH EROS (both *d*- and *l*-amphetamine) showed equivalent peak and overall exposure to ER MAS under fasted conditions.

Introduction

- Amphetamine is a non-catecholamine sympathomimetic amine that stimulates CNS activity. It is indicated for indicated for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD).
- In a separate study, following a single, 18.8 mg oral dose of AMPH EROS, the median (range) time to reach peak plasma concentrations was 4.0 (2 to 7) hours for both *d*-amphetamine and *l*-amphetamine in healthy subjects under fasted conditions.
- For AMPH EROS, food delayed the time to reach peak concentration of both *d*- and *l*-amphetamine by approximately 1 hour. Overall, a high-fat meal increased the average C_{max} of both isomers by about 2% and decreased the AUC by 5-7% (5.7% decrease for d-amphetamine and 7.4% for l-amphetamine).
- Following dosing of the AMPH EROS, the mean (± standard deviation [SD]) plasma terminal elimination half-life of *d*-amphetamine is 12.36 (± 2.95) hours and the mean (± SD) plasma terminal half-life for *l*-amphetamine is 15.12 (± 4.40) hours.
- The objective of this study was to evaluate the comparative bioavailability between extended release oral suspension (EROS), 2.5 mg/mL (18.8 mg amphetamine base per 7.5 mL), and extended-release mixed amphetamine salts capsules, 30 mg (18.8 mg amphetamine base per capsule), after a single dose in healthy subjects, under fasted conditions.

This study was sponsored by Tris Pharma, Inc.

Methods

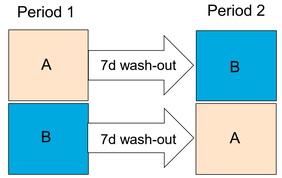
Study Design

- This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative bioavailability study that compared the bioavailability of AMPH EROS to the ER MAS capsule indicated for the treatment of ADHD in children, adolescents, and adults under fasted conditions.
- Bioavailability is assessed upon determination of the rate and extent of absorption of a drug in a biological system. AUC and C_{max} are common PK parameters obtained to estimate the rate and extent of absorption of a drug product. A sampling schedule was designed for this study to ensure that the AUC and C_{max} parameters were adequately assessed from collected plasma. The crossover design allowed for intra-subject PK comparisons.
- To prevent any carryover effect, the two study periods were separated by a washout of at least 7 days, a time interval equivalent to more than 5 times the expected half-lives of *d*-amphetamine and *l*-amphetamine.
- Relative bioavailability between the marketed products was determined by a statistical comparison of the AUC and C_{max} parameters for *d*-amphetamine and *l*-amphetamine.
- Partial AUCs were used to characterize the biphasic release components of the formulations and are recommended in the product-specific Office of Generic Drugs guidance for amphetamine in both AMPH EROS and ER MAS capsule formulations

Treatments Administered

Treatment	Description
A	The test product (7.5 mL of 2.5 mg/mL AMPH EROS) administered after an overnight fast of at least 10 hours.
B	The reference product (one 30 mg ER MAS capsule) administered after an overnight fast of at least 10 hours.

Treatment Sequences



Study Population

- The study population consisted of 36 healthy, non-smoking, male and female volunteers aged 18 to 55 years with BMI ≥19.0 and ≤33.0 kg/m^2.
- Subjects enrolled in the study satisfied the following subject selection criteria no more than 28 days prior to the first drug administration.
- Important exclusion criteria included known history or presence of neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, genitourinary, gastrointestinal, psychiatric, or cardiovascular disease or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results.

Assessments/Statistical Methods

- Primary Endpoint: In order to declare bioequivalence of AMPH EROS to the ER MAS capsule, the 90% confidence intervals (CIs) of the ratios of geometric mean plasma *d*-amphetamine and *l*-amphetamine AUC_{0-5}, AUC_{5-t}, AUC_{inf}, and C_{max} of AMPH EROS in relation to the ER MAS capsule should be between 80.00 and 125.00%, inclusive
- In-house data indicated a CV for *l*-amphetamine AUC of approximately 21%. Assuming a 21% intra-subject variability and a difference between the treatment means of 5% or less, the necessary sample size for a 90% probability of the 90% CI of the treatment means ratio to be within the 80.00 to 125.00% range was estimated to be 26 subjects.

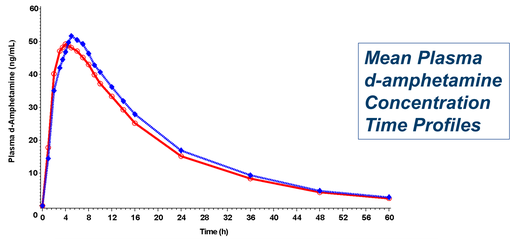
Subject Disposition and Selected Characteristics

Thirty (30) subjects were enrolled in the study and 28 subjects completed the study. Twenty-nine (29) subjects received the test product (as administered in treatment A) and all subjects received the reference product (as administered in treatment B).

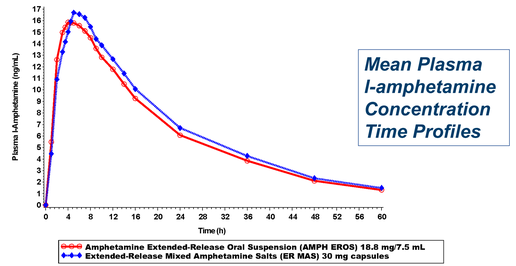
Description	Treatment A	Treatment B	Totals
Randomized	30	30	30
Dosed (Safety Dataset)	29	30	30
Premature DC	1	0	2*
PK Dataset	28	28	28

*Reasons for study discontinuation: Subject decision=1, Dismissed due to non-permitted concomitant medication=1.

Description		Safety Dataset	PK Dataset
Age (years)	Median (min, max)	35 (20-49)	34 (20-49)
	Mean ±SD	35 ±8	34 ±8
Height (in)	Mean ±SD	67.9 ±3.4	67.8 ±3.3
Weight (lb)	Mean ±SD	169.6 ±26.4	168.7 ±26.7
BMI (kg/m^2)	Mean ±SD	25.9 ±26.0	25.8 ±3.5
Sex	Male n (%)	11 (36.7)	10 (35.7)
	Female n (%)	19 (63.3)	18 (64.3)
Race	Black n (%)	17 (56.7)	15 (53.6)
	White n (%)	11 (36.7)	11 (39.3)
	Asian n (%)	1 (3.3)	1 (3.6)
	Multiracial n (%)	1 (3.3)	1 (3.6)
Ethnicity	Hispanic n (%)	2 (6.7)	2 (7.1)
	Non-Hispanic n (%)	28 (93.3)	26 (92.9)



Mean Plasma d-amphetamine Concentration Time Profiles



Mean Plasma l-amphetamine Concentration Time Profiles

Pharmacokinetic Data

***d*-amphetamine**

Parameter	Trt (n)	Geometric Mean	Ratio (%)	90% Confidence Interval	Intrasubject CV (%)
C_{max}	A (28)	50.1	93.2	89.6-96.7	9
	B (28)	53.8			
AUC_t	A (28)	973.2	93.9	89.9-97.9	9
	B (28)	1036.6			
AUC_{0-t}	A (28)	128.9	115.8	106.9-125.5	18
	B (28)	109.5			
AUC_{0-5}	A (28)	175.0	110.5	103.2-118.4	15
	B (28)	158.4			
AUC_{5-t}	A (28)	795.7	91.3	86.8-96.1	11
	B (28)	871.6			
$AUC_{0-\infty}$	A (28)	1014.1	93.4	89.3-98.0	10
	B (28)	1083.6			
T_{max}	A (28)	Median 4.00	Range 2.00-7.00		
	B (28)	Median 5.00	Range 2.00-8.00		

***l*-amphetamine**

Parameter	Trt (n)	Geometric Mean	Ratio (%)	90% Confidence Interval	Intrasubject CV (%)
C_{max}	A (28)	16.2	93.9	90.7-97.1	7
	B (28)	17.3			
AUC_t	A (28)	362.5	94.5	89.9-99.3	11
	B (28)	383.8			
AUC_{0-t}	A (28)	40.1	116.2	107.3-125.8	18
	B (28)	34.3			
AUC_{0-5}	A (28)	55.7	111.1	103.8-118.9	15
	B (28)	50.2			
AUC_{5-t}	A (28)	305.8	92.3	87.1-97.8	13
	B (28)	331.2			
$AUC_{0-\infty}$	A (28)	391.7	94.1	88.8-99.6	13
	B (28)	416.4			
T_{max}	A (28)	Median 4.02	Range 3.00-7.02		
	B (28)	Median 5.00	Range 2.00-9.00		

- The administration of the study drugs was generally well tolerated. The most commonly reported treatment-related TEAE was tachycardia, with 6 events in 5 subjects (16.7%).
- One (1) subject experienced tachycardia after administration of AMPH EROS. Eight (8) TEAEs were related to vital signs and ECG abnormalities. All TEAEs were mild in severity and resolved.
- No SAEs were reported during the conduct of this study.

Conclusions

- The test product, amphetamine extended-release oral suspension (AMPH EROS), 2.5 mg/mL (18.8 mg amphetamine base per 7.5 mL), exhibited comparable total and peak exposure to the reference product, extended-release mixed amphetamine salts (ER MAS) capsules, 30 mg (18.8 mg amphetamine base per capsule), in healthy subjects after a single, oral dose, under fasted conditions.
- Overall, AMPH EROS was well tolerated by the healthy subjects that participated in this study.