Efficacy of Amphetamine Extended-Release Oral Suspension (AMPH EROS) in Children with Attention-Deficit/Hyperactivity Disorder: A Post-hoc Analysis of Effect Sizes Across the Day

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AP, LD, ER, and JCK are all employees of Tris Pharma, Inc., the developer and manufacturer of AMPH ER TAB. SVF and ACC are consultants to Tris Pharma, Inc.

Abstract

Objective: To evaluate the treatment effect size of AMPH EROS (Dyanavel© XR, Tris Pharma, Inc., Monmouth Junction, NJ) in a laboratory classroom study conducted in children aged 6 to 12 with attention-deficit/hyperactivity disorder (ADHD).

Methods: A post-hoc analysis was performed to assess the overall effect size as well as the effect size at each timepoint from early morning through evening (1, 2, 4, 6, 8, 10, 12, and 13 hours postdose) for each efficacy measure evaluated in a 5-week, randomized, dose-optimized, double-blind, placebo-controlled, laboratory classroom assessment, efficacy and safety AMPH EROS study (N=99; Childress, 2018). Change from baseline of the primary (SKAMP-C) and key secondary (SKAMP-A, SKAMP-D, PERMP-T, PERMP-A, PERMP-C) efficacy measures were analyzed using a Mixed-effect Model for Repeat Measurement (MMRM) analysis. Comparisons among treatment were adjusted for multiple comparisons using the Bonferroni method. The effect size was estimated using the Cohen's d method, to determine a "small," (0.2), "medium," (0.5), or "large" (0.8) magnitude of treatment effect (Cohen, 1992).

Results: A large overall effect size of treatment was observed for all primary and key secondary efficacy assessments. Moreover, the SKAMP-C, PERMP-T, PERMP-A, and PERMP-C scores demonstrated a large effect size at each time point evaluated across the day, from 1 hour to 13 hours postdose, and the SKAMP-A and SKAMP-D scores showed a medium to large effect size at each time point.

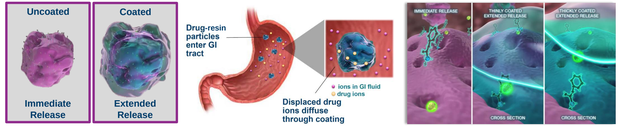
Conclusions: AMPH EROS demonstrated a large and consistent effect size across the day, including early in the morning, in the treatment of symptoms of ADHD in children aged 6-12 years old.

Introduction

- Clinical trials to assess the efficacy of stimulant medications for ADHD typically compare a single active drug treatment with placebo throughout the day.
- However traditional clinical trial designs for ADHD vary between studies and thus don't allow for direct comparisons of efficacy data for different pharmacologic agents in the treatment of ADHD.
- The concept of effect size, was developed to enable more direct comparisons of efficacy data between two studies in order to provide an interpretable value on the direction and magnitude of an effect of a treatment.[1-2]
- Based on analysis by Cohen, effect sizes of 0.2, 0.5, and 0.8, respectively, correspond to a small, medium, and large magnitude of effect.[3]
- The efficacy and safety of AMPH EROS as a treatment for ADHD were established in a laboratory classroom study by Childress *et al.* using the Swanson, Kotkin, Agler, M-Flynn, Pelham (SKAMP) complete and subscores as well as the Permanent Product Measures of Performance (PERMP).[4-6]
- The objective of this study was to perform a post-hoc analysis of the original classroom study in order to evaluate the therapeutic effect size of AMPH EROS in the treatment of children with ADHD. This data can provide practical evaluation of the treatment effect of AMPH EROS versus other available agents and help guide treatment choices.
- Different from other amphetamine formulations for the treatment of ADHD, AMPH EROS is a novel formulation which utilizes the proprietary ion-exchange LiquiXR® technology designed to provide rapid release of active drug followed by a sustained extended release.[7]

LiquiXR© Technology

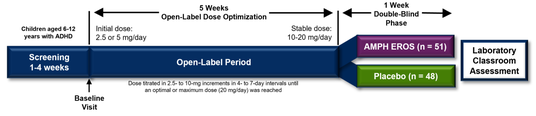
- Millions of micron-sized, ion-exchange, polystyrene resins complex to drug ions forming drug-resin particles
- Polymer coating of varying thickness allows for programmed, extended release of active drug



Methods

Study Design and Population

- The study enrolled 108 boys and girls aged 6 to 12 years diagnosed with ADHD.[4] A total of 99 participants (AMPH EROS, n = 51; placebo, n = 48) completed the study and were included in the intent-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of double-blind study medication and had at least one postdose assessment of the primary efficacy variable (SKAMP-C). Nine participants discontinued from the study.
- The overall study design is provided below, and the complete details of the inclusion and exclusion criteria, methods, and conduct of the parent study have been reported elsewhere.[4]



Assessments/Statistical Methods

- Efficacy assessments were performed on the ITT population,
- Efficacy data were analyzed according to the treatment to which the subject was randomized. Efficacy assessments were collected from the early morning through evening at predose, 1, 2, 4, 6, 8, 10, 12, and 13 hours postdose.
- The efficacy variables used in this analysis were the change from baseline of the following scores: SKAMP Combined (SKAMP-C), Attention (SKAMP-A), and Deportment (SKAMP-D) and the PERMP Total (PERMP-T), Attempted (PERMP-A), and Correct (PERMP-C). These variables were analyzed using an MMRM analysis, which included terms for treatment, time, predose, treatment-by-time interaction, predose-by-time interaction, study center, subject age, and subject sex.
- A significance level of α = 0.05 was used to establish the significance of treatment effect, which was determined using the mixed-effect model adjusted means (LSMEANS). The LSMEANS methodology computed the least-squares means (LS-Means) of fixed effects. Comparisons among treatment accounted for the multiple comparison adjustment using the Bonferroni method.
- All subjects with one dose of double-blind study medication and at least one postdose assessment of the selected variables were included in the analysis without imputation of missing data.
- The effect size was estimated for each variable and for each measurement using Cohen's d method, as the differences between drug effects and placebo effects (treatment effect) divided by their pooled standard deviation (SD).

$$Cohen's\ d = \frac{(Drug\ Effect - Placebo\ Effect)}{Pooled\ Standard\ Deviation\ (SD)}$$

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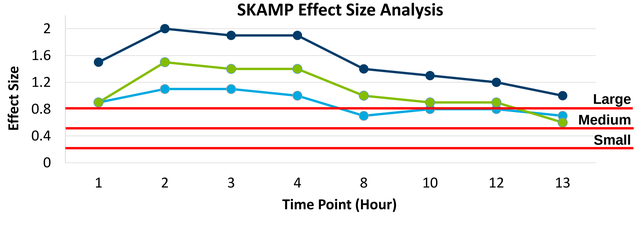
Demographics

Subjects	Placebo (n = 48)	AMPH EROS (n = 51)	Total (N = 99)
Sex, *n* (%)			
Male	32 (66.7)	36 (70.6)	68 (68.7)
Female	16 (33.3)	15 (29.4)	31 (31.3)
Age, years			
Mean (SD)	9.6 (1.76)	9.2 (1.95)	9.4 (1.86)
Median	10.0	9.0	9.0
Range (min, max)	(6, 12)	(6, 12)	(6, 12)
Race, *n* (%)			
White	28 (58.3)	27 (52.9)	55 (55.6)
Black/African American	15 (31.3)	19 (37.3)	34 (34.3)
Other*	5 (10.4)	5 (9.8)	10 (10.1)
Ethnicity, *n* (%)			
Hispanic/Latino	21 (43.8)	18 (35.3)	39 (39.4)
Non-Hispanic/Latino	27 (56.3)	33 (64.7)	60 (60.6)
ADHD Type, *n* (%)			
Predominantly inattentive	8 (16.7)	12 (23.5)	20 (20.2)
Predominantly hyperactive/impulsive	1 (2.1)	0	1 (1.0)
Combined	39 (81.3)	39 (76.5)	78 (78.8)

*Race designation of "other" includes Asian, Native Hawaiian, and biracial (e.g., white and Asian, black and white, white and Native Hawaiian).



Results

Time Point (hour)	SKAMP-C	SKAMP-A	SKAMP-D	PERMP-T	PERMP-A	PERMP-C
1	1.5	0.9	0.9	1.3	1.3	1.3
2	2	1.1	1.5	1.5	1.4	1.4
4	1.9	1.1	1.4	1.4	1.3	1.3
6	1.9	1	1.4	1.4	1.4	1.4
8	1.4	0.7	1	1.3	1.3	1.3
10	1.3	0.8	0.9	1.2	1.2	1.2
12	1.2	0.8	0.9	0.9	0.9	0.9
13	1	0.8	0.6	1	0.9	1
Overall	**1.8**	**0.7**	**1.3**	**1.1**	**1.5**	**1.1**

Discussion

- Clinical studies utilize p-values, a measure of statistical significance, to demonstrate that something nonrandom has occurred. While useful, p-values alone do not provide a complete picture of the efficacy of a treatment.
- Effect size was developed in order to compare the efficacy of different agents, including placebo, by quantifying the size of the difference between treatments.
- Effect size measurements incorporate significance, direction, magnitude and relevance to provide a clinically meaningful picture of the observed effects. It is also useful in standardizing results across different experimental designs in order to compare the efficacy of different agents in the absence of head-to-head trials.
- In this study, the effect sizes for each of the efficacy measures (SKAMP and PERMP scores) showed robust results throughout the day from the first time point measured at 1 hour (onset) through the last time point measured at 13 hours (duration).
- The larger effect size was noted for SKAMP-C indicating that this clinical score was most sensitive to treatment with AMPH EROS
- Meta-analyses to measure the effect size for efficacy of stimulants, based on performance measurements in the patient's environment, have found amphetamines, as class, to range from medium to large effects (0.85 to 1.19) for the treatment of ADHD in children and adolescents.[8]
- The results presented here demonstrate medium to large effects sizes (0.7 to 1.8) for AMPH EROS in the treatment of children and adolescents with ADHD based on behavior measurements from a laboratory classroom environment. While these findings are not commensurate with effects from the patient's environment, they do provide valuable insight into AMPH EROS demonstrating a peak effect beginning early in the morning, remaining consistent throughout the core of the day and slowly tapering down in the evening hours.

Limitations

- As these are post hoc analyses and not part of the *a priori* planned analyses, they were not adequately powered to make direct comparisons of subgroup differences in efficacy variables. The relatively small sample size gives a less precise estimate of the effect size and less generalizability.

Conclusions

- **AMPH EROS demonstrated robust and consistent effects beginning early in the morning and continuing throughout the day in the treatment of symptoms of ADHD in children aged 6 to 12 years old.**