Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose Study to Evaluate the Efficacy and Safety of the Amphetamine Extended-Release Tablet in Adults with Attention-Deficit/Hyperactivity Disorder

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

Abstract

Objectives: To evaluate the efficacy and safety of the Amphetamine Extended-Release Tablet (AMPH ER TAB; Dyanavel® XR Tablet, Tris Pharma, Inc., Monmouth Junction, NJ) in adults with attention-deficit/hyperactivity disorder (ADHD) aged 18 to 60 years.

Methods: In a 5-week forced dose-titration phase, eligible subjects were randomized to either oral double-blind AMPH ER TAB 5 mg starting dose or matching placebo, once daily in the morning beginning the day after the Baseline Visit. Subjects were titrated up (5 mg increments) each week. Safety and efficacy assessments were done weekly. After Visit 3, subjects received 20 mg for 14 (±3) days before Visit 5 (V5). Subjects who could not tolerate study drug were to be discontinued. A Permanent Product Measure of Performance (PERMP) placement test was done at Screening or Baseline. At V5, efficacy assessments included the administration of serial PERMPs predose, 0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours postdose. The primary efficacy endpoint was the mean PERMP-T score across postdose time points during the Visit 5 serial PERMPs. Safety was monitored by AEs assessed at each visit, C-SSRS, vital signs, weight, and assessment of sleep, appetite, mood, and psychotic AEs.

Results: The mean postdose PERMP-T score over all postdose time points at V5 was statistically significantly higher in the AMPH ER TAB group vs placebo (302.8 vs 279.6; p=0.0043). Common adverse events included decreased appetite, insomnia and dry mouth. The majority of treatment-emergent AEs (TEAEs) were mild to moderate in severity, and no SAEs were reported.

Conclusions: AMPH ER TAB demonstrated efficacy in treatment of symptoms of ADHD in adults, with an anticipated safety profile.

Introduction

- Clinical practice guidelines recommend a combination of behavior therapy and medication for treatment of ADHD, and stimulants, including amphetamine, are considered a first-line treatment.
- Extended-release (ER) formulations of amphetamine have demonstrated a wide range of times to onset of efficacy and overall duration of effect.
- Tris Pharma, Inc., has developed a once-daily dose, extended-release tablet formulation that can be chewed or swallowed whole.
- This is a report of the efficacy and safety data from a Phase 3, pivotal clinical trial.
- Previously-reported pharmacokinetic data have demonstrated comparable bioavailability to the amphetamine extended-release (Dyanavel® XR) oral suspension[1].
- The tablet formulation offers dosing flexibility (5, 10, 20 mg sizes) and can be chewed or swallowed whole with no effect on its pharmacokinetics.
- The pharmacokinetic study described above also demonstrated excellent palatability (data presented elsewhere[2]).
- Data on efficacy and safety for AMPH ER TAB will inform healthcare providers when making treatment decisions.

References

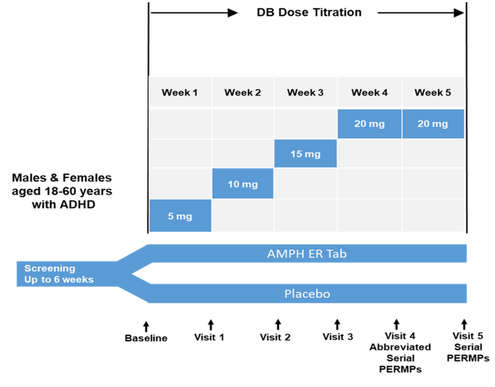
1. Pardo A, Kando JC, King TR, Rafla E, Herman BK. Single-dose pharmacokinetics of amphetamine extended-release tablets compared with amphetamine extended-release oral suspension. CNS Spectr. 2020 Jan 22:1-8. doi: 10.1017/S1092852919001676. Epub ahead of print. PMID: 31964449.

2. Pardo A, King TR, Rafla E, Everitt A, Kando JC. Palatability Assessment of a New Amphetamine Extended-Release Tablet Formulation. Virtual platform presentation delivered at the 2020 AACAP Annual Meeting, 23 October 2020.

Methods

Study Design

- This study employed a 5-week forced-dose titration phase, with eligible subjects (see below) randomized to either oral double-blind amphetamine extended-release tablet (AMPH ER TAB) 5 mg (start dose) or matching placebo. Subjects were titrated up (in 5 mg increments) each week.



- Placebo or test product dose was administered before 10 a.m., with or without food, swallowed whole or chewed.
- After Visit 3 subjects received a final dose of 20 mg for 14 (±3) days before Visit 5.
- Subjects who could not tolerate the study drug were to be discontinued from the study.
- A PERMP placement test was done at Screening or Baseline. PERMP practice sessions were done before/after efficacy and safety assessments during Baseline and Visits 1 to 3.
- An abbreviated administration of serial PERMPs took place at Visit 4 where the PERMP was administered predose, and at 0.5, 1, 2 and 4 hours postdose.
- At Visit 5, efficacy assessments included the administration of serial PERMPs predose and at 0.5, 1, 2, 4, 8, 10, 12, 13, and 14 hours postdose.
- Safety assessments included treatment-emergent adverse events (TEAEs), physical examination, vital signs, body weight, C-SSRS, and direct questioning to assess for sleep, appetite, mood, and psychotic AEs.

Key Inclusion Criteria

Key inclusion criteria included (but were not limited to) the following:

1. Male or female aged 18 to 60 years, diagnosed with ADHD using the DSM-5 criteria based on the Adult ADHD Clinical Diagnostic Scale (ACDS).
2. IQ within normal range based upon clinical opinion of the investigator.
3. Baseline AISRS total score greater than or equal to 26 and baseline score of 4 or higher in CGI-S.
4. Females of childbearing potential must have been non-lactating and must have had a negative serum pregnancy test at Screening and willing to use acceptable, effective methods of contraception. Women of non-childbearing potential were to be permanently sterile or postmenopausal.

Key Exclusion Criteria

- Diagnosis of any DSM-5 active disorder (other than ADHD) with some exceptions.
- Known history of chronic medical illnesses or presence of significant renal or hepatic disease.
- Use of monoamine oxidase inhibitors or tricyclic antidepressants within 30 days of baseline visit or use of atomoxetine within 14 days of baseline visit.
- Known history of allergy/hypersensitivity to amphetamine or study drug.
- History of significant illness requiring hospitalization, or surgery requiring anesthetics within 30 days of baseline visit.
- Known history of lack of response to amphetamine.

Subject Disposition

Subjects	Placebo	AMPH ER TAB	Total
Randomized, n (%)	65	65	130
Enrolled Safety, n (%)	65	62	127
Modified Intent-to-Treat, n (%)	46	45	91
Completed the Study, n (%)	46	45	91
Discontinued, n (%)	19	20	39
Adverse Event	0	3	3
Lost to follow-up	2	4	6
Physician Decision	1	1	2
Protocol Deviation	5	2	7
Withdrawal by Subject	2	2	4
Other	9	8	17

Demography

Subjects	Placebo (n=65)	AMPH ER TAB (n=62)	Total (N=127)
Gender, n (%)			
Male	36 (55)	40 (65)	76 (59)
Female	29 (45)	22 (35)	51 (40)
Age, years			
Mean (SD)	32 (10)	33 (11)	32 (11)
Median	30	30	30
Range (min, max)	18, 58	18, 58	18, 58
Race, n (%)			
Asian	4 (6)	1 (2)	5 (4)
White	52 (80)	52 (84)	104 (82)
Black/African American	9 (14)	7 (11)	16 (13)
Other	0 (0)	2 (3)	2 (2)
Ethnicity, n (%)			
Hispanic/Latino	12 (19)	21 (34)	33 (26)
Non-Hispanic/Latino	53 (82)	41 (66)	94 (74)

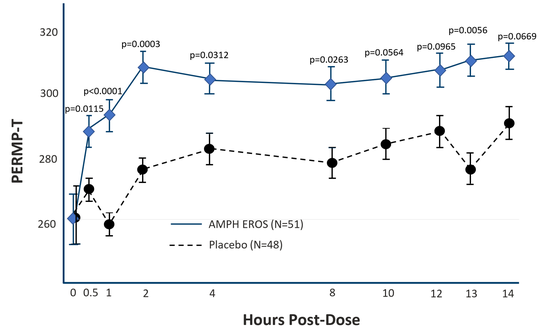
Efficacy Results

Primary Endpoint

- The mean predose PERMP-T scores at Visit 5 in the mITT population were similar between the AMPH ER TAB group (259.5) compared with placebo (260.6).
- At each subsequent visit, mean postdose PERMP-T scores were consistently higher in the AMPH ER TAB group compared with placebo.
- The primary efficacy endpoint was met: the mean postdose PERMP-T score over all postdose time points at Visit 5 was statistically significantly higher in the AMPH ER TAB group (302.8) compared with placebo (279.6) (p-value = 0.0043).

Key Secondary Endpoint

- Statistically significant differences were observed at 0.5 (p=0.0115), 1 (p<0.0001), 2 (0.0003), 4 (0.0312), 8 (p=0.0263), and 13 (p=0.0056) hours postdose.



Safety

- There were no SAEs or deaths during the study. Three subjects (4.8%) in the AMPH ER TAB group experienced AEs that led to discontinuation.
- Larger proportions of subjects experienced AEs and TEAEs in the AMPH ER TAB group (90% and 87%, respectively) than in the placebo group (60% and 54%, respectively). Similarly, about 86% of subjects in the AMPH ER TAB group experienced treatment-related TEAEs compared with 48% of those in the placebo group.
- The most commonly reported (>2%) were insomnia, irritability, initial insomnia, and decreased appetite.

Discussion and Conclusions

- Based on the results of this randomized, double-blind, placebo-controlled, fixed-dose study, amphetamine extended-release tablets were found to be efficacious in the treatment of ADHD in an adult population (ages 18-60 years).
- Based on the results of this clinical study the safety profile of the AMPH ER TAB appears similar to other amphetamine extended-release products.
- The tablet can be chewed or swallowed whole, and may offer a new ADHD treatment option for adults patients based on the tablets' palatability and pharmacokinetic profiles (reported elsewhere)[1,2]