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Prescribing decisions should be made based on the approved package insert.*

Proprietary Drug Name:

Adderall XR®

Generic Drug Name:

Extended release, mixed salts of a single-entity amphetamine product

Therapeutic area and FDA approved indications:

Adderall XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)

Name of Sponsor/Company:

Shire Development, Inc., Wayne, PA, USA

Title of Study:

A Phase IIIb Study to Evaluate the Efficacy and Time Course of Treatment with ADDERALL XR® and STRATTERA® Compared to Placebo on Simulated Driving Safety and Performance and Cognitive Functioning in Adults with Attention Deficit Hyperactivity Disorder (ADHD)

Study Center(s):

Single-center study

Studied period:

25-Feb-2004 – 25-Oct-2004

Phase of Development:

IIIb

Objectives:

Primary

To evaluate the efficacy of treatment with ADDERALL XR and STRATTERA compared to placebo on simulated driving safety and performance of young adults with ADHD as measured by Driving Safety Scores derived by the Driving Simulator.

Secondary

To evaluate the efficacy of treatment with ADDERALL XR and STRATTERA compared to placebo, on the neurocognitive functioning of young adults with ADHD as measured by the CogScreen™-Aeromedical Edition (CogScreen™-AE) Aviator Predictor Score (APS).

To demonstrate the time course of the effects of treatment with ADDERALL XR and STRATTERA compared to placebo, on the simulated driving safety, performance, and neurocognitive functioning of young adults with ADHD as measured by both the Driving Safety Scores on the Driving Simulator and the CogScreen-AE Aviator Predictor Score.

Methodology:

In order to evaluate two different types of ADHD treatments on simulated driving safety, performance, and neurocognitive functioning, this pilot study was divided into two separate cohorts: ADDERALL XR vs. placebo (Cohort I) and STRATTERA vs. placebo (Cohort II). Both cohorts were randomized, single-center, two-way crossovers, designed to evaluate the effects of each drug compared to placebo on simulated driving safety and neurocognitive performance in young adults aged 19-25 diagnosed with ADHD. Cohorts I and II both involved double-blind treatment. The study consisted of a screening period followed by 6 weeks of treatment where subjects were randomized to receive 3 weeks of active treatment and 3 weeks of placebo within the crossover design. Additionally, a follow-up phone call occurred 30 days (±5 days) after the last dose of study drug to query for any new onset serious adverse events (SAEs) and related adverse events (AEs). No new SAEs or related AEs were reported during the follow-up calls.

Subjects stopped taking all psychoactive medication prior to Familiarization Visit 2 (as applicable). The washout period for prior medications allowed for complete clearance of the medication (minimum of five half-lives) and clinical stabilization of the subject prior to Familiarization Visit 2 assessments. Stimulant medications were discontinued at least 7 days prior to the Familiarization Visit, and other psychoactive medications such as antidepressants and STRATTERA required a washout period of at least 28 days prior to the Familiarization Visit.

The following study visits were required for all subjects: Screening Visit 1 (up to 35 days prior to Visit 2), Familiarization Visit 2 (Week 0), Testing Visit I (Week 3), and Testing Visit II (Week 6).

Cohort I (ADDERALL XR vs. placebo) was the first cohort initiated, and upon completion of enrollment, Cohort II (STRATTERA vs. placebo) began enrollment.

Number of subjects (total and for each treatment arm):

Cohort I

In Cohort I, a total of 20 subjects were enrolled, but one subject terminated from the study prior to randomization.

Table I: Subject Disposition for Cohort I (All Enrolled Subjects)

	TPR	ADDERALL XR/ Placebo	Placebo/ ADDERALL XR	Total
Enrolled	1	9 (100.0%)	10 (100.0%)	19 (100.0%)
Randomized	0	9 (100.0%)	10 (100.0%)	19 (100.0%)
ITT	0	8 (88.9%)	7 (70.0%)	15 (78.9%)
PP	0	5 (55.6%)	5 (50.0%)	10 (52.6%)

ITT = full analysis set/intent-to-treat; PP = per protocol; TPR = terminated prior to randomization

Note: Percentages are based on the number of randomized subjects in each column. Total does not include TPR subjects.

Cohort II

In Cohort II, 16 subjects were enrolled and all were randomized.

Table II: Subject Disposition for Cohort II (All Enrolled Subjects)

	TPR	STRATTERA/ Placebo	Placebo/ STRATTERA	Total
Enrolled	0	8 (100.0%)	8 (100.0%)	16 (100.0%)
Randomized	0	8 (100.0%)	8 (100.0%)	16 (100.0%)
ITT	0	8 (100.0%)	8 (100.0%)	16 (100.0%)
PP	0	6 (75.0%)	5 (62.5%)	11 (68.8%)

ITT = full analysis set/intent-to-treat; PP = per protocol; TPR = terminated prior to randomization

Diagnosis and Main Criteria for Admission:

Males or females aged 19-25 years meeting Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV[®]-TR) criteria for primary diagnosis of ADHD who were not naïve to pharmacologic ADHD treatment.

Test Product, Dose and Mode of Administration:

ADDERALL XR is a capsule formulation designed for once-a-day oral administration. During ADDERALL XR treatment, subjects received 20mg (1 x placebo + 1 x 20mg) the first week, followed by 40mg (2 x 20mg) the second week, and 50mg (1 x 20mg + 1 x 30mg) the third week.

During STRATTERA treatment, subjects received 40mg (1 x placebo + 1 x 40mg) the first week, followed by 80mg (2 x 40mg) the second and third weeks.

All study drug was taken orally, once daily in the morning.

Duration of Treatment:

Cohort I: 6 weeks (ADDERALL XR 3 weeks, placebo 3 weeks)

Cohort II: 6 weeks (STRATTERA 3 weeks, placebo 3 weeks)

Reference Therapy, Dose and Mode of Administration:

Placebo (two capsules) was taken orally, once daily in the morning.

Criteria for evaluation:

The primary efficacy measure was Overall Driving Safety Score derived by the driving simulator. Secondary outcome measures were: Driving Safety Scores at individual time points (2, 7, and 12 hours post dose) during Testing Visit I and Testing Visit II, mean CogScreen-AE Aviator Predictor Score, APS at individual time points (0 hours, and 3.5, 8.5, and 13.5 hours post dose) at Testing Visit I and Testing Visit II, the ADHD-rating scale (ADHD-RS), clinical global impressions scale (CGI), and the Self-Rating of Driving Simulator Performance Questionnaire.

Safety measures included: AEs, laboratory screens, physical examination, vital signs, and electrocardiogram (ECG).

Statistical Methods:Primary Efficacy Analysis

The primary efficacy analysis was performed on Overall Driving Safety Score derived from the safety-related driving parameters (speeding tickets, traffic tickets, crashes, crash avoidance rating, time to collision, and speed exceedances). The Overall Driving Safety Score for the three observations obtained at Testing Visits I and II was the primary outcome measure/endpoint. The primary efficacy analysis was based on the ITT population.

The null hypothesis was that there was no difference in the Overall Driving Safety Score between the treatments (placebo vs. ADDERALL XR and placebo vs. STRATTERA). The standard method for two-period crossover designs was used. An analysis of variance (ANOVA) model was fit to the study endpoint. The ANOVA model included terms for sequence, subject within sequence, period, and treatment. Subject within sequence is a random effect and the other model terms were fixed effects. From this ANOVA least squares means for each treatment, estimated treatment differences, and 95% confidence intervals for treatment differences were calculated.

The primary efficacy analysis was also performed using the PP population if there was a substantial difference between the number of subjects in the ITT and PP population.

The analyses were performed for Cohorts I and II separately.

Secondary Efficacy Analyses

The secondary outcomes were analyzed in the same manner as the primary outcome.

The GEE (generalized estimating equations) model with terms treatment and sequence were used to analyze the dichotomized scores for ADHD-RS total score and subscale score, CGI-improvement (CGI-I), and Self-Rating of Driving Simulator Performance.

Safety Analysis

Safety analyses were performed for Cohorts I and II separately.

An overall summary of AEs was presented by treatment, system organ class, and preferred term. Adverse events were also summarized by maximum relationship to study drug and by maximum severity. Summaries included both the number and percentage of subjects experiencing an AE, as well as the number of AEs. Listings were provided for all AEs, all SAEs, and all AEs leading to termination.

Vital signs were summarized with descriptive statistics by treatment and by visit. Height was measured only at screening and summarized with demographics. Physical examination results were presented in a shift table showing results from Screening to Testing Visit II/Early Termination, and a by-subject listing was also provided. The number and percent of normal and abnormal ECG findings were tabulated by visit and a shift table of ECG interpretation (normal, abnormal not clinically significant, abnormal clinically significant) was also provided. Numeric laboratory parameters were summarized with descriptive statistics at Screening and Testing Visit II/Early Termination. A shift table of laboratory values and a by-subject listing of all laboratory tests and abnormal clinically significant laboratory tests were presented.

Summary – Results:

Subject Demographics: In general, demographic characteristics in the population of randomized subjects were similar between Cohort I and Cohort II. The average age in both cohorts was approximately 22 years. Most subjects in both cohorts were male (Cohort I, 89.5%; Cohort II, 87.5%) and Caucasian (Cohort I, 78.9%; Cohort II 56.3%).

Efficacy results: The primary efficacy variable was defined as the Overall Driving Safety Score obtained at Testing Visits I and II. For Cohort I, mean Overall Driving Safety Scores were better in subjects receiving ADDERALL XR (-2.279) compared with subjects receiving placebo (2.442). An analysis of variance revealed that this treatment difference was statistically significant ($p=0.0137$). In contrast, there was no statistically significant difference in Overall Driving Safety Scores observed between subjects receiving STRATTERA (-0.167) compared with subjects receiving placebo (0.146) in Cohort II ($p=0.2932$).

Driving Safety Scores were sustained for the entire 12-hour day for subjects receiving ADDERALL XR compared to placebo. Scores were statistically significantly better in subjects receiving ADDERALL XR compared to those receiving placebo at 7 hours post dose (-2.447 vs. 2.622, $p=0.0134$) and 12 hours (-2.301 vs. 2.465, $p=0.0046$). Driving Safety Scores showed no statistically significant differences at any time points for subjects receiving STRATTERA compared with placebo.

Neurocognitive functioning, as assessed using the Overall CogScreen-AE Aviator Predictor Scores, was statistically significantly improved in both subjects who had been treated with ADDERALL XR compared to placebo (-3.233 vs. -2.446, $p=0.0006$), and in subjects who had been treated with STRATTERA compared with placebo (-2.018 vs. -0.328, $p=0.0029$).

Attention deficit hyperactivity disorder symptoms were significantly improved in subjects receiving ADDERALL XR, as measured by the dichotomized scores for ADHD-RS and CGI-I. Statistically significantly more subjects receiving ADDERALL XR were considered clinically improved, as judged by a $\geq 30\%$ reduction in ADHD-RS total score, compared with placebo (80.0% vs. 13.3%, $p=0.0004$). Further clinical improvements, as judged by CGI-I (very much improved and much improved) were evident in 66.7% of subjects taking ADDERALL XR versus 0.0% of subjects taking placebo.

Improvements in ADHD-RS and CGI-I in subjects receiving STRATTERA were not statistically significantly different from placebo (ADHD-RS improvement: 40.0% vs. 25.0%, $p=0.4078$; CGI-I improvement: 13.3% vs. 6.3%, $p=0.5332$).

Safety results

In Cohort I, the overall incidence of treatment-emergent AEs was higher in subjects receiving ADDERALL XR (75.0%) than in subjects receiving placebo (16.7%). In Cohort II, the overall incidence of treatment-emergent AEs was 68.8% in subjects receiving STRATTERA and 56.3% in subjects receiving placebo.

In Cohort I, the most common treatment-emergent AEs reported by subjects receiving ADDERALL XR were anorexia and weight decreased, both of which were reported with higher frequency in subjects receiving ADDERALL XR (anorexia, 50.0%; weight decreased, 25.0%) compared with subjects receiving placebo (anorexia, 0.0%; weight decreased, 5.6%).

In Cohort II, the most common treatment-emergent AEs reported by subjects receiving STRATTERA were upper abdominal pain and nausea. Both of these events were reported with higher frequency in subjects receiving STRATTERA (abdominal pain upper, 18.8%; nausea, 18.8%) compared with subjects receiving placebo (abdominal pain upper, 0.0%; nausea, 6.3%).

Most AEs reported during the study were mild or moderate, with five subjects reporting severe AEs. Three subjects receiving ADDERALL XR and one subject receiving placebo in Cohort I, and one subject receiving placebo in Cohort II had severe AEs. The only severe AE reported by more than one subject in any treatment group was insomnia, which was reported by two subjects receiving ADDERALL XR.

No serious AEs or deaths occurred in this study. A total of three subjects discontinued from the study due to AEs. One subject was receiving ADDERALL XR, one was receiving placebo in Cohort I, and one was receiving placebo in Cohort II.

In both cohorts, mean changes in laboratory parameters and vital signs were small and not clinically significant. Likewise, no clinically significant abnormal ECG findings were observed at any visit in either cohort, and physical examination results showed no shifts from normal findings at Screening to abnormal at Testing Visit II/Study Termination. While three subjects had clinically significant lab parameters at Testing Visit II, two of the subjects had related values assessed as clinically significant at Screening. One patient in Cohort I had blood in urine (2+) at Testing Visit II. One patient in Cohort II had epithelial cells (2+) and yeast (present) in urine at both Testing II and at Screening. One patient in Cohort II had elevated GGT (52IU/L) and SGPT (107IU/L) at Testing Visit II and elevated SGPT (56IU/L) at Screening.

Overall Summary:

- Results of this study indicate that ADDERALL XR is effective for improving driving safety and neurocognitive performance in young adults with ADHD.
- Significant improvements were observed in reduction of ADHD-RS and CGI-I.
- The study did not support the effectiveness of STRATTERA in improving driving safety in this population.
- Both drugs were well tolerated.

Date of report:

07 June 2005