U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-303/S-009
Drug Name:	Adderall XR ® (SLI381)
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant:	Shire Laboratories
Date:	9/17/2004
Review Priority:	Priority
Biometrics Division:	I (HFD 710)
Statistical Reviewer:	Kun He
Concurring Reviewers:	Kun Jin, , Ph.D.,Team Leader James Hung, Ph.D., Acting Deputy Director
Medical Division:	Neuropharmacological Drug Products (HFD 120)
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Keywords: ANCOVA, ADHD, Adderall XR

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1. Executive Summary

1.1 Conclusions and Recommendations

The conclusion is that the primary analysis for the mean change in ADHD-RS-IV total score from baseline at Week 4 LOCF in the intent-to-treat (ITT) population is significant comparing Adderall XR (10mg/day to 40 mg/day) and placebo in the treatment of adolescents, age 13-17 and weight less than or equal to 75 kg/165 lbs, with Attention Deficit Hyperactivity Disorder (ADHD).

1.2 Brief Overview of Clinical Studies

This was a randomized, double-blind, placebo-controlled trial conducted in 50 centers in USA, evaluating the use of Adderall XR (10mg/day to 40 mg/day) in subjects (age 13-17) with Attention Deficit Hyperactivity Disorder (ADHD). The trial had one 4-week double-blind treatment phase, and followed by a 6-month open-label phase. The primary cohort (designed for the primary objective) consisted of subjects whose weights were less than or equal to 75 kg/165 lbs, and secondary cohort (designed for secondary objective and exploratory analysis) consisted of subjects whose weights were greater than 75 kg/165 lbs. A total of 329 subjects enrolled in the study, and resulted 327 randomized to the double-blind phase. ITT included 287 subjects in the primary cohort, and 40 subjects in the secondary cohort. The primary efficacy endpoint was the mean change in ADHD-RS-IV total score from baseline at Week 4 LOCF in the ITT population. The primary analysis was ANCOVA model with terms for treatment, site, and the corresponding baseline score as the covariate. A closed-testing procedure starting from the highest dose is used to compare each active dose vs. placebo.

1.3 Statistical Issues and Findings

The primary analysis showed that there was a significant difference in favor of Adderall XR, compared to placebo, for the mean change in ADHD-RS-IV from baseline at Week 4 LOCF in the ITT population. Detailed statistics are presented in the following table.

Analyses of ADHD-RS-IV Total Score in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Baseline					
Mean (SD)	35.1 (9.7)	34.9 (10.4)	33.9 (9.1)	35.1 (10.8)	32.6 (10.8)
Endpoint					
Mean (SD)	25.7 (13.4)	20.0 (11.8)	13.3 (10.3)	16.1 (11.0)	16.0 (11.2)
Mean change (SD)	-9.4 (10.6)	-14.9 (12.1)	-20.7 (11.2)	-19.0 (11.1)	-16.5 (11.6)
LS mean difference	--	-5.59	-12.23	-9.23	-8.49
(95% CI)	--	(-9.40, -1.77)	(-16.06, -8.39)	(-13.00, -5.46)	(-12.22, -4.76)
p-value	--	0.0043	<0.0001	<0.0001	<0.0001

2. Introduction

2.1 Overview

Adderall XR is a once-daily, extended-release, single-entity amphetamine produce. Adderall XR was approved by the Agency in 2001 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 and older. Much of the current ADHD literature focuses on school age children (6-12 years old) and there is very limited scientific literature that specifically examines the safety and efficacy of amphetamines in the treatment of adolescents with ADHD.

In this submission, a trial completed was a randomized, double-blind, placebo-controlled conducted in 50 centers in USA, evaluating the use of Adderall XR (10mg/day to 40 mg/day) in subjects (age 13-17) with Attention Deficit Hyperactivity Disorder (ADHD). The trial had one 4-week double-blind treatment phase, and followed by a 6-month open-label phase. The primary cohort (designed for the primary objective) consisted of subjects whose weights were less than or equal to 75 kg/165 lbs, and secondary cohort (designed for secondary objective and exploratory analysis) consisted of subjects whose weights were greater than 75 kg/165 lbs. A total of 329 subjects enrolled in the study, and resulted 327 randomized to the double-blind phase. ITT included 287 subjects in the primary cohort, and 40 subjects in the secondary cohort. The primary efficacy endpoint was the mean change in ADHD-RS-IV total score from baseline at Week 4 LOCF in the ITT population. The primary analysis was ANCOVA model with terms for treatment, site, and the corresponding baseline score as the covariate. A closed-testing procedure starting from the highest dose is used to compare each active dose vs. placebo.

2.2 Data Sources

The path to the CDER Electronic Document Room (EDR) is:

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\\Cdsesub1\n21303\S_009\2004-10-27
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3. Statistical Evaluation

3.1 Evaluation of Efficacy

Texts, tables, and graphs in Sections 3.1.1 – 3.1.7 are mainly adapted from the Applicant's Study Report.

3.1.1 Objective

The primary objective of this study was to assess, under controlled conditions, the safety and efficacy of ADERALL XR (10mg/day to 40 mg/day) compared to placebo in the treatment of adolescents (age 13-17, weighing less than or equal to 75 kg/165 lbs) with ADHD, based on the clinician administered ADHD-Rating Scale (ADHD-RS-IV).

Secondary objective includes to assess the safety and efficacy of ADERALL XR (50mg/day to 60 mg/day) compared to placebo in the treatment of adolescents (age 13-17, weighing over 75 kg/165 lbs) with ADHD, based on the clinician administered ADHD-Rating Scale (ADHD-RS-IV).

3.1.2 Study Design

This study consisted of two parts, Part A and Part B. Part A was a randomized, double-blind, multicenter, placebo-controlled, forced dose titration phase in which subjects took study drug in a blinded fashion for approximately 4 weeks. Part B was a 6-month open-label extension involving subjects from Part A to continue to assess the safety of various doses. This report describes results of Part A only.

There were 2 cohorts of subjects aged 13-17 years old (inclusive): those weighing less than or equal to 75 kg/165 lbs (primary cohort) and those weighing greater than 75 kg/165 lbs 9secondary cohort). The evaluation of the efficacy and safety in both cohorts will be run in parallel.

Approximately 225 subjects weighing less than or equal to 75 kg/165 lbs were to be randomized in a 1:1:1:1:1 ratio (Adderall XR 10 mg, 20 mg, 30 mg, 40 mg, or placebo). All subjects had 10 mg for Week 1, and increased 10 mg each week until reach their object dose level. Approximately 30 subjects weighing greater than 75 kg/165 lbs were to be randomized in a 1:1:1 ratio (Adderall XR 50 mg, 60 mg, or placebo). Subjects in 50 mg group started 20 mg for Week 1, and increased 10 mg each week. Subjects in 60 mg group started 20 mg for Week 1, 40 mg for Week 2, 50 mg for Week 3, and 60 mg for Week 4. The treatment phase lasted approximately 4 weeks. Visits were scheduled 7 days apart during the treatment phase.

3.1.3 Efficacy Measures

The primary efficacy measure was ADHD-RS-IV total score. This rating scale is based on a clinician administered semi-structured interview with the subject's parent (or primary caregiver) and the subject at each applicable visit, beginning with the baseline visit, to capture the ADHA symptoms within each study week. The ADHD-RS-IV consists of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV criteria. Each item is scored from a range of zero (reflecting no symptoms) to three (reflecting severe symptoms) with total scores ranging from 0 to 54.

The primary endpoint was defined as the change from baseline on the ADHD-RS-IV total score at the last treatment week of double-blind treatment phase.

Secondary efficacy measures included the CGI-I (CGI-improvement) rating scale. Rating was completed with respect to ADHD symptoms relative to the baseline.

3.1.4 Statistical Analysis Plan

The primary analysis was a two-way analysis of covariance (ANCOVA) model with terms for treatment of each active dose vs. placebo, site, and the corresponding baseline score as the covariate, using ITT population. A closed-testing procedure starting from the highest dose is used.

The subject's score on CGI-I was dichotomized into two categories, with "very much improved" and "much improved" going into one category (improved) and the rest into the other category (not improved) prior to analysis. The dichotomized CGI-I was analyzed using a CMH test adjusting for study site between active doses combined vs. placebo. The significant treatment effect of each active dose vs. placebo was based on a closed-testing procedure starting from the highest dose.

3.1.5 Protocol Amendments and Deviations

There was one amendment to the final statistical analysis plan issued on July 14, 2003. The amendment was issued on December 5, 2003 and implemented the following changes: described how sites would be pooled; indicated that the overall test of all active vs. placebo did not need to be significant before each dose was compared to placebo; added efficacy analyses for subjects with low and high baseline ADHD severity both by intended dose and final dose; and added the qualitative, categorized analysis of vital signs and ECG parameters.

3.1.6 Study Population

A total of 329 subjects were enrolled in the study. Two subjects terminated prior to randomization and thus, 327 subjects were randomized. Of these, 287 were in the primary cohort and 40 were in the secondary cohort.

The disposition of all patients randomized in the study for the primary cohort is presented in Table 3.1.6.1.

Table 3.1.6.1 Disposition of Patients (Primary Cohort)

	Placebo	10 mg	20 mg	30 mg	40 mg	Total
Enrolled	54	56	56	58	63	287
Randomized	54	56	56	58	63	287
ITT	52 (96.3%)	54 (96.4%)	53 (94.6%)	58 (100%)	61 (96.8%)	278 (96.9%)
Primary reason for discontinuation						
Adverse event(s)	0	1 (1.8%)	1 (1.8%)	1 (1.7%)	2 (3.2%)	5 (1.7%)
Protocol violation	1 (1.9%)	3 (5.4%)	0	0	1 (1.6%)	5 (1.7%)
Withdrew consent	0	2 (3.6%)	2 (3.6%)	1 (1.7%)	5 (7.9%)	10 (3.5%)
Lost to follow-up	2 (3.7%)	1 (1.8%)	1 (1.8%)	1 (1.7%)	1 (1.6%)	6 (2.1%)
Other	1 (1.9%)	0	1 (1.8%)	0	1 (1.6%)	3 (1.0%)

The demographic and other baseline characteristics for the primary cohort are presented by in Table 3.1.6.2.

Table 3.1.6.2 Demographic and Baseline of the Primary Cohort (All Randomized)

Parameter	Placebo (N=54)	10 mg (N=56)	20 mg (N=56)	30 mg (N=58)	40 mg (N=63)	Total (N=287)
Age (years)						
Mean (SD)	14.5 (1.3)	14.4 (1.2)	14.3 (1.2)	14.2 (1.2)	14.0 (1.2)	14.2 (1.2)
Age category						
13-14	32 (59.3%)	30 (53.6%)	37 (66.1%)	37 (63.8%)	46 (73.0%)	182 (63.4%)
15-17	22 (40.7%)	26 (46.4%)	19 (33.9%)	21 (36.2%)	17 (27.0%)	105 (36.6%)
Gender						
Male	36 (66.7%)	35 (62.5%)	38 (67.9%)	38 (65.5%)	40 (63.5%)	187 (65.2%)
Female	18 (33.3%)	21 (37.5%)	18 (32.1%)	20 (34.5%)	23 (36.5%)	100 (34.8%)
Ethnic origin						
White	40 (74.1%)	40 (71.4%)	42 (75.0%)	43 (74.1%)	49 (77.8%)	214 (74.6%)
Black	11 (20.4%)	10 (17.9%)	9 (16.1%)	8 (13.8%)	6 (9.5%)	44 (15.3%)
Hispanic	3 (5.6%)	2 (3.6%)	3 (5.4%)	5 (8.6%)	6 (9.5%)	19 (6.6%)
Asian or Pacific Islander	0	0	0	0	0	0
Native American	0	2 (3.6%)	0	0	2 (3.2%)	4 (1.4%)
Other	0	2 (3.6%)	2 (3.6%)	2 (3.4%)	0	6 (2.1%)
Weight at baseline (lb)	131.5	125.9	125.3	128.6	125.3	127.2
Mean (SD)	(18.1)	(22.2)	(20.4)	(18.8)	(22.3)	(20.5)
Height at screening (inches)	65.5	64.2	64.5	64.1	64.4	64.5
Mean (SD)	(3.6)	(3.6)	(3.7)	(3.1)	(3.6)	(3.5)
BMI at baseline	21.6	21.4	21.2	22.0	21.1	21.4
Mean (SD)	(2.8)	(2.6)	(2.9)	(2.9)	(2.6)	(2.8)
Type of ADHD						
Inattentive	24 (44.4%)	20 (35.7%)	25 (44.6%)	20 (34.5%)	26 (41.3%)	115 (40.1%)
Hyperactive/Impulsive	0	4 (7.1%)	2 (3.6%)	1 (1.7%)	2 (3.2%)	9 (3.1%)
Combined	30 (55.6%)	32 (57.1%)	29 (63.8%)	37 (63.8%)	35 (55.6%)	163 (56.8%)
Years since ADHD diagnosis: Mean (SD)	4.35 (4.16)	5.44 (3.97)	5.11 (4.41)	4.87 (4.12)	5.76 (4.07)	5.13 (4.14)
Number of subjects with recent prior ADHD treatment	7 (13.0%)	6 (10.7%)	13 (23.2%)	16 (27.6%)	17 (27.0%)	59 (20.6%)

The disposition of all patients randomized in the study for the secondary cohort is presented in Table 3.1.6.3, and the demographic and other baseline characteristics for the secondary cohort are presented by in Table 3.1.6.4, respectively.

Table 3.1.6.3 Disposition of Patients (Secondary Cohort)

	Placebo	50 mg	60 mg	Total
Enrolled	15	15	10	40
Randomized	15	15	10	40
ITT	15 (100%)	15 (100%)	10 (100%)	40 (100%)
Primary reason for discontinuation				
Adverse event(s)	0	2 (13.3%)	1 (10%)	3 (7.5%)
Lost to follow-up	1 (6.7%)	0	0	1 (2.5%)

Table 3.1.6.4 Demographic and Baseline of the Secondary Cohort (ITT)

Parameter	Placebo (N=15)	50 mg (N=15)	60 mg (N=10)	Total (N=40)
Age (years)				
Mean (SD)	15.3 (1.2)	15.4 (1.4)	15.4 (1.2)	15.4 (1.2)
Age category				
13-14	4 (26.7%)	6 (40.0%)	3 (30.0%)	13 (32.5%)
15-17	11 (73.3%)	9 (60.0%)	7 (70.0%)	27 (67.5%)
Gender				
Male	14 (93.3%)	14 (93.3%)	8 (80.9%)	36 (90.0%)
Female	1 (6.7%)	1 (6.7%)	2 (20.0%)	4 (10.0%)
Ethnic origin				
White	9 (60.0%)	11 (73.3%)	6 (60.0%)	26 (65.0%)
Black	4 (26.7%)	1 (6.7%)	2 (20.0%)	7 (17.5%)
Hispanic	2 (13.3%)	2 (13.3%)	2 (20.0%)	6 (15.0%)
Asian or Pacific Islander	0	0	0	0
Native American	0	1 (6.7%)	0	1 (2.5%)
Weight at baseline (lb)	190.5	189.6	191.1	190.3
Mean (SD)	(35.2)	(22.1)	(15.0)	(26.0)
Height at screening (inches)	68.7	71.1	69.3	69.8
Mean (SD)	(3.0)	(2.6)	(3.5)	(3.1)
BMI at baseline	28.4	26.4	28.0	27.5
Mean (SD)	(4.9)	(2.9)	(2.2)	(3.7)
Type of ADHD				
Inattentive	6 (40.0%)	8 (53.3%)	3 (30.0%)	17 (42.5%)
Combined	9 (60.0%)	7 (46.7%)	7 (70.0%)	23 (57.5%)
Years since ADHD diagnosis: Mean (SD)	4.84 (5.19)	8.67 (4.03)	6.34 (4.62)	6.65 (4.83)
Number of subjects with recent prior ADHD treatment	2 (13.3%)	4 (26.7%)	1 (10.0%)	7 (17.5%)

3.1.7 Applicant's Efficacy Results

The primary analysis was a two-way analysis of covariance (ANCOVA) model with terms treatment of each active dose vs. placebo, site, and the corresponding baseline score as the covariate, using ITT population. A closed-testing procedure starting from the highest dose is used.

Table 3.1.7.1 presents the primary analyses results of the primary cohort at Week 4 LOCF.

Table 3.1.7.1 Analyses of ADHD-RS-IV Total Score in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Baseline					
Mean (SD)	35.1 (9.7)	34.9 (10.4)	33.9 (9.1)	35.1 (10.8)	32.6 (10.8)
Endpoint					
Mean (SD)	25.7 (13.4)	20.0 (11.8)	13.3 (10.3)	16.1 (11.0)	16.0 (11.2)
Mean change (SD)	-9.4 (10.6)	-14.9 (12.1)	-20.7 (11.2)	-19.0 (11.1)	-16.5 (11.6)
LS mean difference	--	-5.59	-12.23	-9.23	-8.49
(95% CI)	--	(-9.40, -1.77)	(-16.06, -8.39)	(-13.00, -5.46)	(-12.22, -4.76)
p-value	--	0.0043	<0.0001	<0.0001	<0.0001

P-values in the last row in the above table are for each pair's comparisons with placebo.

Table 3.1.7.2 presents the primary analyses results of the primary cohort at Week 4 OC.

Table 3.1.7.2 Analyses of ADHD-RS-IV Total Score in the Primary Cohort (ITT-OC)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Baseline					
Mean (SD)	35.1 (9.7)	34.9 (10.4)	33.9 (9.1)	35.1 (10.8)	32.6 (10.8)
Endpoint at Week 4					
N	50	49	50	55	53
Mean (SD)	25.5 (13.2)	19.3 (11.7)	13.1 (10.1)	15.6 (10.9)	15.7 (11.6)
Mean change (SD)	-9.6 (10.2)	-16.0 (12.0)	-20.8 (11.2)	-19.7 (10.8)	-17.3 (11.4)
LS mean difference	--	-6.23	-12.05	-9.21	-8.31
(95% CI)	--	(-10.11, -2.34)	(-15.91, -8.19)	(-13.02, -5.41)	(-12.15, -4.47)
p-value	--	0.0018	<0.0001	<0.0001	<0.0001

Secondary efficacy measures include the dichotomized CGI-I ("improved", or "not improved"). CMH test adjusting for study site between active doses combined vs. placebo was analysis for the dichotomized CGI-I.

Table 3.1.7.3 presents the analyses results of the dichotomized CGI-I at Week 4 LOCF.

Table 3.1.7.3 Analyses of CGI-I in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)	10-40 mg (N=226)
Dichotomized CGI-I						
Improvement	14 (26.9%)	28 (51.9%)	35 (66.0%)	41 (70.7%)	39 (63.9%)	143 (63.3%)
No improvement	38 (73.1%)	26 (48.1%)	18 (34.0%)	17 (29.3%)	22 (36.1%)	83 (36.7%)
Difference in % with improvement in active group vs. placebo	--	24.9%	39.1%	43.8%	37.0%	36.4%
p-value	--	0.0098	0.0002	<0.0001	0.0001	<0.0001

Table 3.1.7.4 presents the analyses results of the dichotomized CGI-I at Week 4 OC.

Table 3.1.7.4 Analyses of CGI-I in the Primary Cohort (ITT-OC)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)	10-40 mg (N=226)
Dichotomized CGI-I						
N	50	49	50	55	53	207
Improvement	13 (26.0%)	28 (57.1%)	35 (70.0%)	39 (70.9%)	36 (67.9%)	138 (66.7%)
No improvement	37 (74.0%)	21 (42.9%)	15 (30.0%)	16 (29.1%)	17 (32.1%)	69 (33.3%)
Difference in % with improvement in active group vs. placebo	--	31.1%	44.0%	44.9%	41.9%	40.7%
p-value	--	0.0043	0.0001	<0.0001	0.0001	<0.0001

The following tables present results for the secondary cohort. Table 3.1.7.5 presents the analyses results of the secondary cohort at Week 4 LOCF.

Table 3.1.7.5 Analyses of ADHD-RS-IV Total Score in the Secondary Cohort (ITT-LOCF)

	Placebo (N=15)	50 mg (N=15)	60 mg (N=10)
Baseline			
Mean (SD)	35.7 (8.7)	30.4 (10.2)	32.3 (8.6)
Endpoint			
Mean (SD)	23.1 (13.1)	13.5 (8.9)	18.3 (11.5)
Mean change (SD)	-12.5 (10.1)	-16.9 (12.4)	-14.0 (12.5)
LS mean difference	--	-5.63	-1.41
(95% CI)	--	(-17.08, 5.83)	(-13.97, 11.15)
p-value	--	0.3145	0.8156

Table 3.1.7.6 presents the analyses results of the secondary cohort at Week 4 OC.

Table 3.1.7.6 Analyses of ADHD-RS-IV Total Score in the Secondary Cohort (ITT-OC)

	Placebo (N=15)	50 mg (N=15)	60 mg (N=10)
Baseline			
Mean (SD)	35.7 (8.7)	30.4 (10.2)	32.3 (8.6)
Endpoint at Week 4			
N	14	13	9
Mean (SD)	22.6 (13.4)	14.3 (9.2)	17.3 (11.8)
Mean change (SD)	-12.6 (10.4)	-15.9 (12.8)	-15.8 (11.9)
LS mean difference	--	-3.24	-1.20
(95% CI)	--	(-16.06, 9.58)	(-15.88, 13.48)
p-value	--	0.5943	0.8626

Table 3.1.7.7 presents the analyses results of the dichotomized CGI-I at Week 4 LOCF.

Table 3.1.7.7 Analyses of CGI-I in the Secondary Cohort (ITT-LOCF)

	Placebo (N=15)	50 mg (N=15)	60 mg (N=10)	50-60 mg (N=25)
Dichotomized CGI-I				
Improvement	7 (46.7%)	11 (73.3%)	6 (60.0%)	17 (68.0%)
No improvement	8 (53.3%)	4 (26.7%)	4 (40.0%)	8 (32.0%)
Difference in % with improvement in active group vs. placebo	--	26.7%	13.3%	21.3%
p-value	--	0.7316	0.4328	0.4072

Table 3.1.7.8 presents the analyses results of the dichotomized CGI-I at Week 4 OC.

Table 3.1.7.8 Analyses of CGI-I in the Secondary Cohort (ITT-OC)

	Placebo (N=15)	50 mg (N=15)	60 mg (N=10)	50-60 mg (N=25)
Dichotomized CGI-I				
N	14	13	9	22
Improvement	7 (50.0%)	9 (69.2%)	6 (66.7%)	15 (68.2%)
No improvement	7 (50.0%)	4 (30.8%)	3 (33.3%)	7 (31.8%)
Difference in % with improvement in active group vs. placebo	--	19.2%	16.7%	18.2%
p-value	--	1.0000	0.3173	0.6473

3.1.8 Reviewer's Analysis

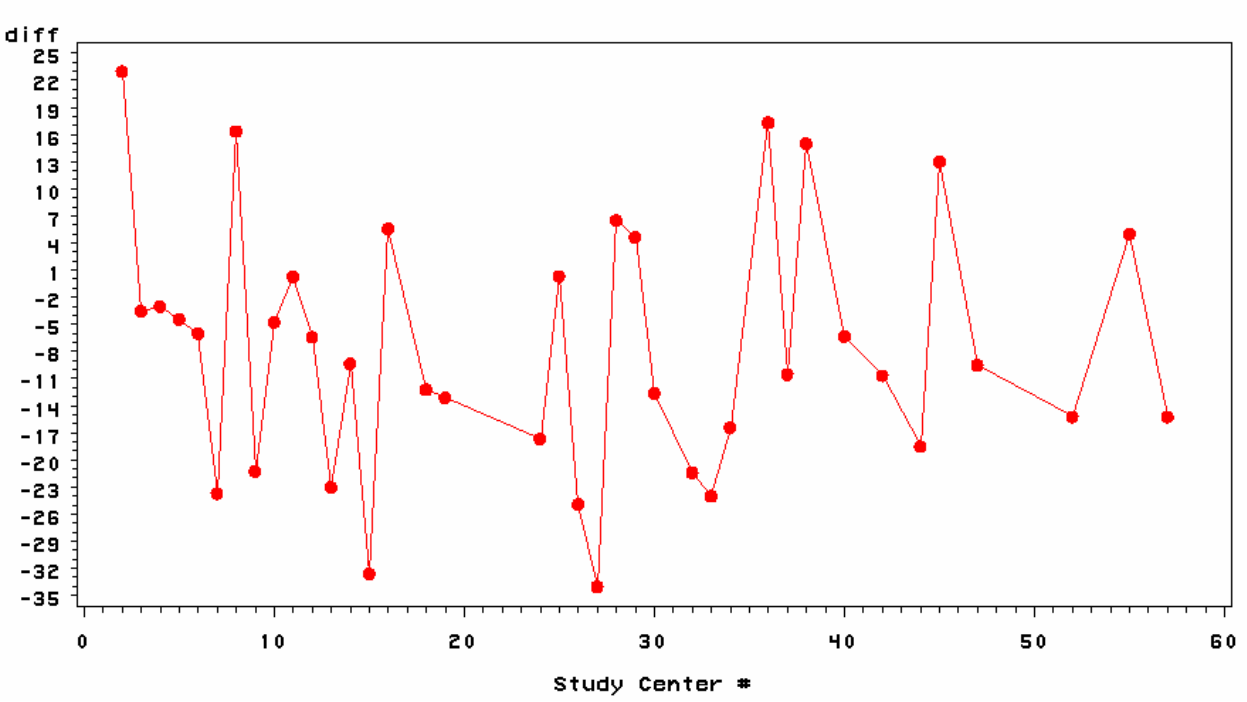
The reviewer validated the sponsor's analysis according to the protocol.

Wilcoxon two-sample test gives p-values .0231 for 10 mg vs. placebo, .0001 for 20 mg vs. placebo, .0001 for 30 mg vs. placebo, and .0018 for 40 mg vs. placebo, respectively.

Table 3.1.8.1 presents difference of the mean change in ADHD-RS-IV at Week 4 LOCF by center.

Table 3.1.8.1 Mean Change of ADHD-RS_IV by Center for Primary Cohort (ITT-LOCF)

Obs	CENTER	n_t	mean_t	n_p	mean_p	diff
1	2	1	-3.0000	1	-26.0000	23.0000
2	3	10	-14.2000	3	-10.6667	-3.5333
3	4	12	-10.3333	3	-7.3333	-3.0000
4	5	7	-9.4286	1	-5.0000	-4.4286
5	6	2	-14.0000	1	-8.0000	-6.0000
6	7	7	-21.7143	1	2.0000	-23.7143
7	8	8	-7.6250	1	-24.0000	16.3750
8	9	4	-18.2500	1	3.0000	-21.2500
9	10	4	-25.7500	1	-21.0000	-4.7500
10	11	7	-27.7143	2	-28.0000	0.2857
11	12	5	-27.4000	1	-21.0000	-6.4000
12	13	1	-27.0000	1	-4.0000	-23.0000
13	14	7	-23.8571	2	-14.5000	-9.3571
14	15	5	-20.6000	1	12.0000	-32.6000
15	16	7	-10.4286	1	-16.0000	5.5714
16	18	7	-16.7143	2	-4.5000	-12.2143
17	19	8	-16.6250	2	-3.5000	-13.1250
18	20	5	-29.0000	.	.	.
19	21	3	-11.3333	.	.	.
20	22	2	-7.5000	.	.	.
21	24	3	-8.6667	1	9.0000	-17.6667
22	25	3	-18.6667	1	-19.0000	0.3333
23	26	12	-25.9167	3	-1.0000	-24.9167
24	27	2	-31.0000	1	3.0000	-34.0000
25	28	2	-12.5000	1	-19.0000	6.5000
26	29	8	-16.3750	2	-21.0000	4.6250
27	30	5	-11.6000	1	1.0000	-12.6000
28	32	5	-22.4000	1	-1.0000	-21.4000
29	33	3	-22.0000	1	2.0000	-24.0000
30	34	5	-18.4000	2	-2.0000	-16.4000
31	36	3	-11.6667	1	-29.0000	17.3333
32	37	13	-15.5385	3	-5.0000	-10.5385
33	38	1	-1.0000	1	-16.0000	15.0000
34	40	3	-13.3333	1	-7.0000	-6.3333
35	41	1	-15.0000	.	.	.
36	42	3	-19.6667	1	-9.0000	-10.6667
37	44	4	-32.5000	1	-14.0000	-18.5000
38	45	4	-19.0000	1	-32.0000	13.0000
39	46	3	-30.6667	.	.	.
40	47	6	-15.5000	1	-6.0000	-9.5000
41	48	2	-20.0000	.	.	.
42	49	5	-13.2000	.	.	.
43	50	1	-8.0000	.	.	.
44	51	3	-19.6667	.	.	.
45	52	4	-13.2500	1	2.0000	-15.2500
46	54	2	-17.5000	.	.	.
47	55	2	-14.0000	1	-19.0000	5.0000
48	56	2	-30.0000	.	.	.
49	57	4	-21.2500	1	-6.0000	-15.2500



After removing both centers 15 and 27, ANCOVA (combined active doses vs. placebo) gives p-value .0001.

3.2 Evaluation of Safety

See Clinical Review.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Since the Study was not powered for subgroup analyses, analytical analysis is not performed. Table 4.1.1 presents the mean change in ADHD-RS-IV from baseline at Week 4 LOCF for the primary cohort by gender for ITT population.

Table 4.1.1 Mean Change from Baseline in ADHD-RS-IV in the Primary Cohort by Gender

Gender	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Male	35	33	37	38	39
Baseline	35.5	36.7	33.6	36.3	33.9
Endpoint	27.6	18.9	13.2	16.5	16.6

Mean Change	-7.9	-17.8	-20.4	-19.8	-17.3
Female	17	21	16	20	22
Baseline	34.4	32.1	34.7	32.8	30.1
Endpoint	21.9	21.7	13.3	15.3	15.0
Mean Change	-12.4	-10.4	-21.4	-17.5	-15.1

Except for female in 10 mg group, subjects in all other Adderall XR groups had more changes than those in placebo group.

Table 4.1.2 presents the mean change in ADHD-RS-IV from baseline at Week 4 LOCF for the primary cohort by age for ITT population. Subjects in all Adderall XR groups had more changes than those in placebo group.

Table 4.1.2 Change from Baseline in ADHD-RS-IV in the Primary Cohort by Age

Age	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
13-14	31	30	37	37	44
Baseline	36.1	36.6	35.9	36.0	32.3
Endpoint	28.1	19.4	14.6	15.9	16.3
Mean Change	-8.0	-17.2	-21.4	-20.1	-16.0
15-17	21	24	16	21	17
Baseline	33.6	32.8	29.3	33.6	33.2
Endpoint	22.3	20.8	10.2	16.4	15.3
Mean Change	-11.3	-12.1	-19.1	-17.2	-17.9

Table 4.1.3 presents the mean change in ADHD-RS-IV from baseline at Week 4 LOCF for the primary cohort by race (white vs. non-white) for ITT population. Subjects in all Adderall XR groups had more changes than those in placebo group.

Table 4.1.3 Change from Baseline in ADHD-RS-IV in the Primary Cohort by Race

Race	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
White	38	38	39	43	47
Baseline	33.2	35.5	33.2	35.2	31.4
Endpoint	21.9	19.4	12.6	16.3	15.2
Mean Change	-11.3	-16.1	-20.6	-19.0	-16.2
Non-White	14	16	14	15	14
Baseline	40.1	33.5	35.9	34.7	36.5
Endpoint	36.1	21.5	15.1	15.5	18.9
Mean Change	-4.0	-12.0	-20.9	-19.2	-17.6

4.2 Other Special/Subgroup Populations

Table 4.2.1 presents the mean change in ADHD-RS-IV from baseline at Week 4 LOCF for the primary cohort by type of ADHD for ITT population. Since the Study was not powered for subgroup analyses, analytical analysis is not performed. Subjects in all Adderall XR groups had more changes than those in placebo group.

Table 4.2.1 Change from Baseline in ADHD-RS-IV in the Primary Cohort by Type of ADHD

Type of ADHD	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Inattentive	23	20	25	20	26
Baseline	29.7	29.3	29.3	29.4	26.3
Endpoint	18.4	14.9	10.9	14.1	12.5
Mean Change	-11.3	-14.4	-18.4	-15.3	-13.8
Hyperactive/Impulsive or combine	29	34	28	38	35
Baseline	39.3	38.2	38.1	38.1	37.3
Endpoint	31.6	23.0	15.4	17.1	18.7
Mean Change	-7.7	-15.2	-22.7	-21.0	-18.6

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The primary analysis showed that there was a significant difference in favor of Adderall XR, compared to placebo, for the mean change in ADHD-RS-IV from baseline at Week 4 LOCF in the ITT population, and there was a significant difference in favor of Adderall XR for the proportion of subjects with a score of much improved or very much improved on the CGI-I at Week 4 LOCF. Detailed statistics are presented in the following tables.

Table 5.1.1 Analyses of ADHD-RS-IV Total Score in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)
Baseline					
Mean (SD)	35.1 (9.7)	34.9 (10.4)	33.9 (9.1)	35.1 (10.8)	32.6 (10.8)
Endpoint					
Mean (SD)	25.7 (13.4)	20.0 (11.8)	13.3 (10.3)	16.1 (11.0)	16.0 (11.2)
Mean change (SD)	-9.4 (10.6)	-14.9 (12.1)	-20.7 (11.2)	-19.0 (11.1)	-16.5 (11.6)
LS mean difference	--	-5.59	-12.23	-9.23	-8.49
(95% CI)	--	(-9.40, -1.77)	(-16.06, -8.39)	(-13.00, -5.46)	(-12.22, -4.76)
p-value	--	0.0043	<0.0001	<0.0001	<0.0001

Table 5.1.2 Analyses of CGI-I in the Primary Cohort (ITT-LOCF)

	Placebo (N=52)	10 mg (N=54)	20 mg (N=53)	30 mg (N=58)	40 mg (N=61)	10-40 mg (N=226)
Dichotomized CGI-I						
Improvement	14 (26.9%)	28 (51.9%)	35 (66.0%)	41 (70.7%)	39 (63.9%)	143 (63.3%)
No improvement	38 (73.1%)	26 (48.1%)	18 (34.0%)	17 (29.3%)	22 (36.1%)	83 (36.7%)
Difference in % with improvement in active group vs. placebo	--	24.9%	39.1%	43.8%	37.0%	36.4%
p-value	--	0.0098	0.0002	<0.0001	0.0001	<0.0001

5.2 Conclusions and Recommendations

The conclusion is that the primary analysis for the mean change in ADHD-RS-IV total score from baseline at Week 4 LOCF in the ITT population is significant comparing Adderall XR (10mg/day to 40 mg/day) and placebo in the treatment of adolescents, age 13-17 and weight less than or equal to 75 kg/165 lbs, with Attention Deficit Hyperactivity Disorder (ADHD). The analysis for the dichotomized CGI-I is also significant in favor of Adderall XR for the proportion of subjects with a score of much improved or very much improved at Week 4 LOCF.

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