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:	21-121
Drug Name:	Concerta, S-008 (methylphenidate HCl) Extended-release Tablets
Indication(s):	ADHD in Adolescents
Applicant:	McNeil Consumer & Specialty Pharmaceuticals
Date(s):	October 23, 2003
Review Priority:	Priority
Biometrics Division:	Division of Biometric I
Statistical Reviewer:	Fanhui Kong, PhD
Concurring Reviewers:	Kun Jin, PhD, Kooros Mahjoob, Ph.D.
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Keywords: Concerta, ADHD, randomized double-blind clinical trial, ANCOVA, CGI, CCI, ITT, LOCF.

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1. EXECUTIVE SUMMARY

The study is entitled "An Evaluation of the Safety and Efficacy of CONCERTA® (up to 72 mg daily) in Adolescents with Attention Deficit Hyperactivity Disorder (ADHD)" with the primary objective to evaluate the safety and efficacy of CONCERTA® (up to 72 mg daily) in adolescents with Attention Deficit Hyperactivity Disorder (ADHD).

1.1 Conclusions and Recommendations

In the LOCF analysis of the pivotal Study 01-146, treatment significantly reduced the ADHD total score at the end of double blind randomized treatment phase therefore supports the claim that the use of Concerta is more effective than placebo in improving clinical conditions of the children with ADHD. The treatment effect was found in both groups of sex. Yet such an effect was less obvious in the Noncaucasian group. In addition to being nonsignificant, the magnitude of the effect in the Noncaucasian group was much smaller compared to the Caucasian group. In addition, nonparametric test results also supported the overall significance claims by the sponsor.

1.2 Brief Overview of Clinical Studies

This submission of efficacy study consisted of one Phase III, randomized, double-blind, parallel group multi-center, placebo-controlled study that evaluated the efficacy and safety of Concerta up to 72 mg per day versus placebo in the treatment of adolescents with ADHD in addition to approved daily doses of 18 mg, 36 mg, and 54 mg. There were 5 arms in this study: arms of daily doses of 18 mg, 36 mg, 54 mg, 72mg and placebo.

This study was composed of four phases: screening, open-label titration, randomized double-blind, and open-label follow-up. Overall, 220 subjects entered the titration phase of the study, 177 subjects were randomized to the double-blind phase and 171 subjects entered the open-label phase. Sixty-six (37.3%) subjects were titrated to CONCERTA 72 mg per day as their individualized dose. In the double-blind phase, 87 subjects were assigned to four arms of CONCERTA and 90 subjects to placebo.

1.3 Statistical Issues and Findings

There was 25% dropout in the double blind phase and the method of LOCF was acceptable for the imputation of the missing data. The significance of the treatment effect on the primary endpoint of the reduction of ADHD total score at the end of double blind phase was consistent in both sex groups, such an effect didn't seem to be obvious in the Noncaucasian group.

According to the protocol, the baseline measure of the efficacy endpoints was made before the titration phase which was up to four weeks before randomization. One of the concerns of such study design is the rebound of the patients who were assigned to use placebo after the titration phase, due to the sudden withdraw of treatment for placebo patients. Such a rebound could make the treatment effect look more significant. After careful study of the change of the ADHD total score, we did not find enough evidence to believe that the significance of the treatment effect was mainly caused by the rebound.

2. INTRODUCTION

2.1 Overview

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder that begins in childhood and is characterized by developmentally inappropriate inattention, hyperactivity and impulsiveness; this could have negative impact on educational, occupational and social outcomes and is associated with an increased risk of other mental health disorders. ADHD represents a common psychiatric disorder in children, affecting approximately 3% to 7% of the school-age population [1]. Boys are at six to nine times greater risk of developing ADHD than girls [2].

Stimulant treatment is the mainstay of pharmacologic treatment for ADHD. Methylphenidate is the most commonly prescribed and most frequently studied stimulant medication in this disorder. As a long-acting form of methylphenidate designed for 12-hour duration, CONCERTA was approved in the United States in August 2000 for the treatment of ADHD. CONCERTA is indicated in the United States for the treatment of ADHD with a maximum daily dose of 54 mg. In this submission, the sponsor presented efficacy results from one randomized controlled clinical study of CONCERTA in doses up to 72 mg/day in adolescents with ADHD and two long-term safety and effectiveness studies.

A full statistical reviewed was conducted on one controlled clinical trial (Study 01-146) studying the efficacy and safety of CONCERTA in doses up to 72 mg/day in adolescents with ADHD in addition to approved daily doses of 18 mg, 36 mg, and 54 mg. There were 5 arms in this study: arms of daily doses of 18 mg, 36 mg, 54 mg, 72mg and placebo.

This study was composed of four phases: screening, open-label titration, randomized double-blind, and open-label follow-up. Overall, 220 subjects entered the titration phase of the study, 177 subjects were randomized to the double-blind phase and 171 subjects entered the open-label phase. Sixty-six (37.3%) of the 177 subjects randomized in the study needed to be titrated to CONCERTA 72 mg as their individualized dose, 72 mg was required to achieve the pre-specified level of improvement. In the double-blind phase, 87 subjects were assigned to CONCERTA and 90 subjects to placebo.

2.2 Data Sources

The applicant study reports for the efficacy and safety of pivotal Study 01-146 were provided both in paper and electronically. The paper version was given in Section 8, Volume 2 pages 1-193, with supporting tables and figures in Section 8, Volume 2 pages 194-644. Literature references were given in Section 8, Volume 2 pages 645-646. In addition, the same study and the open label clinical studies C-98-012 and C-99-018 were summarized in Section 8, Volume 78 pages 1-270. The references were given in Section 8, Volume 78 pages 271-272. Analysis data sets were provided electronically on \\Cdsesub1\n21121\S_008\2003-09-15\crt\datasets.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

The study was conducted from April 1, 2002 to October 16, 2002. The objective of this study was to evaluate the safety and efficacy of treatment with CONCERTA (up to 72 mg daily) in adolescents with ADHD. This was a multicenter study in adolescents aged 13 to 18 years with ADHD which was composed of four phases: screening, open-label titration, randomized, double-blind, and open-label follow-up. At screening, the diagnosis of ADHD was established through clinical evaluation by the investigator according to DSM-IV scale. Eligible subjects were then evaluated after a one-week washout period by their respective parents/caregivers, and investigators regarding their behavior, while off medication as a baseline measure in the efficacy analysis.

In the open-label titration phase, subjects initiated treatment with one 18 mg tablet of CONCERTA daily. The dose was increased in 18 mg increments approximately every 7 days (±2 days) to a maximum of 72 mg daily until an individualized dose was identified. The dose for each subject was 18, 36, 54, or 72 mg, which produced the criterion of >30% improvement in ADHD symptoms from baseline with tolerable safety for a given subject. This was then the dose administered in the randomized double-blind phase in treatment group.

Subjects were then randomized to receive either their individualized CONCERTA dose or a matched placebo for two weeks in double-blind phase. At the end of each week of the double-blind phase, the subject was assessed over the previous week by the parent/caregiver, the subject and the investigator. Additionally, on a twice-weekly basis, a telephone interview was conducted with the parent/caregiver to determine the Child Conflict Index.

Subjects who successfully completed the double-blind phase of the trial were then eligible to receive CONCERTA for an eight-week open-label follow-up phase. Also, subjects who experienced intolerable lack of efficacy during the double-blind phase were allowed to discontinue that phase prematurely, and then they were allowed to enroll directly into the open-label follow-up phase with the individualized dose of CONCERTA identified in the titration phase. Clinical site staff telephoned the subject's parent/caregiver every two weeks between monthly visits to assess dosing compliance and any potential adverse events. Dosing compliance and safety assessments were also made at monthly site visits.

The protocol was first issued on November 9, 2001 and amended twice on January 3, 2002 and April 29, 2002, respectively. Approximately 200 subjects were planned in the protocol to be enrolled into the titration phase to target 126 evaluable subjects at the completion of the double-blind phase. In the following review, Tables 3.1.1 to 3.1.4 are taken directly from sponsor's Study Report.

3.1.2 Primary and Secondary Endpoints

The primary efficacy endpoint was the change from baseline to the end of the randomized double-blind phase of the mean total score of the ADHD Rating Scale as evaluated by the investigator.

Secondary endpoints specified in the statistical analysis plan included:

- The change from baseline of the mean total score of the ADHD Rating Scale as evaluated by the parent/caregiver (double-blind and titration phases) and investigator (titration phase).

- The Global Assessment of Effectiveness evaluated by the investigator (double-blind and titration phases).

- The Global Improvement subscale of the Clinical Global Impression (CGI) measured by the investigator (double-blind phase).

- The total score of the Conners-Wells' Self Report Scale as measured by the subject (double-blind phase).

- The average score of the Child Conflict Index (CCI) as evaluated by the parent/caregiver (double-blind phase).

3.1.3 Patient Disposition, Demographic and Baseline Characteristics

There were 220 subjects enrolled into the open-label titration phase and 177 subjects randomized into the double-blind phase. There were 133 subjects that completed the two-week double-blind phase. There were 171 subjects who entered the open-label follow-up phase.

For the total of 177 subjects who were randomized, 175 were included in the intent-to-treat analysis and 156 were included in the per-protocol analysis. Two subjects were excluded from the intent-to-treat analysis, one for not taking study medication in the double-blind phase and one for not having a post-randomization value of the investigator ADHD rating scale. Reasons for exclusion from the per-protocol analysis were as follows: last visit date more than one day from the date of last dose during the double-blind phase, concomitant medication/product violations, less than 80% compliance and study dose violation.

For all subjects enrolled in the titration phase, there were no significant differences among CONCERTA doses regarding gender, race, age, weight, height, and for the percentage of subjects taking concomitant medications. For the intent-to-treat population during the double-blind phase, there were no significant differences between Any CONCERTA group and placebo in race, age, weight, height, and percentage of subjects taking concomitant medications (Table 3.1.1). However, there were significantly ($p=0.0431$) more males in the placebo group (86.5%) than in the Any CONCERTA group (74.4%). For subjects enrolled in the open-label follow-up phase, there were no significant differences among CONCERTA doses regarding gender, race, age, weight, and height. There was a borderline significant ($p=0.0583$) difference among CONCERTA doses in the percentage of subjects with changes since the double-blind phase in the use of concomitant medications. There was a general trend of decreased change since the double-blind phase in use of concomitant medication with increasing CONCERTA dose.

Table 3.1.1 Baseline/Demographic Characteristic by Treatment for Intent to Treat (ITT) Subjects in Randomized Double-Blind Phase

		CONCERTA						
Characteristic	Placebo (N=89)	18 mg (N=4)	36 mg (N=25)	54 mg (N=24)	72 mg (N=33)	Any CONCERTA (N=86)	Total Subjects (N=175)	p-Value[a]
Gender								0.0431
Male	77 (86.5%)	2 (50.0%)	19 (76.0%)	18 (75.0%)	25 (75.8%)	64 (74.4%)	141 (80.6%)	
Female	12 (13.5%)	2 (50.0%)	6 (24.0%)	6 (25.0%)	8 (24.2%)	22 (25.6%)	34 (19.4%)	
Race								0.1903
Caucasian	67 (75.3%)	3 (75.0%)	17 (68.0%)	18 (75.0%)	26 (78.8%)	64 (74.4%)	131 (74.9%)	
African-American	15 (16.9%)	0 (0.0%)	4 (16.0%)	1 (4.2%)	4 (12.1%)	9 (10.5%)	24 (13.7%)	
Other	7 (7.9%)	1 (25.0%)	4 (16.0%)	5 (20.8%)	3 (9.1%)	13 (15.1%)	20 (11.4%)	
Age (y)								
Mean (SD)	14.5 (1.4)	14.5 (1.7)	14.4 (1.5)	14.5 (1.4)	15.4 (1.8)	14.8 (1.6)	14.6 (1.5)	0.1350
Range	13.0-18.0	13.0-17.0	13.0-18.0	13.0-18.0	13.0-18.0	13.0-18.0	13.0-18.0	
Distribution of Age (y)								
13	29 (32.6%)	1 (25.0%)	8 (32.0%)	8 (33.3%)	6 (18.2%)	23 (26.7%)	52 (29.7%)	
14	22 (24.7%)	2 (50.0%)	8 (32.0%)	5 (20.8%)	7 (21.2%)	22 (25.6%)	44 (25.1%)	
15	17 (19.1%)	0 (0.0%)	3 (12.0%)	6 (25.0%)	5 (15.2%)	14 (16.3%)	31 (17.7%)	
16	11 (12.4%)	0 (0.0%)	3 (12.0%)	3 (12.5%)	4 (12.1%)	10 (11.6%)	21 (12.0%)	
17	9 (10.1%)	1 (25.0%)	2 (8.0%)	1 (4.2%)	6 (18.2%)	10 (11.6%)	19 (10.9%)	
18	1 (1.1%)	0 (0.0%)	1 (4.0%)	1 (4.2%)	5 (15.2%)	7 (8.1%)	8 (4.6%)	
Weight (kg)								0.8398
Mean (SD)	65.7 (18.5)	66.6 (5.8)	63.6 (17.5)	64.8 (13.1)	69.1 (17.2)	66.2 (15.9)	65.9 (17.2)	
Range	34.9-128.9	59.5-73.5	34.1-116.2	40.1-90.3	50.8-124.4	34.1-124.4	34.1-128.9	
Height (cm)								0.4795
Mean (SD)	167.6 (9.6)	170.8 (13.9)	167.1 (10.3)	167.3 (9.3)	170.4 (8.7)	168.6 (9.5)	168.1 (9.6)	
Range	142.2-186.7	156.2-186.7	148.6-181.6	149.9-186.2	154.9-188.0	148.6-188.0	142.2-188.0	
Concomitant Medication								0.3803
No	27 (30.3%)	0 (0.0%)	6 (24.0%)	10 (41.7%)	5 (15.2%)	21 (24.4%)	48 (27.4%)	
Yes	62 (69.7%)	4 (100.0%)	19 (76.0%)	14 (58.3%)	28 (84.8%)	65 (75.6%)	127 (72.6%)	

a: Gender, race, concomitant medication were analyzed with Chi-Square tests. Age, weight and height were analyzed with one-way analyses of variance. P-Value compared Any CONCERTA vs. placebo.

Table 3.1.2 shows baseline evaluation scores for subjects included in the intent-to-treat analysis and the results of statistical comparisons between CONCERTA and placebo. There were no significant differences between Any CONCERTA and placebo for any evaluation score.

Table 3.1.2 Mean Baseline Evaluation Scores by Treatment for Intent to Treat (ITT) Subjects in Randomized Double-Blind Phase

Characteristic[a]	Placebo	CONCERTA					p-Value[b]
		18 mg	36 mg	54 mg	72 mg	Any CONCERTA	
Total Score of ADHD Rating Scale (Investigator),							
N	89	4	25	24	33	86	
Mean	30.99	25.50	30.28	32.88	32.27	31.55	0.7042
SD	9.64	7.05	8.29	9.54	10.31	9.42	
Min, Max	10,54	18,32	18,47	11,52	8,54	8,54	
Total Score of ADHD Rating Scale (Parent)							
N	89	4	25	24	33	86	
Mean	30.99	21.25	30.20	31.25	31.70	30.65	0.9324
SD	11.55	2.22	9.87	9.13	10.46	9.81	
Min, Max	6,54	19,24	18,48	15,52	7,51	7,52	
Total Score of Conners-Wells' Self Report Scale (Subject)							
N	89	4	25	23	33	85	
Mean	94.02	73.28	87.23	96.05	89.42	89.81	0.5847
SD	49.20	18.50	41.48	42.39	43.38	41.44	
Min, Max	9,221	48,92	11,194	28,167	11,227	11,227	
Child Conflict Index (Parent)							
N	88	4	25	24	33	86	
Mean	0.259	0.302	0.304	0.295	0.265	0.286	0.3048
SD	0.182	0.123	0.181	0.179	0.174	0.174	
Min, Max	0.00,0.72	0.19,0.47	0.07,0.76	0.00,0.67	0.05,0.78	0.00,0.78	

a: Baseline scores are not presented for the global evaluation parameters, Clinical Global Impression and Global Assessment of Effectiveness

b: ANOVA models with treatment (Any CONCERTA vs. placebo) and site as factors.

The primary reasons for withdrawal during the double-blind phase are: adverse events, lost to follow-up, lack of efficacy, protocol violation. Table 3.1.3 summarizes the number and percent of subjects who withdrew from the double-blind phase of the study. Forty-four subjects (24.9%) discontinued prematurely. Of these, six subjects discontinued from the study and did not enter the open-label phase of the study. All of the 37 subjects who discontinued for lack of efficacy entered the open-label phase. Additionally, one subject with a protocol deviation (outside visit window) continued into the open-label phase.

Table 3.1.3 Disposition of Subjects during the Randomized Double-Blind Phase by Treatment Group

		CONCERTA				
Characteristics	Placebo	18 mg	36 mg	54 mg	72 mg	Any CONCERTA
Subjects Randomized	90 (100.0%)	5 (100.0%)	25 (100.0%)	24 (100.0%)	33 (100.0%)	87 (100.0%)
Subjects Dispensed the Double-Blind Study Medication	90 (100.0%)	5 (100.0%)	25 (100.0%)	24 (100.0%)	33 (100.0%)	87 (100.0%)
Subjects Completing the Double-Blind Phase	62 (68.9%)	4 (80.0%)	22 (88.0%)	20 (83.3%)	25 (75.8%)	71 (81.6%)
Subjects Discontinuing from the Double-Blind Phase	28 (31.1%)	1 (20.0%)	3 (12.0%)	4 (16.7%)	8 (24.2%)	16 (18.4%)
Reason for Discontinuation						
Adverse Events	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-Up	2 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lack of Efficacy[a]	23 (25.6%)	1 (20.0%)	1 (4.0%)	4 (16.7%)	8 (24.2%)	14 (16.1%)
Protocol Violations	2 (2.2%)	0 (0.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)	2 (2.3%)

a: Protocol allowed subjects exhibiting intolerable lack of efficacy to discontinue the double-blind phase and enroll directly into the open-label phase. All subjects discontinuing due to lack of efficacy enrolled directly into the open-label phase.

3.1.4 Statistical Methodologies Used

In this study, statistical tests were all two-sided with a significance level of 0.05. The last observation carried forward (LOCF) technique was used to define the measures at the end of the randomized double-blind phase. A change from baseline in total score of the ADHD rating scale rated by investigator at the end of the randomized double-blind phase was evaluated as the primary efficacy endpoint for ITT population. The total ADHD score rated by investigator was summarized by treatment group (Placebo, CONCERTA 18 mg, 36, mg, 54 mg, 72 mg and Any CONCERTA) at baseline and each study week, with descriptive statistics. An analysis of covariance (ANCOVA) with study site and treatment group (Placebo vs. Any CONCERTA) as factors and the baseline value as a covariate was used to test for differences between treatment groups in changes from baseline. The treatment-by-site interactions were examined at a significance level of α=0.10.

The Cochran-Mantel-Haenszel test stratified by study site was used to compare treatment differences between placebo and Any CONCERTA during the double-blind phase for Global Assessment of Effectiveness and Global Improvement subscale of the Clinical Global Impression (CGI). The ANCOVA method was also used for all other secondary efficacy measures.

3.1.5 Results by the Sponsor

3.1.5.1 Primary Endpoint Results

The analyses of the efficacy data were conducted using the ITT population for both primary and all secondary efficacy variables. The similar analyses of efficacy data were also conducted for the PP population. Primary inferences were based on the ITT population using LOCF dataset at the end of the randomized double-blind phase. Negative changes from baseline for ADHD Total score indicated an improvement for the patient.

The primary endpoint for assessing efficacy in the treatment of ADHD was the change from baseline at the end of the randomized double-blind phase for the mean total score of the ADHD Rating Scale as

evaluated by the investigator. The results for the primary efficacy endpoint are shown in Table 3.1.4. Subjects taking Any CONCERTA dose had significantly greater (p = 0.0010) improvements in the investigator-evaluated ADHD Rating Scale than subjects taking placebo (mean change: Any CONCERTA = -14.93, placebo = -9.58).

Table 3.1.4 Mean Change from Baseline at the End of the Randomized Double-Blind Phase by Dose Group for ADHD Total Score (Investigator), Intent-to-Treat Population

			CONCERTA					
	Statistics	Placebo	18 mg	36 mg	54 mg	72 mg	Any CONCERTA	p-Value[a]
Baseline	N	89	4	25	24	33	86	
	Mean	30.99	25.50	30.28	32.88	32.27	31.55	
	SD	9.64	7.05	8.29	9.54	10.31	9.42	
	Min, Max	10, 54	18, 32	18, 47	11, 52	8, 54	8, 54	
End of RDB[b]	N	89	4	25	24	33	86	
	Mean	21.40	8.00	17.96	16.25	16.91	16.62	
	SD	13.44	1.83	10.30	11.45	11.76	11.03	
	Min, Max	1, 54	6, 10	0, 44	3, 44	0, 46	0, 46	
Change from Baseline at End of RDB[b]	N	89	4	25	24	33	86	
	Mean	-9.58	-17.50	-12.32	-16.63	-15.36	-14.93	0.0010
	SD	9.73	8.81	9.93	10.12	11.91	10.72	
	Min, Max	-34, 9	-25, -8	-33, 7	-41, 6	-37, 9	-41, 9	

a: ANCOVA models with treatment (placebo or Any CONCERTA) and site as factors and the corresponding baseline total score as a covariate.
b: Last observation carried forward at the end of randomized double-blind phase. Abbreviations: RDB=randomized double-blind.

3.1.5.2 Secondary Endpoint Results

Secondary efficacy endpoints for the double-blind phase included change from baseline for the mean total score of the ADHD Rating Scale as evaluated by the parent/caregiver, the Global Assessment of Effectiveness (GAE), the Global Improvement subscale of the Clinical Global Impression (CGI), the total score of the Conners-Wells' Self Report Scale, and the average score of the Child Conflict Index (CCI). Results for all secondary endpoints for the double blind phase and their statistical significance levels of Any CONCERTA dose compared to placebo are showed in Table 3.1.5.

For parent-evaluated ADHD Rating Scale, subjects taking Any CONCERTA dose had significantly (p = 0.0077) greater improvements in the parent-evaluated ADHD Rating Scale than subjects taking placebo (mean change: Any CONCERTA = -14.00, placebo = -10.14).

For the global assessment of effectiveness, 51.2% of subjects treated with Any CONCERTA dose were evaluated to have good or excellent effectiveness compared to 32.6% of placebo-treated subjects. This result was statistically significant (p = 0.0043).

For the Global Improvement subscale of the Clinical Global Impression, significant differences (p = 0.0113) were found by the investigator in favor of the group of Any CONCERTA compared to placebo. A greater percentage of subjects taking Any CONCERTA dose were 'much improved' or 'very much improved' (51.8%) compared to subjects taking placebo (31.0%).

For the Conners-Wells' Self Report Scale, Any CONCERTA group reported significantly (p = 0.0011) greater improvements compared to subjects taking placebo (mean change: Any CONCERTA = -31.70, placebo = -18.70).

For the average score of the Child Conflict Index as evaluated by the parent, the group of Any CONCERTA was significantly (p = 0.0051) more effective compared to placebo (mean change: Any CONCERTA = -0.098, placebo = -0.016). For Any CONCERTA, this change represents a 34.3% improvement in the Child Conflict Index from baseline.

Table 3.1.5 Secondary Efficacy Measure at the End of Double Blind Phase for ITT Population—LOCF Analysis

Secondary Efficacy Endpoint	Placebo	CONCERTA					P-value [b]
		18 mg	36 mg	54 mg	72 mg	Any Concerta	
ADHD (Parent/Caregiver)							
Mean change from baseline (SD)[a]	-10.14 (10.0)	-13.75 (5.68)	-13.32 (10.37)	-14.08 (8.94)	-14.48 (11.86)	-14.0 (10.31)	0.0077
Min, Max	-37, 10	-18, -6	-32, 8	-35, 7	-39, 6	-39, 8	
N	89	4	25	24	33	86	
GAE (Investigator) (%)							
Poor	42 (47.2)	0 (0.0)	8 (32.0)	6 (25.0)	11 (33.3)	25 (29.1)	0.0043
Fair	18 (20.2)	0 (0.0)	6 (24.0)	7 (29.2)	4 (12.1)	17 (19.8)	
Good	24 (27.0)	2 (50.0)	7 (28.0)	7(29.2)	11 (33.3)	27 (31.4)	
Excellent	5 (5.6)	2 (50.0)	4 (16.0)	4 (16.7)	7 (21.2)	17 (19.8)	
N	89	4	25	24	33	86	
CGI (Investigator) (%)							
Very much improved	7 (8.0)	0 (0.0)	3 (12.5)	3 (12.5)	6 (18.2)	12 (14.1)	0.0113
Much improved	20 (23.0)	4 (100.0)	8 (33.3)	9 (37.5)	11 (33.3)	32 (37.6)	
Minimally improved	15 (17.2)	0 (0.0)	5 (20.8)	7 (29.2)	5 (15.2)	17 (20.0)	
No change	32 (36.8)	0 (0.0)	4 (16.7)	4 (16.7)	5 (15.2)	13 (15.3)	
Minimally worse	8 (9.2)	0 (0.0)	4 (16.7)	0 (0.0)	4 (12.1)	8 (9.4)	
Much worse	4 (4.6)	0 (0.0)	0 (0.0)	1 (4.2)	2 (6.1)	3 (3.5)	
Very much worse	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
N	87	4	24	24	33	85	
Conners-Wells Self Report Scale							
Mean change from baseline (SD)[a]	-18.70 (26.94)	-11.04 (14.02)	-33.95 (33.34)	-34.87 (32.57)	-30.30 (23.52)	-31.70 (28.96)	0.0011
Min, Max	89, 63	-27, 7	-119, 14	-79. 47	-101, 10	-119, 47	
N	89	4	25	23	33	85	
CCI (Parent/Caregiver)							
Mean change from baseline (SD)[a]	-0.016 (0.15)	-0.218 (0.15)	-0.064 (0.156)	-0.107 (0.219)	-0.103 (0.192)	-0.098 (0.189)	0.0051
Min, Max	-0.36, 0.33	-0.39, -0.02	-0.33, 0.21	-0.45, 0.31	-0.53, 0.33	-0.53, 0.33	
N	88	4	25	24	33	86	

a: ANCOVA models with treatment (placebo or Any CONCERTA) and site as factors and the corresponding baseline total score as a covariate.
b: Last observation carried forward at the end of randomized double-blind phase.

3.1.6 Reviewer's Findings

Using the ITT-LOCF data set provided by the sponsor, the reviewer duplicated the sponsor's analysis according to the protocol and obtained the same results for LOCF analyses. These results are depicted in Table 3.1.6.

Table 3.1.6 Efficacy for the Reduction of ADHD Total Score at Week 2 ITT Population

Primary Efficacy Endpoint	Placebo	CONCERTA					P-value [a]
		18 mg	36 mg	54 mg	72 mg	Any Concerta	
ADHD--LOCF							
Mean change from baseline (SD)[b]	-9.58 (9.73)	-17.5 (8.81)	-12.32 (9.93)	-16.63 (10.12)	-15.36 (11.91)	14.93 (10.72)	0.001
Min, Max	-34, 9	-25, -8	-33, 7	-41, 6	-37, 9	-41, 9	
N	89	4	25	24	33	86	
ADHD--OC							
Mean change from baseline (SD)[b]	-12.19 (8.36)	-17.5 (8.81)	-11.68 (9.49)	-17.8 (9.76)	-18.73 (10.39)	-16.25 (10.14)	0.029
Min, Max	-28, 8	-25, -8	-28, 7	-41, -1	-37, 8	-41, 8	
N	63	4	22	20	26	72	

a: ANCOVA models with treatment (placebo or Any CONCERTA) and site as factors and the corresponding baseline total score as a covariate.
b: Last observation carried forward at the end of randomized double-blind phase.

Normality assumption was tested both for the ADHD Total score and its reduction from baseline to the end of the randomized double-blind phase. Kolmogorov-Smirnov D test and the Shapiro-Wilks test gave p-values of 0.063 and 0.0004 for ADHD Total score for treatment group and 0.016 and 0.003 for placebo group. These tests gave p-values of 0.15 and 0.80 for the change from baseline of the ADHD Total score for treatment group and 0.15 and 0.37 for placebo group. On the other hand, the distributions for the reduction from baseline for ADHD total score was less skewed and the histograms were more bell shaped. These results indicated that the normality assumption for the primary endpoint of the change from baseline of ADHD total score was more appropriate than the ADHD total score itself. As an alternative, the reviewer performed nonparametric tests. The Wilcoxon and Kruskal-Wilks tests gave p-values of 0.025 and 0.024, respectively. These results confirmed the testing results in Table 3.1.6.

Parallelism of the regression lines for the placebo and Any Concerta groups was tested by testing the interaction between the baseline ADHD Total score and the treatment indicator. This test yielded a significant result with a p-value of 0.022, indicating a non-parallelism between the regression lines of two treatment groups.

3.2 Evaluation of Safety

See medical review for details.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The effect of sex on the primary outcome was evaluated by testing the significance of sex as a covariate in the model. The p-value of the test was 0.076 so sex had a board line significant difference on the reduction of ADHD Total score at the end of double-blind randomized treatment phase. To see the trend of sex in the effect of Concerta, the following table gives t-test results for the treatment differences by sex. Change is the mean change of ADHD Total score from baseline to the end of double blind phase. Trt_effect is the difference between Change of Any Concerta and Placebo.

Table 4.1.1 Treatment Effect on the Change of ADHD Total Score in both Sex Groups at the end of Double Blind Phase

Sex	Therapy	Patient	Change	Trt_effect	p-Value
Male	**Any Concerta**	64	-15.70	-5.34	0.002
	Placebo	77	-10.36		
Female	**Any Concerta**	22	-12.68	-8.1	0.04
	Placebo	12	-4.58		

The above table shows that Concerta has statistically significant effect on the change of ADHD Total score in both sex groups. However, without the adjustment of other covariates, the nominal p-value should be interpreted with care.

The effect of race on the primary outcome was evaluated by testing the significance of race as a covariate in the model. Given that about 75% of the patients were Caucasian, we separated the population into two groups: Caucasian and Noncaucasian. The p-value of the test was 0.998 so race did not make a significant difference on the reduction of ADHD Total score at the end of double blind phase. To see the trend of race on the effect of Concerta, the following table gives t-test results on the treatment differences by race. Change is the mean change of ADHD Total score from baseline to the end of double blind phase. Trt_effect is the difference between Change of Any Concerta and Placebo. Given that the magnitude of the treatment effect is much smaller in Noncaucasian group, the treatment effect does not seem to be obvious in this group.

Table 4.1.2 Treatment Effect on the Change of ADHD Total Score in Race Groups at the end of Double Blind Phase

Race	Therapy	Patient	Change	Trt_effect	p-Value
Caucasian	**Any Concerta**	64	-15.05	-6.44	0.0005
	Placebo	67	-8.61		
Noncaucasian	**Any Concerta**	22	-14.59	-2.05	0.5
	Placebo	22	-12.55		

The age of the population is from 13 to 18 so the age difference is of little concern.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The study did not include an interim analysis. The percentage of drop out in the double blind phase was 25% and the LOCF was employed for the imputation of the missing data. The significance of the treatment effect on the primary endpoint of the reduction of ADHD total score at the end of double blind phase is consistent in both sex groups, such an effect seems to be mainly in the Caucasians only.

According to the protocol, the baseline measure of the efficacy endpoints was made before the titration phase which was up to four weeks, before the subjects were randomized into the double-blind phase. Then at the end of Week 2 of the double-blind phase, subjects were compared for their efficacy endpoints, see the Final Report Section 8, Volume 2, page 44. One of the concerns of such study design is the rebound of the placebo patients after the titration phase. Due to the sudden withdraw of treatment for placebo patients during the double-blind phase, their ADHD total score could rebound so the reduction of ADHD total score in this group could disappear. Such a rebound could make the treatment effect look more significant.

To study such a possible rebound, we computed the mean change of the patients in both treatment groups in both weeks of double-blind phase. There are 89 patients in the placebo group and 86 patients in the treatment group. The means and standard deviations of the ADHD total score at the end of titration and in the two weeks of double-blind phase are depicted in Table 4.1.3. There were some rebound after the randomization. The p-values of the reductions from the end of titration of both weeks in both treatment groups were all <0.0001. But the reductions in the placebo were more dramatic. On the other hand, compared to baseline which was before the titration, the reduction in the placebo did not disappear. So there was not enough evidence to believe that the significance of the treatment effect was mainly caused by the rebound.

Table 4.1.3 Change of ADHD Total Score at the end of Titration Phase and in the Double Blind Phase in Both Treatment Groups

Treatment Group	End of Titration	First Week of RDB	Second Week of RDB
Concerta	-20.88 (7.56) n=86	-15.38 (10.47) n=86	-16.25 (10.14) N=72
Placebo	-20.36 (8.21) n=89	-8.97 (10.01) n=89	-12.19 (8.36) N=63

We also performed subgroup analysis of the treatment effect for each dose group even though these groups are self-selected. Such an analysis will give a better idea of which group contributes to the overall treatment effect. The results are depicted in the following table. It seems that the dose groups of 54mg and 73mg contribute the most while the group of 36mg contributes the least. The group of 18mg has only 4 patients so it is too small for any reliable results.

Table 4.1.4 Treatment Effect on the Change of ADHD Total Score at the end of Double Blind Phase in the Dose Groups

Dose Group	Treatment Group	Placebo Group	Trt_effect	p-Value
18 mg/day (SD)	-17.5 (8.81) n=4	-9.58 (9.73) n=89	-7.92 (9.70)	0.11
36 mg/day (SD)	-12.32 (9.93) n=25	-9.58 (9.73) n=89	-2.74 (9.77)	0.22
54 mg/day (SD)	-16.63 (10.12) n=24	-9.58 (9.73) n=89	-7.04 (9.81)	0.002
72 mg/day (SD)	-15.36 (11.91) n=33	-9.58 (9.73) n=89	-5.78 (10.36)	0.007

5.2 Conclusions and Recommendations

In this submission, the sponsor conducted one Phase III, placebo controlled clinical trial study that evaluated the efficacy and safety of Concerta versus placebo in the treatment of children with ADHD.

In the LOCF analysis of the pivotal Study 01-146, treatment significantly reduced the ADHD Total score at the end of double blind randomized treatment phase compared to placebo therefore supported the conclusion that the use of Concerta was more effective than placebo in improving clinical conditions of the adolescents with ADHD. The model assumptions made by the sponsor on the primary endpoints were checked by the reviewer and were found to be acceptable. In addition to the adjustment of covariates in the models presented, the significance of covariates sex and race was tested in the ANCOVA model. Sex was found to be board line significant and the treatment effect was found in both sex groups. Race was not significant in the overall ANCOVA model. However, the treatment effect of Concerta was not obvious in the Noncaucasian group. Even though the Noncaucasian group had an effect of the same direction and the sample size was quite small, its magnitude was much smaller compared to the Caucasian group. In addition, the Wilcoxon nonparametric test was used to test the significance of the treatment effect. The results provided adequate evidence to support the claims proposed in the NDA.

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