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Name of Sponsor/Company	Ortho-McNeil Janssen Scientific Affairs, L.L.C.
Name of Finished Product	CONCERTA®
Name of Active Ingredient(s)	methylphenidate HCl

Protocol No.: CONCERTA-ATT-4080

Title of Study: Double-Blind, Randomized, Placebo-Controlled, Crossover Study Evaluating the Academic, Behavioral and Cognitive Effects of CONCERTA® on Older Children with ADHD

Study Name: OMJSA - The ABC Study

Principal Investigator: Multi-center, see Appendix 1.4.

Publication (Reference): None.

Study Period: 08 December 2008 to 26 June 2009

Phase of Development: 4

Objectives: The objective of this study was to evaluate the effect of CONCERTA® (methylphenidate HCl extended release tablets) versus placebo on a variety of measures evaluating academic performance, cognition, and social behavior in older children with Attention Deficit Hyperactivity Disorder (ADHD). Secondary objectives included characterizing the response during the Dose Adjustment Period and monitoring safety throughout the study.

Methods: This study was a multi-center, randomized, double-blind, 2-period, 2-treatment, crossover design conducted in the United States in children 9 through 12 years of age with ADHD. The study compared CONCERTA with placebo in a classroom setting, following individualized, open-label dose optimization, to evaluate the efficacy of CONCERTA in reducing academic impairment and improving social behavior and cognition.

Screening/Washout Phase: Subjects who were either not taking medication for ADHD, or were currently taking an ADHD medication (at less than the highest approved dose for their age, who demonstrated inadequate effect, and had no known tolerability experience that would preclude dose increase), completed a washout phase for at least 5 half-lives of the given medication before completing baseline assessments (approximately 3 to 6 days, depending on the medication). All subjects who successfully completed screening were eligible to enroll in the open-label portion of the study.

Open-Label Dose Adjustment Period: This period varied in duration from 1 to 6 weeks, depending on the response of the subject at each visit. During the Dose Adjustment Period, subjects initiated treatment with open-label CONCERTA at 18 mg/day on a once-a-day regimen and continued with incremental increases of 18 mg/day every 3 to 7 days until an optimal individualized dose was achieved, up to a maximum dose of 54 mg/day. Subjects who achieved an optimal dose during the Dose Adjustment Period were randomized and entered the Double-Blind Assessment Period provided they met the following additional criteria: 1) a CGI of "very much improved" or "much improved" and 2) Attention Deficit Hyperactivity Disorder Rating Scale (ADHD RS) -IV home version total and subscale scores ≤75th percentile for the subject's age and gender. In addition to those subjects who reached the criterion range of total and subscale scores ≤75th percentile for age and gender, continuation into the Double-Blind Assessment Period was also allowed for subjects who titrated to 54 mg/day or their maximum tolerated dose (if a one-time dose decrease by 18 mg had been required for tolerability, with a minimum dose of 18 mg/day) and whose ADHD RS-IV total or subscale scores were >75th percentile, but both total and subscale scores were <85th percentile for age and

gender. Each subject also completed a "practice" laboratory school day after reaching their optimal individualized dose.

Double-Blind Assessment Period: Subjects randomly assigned into the double-blind crossover sequences continued to take open-label CONCERTA at the optimal dose identified during the Dose Adjustment Period, except on the laboratory assessment days. The 2 full-day laboratory classroom sessions were scheduled within 6 weeks following successful completion of the Dose Adjustment Period. The 2 laboratory days were separated by at least 7 days. Subjects did not take their CONCERTA on the morning of a scheduled laboratory assessment day. On the scheduled laboratory assessment day, subjects were randomly assigned in a crossover fashion to 1 of 2 treatment sequences (CONCERTA/placebo or placebo/CONCERTA). Subjects received CONCERTA or placebo on the first laboratory school assessment day and the other treatment on the second laboratory assessment day. The final study visit was completed within 2 weeks of the last laboratory school day.

The laboratory classroom schools, affiliated with each study site, were staffed by qualified raters, chosen by the principal investigator based on skills and experience. Within these classrooms, raters were used consistently during the different laboratory assessment days and across cohorts of subjects evaluated in the laboratory schools. In addition, raters received training on study procedures at the investigators' meeting prior to the start of the study. These steps contributed to the overall consistency and quality of the data.

Number of Subjects (planned and analyzed): Planned: Approximately 90 children, 9 to 12 years of age, were planned for enrollment into the open-label treatment period. Upon successful titration to an optimal individualized dose, approximately 75 children were to be randomly assigned to 1 of 2 treatment sequences. The sample size was computed to be 33 randomly assigned subjects per dosing sequence. Analyzed: A total of 89 subjects were enrolled. The number of subjects analyzed was 89 for the safety analysis set and 68 for the efficacy (intent-to treat [ITT]) analysis set, with 34 subjects randomly assigned to placebo/CONCERTA, 34 subjects randomly assigned to CONCERTA/placebo treatment, and 21 subjects were not randomly assigned into double-blind treatment.

Diagnosis and Main Criteria for Inclusion: Males and females ages 9 to 12 years (inclusive) who **a)** had an ADHD diagnosis of all subtypes (except Not Otherwise Specified) as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR™), and supported by the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime version (K-SADS-PL); **b)** had a Children's Global Assessment Scale (C-GAS) rating of 41-70 inclusive (part of the K-SADS-PL); **c)** had a ADHD RS-IV total or subscale scores ≥90th percentile relative to the general population of children by age and gender; **d)** read and understood English; **e)** had the ability to attend school regularly, **f)** were willing to adhere to prohibitions and restrictions specified in protocol; and **g)** had informed consent signed by parent or legally acceptable representative (and gave assent if able to understand the nature of the study, depending on institutional policies). Subjects enrolled also could have had mild or moderate learning disabilities (LD), anxiety or depression, but not severe LD, anxiety, or depression. Among the exclusionary criteria, subjects could not have had an estimated full-scale IQ of 80 or below; a clinically significant risk of suicidality; known severe gastrointestinal (GI) narrowing or significant GI problems; or a history of hypersensitivity to methylphenidate or any of the components of CONCERTA.

Test Product, Dose and Mode of Administration, Batch No.: CONCERTA Batch Numbers: 0718437 (18 mg), 0718438 (36 mg), and 0718440 (54 mg); companion Placebo Batch Numbers: 0712540 (18 mg), 0517770 (36 mg), and 0517691 (54 mg).

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: Open-label dose titration to an optimized CONCERTA dose for up to 42 days during the Dose Adjustment Period; continued open-label CONCERTA dose for up to 28 days (1 month) before double-blind treatment with either CONCERTA or matching placebo for the 2 laboratory school days; at least 7 days open-label CONCERTA between laboratory school days; and up to 14 days open-label CONCERTA dosing until the final study visit. All dosing was once a day.

Criteria for Evaluation: Efficacy measures are listed below and grouped by time period when conducted.

Efficacy Measure	Description
Dose Adjustment Period (and Final Visit)	
ADHD RS-IV – Home Version	(ADHD Rating Scale-IV)
ADHD RS-IV – School Version	(ADHD Rating Scale-IV)
GAE	(Global Assessment of Effectiveness) - by parent
CGI-S	(Clinical Global Impressions Scale of Severity) - by clinician
CGI-I	(Clinical Global Impression - Improvement) - by clinician
CCI	(Child Conflict Index) – parent/caregiver completed it by phone interview with the site

Double-Blind Assessment Period	Details
PERMP attempted score	Permanent Product Math Test
SKAMP Scale - attention and deportment scores	Swanson, Kotkin, Alger, M-Flynn and Pelham
Grammar Task	Exploratory evaluation
THS-R	Test of Handwriting Skills (Revised)
Homework Tasks	Including GSRT (Gray Silent Reading Test) and exploratory evaluations ("homework" activity packet, including short story, root word, alphabetize list, multiple meanings, sentence completion, word search, and decode sentence)
TOVA sub-tests	Test of Variables of Attention
DIBELS	Dynamic Indicators of Basic Early Literacy Skills
Digit Span subtest from WISC-III-PI	Wechsler Intelligence Scale for Children – 3rd ed. Instrument for auditory working memory
WRAML Finger Windows	Wide Range Assessment of Memory and Learning; instrument for visual-spatial working memory

Final Study Visit	Details
Homework Questionnaire	Completed by parent
Treatment Preference and Satisfaction	Completed by parent
ADHD RS-IV – Home Version	Completed by parent
ADHD RS-IV – School Version	Completed by teacher
GAE	Global Assessment of Effectiveness – completed by parent
CGI-S	Clinical Global Impressions Scale of Severity – completed by clinician
CGI-I	Clinical Global Impression - Improvement – completed by clinician
CCI	Child Conflict Index – interview with parent/caregiver by study staff

Safety: Evaluations included adverse events (AEs), vital signs, body weight measurements, clinical laboratory testing at screening (CBC, complete chemistry panel, and liver function tests [LFTs]), urine drug screen, pregnancy test (if applicable), physical examinations, 12-lead electrocardiograms (ECGs), concomitant medications, and the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL) including items specifically dealing with suicidal thinking.

Statistical Methods: Demographic and baseline characteristics were summarized using descriptive statistics.

All efficacy endpoints collected during the Double-Blind Assessment Period were based on the ITT "as treated" analysis set (all subjects who were randomly assigned, received at least 1 dose of study drug, and had any primary efficacy data during the Double-Blind Assessment Period). All efficacy data collected during the Dose Adjustment Period were based on the dose adjustment analysis set (all subjects who received at least 1 dose of study drug and had any efficacy data during the Dose Adjustment Period). All subjects who took at least 1 dose of study drug and had safety data were included in the safety analysis set.

The primary efficacy endpoints in this study were the observed scores of the Permanent Product Math Test (PERMP) number attempted and PERMP number correct at 4 hours. These endpoints were analyzed using a repeated measures mixed model with terms for time, treatment, time-by-treatment interaction, subject, sequence, and period, and with appropriate contrast statement in the model. Hypotheses corresponding to these endpoints were tested using a Hochberg step-up procedure, which begins by adjusting the p-value for the least significant test and steps up to the most significant. Both tests must be significant at the 5% level in order to proceed.

The SKAMP-Deportment (SKAMP-D), SKAMP Composite, and SKAMP-Attention (SKAMP-A) endpoints were also analyzed using a repeated measures model. The remaining secondary efficacy endpoints were analyzed using a general linear mixed model. The hypotheses corresponding to these secondary endpoints were tested using a fixed-sequence gatekeeper approach. In this approach, a sequence of multiple hypotheses was tested one by one to maintain the overall Type I error rate at the 5% level. The fixed sequence proceeded with the first endpoint tested at the 5% level. If the null hypothesis was rejected, then the second endpoint was tested. Once the p-value for a test of any endpoint exceeded 5%, no unqualified statements were to be made for the remaining endpoints. The order of these tests is provided below:

3.SKAMP-D at 4 hours	15. DIBELS
4. SKAMP Composite score at 4 hours	16. Digit Span forwards
5. SKAMP-A at 4 hours	17. TOVA Omissions
6. TOVA ADHD Score	18. Grammar Task
7.TOVA RT	19. Homework task: short story with questions for comprehension
8 TOVA RT variability	20. Homework task: identify the root word
9. Finger Windows – backwards	21. Homework task: alphabetize list of words
10. Finger Windows – forward	23. Homework task: identify multiple meanings for words
11. TOVA Commissions	23. Homework task: complete sentences using words provided
12. Digit Span backwards	24. Homework task: word search
13. Reading comprehension (GSRT)	25. Homework task: decode the mystery sentence
14. TSH-R, handwriting skills standard score	--

Safety measures including AEs were summarized descriptively. The K-SADS-PL suicide total subscores at the final visit were compared by a paired t-test to the scores at the screening visit for overall subjects in the safety analysis set.

RESULTS:

SUBJECT POPULATION: Eighty-nine subjects comprised the safety analysis set in this study. Mean age for these subjects was 10.2 years, and there was a higher percentage of male (67.4%) than female (32.6%) subjects. Most subjects were not of Hispanic or Latino ethnicity (88.8%). Thirty-seven percent of all subjects had received previous medication for ADHD; however, the majority of subjects (70 of 89, 78.7%) were not currently taking medication for ADHD. The ADHD diagnosis subtype composition was predominantly 'combined' (56.2%). Thirty-five subjects (39.3%) were diagnosed with the ADHD subtype of 'inattentive' and 4 subjects (4.5%) were diagnosed with ADHD subtype of hyperactive-impulsive. Anxiety was reported in 8 subjects (9.0%) and depression in 1 subject (1.1%) at baseline. Learning disability (data available for 84 subjects) was absent in 60.7% of subjects and was present as mild or moderate in 36.9% of subjects. No subject upon study entry or at the final visit had evidence of suicidal thoughts on any of the 5 K-SADS-PL suicidal items.

EFFICACY RESULTS: Hypotheses for the 2 primary efficacy endpoints and 7 of the 23 secondary efficacy endpoints in the pre-specified fixed-sequence gatekeeper approach were statistically significant for the comparison between CONCERTA and placebo.

The difference between placebo and CONCERTA was statistically significant ($p<0.0001$) not only at the 4-hour primary efficacy endpoint (PERMP-attempted), but also from 1 hour until 12.5 hours for the PERMP-attempted, for the PERMP-correct, and for the SKAMP Composite. The onset of this treatment effect was as early as 1 hour after dosing (the first time point assessed) and was maintained over the last time point assessed (at 12.5 hours after dosing). Therefore, the offset of effect and duration of effect could not be definitively determined.

For the 23 secondary efficacy endpoints, the treatment difference between placebo and CONCERTA was statistically significant ($p\leq0.05$) for the SKAMP-D, SKAMP-A, TOVA ADHD score; the TOVA Reaction Time; the TOVA Reaction Time-Variability; and the Finger Windows Backwards. These assessments included evaluation of the subject's functioning for classroom behavior, attention, response times, and visual working memory. Although testing of the additional endpoints in the gatekeeper sequence was still

performed because of the pre-specified analysis plan, no unqualified statements about statistical significance were suggested and these endpoints are not discussed here.

The protocol provided an opportunity to explore how treatment satisfaction, as a yes/no dichotomized response reported by the parent/caregiver at the final visit, was related to several efficacy domains measured in this study. The majority of parents/caregivers were satisfied with CONCERTA treatment in each efficacy domain. At the final visit of the Dose Adjustment Period, 52 of 69 parents/caregivers (75.3%) responded that they were extremely or very pleased with CONCERTA for their child's ADHD symptoms, 81.2% responded that their child had benefitted "a lot" from CONCERTA, and 89.9% would recommend CONCERTA to someone else with this condition.

Subjects with the inattentive ADHD subtype showed similar decreases in impairment as measured by PERMP and SKAMP compared to decreases observed in subjects with the combined ADHD subtype. Subjects who were classified as learning disabled also showed similar improvement in PERMP and SKAMP scores as subjects who were classified as not having a learning disability during treatment with CONCERTA.

For the ADHD RS-IV home version, mean total scores decreased from baseline at all dose adjustment visits and at the final visit with open-label CONCERTA treatment, indicating improvement in the child's behavior. At both the final dose adjustment visit and the final visit for subjects that were optimized at each dose level, mean total scores were significantly decreased from baseline for subjects at all dose levels. For the ADHD RS-IV school version, mean total scores significantly decreased from baseline at the final dose adjustment visit ($p<0.0001$) and at the final visit ($p=0.0026$) for subjects who optimized at the 54 mg dose.

SAFETY RESULTS: CONCERTA at all doses (18 mg, 36 mg, and 54 mg) was safe and well-tolerated by the 9- to 12-year old subjects in this study. Among the 68 randomly assigned subjects, the final selected dose of CONCERTA was 54 mg per day for 50 subjects (73.5%); 36 mg per day for 12 subjects (17.6%); and 18 mg per day for 6 subjects (8.8%). A total of 82 subjects (92.1%) experienced a treatment-emergent adverse event (TEAE) during the course of the study. Most of these subjects (81 subjects, 91.0%) had TEAEs that were reported as mild or moderate in intensity. There were no unexpected TEAEs, SAEs, or deaths during the study. There were 2 subjects with TEAEs that resulted in study discontinuation during the Open-Label Dose Adjustment Period (Subject 201011: moderate nausea, vomiting, and lethargy and mild sore throat; Subject 201013: mild substance-induced mood disorder with depressive features, moderate irritability, and severe initial insomnia). There were 5 subjects (5.6%) who experienced 8 TEAEs that required a dose adjustment, but none were severe.

STUDY LIMITATIONS: 1) There is limited information on the response and associated variability for some of the efficacy measures, and it was anticipated that the study might be underpowered to achieve statistical significance for some of those endpoints. In consideration of this limitation, the statistical analysis plan provided for the combination of data from this study with data from a concurrent, companion study of identical design that was conducted independently. 2) Some efficacy measures are relatively new and have not been fully validated. 3) Only subjects who met the optimized dose criteria were randomized, thus CONCERTA non-responders were not evaluated in this study. By the final visit of the Dose Adjustment Period, 39 of 77 subjects (50.6%) met the optimized dose criteria and 38 subjects (49.4%) did not achieve all three optimized dose criteria. 4) The order of the endpoints in the gatekeeper was predetermined based on the expectation of achieving nominal p-values <0.05. More accurate estimates would have resulted in more endpoints fulfilling the gatekeeper criteria. 5) The preference in those parents who had no prior experience with pharmacologic treatment cannot be determined and, therefore, there was not a basis for comparison with current intervention.

CONCLUSION: The results of this study indicate that CONCERTA at dose levels of 18 mg, 36 mg, or 54 mg compared with placebo is effective in the treatment of ADHD across a broad range of measures in the 9- to 12-year-old population with various subtypes of ADHD. CONCERTA showed treatment effect at 1 hour after dosing that persisted through 12.5 hours after dosing compared to placebo.

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