SYNOPSIS

Name of Sponsor/Company: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Name of Finished Product: CONCERTA® Name of Active Ingredient(s): methylphenidate HCl	

Protocol No.: 12-101

Title of Study: A Multi-Center Randomized Parallel Group Study Evaluating Treatment Outcomes of CONCERTA® (Extended Release Methylphenidate) and Strattera™(Atomoxetine) in Children With Attention-Deficit/Hyperactivity Disorder

Investigators: 323 sites

Publication (Reference): Advances in Therapy. 22(5):498-512, 2005 Sep-Oct. and J Natl Med Assoc. 2005 Oct;97(10 Suppl):11S-16S.

Study Period: 04 July 2003 to 30 November 2003	**Phase of development:** 4

Objectives: The objective of this study was to evaluate and better understand treatment outcomes of CONCERTA and Strattera in patients with attention-deficit/hyperactivity disorder as evaluated by physicians and parents in a broad-based clinical use setting.

Methodology: This was a Phase 4 open-labeled parallel design multi-center study. Approximately 1,000 clinical sites were expected to enroll 6 patients with 4 patients randomly assigned to receive CONCERTA and 2 patients randomly assigned to receive Strattera. Specific study medication assignment was printed on the case report form (CRF). Study medication was to be taken once each day as dictated by the package insert supplied with the study kit. The study medication was to be titrated as considered appropriate by the physician following the patient. Investigators and parents completed efficacy assessments at the screening visit and 3 visits (1 telephone visit and 2 clinic visits) over a treatment period of 21 days. Adverse events, vital sign measurements, height, and weight were recorded.

Number of Subjects (planned and analyzed): 6000 planned; 1329 enrolled; 1323 analyzed.

Diagnosis and Main Criteria for Inclusion: Patients were enrolled in the study provided they satisfied the following inclusion criteria: 1. Male and female patients from the age of 6 to 12 years. 2. Patients who met the DSM-IV criteria for a primary diagnosis of ADHD of any subtype. 3. Patients may have been newly diagnosed with ADHD and not on treatment. 4. Patients must have had a score of 24 or higher on the ADHD Rating Scale (ADHD–RS) at screening. 5. Physician must have rated the patient as “Moderately ill” or worse on the Clinical Global Impression – Severity of Illness (CGI-S) at screening. 6. Patients may have been enrolled who were not receiving adequate treatment for ADHD. 7. The patient and parent must have been able to understand the information and complete the forms provided to them and must have been able to give written informed consent, and assent, where applicable.

Patients were excluded from participation in the study if they fulfilled any of the following criteria: 1. The patient was a female who had experienced menarche. 2. The patient had an eating or substance disorder or co-morbid psychiatric condition other than oppositional defiant disorder. 3. The patient had a history of seizure, tic disorder, mental retardation, severe developmental disorder (i.e. severe cerebral palsy, autism) or family history of Tourette’s Disorder. 4. The patient required medications as excluded by the package inserts for CONCERTA or Strattera. 5. The patient had been diagnosed with hyperthyroidism or glaucoma. 6. Patients who were known to be non-responders to treatments indicated for ADHD.

Test Product, Dose and Mode of Administration, Batch No.: The commercially available form of CONCERTA in commercially available dosage strengths was used in this study. Study drug was to be taken orally once each day. Patients randomly assigned to extended-release methylphenidate began treatment with 18 mg/day. The study medication was to be titrated as considered appropriate by the patient's physician.

SYNOPSIS (CONTINUED)

Reference Therapy, Dose and Mode of Administration, Batch No.: The commercially available form Strattera in commercially available dosage strengths was used in this study. Study drug was to be taken orally once each day. Patients randomly assigned to atomoxetine began treatment with 0.5 mg/kg/day. The study medication was to be titrated as considered appropriate by the patient's physician.

Duration of Treatment: 21 days

Criteria for Evaluation:

Efficacy: The physician's evaluation of treatment outcomes was assessed by the ADHD-RS and Clinical Global Impression-Improvement of Illness scale (CGI-I). The parent's evaluation of treatment outcomes was assessed by the Parent Satisfaction Questionnaire (PSQ).

Safety: Safety assessment consisted of the monitoring of adverse events, vital sign measurements, and body weight.

Statistical Methods: For ADHD-RS, the primary efficacy end point, observed and change from baseline measures for ADHD-RS total scores were summarized by descriptive statistics and analyzed by repeated measures of analysis of covariance. For CGI-I and PSQ, the secondary efficacy end points, CGI-I and each PSQ item separately were summarized by descriptive statistics and frequency distributions. Treatment effects were tested by chi-square statistics. Onset of effect was assessed by PSQ on Days 2 to 13. For ADHD-RS, the following subgroup analyses were performed: sex, race, and prior therapy with ADHD. The incidence of treatment-emergent adverse events was calculated, and actual and change from baseline values for vital sign measurements, height, and weight were provided.

SUMMARY - CONCLUSIONS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS: A total of 1,323 patients were randomly assigned to open-label study medication (850 CONCERTA, 473 Strattera). Data were available for 1,226 patients at the telephone visit at 1 week (after beginning study medication), 1,161 patients at the clinic visit at 2 weeks, and 1,093 patients at the clinic visit at the end of the study at 3 weeks. There was no record of whether patients completed the study and the 1,093 patients with information at the final visit include some patients who discontinued early. The mean (SD) age of patients in this study was 8.9 (2.06) years. The majority of patients were male (74.3%) and Caucasian (76.7%). The severity of ADHD was slightly greater in the CONCERTA group compared with the Strattera group; the mean total ADHD-RS scores at baseline were 39.9 and 38.6, respectively. The mean (SD) exposure was 21.8 (7.1) days and 21.3 (7.2) days for the CONCERTA and Strattera groups, respectively. The mean (SD) prescribed dose at the final visit was 32.7 (12.1) mg per day of CONCERTA and 36.7 (15.4) mg per day (1.1 mg/kg/day, SD 0.4) of Strattera.

EFFICACY RESULTS: Significantly greater improvement was observed in investigator evaluated ADHD-RS scores at each post baseline evaluation among patients receiving CONCERTA than among patients receiving Strattera. At the end of the study, mean decreases from baseline ADHD-RS scores were 20.4 for the CONCERTA group and 15.7 for the Strattera group ($P < 0.001$). A trend was noted toward greater between-treatment differences over time (2.77, 3.44, and 4.24 at Weeks 1, 2, and 3, respectively; $P < 0.001$). At all visits, the CGI-I responses considered "improved" were greater for the CONCERTA group compared with the Strattera group ($P < 0.001$). The mean estimated treatment effect was calculated for each day of assessment for the PSQ. The results were consistently and statistically significant in favor of CONCERTA; however, the magnitude of the treatment effect was a modest 2 units. At the end of the study parents were asked to compare their child's behavior at that point in time compared with behavior on previous medications for ADHD (PSG Question #11) and to indicate their overall level of satisfaction with the medication given their child during the study (PSQ Question #12); for both questions a higher proportion of subjects in the CONCERTA group were in the "better than" and "satisfied" ends of the scales, respectively, than the Strattera group ($P < 0.001$). Also, at the end of the study, parents were asked to indicate if they planned to continue their child on the same medication that was taken during the study. A slightly higher proportion of parents in the CONCERTA group (88.8%) than in the Strattera group (82.4%) responded "Yes" to this question ($p=0.003$). A subgroup analysis of ADHD-RS found CONCERTA to be more effective than Strattera in both males and females, in both Caucasians and non-Caucasians, and in both prior therapy naïve and experienced patients.

SAFETY RESULTS: The overall incidence of adverse events was similar for both treatment groups, 26.3% for CONCERTA compared with 28.3% for Strattera. Incidences of treatment related adverse events were also similar, 22.5% for CONCERTA compared with 25.6% for Strattera. Most adverse events were categorized as mild and not serious. A greater proportion of patients in the Strattera group experienced nausea, fatigue, somnolence, and sedation; insomnia and appetite decreased were more common in the CONCERTA group. Percentages of patient withdrawals attributed to adverse events were similar in both treatment groups, 4.8% for CONCERTA compared with 5.5% for Strattera. Serious adverse events were reported in 7 (0.8%) patients in the CONCERTA group and in 1 (0.2%) patient in the Strattera group. In 4 CONCERTA patients, the serious adverse events were considered by the

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investigator to be unrelated to the study medication (vomiting, ". . .agitated . . threatening . .", distress in 2 patients); in 2 CONCERTA patients (paranoia, crying , anger, and aggression in 1 patient; licking table in 1 patient) and in 1 Strattera patient (prolonged crying and fears of death for self and family) the investigator considered the relationship to study medication to be probable; and in 1 CONCERTA patient (mania) the investigator considered the relationship to study medication to be certainly related. Differences between treatment groups on vital signs, height and weight were small and clinically insignificant.

CONCLUSION: This large, prospective, randomized, open-label study compares once-daily CONCERTA and Strattera in children with ADHD. Although community-based studies often lack the control of randomized placebo-controlled trials, the results of this comparison demonstrate significantly greater symptom improvement with CONCERTA compared with Strattera at Weeks 1, 2, and 3, with a similar rate of adverse events.

Date of the report: Date of Clinical Study Report: 29 October 2004

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