

FINAL CLINICAL STUDY REPORT SYNOPSIS

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| <u>Name of Sponsor/Company</u> | Johnson & Johnson Pharmaceutical Research & Development | |
| <u>Name of Finished Product</u> | CONCERTA® | |
| <u>Name of Active Ingredient(s)</u> | Methylphenidate HCl | |
| Protocol No.: CR011557 | | |
| Title of Study: Clinical Study Report of An Open-Label, Dose-Titration, Long-Term Safety Study to Evaluate CONCERTA® at Doses of 36 mg, 54 mg, 72 mg, 90 mg, and 108 mg per day in Adults with Attention Deficit Hyperactivity Disorder | | |
| Study Initiation/Completion Dates: 08 May 2006 to 16 Aug 2007 | | Phase of Development: 3 |
| Objectives: The primary objective of this study was to evaluate the safety of CONCERTA® (methylphenidate HCl) extended-release tablets at doses of 36 mg up to 108 mg per day in adults with Attention Deficit Hyperactivity Disorder (ADHD). | | |
| <p>Methodology: This was a multi-center, open-label, dose-titration, long-term safety study in adult subjects diagnosed with chronic, symptomatic ADHD from childhood conducted in the United States. Approximately 450 subjects were to be enrolled for either a 6-month or 1-year duration, as assigned at screening. (Subjects enrolled during the first 3 months of the study were assigned to a 1-year duration; subjects enrolled after this time were assigned to a 6-month duration.) Subjects who completed Study 02-159 (randomized, double-blind, placebo-controlled study) could also be enrolled into Study 12-304.</p> <p>At the Baseline Visit, following a 7- to 14-day washout period during which all ADHD medication was discontinued, eligible subjects were evaluated: formal diagnosis of ADHD was confirmed using the Adult ADHD Clinical Diagnostic Scale (ACDS), Version 1.2, and subjects were to have met full diagnostic criteria for ADHD (any type: Combined, Predominantly Inattentive, or Predominantly Hyperactive-Impulsive) according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV). Inclusion criteria included Global Assessment of Functioning (GAF) Scale score of 41 through 60, inclusive, and Adult ADHD Investigator Symptom Rating Scale (AISRS) score of at least 24.</p> <p>Subjects began treatment with 36 mg of CONCERTA per day. During the Titration Period, the dose was increased in 18-mg increments every 7 (+/-2) days from 36 mg up to a maximum of 108 mg per day. Dose increase stopped once there was a 30% improvement on the AISRS score and a Clinical Global Impression-Improvement (CGI-I) score of 1 or 2. Dose reduction was required for resting heart rate >100 beats per minute (bpm), systolic BP >140 mmHg, or diastolic BP >90 mmHg (average of triplicate measurements). If a limiting adverse event occurred, the dose was reduced by 18 mg, and this was then the individualized dose. Subjects unable to tolerate the 36 mg dose were discontinued.</p> <p>Following the Titration Period, subjects returned monthly. Those who tolerated their individualized dose continued at that dose for the duration of the study. Subjects who did not tolerate a particular dose returned to the previous dose. Dose reduction could occur as necessary throughout the study to a minimum dose of 36 mg/day; subjects who were unable to tolerate the 36-mg dose were discontinued from the study. Dose increase could occur in 18-mg increments as needed to a maximum dose of 108 mg.</p> <p>Throughout the study, vital signs and weight were obtained, adverse events and concomitant medications were recorded, subject diaries were photocopied and reviewed, and medication compliance was assessed.</p> <p>Subjects included in the safety and efficacy analysis were those who enrolled and took at least 1 dose of study medication. This analysis was based on descriptive statistics only, due to the open-label, non-randomized nature of this study.</p> | | |
| Criteria for Evaluation: | | |
| <p>Efficacy: Throughout the study (Titration and Observation Periods), efficacy was evaluated by total scores and changes from baseline in AISRS and Global Assessment of Effectiveness (GAE). During the Titration Period, efficacy was evaluated by total scores and changes from baseline in CGI-I and Clinical Global Impression Severity (CGI-S).</p> <p>Safety: Safety was assessed by adverse events, vital signs, and weight monitored throughout the study. An electrocardiogram (ECG) was performed at screening, baseline, after each dose increase and at Months 3, 6, 9, and 12, or early withdrawal. In addition, each subject had a physical examination and fasting blood samples collected for clinical laboratory tests at screening, Month 6, and Month 12 or early withdrawal. Adverse events were classified</p> | | |

SYNOPSIS (CONTINUED)

according to the Medical Dictionary for Regulatory Activities (MedDRA) version 9.0. Adverse events and other safety parameters were assigned to dose category according to the dose at first occurrence; these summaries of safety parameters by dose category were not adjusted for duration of exposure. Cardiovascular and psychiatric adverse events of interest were identified by primary term and summarized.

SUMMARY - CONCLUSIONS

For this study, there were 560 enrolled subjects, of which 550 subjects were evaluable for safety and efficacy; 258 subjects consented to the 6-month study period and 292 subjects consented to the 12-month study period. Of the evaluable subjects, 15% (84 subjects: 38 CONCERTA and 46 placebo during double-blind treatment) previously participated in Study 02-159.

EFFICACY RESULTS:

Adults taking CONCERTA demonstrated improvement in all efficacy evaluations performed, according to descriptive statistics. AISRS total scores and GAE scores were evaluated during both the Titration and Observation Periods, while CGI-I and CGI-S subscale scores were evaluated only during the Titration Period.

- For AISRS total scores, the mean changes from baseline at the Final Titration Visit and the Final Study Visit indicated improvement during both the Titration and Observation Periods: Final Titration Visit -17.2 (SD 10.10; AISRS total score 21.1 [SD 10.80]; n=539) and Final Study Visit -18.7 (SD 11.96; AISRS total score 19.5 [SD 11.77]; n=438). The AISRS total score ranged from 0 to 54; lower scores indicate an improvement.
- Mean GAE scores improved during the Titration Period (not assessed at baseline): 0.7 (SD 0.83; n=538) at Titration Visit 1 to 1.8 (SD 0.94; n=538) at the Final Titration Visit. The mean GAE score at the Final Study Visit of the Observation Period was also 1.8 (SD 1.07; n=432). For the GAE, assessment of efficacy was evaluated based on a 4-point scale: 0=Poor, 1=Fair, 2=Good, 3=Excellent.
- The mean CGI-I subscale scores improved during the Titration Period (not assessed at baseline): 3.3 (SD 0.80; n=521) at Titration Visit 1 to 2.2 (SD 0.92; n=521) at the Final Titration Visit. For the CGI-I, assessment of improvement was evaluated based on a 7-point scale from 1 (very much improved) to 7 (very much worse).
- The mean CGI-S subscale score improved during the Titration Period: the mean CGI-S subscale score at baseline was 4.6 (SD 0.69; n=550) and the mean change from baseline at the Final Titration Visit was -1.4 (SD 1.04; CGI-S subscale score 3.2 [SD 1.05]; n=521). For the CGI-S, assessment of severity of illness was based on a 7-point scale from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).

SAFETY RESULTS:

- Overall, adverse events were reported by 504 subjects (91.6%); 451 subjects (82.0%) had drug-related adverse events, most of which were mild or moderate in intensity.
- There were no deaths during the study. Eight subjects (1.5%) experienced a total of 10 treatment-emergent serious adverse events, which included asthma exercise induced, non-cardiac chest pain, arthropod sting, subdural hematoma, diabetic ketoacidosis, syncope, pneumonia, asthma, fall, and spinal cord compression. No serious adverse event was considered related to study medication, and all serious adverse events except spinal cord compression resolved. Treatment was discontinued for 3 subjects with serious adverse events: non-cardiac chest pain on 36 mg of CONCERTA, subdural hematoma on 108 mg of CONCERTA, and fall and spinal cord compression in one subject on 108 mg of CONCERTA.
- One hundred subjects (18.2%) discontinued due to adverse events; adverse events causing withdrawal reported for equal to or greater than 2% of subjects included anxiety and insomnia.
- Adverse events that were reported in at least 20% of subjects included decreased appetite, headache, and insomnia. Adverse events that were reported in at least 10% but less than 20% of subjects included dry mouth, anxiety, heart rate increased, upper respiratory tract infection, nausea, and irritability. Dizziness, initial insomnia, feeling jittery, weight decreased, fatigue, blood pressure increased, nasopharyngitis, and tachycardia were adverse events experienced by at least 5% but less than 10% of subjects.
- Adverse events considered by the investigator to be related to the study drug that were experienced by greater than 10% of subjects included decreased appetite, insomnia, headache, dry mouth, and anxiety; 92 subjects (16.7%) discontinued due to drug-related adverse events.
- Adverse event time-to-onset analysis showed that the greatest occurrence of new adverse events was during the first time period, Day 1 to 30, with 453 of 550 subjects (82.4%) experiencing new adverse events. Thereafter, the occurrence of new adverse events was less than during the first time period.

SYNOPSIS (CONTINUED)

- A total of 167 subjects (30.4%) had a dose reduction due to an adverse event or increases above protocol-defined limits in heart rate or blood pressure. Heart rate increased was the most common adverse event leading to dose reduction of CONCERTA. Other adverse events leading to dose reduction that were reported for $\geq 2\%$ of subjects included blood pressure increased, irritability, feeling jittery, tachycardia, diastolic blood pressure increased, insomnia, anxiety, and dizziness.
- Overall, 137 (24.9%) subjects reported adverse events of special interest; 128 (23.3%) subjects had adverse events that were cardiovascular in nature and 10 (1.8%) subjects had adverse events that were psychiatric in nature. The most frequently occurring cardiovascular adverse events of special interest ($>4\%$ of subjects) were palpitations and blood pressure increased; psychiatric adverse events of special interest reported in more than 1 subject were mania (0.5%), aggression (0.4%), and paranoia (0.4%).
- No remarkable differences were observed in the mean change from Screening to the Final Visit for any hematologic or chemistry parameter evaluated. The mean increases in systolic and diastolic blood pressure were 2.6 mmHg and 1.9 mmHg, respectively. The mean increase in heart rate was 4.1 bpm at the Final Visit. This observation is consistent with known effects of stimulant medications. The mean decrease in weight from baseline to the Final Visit was 2.3 kg. There were no clinically relevant changes in ECGs.
- Minimal change was observed at the Final Visit for both the HAM-A (mean score at baseline, 6.4; final visit, 6.3) and HAM-D (mean score at baseline, 5.0; final visit, 5.2), indicating no change in anxiety and depression, respectively, during the study.

CONCLUSION:

CONCERTA extended-release tablets, in a dose range of 36 to 108 mg/day, were generally safe and well tolerated in adult subjects with ADHD in this study treated for up to 1 year. There were no unexpected safety or tolerability findings in this long-term study compared with findings from randomized, double-blind, placebo-controlled studies of shorter duration.

Issue Date of the Clinical Study Report: 19 February 2008

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