SYNOPSIS

Issue Date: 20 December 2010
Document No.: EDMS-ERI-13759082:1.0

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

Protocol No.: CONCERTA-ATT-3014

Title of Study: A Placebo-controlled, Double-blind, Parallel-group, Individualized Dosing Study Optimizing Treatment of Adults with Attention Deficit Hyperactivity Disorder to an Effective Response with OROS® Methylphenidate

NCT No.: ClinicalTrials.gov identifier: NCT00937040

Clinical Registry No.: CR015058

Investigator(s): Multicenter study in the Unites States (US)

Study Center(s): 35

Publication (Reference): None

Study Period: 22 July 2009 to 28 February 2010; database lock was 20 May 2010

Phase of Development: 4

Objectives: The primary objective of this study was to compare the response of attention deficit hyperactivity disorder (ADHD) in adults treated with OROS MPH or treated with placebo, as measured by a reduction in ADHD symptoms when following a dosing regimen that targeted a score of less than 18 on the Adult ADHD Investigator Symptom Rating Scale (AISRS v1.1). Secondary objectives were: to assess symptom improvement by utilizing additional assessments by investigator, by subject, by spouse/ significant other, or other adult in household, and with computerized systems; to compare investigator (AISRS v1.1) and subject ADHD Adult Self-Report Scale (ASRS v1.1) rating of ADHD symptoms, in order to test the utility of subject self-assessment when adjusting OROS MPH dose to achieve individualized response in adults with ADHD; and to assess safety. An exploratory objective was to collect information about sleep in adults with ADHD to increase understanding of the interrelationships among sleep, ADHD, and the use of OROS MPH in the treatment of ADHD.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group study conducted at multiple sites in the United States that evaluated OROS MPH by using an individualized dose in subjects with ADHD.

Screening/Baseline Period (Visit 1/1A): After subjects were allocated to random treatment assignment (Day 0) to receive either OROS MPH or placebo based on a computer-generated randomization schedule prepared by Johnson & Johnson Pharmaceutical Research & Development (J&JPRD), subjects completed screening/baseline assessments. Subjects started the first dose of study drug the day after randomization (on Day 1) and were enrolled in the study until Day 42. Subjects in the OROS MPH group took one 18 mg tablet/day, and subjects in the placebo group took 1 matching placebo tablet/day for the first week of treatment.

Dose Adjustment Period (DAP) comprised of 4 DAP visits (allowable visit window of ±2 days): The dose of study drug could have been adjusted at Visits 2, 3, 4, and 5 (Days 7, 14, 21, and 28, respectively). Daily dose options were 18 mg, 36 mg, 54 mg, or 72 mg, with selection based on investigator's consideration of efficacy and tolerability. The subject completed the ASRS-v1.1 symptom checklist and the 24-hour

symptom assessment, and also reported any adverse events (AEs) at each DAP visit. After the investigator completed the AISRS and CGI-I assessments at each DAP visit, the investigator determined the subject's daily dose. The dose was maintained or adjusted up or down by 18-mg steps, but the adjusted daily dose was not allowed by protocol to go below 18 mg/d or above 72 mg/d. At Visit 5, no dose increase was allowed. Subjects who were unable to tolerate 18 mg daily were discontinued from the study.

Assessment Period (14 days) starting following Visit 5: The subject continued on the dose of study drug prescribed at the last of the DAP visits, without dose adjustment. At the end of this period, subjects returned for the Final Evaluation Visit (Visit 6 [Day 42 with visit window of -2/+6 days]) to complete the final safety and efficacy assessments, including computerized testing. Visit 6 was scheduled to occur between 3 to 8 hours after the expected time of the subject taking their daily dose of study drug. For all subjects at a subset of study sites, the Final Evaluation Visit also entailed an Extended Assessment Day (EAD), where efficacy measures to determine the onset and duration of drug effect were completed. Any subject who discontinued from the study (after randomization) also completed the Final Evaluation Visit / Early Termination Visit procedures.

Number of Subjects (planned and analyzed): Planned: approximately 350 subjects. Analyzed: screened (447), randomized (357), safety analysis set (349), and intent-to-treat (ITT) analysis set (341).

Diagnosis and Main Criteria for Inclusion: Subjects enrolled were required to meet the following acceptance criteria: **1.** Males and females, 18 to 65-years old (inclusive). **2.** Clinical diagnosis of ADHD (any type: Combined, Predominantly Inattentive, or Predominantly Hyperactive-Impulsive) as defined by the DSM-IV criteria adapted for adults. With regard to the diagnosis, subjects had to**: a)** Describe a chronic course of ADHD symptoms from childhood to adulthood, with impairing symptoms present before age of 7 years, and continue to meet full Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. **b)** Have the diagnosis confirmed by using the Adult ADHD Clinical Diagnostic Scale version 1.2 and the MINI International Neuropsychiatric Interview to identify other entities in the differential diagnosis of ADHD. **c)** Have an AISRS score greater than 24. **3.** Be in general good health. **4.** Women had to be postmenopausal (for at least 12 months), surgically sterile, abstinent, or if sexually active, be practicing a highly effective method of birth control. **5.** Have signed an informed consent document. **6.** Had a negative urine drug screen. **7.** Be able to read and understand English.

Among the exclusionary criteria, subjects could not have had: a significant history of cardiovascular disease or cardiovascular disease detectable via electrocardiogram (ECG) putting participant at risk; history of diagnosis of substance or alcohol dependence or admission/hospitalization for rehabilitation for dependence; concurrent neurologic or psychiatric diagnosis; inability to swallow study drug whole or a preexisting narrowing of the gastrointestinal (GI) tract; pregnancy or breastfeeding; known allergies, hypersensitivity, or intolerance to OROS MPH or its excipients.

Test Product, Dose and Mode of Administration, Batch No.:
OROS MPH: 0904922 (18 mg), 0904924 (36 mg), and 0904925 (54 mg).
Placebo: 8MDO353-X (18 mg), 8NDO428-X (36 mg), and 8MDO352-X (54 mg).

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

Duration of Treatment: 42 days of double-blind treatment as planned by protocol: 28 days during the DAP and 14 days during the Assessment Period.

Criteria for Evaluation: ADHD symptoms and efficacy measures are listed below and grouped by study period when conducted.

Assessment Measure	Description
Screening/Baseline Period	
ACDS v1.2	(Adult ADHD Clinical Diagnostic Scale)
ADHD-RS-IV	(ADHD Rating Scale IV - designated observer)
AIM-A	(ADHD Impact Model™ - Adult)
AISRS v1.1	(18-item Core ADHD Symptom List)
ASRS Symptom Checklist v1.1	(ADHD Adult Self-Report Scale)
BRIEF-A	(Brief Rating Inventory of Executive Function – Adult Version)
CGI-S	(Clinical Global Impressions Scale of Severity)
Clinician's Global Assessment of Anxiety	-
Clinician's Global Assessment of Depression	-
Computerized Assessments (CNSVS)	(Cognitive/Executive Function)
DAS	(Dyadic Adjustment Scale)
ECG	(electrocardiogram)
EWPS	(Endicott Work Productivity Scale)
ESS	(Epworth Sleepiness Scale)
HAM-A	(Hamilton Anxiety Rating Scale)
HAM-D	(Hamilton Depression Rating Scale)
ISST-Plus	(InterSePT Scale for Suicidal Thinking – Plus)
Laboratory Assessments	(clinical hematology and chemistry, urine drug screen, urine pregnancy test)
MINI	(International Neuropsychiatric Interview-MINI)
PERMP [a]	(Permanent Product Math Test)
Physical Examination	-
PSQI	(Pittsburgh Sleep Quality Index)
Dose Adjustment Period	**Description**
Actigraphy	-
AISRS v1.1	(18-item Core ADHD Symptom List)
ASRS Symptom Checklist v1.1	-
CGI-I	(Clinical Global Impression – Improvement of ADHD)
ISST – Plus	(InterSePT Scale for Suicidal Thinking – Plus)
PERMP [a]	(Permanent Product Math Test)
Subject 24-h Symptom Assessment	-
Assessment Period	**Description**
Actigraphy	-
ADHD-RS-IV	(ADHD Rating Scale-IV)
AIM-A	(ADHD Impact Model™ - Adult)
AISRS v1.1	(18-item Core ADHD Symptom List)
ASRS Symptom Checklist v1.1	-
BRIEF-A	(Brief Rating Inventory of Executive Function – Adult Version)
CGI-S	(Clinical Global Impressions Scale of Severity)
CGI-I	(Clinical Global Impressions Scale – Improvement of ADHD)
Clinician's Global Assessment of Anxiety	-
Clinician's Global Assessment of Depression	-
Computerized Assessments - CNSVS [a,b]	(Same Cognitive/Executive Function tests as conducted at screening)
DAS	(Dyadic Adjustment Scale)
EWPS	(Endicott Work Productivity Scale)
ESS	(Epworth Sleepiness Scale)
HAM-A	(Hamilton Anxiety Rating Scale)
HAM-D	(Hamilton Depression Rating Scale)
ISST-Plus	(InterSePT Scale for Suicidal Thinking – Plus)
PERMP [a]	(Permanent Product Math Test)
PSQI	(Pittsburg Sleep Quality Index)
Exit Interview	-
Satisfaction with Treatment	-
Self-Assessments	-
Subject 24-h Symptom Assessment	-

[a] Assessment conducted at the EAD study sites only.
[b] Some computerized tests were performed one time, some repeated, for subjects at the EAD study sites.
KEY: ADHD=attention deficit hyperactivity disorder; AISRS=Adult ADHD Investigator Symptom Rating Scale; CNSVS=Central Nervous System Vital Signs.

Safety: Evaluations included AEs; vital signs, HAM-A, HAM-D, ISST-Plus, global assessments of anxiety and of depression) as evaluations of co-morbid psychiatric conditions, body weight, urine pregnancy test (if applicable), concomitant medications, and medical and psychiatric history. Clinical laboratory tests including the urine drug screen, 12-lead ECGs, and physical examinations were only conducted at Screening/Baseline to determine eligibility.

Statistical Methods:
Sample size: From a descriptive assumption (detectable mean difference between OROS MPH and placebo in change from baseline AISRS score of 4.1 points (±SD of 11.114) and the normality assumption, it was estimated that approximately 312 subjects (156 subjects for each treatment group) provided 90% power to determine if OROS MPH was statistically different from placebo at an overall alpha level of 5%. Assuming 10% non-evaluable subjects, approximately 350 adult subjects with ADHD were planned to be enrolled to achieve an ITT analysis set of 312 subjects. No formal sample size calculation was performed for the EAD subset comparison, although adequate sample size was estimated at 75-90 subjects based on pivotal studies in children with ADHD in simulated classroom settings of OROS MPH.

Analysis sets: The safety analysis set was defined as all subjects who took at least 1 dose of study drug. The ITT was defined as all subjects who were randomly assigned, received at least 1 dose of study drug, and had efficacy data after baseline (not including ASRS).

The primary efficacy endpoint (change in AISRS from baseline to endpoint) was analyzed and tested at a 2-sided 0.05 alpha level. Descriptive summaries of the total AISRS score and change from baseline AISRS score were presented for each visit by treatment group and by final OROS MPH dose. The statistical significance of the difference between OROS MPH and placebo treatment groups in the mean change from baseline AISRS total score at the endpoint was assessed using an analysis of covariance model (ANCOVA) with treatment and pooled study center as factors, baseline AISRS total score as covariate, and treatment-by-center interaction and treatment-by-baseline AISRS total score as interaction terms. Homogeneity of treatment effect across pooled study centers and baseline severity was assessed by testing the treatment-by-center interaction and treatment-by-baseline AISRS total score interaction terms, which were dropped from the model if not significant at the 0.10 alpha level. Assuming the model with only the main effects, the treatment effect of OROS MPH was estimated by computing the difference in least-squares means (LSM) of OROS MPH and placebo from the ANCOVA model. The statistical significance of the OROS MPH treatment effect was assessed by the p-value and the corresponding 95% confidence interval around the difference in LSM. The assumptions of normality and homogeneity of variance were investigated using residual diagnostics. If these assumptions were violated, appropriate nonparametric analysis was performed to compare the 2 treatment groups. Lastly, due to the anticipated dropout rate (approximately 30%), a sensitivity analysis of the primary efficacy endpoint was performed using the Baseline Observation Carried-Forward approach for subjects who dropped out early.

The secondary efficacy endpoints were analyzed and tested at a 2-sided 0.05 alpha level, using a fixed sequence gatekeeper approach. A sequence of multiple hypotheses (that OROS MPH would be superior to placebo) was tested individually, one after the other, in order to maintain the overall Type I error at 0.05. If the null hypothesis was rejected, then the next-in-sequence 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 sequence of testing, in order, is listed below. Analysis of other exploratory efficacy endpoints that were not part of the fixed gatekeeper testing sequence was performed at a 2-sided 0.05 level without adjustment for multiplicity. These were the 3 exploratory sleep variables (actigraphy, PSQI, and the ESS) and the EAD variables.

1	Reaction Time / Information Processing Speed Domain Score (derived from Stroop Test)	9	Satisfaction with treatment questionnaire (subject)
2	Vigilance Domain Score (derived from CPT)	10	Responder rate (defined as percentage of subjects with AISRS < 18 at final visit)
3	Cognitive Flexibility Domain Score (derived from SAT)	11	CGI-I
4	Symbol Digit Modalities Test (SDMT)	12	ADHD RS IV (Significant Other)
5	BRIEF-A (subject)	13	BRIEF-A Informant Report Form
6	AIM-A (subject)	14	DAS (designated observer)
7	EWPS (subject)	15	Satisfaction with treatment questionnaire (designated observer)
8	Dyadic Satisfaction subscale of the Dyadic Adjustment Scale (DAS) (subject)		

Additionally, as a secondary efficacy variable, the Responder rate for the AISRS (percentage of subjects with AISRS <18 at endpoint) was analyzed using the Cochran-Mantel-Haenszel (CMH) test controlling for

pooled center. Also a subgroup analysis of the change from baseline in AISRS as assessed by the investigator at endpoint was compared between the OROS MPH and placebo treatment groups separately by the subgroups of subjects rated at screening on the Global Assessment of Anxiety (none or mild) and Global Assessment of Depression (none or mild).

Descriptive statistics were utilized to summarize demographic and baseline characteristics, protocol deviations, concomitant medications, compliance, extent of exposure, evaluation of the dosing scheme, and safety.

RESULTS:

STUDY POPULATION: Three hundred forty-nine subjects comprised the safety analysis set in this study. The mean age was 35.8 years, and there was a slightly higher percentage of male (52.7%) than female (47.3%) subjects. None of the subjects was currently taking medication for ADHD. Most subjects did not have anxiety or depression (63.0% or 85.1%, respectively) at baseline. The ADHD diagnosis subtype composition was predominantly combined ADHD (81.1%), with the remaining subjects diagnosed with inattentive ADHD (17.5%) and hyperactive-impulsive ADHD (1.4%). The baseline mean AISRS score (37.4) was representative of moderate ADHD symptoms. The demographic and baseline characteristics were similar between treatment groups.

For subjects who reached an individually determined dose, 141 of 178 subjects (79.2%) randomized to OROS MPH and 138 of 179 subjects (77.1%) randomized to placebo completed the study. Considering both treatment groups, 78 (21.8%) subjects discontinued from the study. The most common reasons for discontinuation were lost to follow-up (6.7%) and withdrawal of consent (5.6%). Protocol deviations were reported in 13.8% of subjects. The most common deviation was noncompliance with study medication (defined as compliance <80% or >120% of intended doses), reported in 4.6% of subjects in each group during the Assessment Period. Despite this compliance deviation, during the Assessment Period 94.7% of subjects were compliant, and compliance was similar between treatment groups.

Duration of exposure was as planned. During the DAP, 174 subjects received OROS MPH for a mean of 26 days (mean average daily dose of 35.68 mg). During the Assessment Period, 142 subjects received OROS MPH for a mean of 15.0 days (mean average daily dose of 54.89 mg). As for the individualized final dose, although greater percentages of subjects in both treatment groups were at the 72 mg/d dose, the final placebo dose (72 mg/d level) was predominant (59.3% of subjects), compared with 39.1% of subjects at the OROS MPH 72 mg/d dose.

EFFICACY RESULTS: The primary efficacy variable, change from baseline to endpoint in AISRS total score, was statistically significant ($p<0.001$) by treatment for the ITT analysis set. At the other time points after baseline (Visits 2 through 6), these differences were also statistically significant by treatment ($p\leq0.034$). Greater mean decreases from baseline (improvement) were observed in the OROS MPH group than in the placebo group, indicating that subjects had reduction in ADHD symptoms after treatment with their individualized OROS MPH dose than with placebo. Of the subjects who reached the 72 mg/d dose (or the equivalent of matched placebo tablets) at Visit 5 (141 and 145 subjects, respectively), 56 subjects (39.7%) of the placebo group and 93 subjects (64.1%) of the OROS MPH group achieved the treatment goal of an AISRS score less than 18; and 75 subjects (53.2%) of the placebo group and 114 subjects (78.6%) of the OROS MPH group achieved a 30% decrease in AISRS score.

Since the first of the 15 major secondary efficacy variables (reaction time) did not meet the fixed gatekeeper sequence criteria of $p\leq0.05$, no unqualified statements about statistical significance for any of the secondary variables can be made. While nominal p-values were <0.05 for AISRS responder rates (AISRS total score <18, a score not warranting an ADHD diagnosis), at endpoint 45.0% and 30.8% of subjects in the OROS MPH and placebo groups, respectively, were responders (nominal p=0.008). These results did not meet the criteria of maintaining overall Type I error below 5% after adjusting for multiplicity.

Exploratory secondary efficacy variables did not achieve statistical significance with adjustments for multiplicity. Two domains of neurocognition (executive functioning and composite memory) had nominal p-values >0.05.The ASRS total score at endpoint had a greater decrease in score (improvement) in the

OROS MPH group than score in the placebo group (nominal p<0.001).When an agreement analysis of the AISRS and ASRS scores was performed, concordance of total scores (0.51 concordance correlation coefficient) and subset scores (0.45) were observed.

For the sleep assessments, the mean changes from baseline were not statistically significantly different by treatment for overall quality of sleep (PSQI scores); for less daytime sleepiness the between treatment ESS score nominal p-value was p=0.007. For actigraphy results at endpoint, there were no statistically significant differences by treatment for the sleep interval variables (e.g., sleep onset latency, total and average activity, and sleep efficiency %), or for the active interval or daily interval variables. For the PSQI, ESS, and quantitative, wrist-watch actigraphy results taken together, OROS MPH was similar to placebo treatment in its effect on the overall quality of sleep and on numerous aspects of sleep within the sleep, active, and daily intervals of full 24-hour days for the duration of the study.

The Extended Assessment Day provided data to evaluate the time course of study drug effect for 4 neurocognition domains, the PERMP Attempted, and PERMP Correct using time points starting before dosing and following dosing from 1 through 12 hours. These assessments did not provide evidence of treatment effect in this study, and no conclusions about time course are drawn.

SAFETY RESULTS: The safety and tolerability of OROS MPH at all daily doses (18, 36, 54, and 72 mg) for 18- to 65-year old, male and female subjects in this study did not identify any clinically meaningful difference from prior studies.

The frequencies of treatment emergent adverse events (TEAEs) in this study were 72.4% in the OROS MPH group and 49.7% in the placebo group. There were no unexpected TEAEs or SAEs, and no deaths. Headache was the most commonly reported TEAE in both treatment groups (19.0% and 11.4% in the OROS MPH and placebo groups, respectively). The majority of subjects in both treatment groups were reported with mild or moderate TEAEs; 9 subjects were reported with severe TEAEs (3.4%, OROS MPH; 1.7%, placebo). Treatment-emergent AEs, considered by the investigator to be study drug-related, were observed in 61.5% and 32.0% of subjects in the OROS MPH and placebo groups, respectively. Thirteen subjects discontinued from the study because of a TEAE (4.6%, OROS MPH; and 2.9%, placebo), including 1 placebo subject with an SAE of suicidal ideation. Vital sign results demonstrated changes that were within normal expected variations. No subject in the OROS MPH or placebo group experienced severe symptoms of anxiety or depression at the Final Visit. The ISST-Plus Part I and Part III scores demonstrated no increase in suicidal thinking between Baseline and Final Visits.

STUDY LIMITATIONS: 1) There is limited information on the response and associated variability for 4 sponsor-designed, secondary efficacy measures. 2) Unanticipated failures in data capture and/or transfer occurred during administration of computerized assessments completed by a subset of subjects. Also, at 7 sites (including 2 Extended Assessment Day sites), procedures to set up the computerized CNSVS assessments were not performed correctly at baseline for all subjects, leading to missing data. Thus, fewer subjects had data available for analysis. Statistical significance was not attained; no unqualified statistical statements could be made for any of the secondary efficacy variables.

CONCLUSIONS: The results of this Phase 4 study indicate that OROS MPH at the individualized daily dose (chosen from options of 18 mg, 36 mg, 54 mg, and 72 mg) compared with placebo is effective in the treatment of ADHD when assessed by the AISRS and ASRS in the 18- to 65-year old adult population (males and females) with various subtypes of ADHD. All 4 individualized dose levels of OROS MPH were associated with incidence and severity of AEs generally consistent with previous studies. This study showed that achieving a balance of efficacy and safety considerations with treatment was possible across the spectrum of all 4 final OROS MPH doses.