1. SYNOPSIS

Name of Sponsor/Company Johnson & Johnson Pharmaceutical Research & Development ***Name of Finished Product:*** CONCERTA® ***Name of Active Ingredient:*** methylphenidate HCl	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of Study: A Placebo-Controlled, Double-Blind, Parallel-Group, Dose-Titration Study to Evaluate the Efficacy and Safety of CONCERTA® in Adults with Attention Deficit Hyperactivity Disorder at Doses of 36 mg, 54 mg, 72 mg, 90 mg, or 108 mg per day.

Coordinating Investigator: Lenard Adler, M.D. - [redacted] Harbor Healthcare System Veterans' Affairs MedicalCenter (VANYHHS), [redacted] USA

Publication (reference): Not applicable

Study Period: ***Phase of Development:*** 3
Date of first enrollment: 8 May 2006
Date of last completed: 21 November 2006

Objectives: The primary objective of this study was to evaluate the efficacy and safety of CONCERTA® (methylphenidate HCl) extended-release tablets at five dose levels (36 mg, 54 mg, 72 mg, 90 mg, or 108 mg per day) compared to placebo in adults with Attention Deficit Hyperactivity Disorder (ADHD).

Methodology: This was a randomized, placebo-controlled, double-blind, parallel-group, dose-titration study conducted in the US at 27 investigative sites. At screening, the diagnosis of ADHD (DMS-IV criteria) was established through clinical evaluation by the investigator. The subject must have described a chronic course of ADHD symptomatology from childhood to adulthood. Previous formal diagnosis and/or treatment were not required.

A total of 229 adult subjects were enrolled. At the Screening Visit, subjects being treated with medication for ADHD washed out from all ADHD medication for seven to 14 days prior to the Baseline Visit. Subjects who received atomoxetine HCl returned for their Baseline Visit within a ten to 14 day window. At the Baseline Visit, the subject's diagnosis of ADHD was confirmed by the Adult ADHD Clinical Diagnostic Scale (ACDS) Version 1.2. The subject had to meet 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) with symptoms present before age seven years and must have continued to meet DSM-IV criteria at the time of assessment. At the Baseline Visit, the eligible subject and the investigator completed rating scales assessing the subject's behavior while taking no medication for ADHD. The Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D) were administered at the Baseline Visit to identify significant psychiatric co-morbidities that would exclude the subject. Subjects with a Global Assessment of Functioning (GAF) Scale score of 41 to 60, inclusive, and an Adult ADHD investigator Symptom Rating Scale (AISRS) score of 24 or greater at the Baseline Visit were eligible to enter the study. At the Baseline Visit, eligible subjects were randomized in a 1:1 ratio to either CONCERTA or placebo.

All subjects initiated treatment with 36 mg of study medication and continued with incremental increases of 18 mg every seven days (+/- 2 days) until an individualized dose was achieved, defined as when: AISRS decreased by 30 percent from baseline and a Clinical Global Impression-Improvement (CGI-I) rating of one (very much improved) or two (much improved) was achieved, or titration to the maximum dose of 108 mg was achieved. If

a limiting adverse event occurred, the dose was titrated downward by 18 mg. This dose was then the subject's individualized dose. Titration downward was required for resting heart rate >100 beats per minute (bpm), systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg (average of triplicate measurements), and for adverse events at the discretion of the investigator. Subjects could have their dose titrated down once during their participation in the study, and their dose could not be up-titrated again for the duration of their participation in the study. Subjects unable to tolerate the initial dose of 36 mg were discontinued from the study.

Once an individualized dose was achieved, subjects remained on that dose for the remaining duration of the titration period and for the two weeks prior to the Final Visit/Two Week Efficacy Assessment Visit. Subjects were to complete all study visits regardless of the visit at which their individual dose was identified. Table 1-1 summarizes the treatment schedule for the study. At the Baseline Visit, subjects were randomized and instructed to begin study medication the following day.

Table 1-1: Treatment Schedule

Visit	Screening Visit[a]	Baseline Visit	Titration Visit 1 [b]	Titration Visit 2 [b]	Titration Visit 3 [b]	Titration Visit 4 [b]	Titration Visit 5 [b]	Final Visit/ 2 Week Efficacy Assessment
Study Day	Day	Day[a] 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 49
	-14 to -7		+/-2 days	+/- 2 days	+/-2 days	+/- 2 days	+/- 2 days	+/- 2 days
Dose Evaluation	Washout from ADHD medication 7-14 days as needed		36 mg Placebo	54 mg Placebo	72 mg Placebo	90 mg Placebo	108 mg Placebo	Individualized Dose

a: Subjects that were being treated for ADHD at screening had to washout from all ADHD medication for seven to 14 days. Subjects on atomoxetine HCl returned for Baseline within a 10 to 14 day window.
b: Doses were titrated until the individualized dose was achieved. All visits were required, even if a subject had achieved an individualized dose.

Number of Subjects (planned and analyzed): Approximately 260 subjects were to be screened to enroll 208 evaluable subjects. A total of 348 subjects were screened and 229 subjects were enrolled.

Diagnosis and Main Criteria for Inclusion: Clinical diagnosis of ADHD, age 18 to 65 years at the Screening Visit and at least the state-specific age of majority.

Test Product, Dose and Mode of Administration, Batch Number: CONCERTA (methylphenidate HCl) extended release over-encapsulated tablets, 36 mg and 54 mg taken orally, once daily. All dose levels in the study (36 mg, 54 mg, 72 mg, 90 mg or 108 mg) were supplied as an appropriate combination of 36 and/or 54 mg tablets and/or matching placebo tablets. Batch numbers: 0541990 (36 mg tablets) and 0541991 (54 mg tablets).

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Duration of Treatment: The titration period was designed to take up to 35 days followed by a 14-day efficacy assessment period. Subjects in the placebo group received placebo for the duration of the study. Subjects randomized to CONCERTA began treatment at 36 mg and received incremental increases of 18 mg every seven days (+/- 2 days) until their individualized dose was achieved or the maximum dose of 108 mg was achieved. Subjects could be on study drug for a total duration of 51 days.

Reference Therapy, Dose and Mode of Administration, Batch Number: Over-encapsulated OROS placebo tablets, identical in appearance to the CONCERTA dosage forms (36 mg or 54 mg) taken orally, once daily. Batch number: 0517770

Criteria for Evaluation:
Efficacy:
Primary efficacy variable: change from baseline in the AISRS total score as assessed by the investigator at the Final Visit (last observation carried forward; LOCF)

Secondary efficacy variables:

In order to protect the Type I error rate, a pre-defined closed, stepwise procedure was used. In this procedure, the secondary endpoints were analyzed sequentially and were only considered statistically significant at the 0.05 level if the endpoint was individually significant at the 0.05 level and previous endpoints in the hierarchy were significant at the 0.05 level. The secondary endpoints were assessed in the following order:

- CGI-I last score provided during the study
- Conners' Adult ADHD Rating Scale-Self-Report: Short Version (CAARS-S:S) total score change from baseline (last score provided during the study)
- Responder defined as a subject who has a 30% improvement (without rounding) in the AISRS score from baseline and has a CGI-I of much improved or very much improved (last score provided during study)
- Sheehan Disability Scale change from baseline score for the "work" question
- CGI-Severity (CGI-S) last score provided during the study
- ADHD Impact Module for Adults (AIM-A™) work/home/school domain (change from baseline)

Secondary efficacy variables excluded from the hierarchy included:

- Change from baseline in the AISRS as completed by the investigator at each Titration Visit
- Change from baseline in the AISRS as completed by the investigator at the end of the study or the last score provided during the study, based upon mg/kg dosing groups (mg/kg ranges for groups to be determined)
- Global Assessment of Effectiveness (GAE) measured at each Titration Visit, and at the end of the study or the last score provided during the study
- CGI-I measured at each Titration Visit
- Change from baseline of the CGI-S measured at each Titration Visit
- Change from baseline in the Sheehan Disability Scale, Social Life and Family Life subscales, at the end of the study
- Change from baseline in total score of the CAARS-S:S measured at each Titration Visit

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- Change from baseline in the Q-LES-Q-SF measured at the end of the study.
- Change from Baseline in the AIM-A at the end of the study
- Responder defined as a subject who had a 30% improvement in the AISRS score from baseline and had a CGI-I of ≤ 2 (either very much improved or much improved) measured at each Titration Visit
- Responder defined as a subject who had a 30% improvement in the AISRS score from baseline measured at each Titration Visit, and at the end of the study or the last score provided during the study
- Responder defined as a subject who had a score on the CGI-I of ≤ 2 (either very much improved or much improved) measured at each Titration Visit, and at the end of the study or the last score provided during the study

Safety: Safety assessments consisted of monitoring adverse events and vital signs throughout the course of the study. Each subject had an electrocardiogram (ECG) performed at screening, baseline, at the visit subsequent to each upward dose titration, and at the Final Visit/Two Week Efficacy Assessment Visit. Physical exams and laboratory tests were performed at screening and the Final Visit/Two Week Efficacy Assessment Visit. The HAM-A and HAM-D were administered at the Baseline Visit and Final Visit/Two Week Efficacy Assessment Visit.

Statistical Methods: The Intent-to-Treat (ITT) Population included all subjects randomized and dispensed study medication. The Safety Population included all subjects who took at least one dose of study medication. The ITT Population was used for the efficacy analyses and the Safety Population for the safety analyses.

For the primary efficacy variable, analysis of covariance (ANCOVA) with change from baseline as a dependent variable, treatment and study site as factors, and the corresponding baseline score as a covariate was used to evaluate the difference between All CONCERTA and placebo.

For the secondary efficacy variables of AISRS, CGI-S, and CAARS-S:S, and the Quality-of-Life measures from the Sheehan Disability scale, Q-LES-Q-SF total score and AIM-A, ANCOVA with change from baseline score as a dependent variable; treatment group and study site as factors and the corresponding baseline score as a covariate was used to evaluate the difference between All CONCERTA and placebo.

The secondary efficacy variables, GAE and CGI-I, were analyzed using analysis of variance (ANOVA) with treatment group (All CONCERTA, placebo) and study site as factors.

Three Responder analyses were performed using a Cochran-Mantel-Haenszel test comparing responder status (responder vs. non-responder) by treatment group (All CONCERTA, placebo) stratified by study site.

Analyses of data involving changes from baseline to endpoint used the last observation carried forward (LOCF) approach. For the primary efficacy analysis, for subjects who had no post baseline AISRS assessment, the baseline observation was carried forward (BOCF); no change was assumed.

To protect the Type I error rate, a pre-defined closed, stepwise procedure was used as described above.

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Safety: Adverse events were classified according the Medical Dictionary for Regulatory Activities (MedDRA) dictionary with the incidence of adverse events tabulated by treatment group (All CONCERTA, placebo), primary system organ class, and MedDRA preferred terms. Additional summaries displayed adverse events by the associated CONCERTA dose and placebo. Narrative summaries were provided for serious adverse events and adverse events leading to discontinuation. Descriptive statistics of ECG and laboratory tests were summarized by treatment group (All CONCERTA, placebo) and by the associated CONCERTA dose at each visit.

Weight and vital signs, HAM-A and HAM-D were summarized by treatment group (All CONCERTA, placebo) and by the associated CONCERTA dose at each visit.

Summary – Conclusions:

Subject and Treatment Information:

Overall, 229 subjects were randomized to treatment (113 to CONCERTA® and 116 to placebo). Three subjects did not meet inclusion/exclusion criteria, but were randomized. These subjects were randomized to CONCERTA but did not receive study medication. Therefore, 226 subjects were included in the ITT Population and 226 subjects were included in the Safety Population, 110 and 116 in the CONCERTA and placebo groups, respectively. The majority of the ITT Population (N=226) was male (56.2%), white (86.3%), non-Hispanic (88.1%) and had an ADHD subtype of combined (80.1%). The mean age of subjects was 39.0 years.

Efficacy Results:

Table 1-2 summarizes the efficacy endpoints for the ITT Population. Adult subjects treated with CONCERTA had a statistically significant improvement in the AISRS total score from baseline to endpoint, the primary efficacy variable, compared to subjects receiving placebo, p=0.012. CONCERTA was statistically significantly superior to placebo for the secondary endpoints: CGI-I score at endpoint, p=0.008; improvement in the CAARS-S:S total score from baseline to the endpoint, p=0.029; for the definition of Responder; subjects with both a 30% improvement in AISRS score and a CGI-I rating of much or very much improved, at endpoint, p=0.009. By virtue of a step-down procedure that controlled the overall Type I error rate, CONCERTA showed greater improvement, but not a statistically significant difference, for the following secondary endpoints: the Work subscale of Sheehan Disability Scale at endpoint, p=0.397; the CGI-S score from baseline to endpoint, unadjusted, nominal p-value of 0.009; the AIM-A Work/Home/School Domain score from baseline to endpoint, unadjusted, nominal p-value of 0.016.

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Table 1-2: Summary of Efficacy Endpoints at Final Visit (LOCF) – Intent-to-Treat Population

Variable[a]	All CONCERTA	Placebo	p-Value[b]
Primary			
AISRS: Change from Baseline			
N	110	116	
LSMean ± SEM	-10.6 ± 1.09	-6.8 ± 1.06	0.012
Secondary			
CGI-Improvement:			
N	103	115	
LSMean ± SEM	3.0 ± 0.11	3.4 ± 0.11	0.008
CAARS-S:S Total Score: Change from baseline			
N	102	115	
LSMean ± SEM	-12.7 ± 1.45	-8.3 ± 1.37	0.029
Responder defined as: Subjects with 30% improvement in AISRS Score and a CGI-Improvement rating of much or very much improved, % (n/N)	36.9 (38/103)	20.9 (24/115)	0.009
Sheehan Disability Scale - Work: Change from baseline			
N	90	99	
LSMean ± SEM	-1.3 ± 0.25	-1.0 ± 0.24	0.397
CGI-Severity: Change from baseline			
N	103	115	
LSMean ± SEM	-0.9 ± 0.11	-0.5 ± 0.10	Not Tested[c]
AIM-A: Work/Home/School Domain: Change from baseline			
N	94	107	
LSMean ± SEM	16.5 ± 2.37	8.6 ± 2.24	Not Tested[c]

a: Lower values indicate greater improvement for AISRS, CGI-Improvement, CAARS-S:S Total Score, Sheehan Disability Score- Work, and CGI-Severity. Higher values indicate greater effectiveness for AIM-A Work/Home/School Domain.

b: Tests for significant treatment differences for AISRS total score, CAARS-S:S Total Score, Sheehan Disability Score - Work, CGI-Severity, and AIM-A Work/Home/School Domain with ANCOVA model. Tests for significant treatment differences for CGI-Improvement with ANOVA model. Tests for significant treatment differences for responder analysis with Cochran-Mantel-Haenszel row means score.

c: Formal testing was not performed due to multiple-testing hierarchy. Nominal p-values: CGI-Severity nominal p-value = 0.009, AIM-A Work/Home/School Domain nominal p-value = 0.016.

Note: The number of subjects reported for each variable is not the same because the baseline value was carried forward to final visit only for the AISRS score.

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Efficacy Results Continued:

d: A post hoc examination of the response rate by dose at which a response first occurred showed that for each dose level, the proportion of adult subjects with ADHD achieving a protocol-defined response was substantially higher on CONCERTA than on placebo. In addition, these data indicate that CONCERTA reduces the symptoms and severity of ADHD across the dose range of 36 to 108 mg per day; 13% of subjects first responded as doses above 72 mg/day (90 mg/day or 108 mg/day). The cumulative number of responders increased with exposure to increasing doses of CONCERTA up to 108 mg/day.

Safety Results:

Study medication was well tolerated. Overall, adverse events were reported by 93 (84.5%) subjects in the All CONCERTA group compared with 74 (63.8%) in the placebo group. No serious treatment emergent adverse events and no deaths were reported in either treatment group. The most commonly reported adverse events reported more frequently in CONCERTA-treated subjects than placebo-treated subjects included decreased appetite (25.5%), headache (25.5%), dry mouth (20.0%), anxiety (16.4%), nausea (12.7%), blood pressure increased (10%), insomnia (9.1%), initial insomnia (7.3%), heart rate increased (7.3%), bruxism (6.4%), irritability (6.4%), and muscle tightness (6.4%). Sixteen (14.5%) and 6 (5.2%) subjects in the All CONCERTA and placebo groups, respectively, discontinued from the study due to adverse events. The mean change in weight from baseline to the Final Visit (LOCF) was -2.2 kg in the All CONCERTA group and +0.2 kg in the placebo group.

The mean change from baseline to Final Visit (LOCF) in systolic and diastolic blood pressure was similar for the CONCERTA and placebo groups, -1.2 mmHg compared to –0.5 mmHg, and +1.1 mmHg compared to +0.4 mmHg, respectively. The mean change from baseline to Final Visit (LOCF) in pulse was greater for the CONCERTA group compared to the placebo group, +3.6 bpm and -1.6 bpm, respectively.

Based on ECG data, a higher percentage of subjects in the All CONCERTA group had a maximum post-baseline heart rate of >100 beats/min (n=5, 4.9%) than in the placebo group (n=1, 0.9%). Similarly, in the All CONCERTA group, the percentage of subjects with a post-baseline increase in heart rate of >25% (n=32, 31.4%) was greater than the percentage of subjects in the placebo group (n=16, 13.9%). There was no evidence of a treatment effect in any of the other ECG interval assessments including corrected QT.

Conclusions:

CONCERTA extended-release tablets, in a dose range of 36 to 108 mg/day, demonstrated efficacy in the treatment of adult subjects with ADHD, as measured by the AISRS, CGI-I, and CAARS-S:S scores and the Responder analysis (as defined by the AISRS and CGI-I scores). A post hoc examination of the response rate by dose at which a response first occurred showed that for each dose level, the proportion of adult subjects with ADHD achieving a protocol-defined response was substantially higher on CONCERTA than on placebo. The cumulative number of responders increased with exposure to increasing doses of CONCERTA up to 108 mg/day.

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Conclusions Continued: Study medication was well tolerated. No serious treatment emergent adverse events and no deaths were reported in either treatment group. No clinically relevant changes in blood pressure, heart rate, or ECGs were observed.		
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