SYNOPSIS

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Name of Sponsor/Company Janssen Ortho Canada Inc.
Name of Finished Product CONCERTA®
Name of Active Ingredient(s) Methylphenidate HCl

Protocol No.: CRO017179

Title of Study: A Randomized, Open-label, Single-dose, Three-way Crossover Study to Determine the Relative Pharmacokinetic Profile of Oral Doses of CONCERTA® Tablets, Ritalin-SR® Tablets and Novo-Methylphenidate ER-C® Tablets under Fasted Condition in Healthy Subjects

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Publication (Reference): None

Study Period: 06 MAY 2010 to 08 JUN 2010

Screening: 06 – 13 MAY 2010
Treatment Period 1: 14 – 16 MAY 2010
Treatment Period 2: 20 – 22 MAY 2010
Treatment Period 3: 28 – 30 MAY 2010
Telephone Follow-up: 29 MAY – 08 JUN 2010

Phase of Development: Phase 1

Objectives: The primary objective of this study was to characterize the rate, pattern and extent of absorption of methylphenidate from CONCERTA®, Ritalin-SR® and Novo-Methylphenidate ER-C® tablets in healthy adult volunteers under fasting conditions.

The secondary objective of this study was to assess the safety and tolerability of all products in healthy adult volunteers under fasting conditions.

Methods: This was a single-centre, randomized, open-label, single-dose, three-way crossover study in 30 healthy adult volunteers. The study consisted of two phases: screening and treatment, including post-treatment follow-up. Screening took place up to 21 days prior to study drug administration. The treatment phase consisted of three 2-night inpatient treatment periods. Eligible subjects were assigned to one of six treatment-sequence groups. Subjects were administered a single oral dose of 54-mg CONCERTA®, 3x20-mg Ritalin-SR®, and 54-mg Novo-Methylphenidate ER-C® (one study drug administration at each of the three treatment periods). At each treatment session, serial pharmacokinetic (PK) sampling and safety assessments (including vital signs, 12-lead electrocardiogram (ECG), clinical laboratory tests, adverse events (AEs)) were conducted up to 24 hours post- washout period between each study drug administration was from 3 to 14 days. A telephone follow-up occurred between 7 and 14 days after the last drug intake.

Number of Subjects (planned and analyzed): Approximately 30 healthy subjects were to be enrolled into this study to ensure that at least 24 subjects completed the study. Twenty four subjects completed all treatment sessions as per protocol and were included in the PK analyses. In addition to the main PK analysis, a supplementary analysis was conducted which excluded a single subject who vomited within 24 hours after dosing. All 30 randomized subjects received at least one treatment and were included in the safety analysis.

Diagnosis and Main Criteria for Inclusion: Healthy subjects between the ages of 18 to 45 years with a body mass index (BMI) between 18.0 and 30.0 kg/m² (inclusive), body weight of not less than 50.0 kg, and blood pressure between 90 and 140 mmHg systolic and 50 and 90 mmHg diastolic were enrolled in this study. Subjects were required to be nonsmokers (or did not use nicotine-containing substances within 2 months of study entry) who did not take prescription or nonprescription medication except for birth control, acetaminophen, or hormonal replacement therapy. Female subjects who were pregnant or wished to become pregnant, or lactating mothers were not enrolled.

Study Treatments, Dose and Mode of Administration, Batch No.:

Test product: Novo-Methylphenidate ER-C® (Teva Canada Ltd., Toronto, ON Canada)

Dose: One 54-mg tablet
Mode of administration: oral
Lot number: 35308907A

Reference product A: CONCERTA® (Janssen-Ortho Inc., Toronto, ON Canada)

Dose: One 54-mg tablet
Mode of administration: oral
Lot number: OBG411

Reference product C: Ritalin-SR® (Novartis Pharmaceuticals Canada Inc., Dorval, QC Canada)

Dose: 3x 20-mg tablets
Mode of administration: oral
Lot number: FGG

Duration of Treatment: Total duration of the study, including the screening phase, treatment phase, washout periods, and follow-up was up to 67 days (approx 10 weeks) for each subject.

Criteria for Evaluation:

Pharmacokinetics:

Plasma samples were analyzed for d- & l- methylphenidate (MPH) concentrations, as well as the metabolite d/l-ritalinic acid (RA). For each subject, the following PK parameters were estimated using non-compartmental analysis:

- Maximum plasma concentration (C_{max})
- Time to reach the maximum plasma concentration (T_{max})
- Minimum plasma concentration (within 24 hours after dosing) ($C_{min)}$
- Time to reach the minimum plasma concentration (within 24 hours after dosing) (T_{min})
- Area under the concentration-time curve (AUC) over the time interval time 0 to time 24 (AUC_{0-24})
- AUC from time 0 to the time of the last quantifiable concentration (AUC_T)
- Partial AUC up to median T_{max} of reference product ($pAUC_{Tmed}$)
- Area under the plasma concentration-time curve from time 0 to infinite time (AUC_{inf}), calculated as the sum of AUC_T and Clast/λ, in which Clast is the last observed quantifiable concentration
- Portion of AUC that is extrapolated to infinity as a percentage of AUCinf ($\%AUC_{inf,ex}$)
- λ, First-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve
- $t_{1/2}$, Elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$

In addition to the protocol-specified parameters, the following partial AUCs were calculated:

- pAUC from time 0 to 3 (and 4) hours post-dose ($pAUC_{0-3}$ and $pAUC_{0-4}$)
- pAUC from 3 (and 4) hours post-dose to 24 hours post-dose ($pAUC_{3-24}$ and $pAUC_{4-24}$)
- pAUC from 3 (and 4) hours post-dose extrapolated to infinity ($pAUC_{3-inf}$ and $pAUC_{4-inf}$)

Safety:

Safety and tolerability endpoints included:

- Clinical laboratory tests (hematology, clinical chemistry, and urinalysis)
- Vital signs
- AEs

- Physical examination
- 12-lead ECG

Statistical Methods:

Sample Size Determination:

The intra-subject CV (Coefficient of Variation) for AUC's and Cmax was estimated to be less than or equal to 15%. Using an estimated intra-subject CV of 15%, a sample of 24 subjects was determined to be sufficient for the point estimator of the ratio of mean PK parameters to fall within 93 and 108 % of the true value with 95% confidence.

Pharmacokinetics:

Statistical analyses of λ and T_{max} were performed on raw data, while C_{max} and AUCs and pAUCs were ln-transformed prior to analysis using a mixed-effect analysis of variance model with treatment, period, and treatment sequence as fixed effects, and subject as a random effect. Ninety percent confidence intervals for the ratio of mean AUCs and C_{max} were constructed using the estimated least squares. Based on correction for measured content, the AUCs and C_{max} ratio estimates and their 90% CIs were also calculated. Correction was made for potency prior to data analysis using a ratio of 0.9, the ratio of the measured drug content of the reference treatment (54mg Concerta) over the measured drug content the test treatment (60mg Ritalin-SR). All other PK parameters were reported using summary statistics.

Safety:

The number and percent of subjects with specific AEs were tabulated by treatment at onset, using MedDRA dictionary terms, and by closest relationship and maximum severity. Descriptive statistics and change from baseline (pre-dose vital signs, labs and ECG) were calculated for each parameter at each scheduled time point. Listings for all safety results were also generated.

RESULTS:

Subject Disposition and Baseline Demographics

As planned, a total of 30 eligible subjects were enrolled and randomized to treatment. Of the 30 randomized subjects, 24 (80.0%) subjects completed the study. All randomized subjects were included in the safety analyses and the 24 completed subjects were included in the PK analyses. Randomized subjects had a mean age of approximately 33 years, a BMI range between 21.1 and 29.6 kg/m^2, inclusive, and most were White (66.7%) and male (70%); the subset of subjects included in the PK analyses did not differ from the entire sample in terms of demographics or baseline characteristics.

Pharmacokinetic Results:

Plasma concentration and concentration ratios over time:

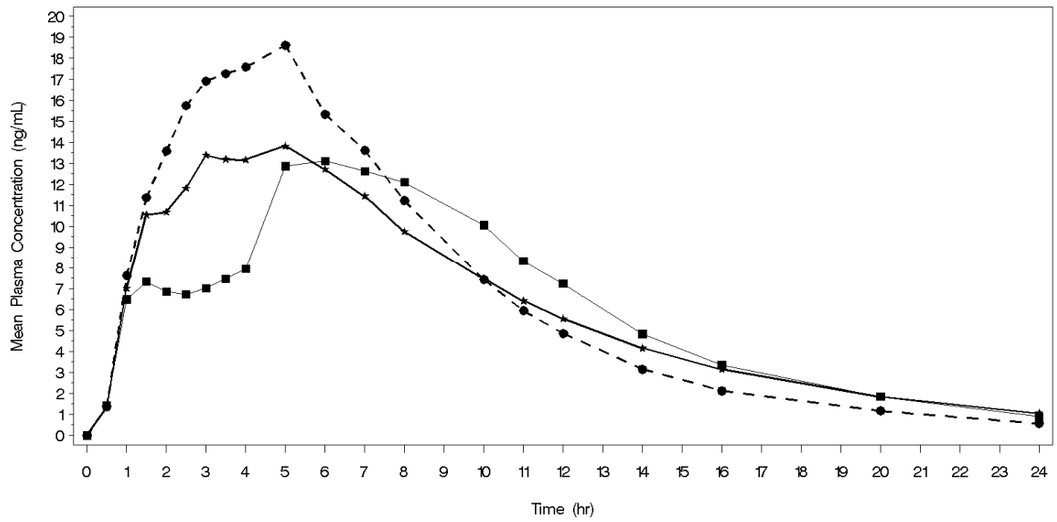
Mean plasma concentration-time curves for d-MPH for both 54-mg CONCERTA® and 60-mg Ritalin-SR® followed the expected temporal patterns that are characteristic for each formulation (Figure 1a); in the case of CONCERTA®, there was a rapid initial increase in mean plasma concentrations of d-MPH to approximately 1.5 hours post-dose (~7.3 ng/mL), followed by a slower rise to peak concentrations (13.1 ng/mL) at 6 hours post-dose. In contrast, mean plasma concentrations of d-MPH following oral administration of 60-mg Ritalin-SR® and 54-mg Novo-MPH ER-C® rose consistently to a single peak of ~18.6 ng/mL and 13.8 ng/mL, respectively, at 5 hours post-dose. Elimination of d-MPH was linear for all 3 products.

The plasma concentration ratio-time profiles between 54-mg CONCERTA® and 54-mg Novo-MPH ER-C® show that d-MPH concentrations were higher following administration of 54-mg Novo-MPH ER-C® than 54-mg CONCERTA® for the first 6 hours post-dose, with a peak difference of ~200% (54-mg Novo-MPH ER-C®/ 54-mg CONCERTA®) at 3 hours post-dose. Similarly, a peak ratio of ~220% was observed at 3 hours post-dose for 60-mg Ritalin-SR® versus 54-mg CONCERTA® following dose normalization (Figure 1b). Plasma concentrations after 7 hours post-dosing were generally lower (~60%) for 60-mg Ritalin-SR® compared to 54-mg CONCERTA®.

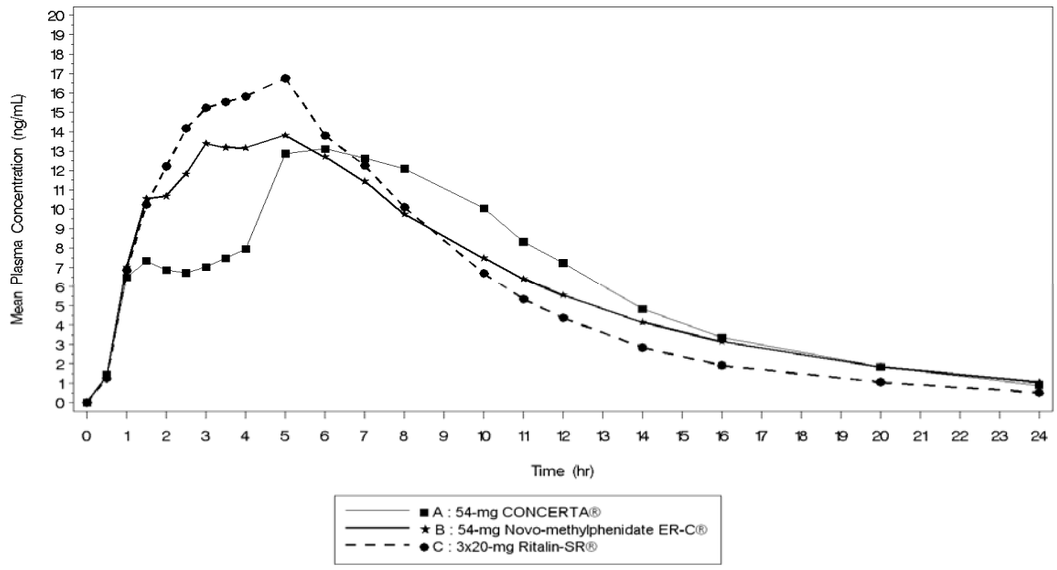
In contrast, dose-corrected plasma concentrations of 60-mg Ritalin-SR® were similar or slightly lower compared with Novo MPH ER-C for the first 7 hours post-dosing, but beyond 7 hours post-dose, the concentration ratios increased steadily to ~210%, indicating plasma concentrations were generally higher for 54-mg Novo-MPH ER-C® compared to 60-mg Ritalin-SR®.

Figure 1. Mean plasma concentration-time curves of d-threo-methylphenidate following oral administration of 54-mg CONCERTA®, Novo-Methylphenidate ER-C® and 60-mg Ritalin-SR® (Evaluable Population, N=24)

(a) Non-dose-corrected



(b) Dose-corrected



Note: in (B), the plasma concentration-time curve for 60-mg Ritalin-SR® was dose-corrected by multiplying concentrations by a coefficient of 54/60.

Analysis of pharmacokinetic parameters:

54-mg CONCERTA® (Reference A) vs. 54-mg Novo-MPH ER-C® (Test)

Peak (C_{max}) and extent (AUC_{0-24} and AUC_{0-inf}) of exposure to d-MPH were similar following oral administration of 54-mg CONCERTA® and 54-mg Novo-MPH ER-C®, consistent with the bioequivalence previously demonstrated for regulatory approval of 54-mg Novo-MPH ER-C®.

Median T_{max} of 54-mg Novo-MPH ER-C® (4 hours) was significantly shorter than that of 54-mg CONCERTA® (6 hours, $p < 0.001$), and using the median T_{max} of 54-mg CONCERTA®, exposure (AUC_{Tmed}) to d-MPH was observed to be significantly higher for the first 6 hours post-dosing with 54-mg Novo-MPH ER-C® (geometric mean [%CV]: 60.9 [32.4] ng/mL*hr) compared to 54-mg CONCERTA® (45.1 [29.4] ng/mL*hr). Analysis of pAUCs confirmed that exposure to d-MPH up to 3 or 4 hours post-dose was significantly higher following administration of 54-mg Novo-MPH ER-C® compared to 54-mg CONCERTA®

60-mg Ritalin-SR® (Reference C) vs. 54-mg Novo-MPH ER-C® (Test)

AUC_{0-24} and AUC_{0-inf} were similar between 54-mg Novo-MPH ER-C® and 60-mg Ritalin-SR®; whereas C_{max} of d-MPH was significantly lower following administration of 54-mg Novo-MPH ER-C® (geometric mean [%CV]: 14.8 [37.6] ng/mL) compared with 60-mg Ritalin-SR® (dose-corrected: 17.3 [37.7]).

T_{max} was similar for both products (median=4 hours), but comparison of AUC_{0-Tmed} (using T_{med} of 60-mg Ritalin-SR® as reference), demonstrated that exposure to d-MPH was significantly lower ($p<0.001$) following 54-mg Novo-MPH ER-C® administration compared to 60-mg Ritalin-SR; however, the 90% CIs of the GM ratio were within the 80.00-125.00 range. For all other pAUCs, the 90% CIs of the GM ratios did not contain 100.00, but were within the 80.00-125.00 range, showing similar exposure within the specified time intervals.

54-mg CONCERTA® (Reference A) vs. 60-mg Ritalin-SR®(Reference C)

AUC_{0-24} and AUC_{0-inf} were similar between 54-mg CONCERTA® and 60-mg Ritalin-SR®, indicating extent of exposure was similar after correcting for dose; however, the dose-corrected C_{max} of 60-mg Ritalin-SR® was significantly higher than the C_{max} of 54-mg CONCERTA®. Using the median T_{max} of either 54-mg CONCERTA® or 60-mg Ritalin-SR®, AUC_{0-Tmed} was significantly higher for 60-mg Ritalin-SR® when dose corrected compared with 54-mg CONCERTA®.

Similar to $AUC_{0\text{-}Tmed}$, exposure to d-MPH up to 3 or 4 hours post-dose was significantly higher following administration of 60-mg Ritalin-SR® compared to 54-mg CONCERTA®;

The mean (SD) apparent terminal elimination half-life of d-MPH was approximately 1 hour longer for 54-mg Novo-MPH ER-C (4.84 [1.18] hours) compared with 54-mg CONCERTA (3.96 [0.62] hours) and 60-mg Ritalin-SR® (3.75 [0.57] hours), which is reflected by the significantly lower λ_z for 54-mg Novo-MPH ER-C® compared to the innovator products.

Safety Results:

There were no serious or life threatening treatment-emergent AEs (TEAEs) reported during the study. No deaths occurred during the study and no subject was discontinued from the study by the investigator due to a TEAE. The majority of TEAEs were judged to be mild in severity; only one subject reported a TEAE of moderate severity (headache) following administration of 54-mg CONCERTA®. No subject experienced a severe TEAE.

The incidence of TEAEs was similar between treatments, ranging between 34.5% (54-mg Novo-MPH ER-C®) and 39.3% (60-mg Ritalin-SR®). The most common TEAE was headache, which was reported by 3 (11.1%) subjects following administration of 54-mg CONCERTA®, and 4 subjects each following administration of 54-mg Novo-MPH ER-C® (13.8%) and 60-mg Ritalin-SR® (14.3%).

Gastrointestinal disorders-related TEAEs occurred at a higher incidence following administration of 54-mg Novo-MPH ER-C® (4 [13.8%] subjects) compared to 60-mg Ritalin-SR® (3 [10.7%] subjects), while treatment with 54-mg CONCERTA® was associated with the lowest incidence (2 [7.4%] subjects). The overall profile of TEAEs observed in this study is consistent with the known pharmacology of MPH.

No notable changes in mean clinical laboratory measures, blood pressure or ECG results were observed between Day -1 and 24 hours post-dosing in the Treatment period for any treatment, and mean post-baseline findings were within normal range.

No clinically significant vital signs, ECG or clinical laboratory assessment results were reported during the study.

Conclusions

The results of this study demonstrate that plasma concentrations of d-MPH were significantly lower in the morning for CONCERTA® compared with both Novo-MPH ER-C® and Ritalin-SR®, whereas plasma concentrations were generally higher for the former in the afternoon and evening, and significantly so compared with Ritalin-SR®. Overall, the PK profiles of 54-mg CONCERTA®, 54-mg Novo-MPH ER-C®, and 60-mg Ritalin-SR® are remarkably different when considering measures beyond those traditionally used to establish bioequivalence.

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