CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS-PSDB-6511694:4.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development	
Name of Finished Product	Paliperidone palmitate	
Name of Active Ingredient	6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyridol[1,2-*a*]pyrimidin-9-yl hexadecanoate	

Protocol No.: CR004195

Title of Study: A Randomized, Double Blind, Parallel-Group Comparative Study of Flexibly Dosed Paliperidone Palmitate (25, 50, 75, or 100 mg eq.) Administered Every 4 Weeks and Flexibly Dosed RISPERDAL® CONSTA® (25, 37.5, or 50 mg) Administered Every 2 Weeks in Subjects With Schizophrenia

Coordinating Investigator: Wolfgang Fleischhacker, M.D. - University Clinic for Psychiatry, Innsbruck; Austria

Publication (Reference): None

Study Period: 25 February 2005 to 10 April 2007 | **Phase of Development:** 3

Objectives: The primary objective was to demonstrate that paliperidone palmitate is not clinically less effective than RISPERDAL CONSTA for the treatment of symptoms of schizophrenia. The safety and tolerability of paliperidone palmitate in maintenance therapy of schizophrenia were also assessed. Secondary objectives included: assessment of the global improvement in severity of illness associated with the use of paliperidone palmitate compared with RISPERDAL CONSTA; assessment of the benefits to personal and social functioning associated with the use of paliperidone palmitate compared with RISPERDAL CONSTA; evaluation of symptomatic remission associated with the use of paliperidone palmitate compared with RISPERDAL CONSTA; and exploration of the pharmacokinetics (PK) of i.m. paliperidone palmitate and the relationship between its PK and the results of the efficacy parameters (e.g., Positive and Negative Syndrome Scale [PANSS]) and safety parameters (e.g., extrapyramidal symptoms [EPS] and adverse events [AEs] of interest).

Methodology: Subjects were screened for medical history and underwent physical and psychiatric evaluation between 1 and 7 days before randomization. Clinical laboratory tests and an ECG were performed. A 5-day washout of disallowed psychotropic medications was to be preferably completed at least 2 days before randomization. Subjects without documented evidence of previous exposure to oral risperidone or paliperidone, or 1 dose of RISPERDAL CONSTA or paliperidone palmitate, underwent a 4-day tolerability test with 3 mg/d paliperidone ER that was to be preferably completed at least 2 days before randomization. At baseline (Day 1), eligible subjects were randomized with equal probability to 1 of 2 double-blind treatment groups: flexibly dosed paliperidone palmitate, 25, 50, 75, or 100 mg eq., or flexibly dosed RISPERDAL CONSTA, 25, 37.5, or 50 mg. Subjects were to receive oral supplementation (placebo in the paliperidone palmitate treatment arm and risperidone 1-6 mg/d in the RISPERDAL CONSTA arm) during the first 4 weeks of the study. Subjects were also to receive oral supplementation (placebo in the paliperidone palmitate treatment arm and risperidone 1-4 mg/d in the RISPERDAL CONSTA arm) during the 3 weeks after every dose increase during the double-blind period.

Number of Subjects (planned and analyzed): Approximately 700 subjects were to be randomized in a 1:1 ratio to receive either flexibly dosed paliperidone palmitate (25, 50, 75, or 100 mg eq.) or flexibly dosed RISPERDAL CONSTA (25, 37.5, or 50 mg). A total of 749 subjects were randomly assigned to treatment, 379 to the paliperidone palmitate group and 370 to the RISPERDAL CONSTA group. A total of 747 randomly assigned subjects who received study drug were analyzed for safety. A total of 674 randomly assigned subjects received study drug, had baseline and post-baseline efficacy assessments, and did not belong to 2 sites excluded from analysis due to Good Clinical Practice (GCP) issues (Intent-to-Treat [ITT] Analysis Set [excluding 2 sites]). A total of 570 randomly assigned subjects received at least 4 injections of double-blind study drug with the time between any 2 injections during the double-blind treatment period not exceeding 35 days; had baseline and post-baseline efficacy assessments; and did not have major protocol violations (Per-Protocol Analysis Set).

Diagnosis and Main Criteria for Inclusion: Men and women (350 in each arm) who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for schizophrenia for at least 1 year (with a PANSS of 60 to 120), aged 18 years or older. An effort was made to randomize a minimum of 50 subjects aged 65 or older.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone palmitate 100 mg eq./mL injectable suspension for administration of 25, 50, 75, or 100 mg eq., batch nos. 04D13/F011, 04E05/F011, 05C24/F013, 05E12/F13, 05I07/F13, 05J19/F13, and 06A24/F13.

SYNOPSIS (CONTINUED)

Reference Therapy, Dose and Mode of Administration, Batch No.: RISPERDAL CONSTA 25-, 37.5-, and 50-mg microspheres for injection of 25, 37.5, or 50 mg, batch nos. 164-0943BB, 164-2194B, 164-0775A, 164-2393CA, 164-2623BA, and 164-2194AB. Risperidone 1-mg tablets for oral supplementation at 1-6 mg/d, batch nos. 04H10/F005, 04K03/F005, 05G12/F005, and 06A27/F005.

Duration of Treatment: One-week screening, washout and tolerability period followed by a 53-week double-blind treatment period.

Criteria for Evaluation:

Pharmacokinetics: Blood samples for PK analysis were collected at baseline and during Week 9, Week 29, Weeks 37 through 43, and at End-of-Study/Early Withdrawal.

Efficacy: Efficacy was assessed by PANSS and Clinical Global Impression-Severity (CGI-S) at baseline and during Week 5, Week 13, Week 25, Week 37, Week 45, and at End-of-Study/Early Withdrawal; in addition, Personal and Social Performance (PSP) scores were obtained at the same time points, excepting Week 5 and Week 45. An exploratory Healthcare Resource Use Questionnaire (HRUQ) was performed at the same time points as the PSP assessment.

Safety: Vital signs, physical examination, clinical laboratory tests, ECGs, EPS scales, injection site pain, and sexual function were monitored at selected time points. Monitoring of concomitant medications and AEs was done throughout the study.

Pharmacogenomics: Blood samples for pharmacogenomic analysis were collected at baseline for those subjects who consented to the genetic component of the study. No genes were genotyped during this study. Genotyping of any genes in the future will be reported separately. In addition, subjects were asked to consent to storage of a DNA sample for future testing of genes related to paliperidone under investigation in this clinical study or genes related to schizophrenia.

Statistical Methods:

Efficacy: The Per-Protocol Analysis Set was the primary population for the noninferiority analysis of the primary efficacy variable. The change from the baseline score at each visit and at end point was analyzed using an ANCOVA model with factors for treatment and country, and baseline PANSS total score as the covariate. The point estimate and 2-sided 95% confidence interval (CI) based on ANCOVA was provided for the difference between RISPERDAL CONSTA and paliperidone palmitate in the change in total PANSS score. Noninferiority of paliperidone palmitate to RISPERDAL CONSTA was to be concluded if the lower limit of the 2-sided 95% CI exceeded –5. At end point, the interaction term between treatment and country was included in the ANCOVA model to be evaluated. All secondary analyses were performed using the ITT Analysis Set (excluding 2 sites), and included ANCOVA analysis with factors for treatment and country and baseline score as a covariate of the change from baseline to end point in CGI-S, PANSS subscales, and PSP. For symptomatic remission and the responder rate, the point estimate and 2-sided 95% CI for the relative risk were provided using a Mantel-Haenszel test controlling for country. Sensitivity analysis was performed using the ITT Analysis Set (excluding 2 sites) and to assess the influence of the IVRS error, exclusion of subjects due to the GCP issue, and baseline body mass index (BMI) on the primary efficacy variable.

Safety: The primary population for the Safety Analysis Set was all subjects who had received at least 1 dose of double-blind study drug and had provided post-baseline safety data. The percentage of subjects with specific treatment-emergent AEs was summarized for each treatment group. Descriptive statistics were calculated for each laboratory analyte at baseline and at each scheduled time point. The effects on cardiovascular variables were evaluated by means of descriptive statistics and frequency tabulations. Descriptive statistics were provided to evaluate changes in vital signs at each scheduled time point. In addition, a frequency table of the occurrence of orthostatic hypotension was presented. Changes from baseline were calculated for each of the EPS scales. The changes from baseline in sexual function, weight, and BMI at each visit and at end point were analyzed using an ANCOVA model with factors for treatment and country, and baseline value as a covariate. The results of injection site evaluations were summarized descriptively at each time point.

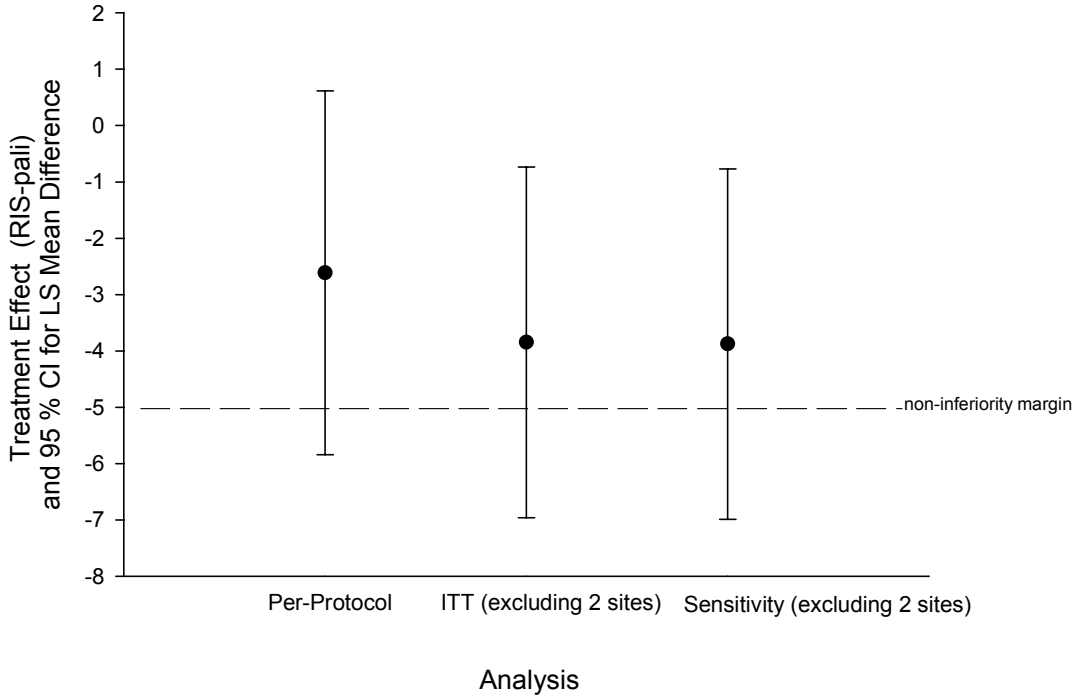
SUMMARY - CONCLUSIONS

PHARMACOKINETICS: In the paliperidone palmitate group, paliperidone plasma concentrations increased in proportion with dose and reached steady state from Day 204 onwards. It is possible that paliperidone plasma concentrations reached steady state before Day 204, because no observations took place between Day 64 and Day 204. Paliperidone plasma concentrations were lower on Day 64 relative to later time points. This may be explained by the long apparent half-life of paliperidone palmitate, and by the time it takes to achieve steady-state plasma concentrations with gluteal injections and without initial doses higher than 50 mg eq. paliperidone palmitate. The paliperidone plasma concentrations observed on Day 64 were lower than active moiety plasma concentrations at equivalent doses of RISPERDAL CONSTA. This may be explained by several factors, such as the different time to steady state following RISPERDAL CONSTA injection compared to paliperidone palmitate injection; oral supplementation with risperidone; and differences in the pharmacokinetic profiles. Due to the latter, it was likely that no trough concentrations were measured in the RISPERDAL CONSTA group.

SYNOPSIS (CONTINUED)

EFFICACY RESULTS: The primary efficacy variable was the change from baseline to end point in total PANSS score. Using last-observation-carried-forward on the Per-Protocol Analysis Set, the mean (SD) change from baseline to end point in total PANSS score was –11.6 (21.22) in the paliperidone palmitate group and –14.4 (19.76) in the RISPERDAL CONSTA group. The difference between paliperidone palmitate and RISPERDAL CONSTA in least-squares means for the change in total PANSS score was 2.6 points (95% CI [–5.84, 0.61]). Similar results were observed when allowance was made for the IVRS error, and when ANCOVA analysis was done using the ITT Analysis Set either including or excluding the 2 sites with the GCP issue. In an exploratory analysis, there was an interaction between treatment and BMI that approached statistical significance (p=0.108) at the 10% level. The point estimate (95% CI) for the difference in least-squares means between paliperidone palmitate and RISPERDAL CONSTA was –0.3 (–4.63, 4.05) for normal-weight subjects (BMI <25 kg/m^2), –0.7 (–5.29, 3.96) for overweight subjects (BMI ≥25 to <30 kg/m^2), and –7.5 (–12.1, –2.82) for obese subjects (BMI ≥30 kg/m^2). The magnitude of the change in total PANSS from baseline to end point in patients receiving paliperidone palmitate was consistent with that observed in clinical studies where statistically significant improvement of paliperidone palmitate over placebo was demonstrated.

Confidence Intervals (95%) for Least-Squares Mean Differences Between Paliperidone Palmitate and RISPERDAL CONSTA for the Change in Total PANSS Score
(Study R092670-PSY-3002)



Note: The per-protocol and ITT (excluding 2 sites) analyses were based on an ANCOVA model including treatment and country as factors and baseline as a covariate. The sensitivity analysis was based on an ANCOVA model with treatment, country, and pre- and post-IVRS error as factors and baseline as a covariate.

Secondary analyses: For CGI-S, the difference in least-squares means between RISPERDAL CONSTA and paliperidone palmitate was –0.2 and the 95% CI was (–0.41, –0.06). For PSP, the difference in least-squares means between RISPERDAL CONSTA and paliperidone palmitate was 1.7 and the 95% CI was (–0.61, 3.97), suggesting no difference between the treatment groups. For PANSS responders, the point estimate (95% CI) of the relative risk of paliperidone palmitate vs. RISPERDAL CONSTA for subjects who improved from baseline by 30% or more was 0.8 (0.70, 0.95). For PANSS subscales, RISPERDAL CONSTA was associated with a numerically larger mean improvement in treating positive symptoms, uncontrolled hostility and excitement, and anxiety or depression compared to paliperidone palmitate. For symptomatic remission, the point estimate (95% CI) of the relative risk of paliperidone palmitate vs. RISPERDAL CONSTA was 0.8 (0.66, 1.07). For the HRUQ, the number of subjects in each treatment group who were hospitalized or outpatients in the previous 3 months was lower at the end of the study than at the beginning.

SAFETY RESULTS:

The most common treatment-emergent AEs reported were insomnia, psychotic disorder, schizophrenia, and anxiety. There were more psychiatric disorder-related serious AEs (25% vs. 20%) and psychiatric disorder AEs leading to discontinuation

SYNOPSIS (CONTINUED)

(5% vs. 3%) in the paliperidone palmitate group than in the RISPERDAL CONSTA group. In addition, a larger proportion

Overall Summary of Treatment-Emergent Adverse Events
(Study R092670-PSY-3002: Safety Analysis Set)

	R092670 (N=379) n (%)	RISPERDAL CONSTA (N=368) n (%)
TEAE	289 (76)	289 (79)
Possibly related TEAE[a]	137 (36)	139 (38)
1 or more serious TEAE	111 (29)	80 (22)
TEAE leading to permanent stop	25 (7)	23 (6)
TEAE leading to death	3 (1)	1 (<1)

[a]Study drug relationships (as assessed by the site investigator) of possible, probable, and very likely are included in this category.
TEAE=treatment-emergent adverse event.

(18% vs. 14%) of subjects in the paliperidone palmitate group had a severe psychiatric disorder AE (primarily psychotic disorder and schizophrenia). This was consistent with lower paliperidone plasma levels in the paliperidone palmitate group compared to active moiety plasma levels in the RISPERDAL CONSTA group. Prolactin levels increased from baseline to the end of the study in both males and females. There were slight increases in mean body weight and BMI from baseline to the end of the study for subjects in the RISPERDAL CONSTA group. Sexual function was not notably affected by treatment with either drug.

CONCLUSION: Based on the predetermined margin of 5 points in the total PANSS score, paliperidone palmitate was not demonstrated to be noninferior to RISPERDAL CONSTA. In general, paliperidone palmitate was safe and well tolerated. The low initial plasma concentration of paliperidone may have led to a higher incidence of psychiatric adverse events and higher rate of withdrawal due to lack of efficacy compared to RISPERDAL CONSTA. The dosing regimen of 50 mg eq. injections on Day 1 and Day 8 in the gluteal muscle may have led to low initial plasma concentrations of paliperidone that resulted in paliperidone palmitate not being demonstrated to be noninferior to RISPERDAL CONSTA. This result suggests that the dosing regimen used in this study may need to be adjusted to optimize plasma concentrations.

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