

CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS-PSDB-9269044:2.0

<u>Name of Sponsor/Company</u>	Johnson & Johnson Pharmaceutical Research & Development	
<u>Name of Finished Product</u>	Paliperidone palmitate	
<u>Name of Active Ingredient</u>	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.: CR004198		
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating Paliperidone Palmitate in the Prevention of Recurrence in Subjects With Schizophrenia		
Coordinating Investigator: Margarita Morozova, M.D., Mental Health Research Center of Russian Academy of Medical Sciences, Moscow; Russia		
Publication (Reference): None		
Study Period: 4 March 2005 to 16 February 2007		Phase of Development: 3
<p>Objectives: The primary objectives of this study were to evaluate the efficacy of paliperidone palmitate compared with placebo in the prevention of recurrence of the symptoms of schizophrenia, and to assess the safety and tolerability of paliperidone palmitate (R092670) in subjects with schizophrenia.</p> <p>Secondary objectives included the following: (1) evaluation of the improvement in the positive and negative symptoms of schizophrenia associated with the use of paliperidone palmitate compared with placebo; (2) evaluation of the global improvement in severity of illness associated with the use of paliperidone palmitate compared with placebo; (3) evaluation of the benefits to personal and social functioning of paliperidone palmitate compared with placebo; and (4) assessment of symptom reduction and stability of symptoms of schizophrenia during the transition and maintenance phases, respectively.</p> <p>The objective of the open-label extension (OLE) phase was to evaluate the long-term safety and tolerability of paliperidone palmitate.</p>		
<p>Methodology: This study is a randomized, double-blind (DB), placebo-controlled, parallel-group, multicenter study designed to evaluate the efficacy of paliperidone palmitate (a long acting i.m. injectable formulation) compared with placebo in preventing recurrence of schizophrenic symptoms in subjects with schizophrenia. Paliperidone palmitate was administered by i.m. gluteal injection. The first 2 doses were separated by 1 week followed by injections every 4 weeks. The study consisted of 5 phases: screening/washout/tolerability phase (up to 7 days); a 9-week open-label transition (TR) phase (50 mg eq. on Days 1 and 8, and a flexible dose of 25, 50, or 100 mg eq. at Week 5); a 24-week open-label maintenance (MA) phase (flexible dose of 25, 50, or 100 mg eq. at Weeks 9, 13, 17, and 21, with no further dose adjustments during the last 12 weeks thereafter); a randomized, DB, placebo-controlled recurrence prevention phase of variable duration (placebo or a fixed dose of paliperidone palmitate equivalent to the dose received at the end of the maintenance phase); and an optional 52-week OLE phase for those subjects completing the placebo-controlled DB recurrence prevention phase or for those subjects who had received at least 1 injection of study drug when the DB recurrence prevention phase was stopped. Data collected from study start through the end of the DB recurrence prevention phase of the study are summarized in the main text of this report, while results of the OLE phase are provided in Appendix 3.</p>		
<p>Number of Subjects (planned and analyzed): The planned sample size to be enrolled was 854 subjects, based on the expectation that 384 randomized subjects would provide 136 recurrence events during the DB phase. Of the 849 subjects enrolled in the TR phase (all treated analysis set), 681 (80%) subjects entered the MA phase, and 410 (48%) subjects were randomized to DB treatment (placebo, n=204; paliperidone palmitate, n=206). The intent-to-treat (ITT) efficacy analysis set for the final analysis included 408 subjects (placebo, n=203; paliperidone palmitate, n=205); these subjects also comprised the DB safety analysis set. At the time of the interim efficacy analysis (which was considered the primary efficacy analysis, see Statistical Methods section of this synopsis), 312 subjects (placebo, n=156; paliperidone palmitate, n=156) were randomized into the DB phase of the study and received at least 1 dose of DB study medication (interim analysis ITT analysis set). Overall, 388 subjects entered the OLE phase.</p>		
<p>Diagnosis and Main Criteria for Inclusion: Eligible subjects were men and women between the ages of 18 and 65 years, with a diagnosis of schizophrenia based on Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. (DSM-IV) criteria. Both stable and symptomatic subjects were eligible for recruitment. To enter the DB phase, subjects had to first achieve and maintain symptom control during the TR/MA phase.</p>		
<p>Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER 3-mg tablets for oral administration, batch nos. 0426909/F016, 0500130/F016, and 0602599/F039. Paliperidone palmitate eq. 100 mg/mL suspension for 25, 50, 75, or 100 mg eq. i.m. administration, batch nos. 04D13/F011, 04F01/F011, 05C24/F013, 05E12/F013, 05J19/F013, 05E12/F013,</p>		

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05I07/F013, 06D10/F013, 06A24/F013, 06H02/F013, and 06K22/F013.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo, Intralipid® 20% injectable emulsion (batch nos. 05D19/F00 and 06E10/F00).

Duration of Treatment: Study medication was administered for 9 weeks during the TR phase, 24 weeks during the MA phase, and a variable length of time during the DB recurrence prevention phase (until recurrence event, withdrawal, or DB phase termination; median duration of DB treatment, paliperidone palmitate: 171 days [range, 1 to 407 days]; placebo, 105 days [range, 8 to 441 days]). In addition, an oral tolerability test, in which subjects were given up to 4 days of treatment with ER OROS paliperidone 3 mg/day, was to be administered during the screening phase for subjects without evidence of prior exposure to risperidone or paliperidone. During the OLE phase, subjects received paliperidone palmitate injections every 4 weeks for 52 weeks or 12 injections (median duration of exposure during OLE phase was 338 days [range, 10 to 390 days]). Additionally, ER OROS paliperidone supplementation was allowed during the first 8 weeks of OLE for all subjects.

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the time from randomization to treatment in DB to the first recurrence event in the DB phase. Efficacy analyses in the DB phase were performed comparing paliperidone palmitate with placebo. Secondary efficacy variables were assessed for the TR/MA phases based on the change from TR baseline and for DB phase based on the change from DB baseline. For the OLE phase, evaluations were based on the change from OLE baseline and transition baseline. Secondary efficacy assessments included Positive and Negative Syndrome Scale (PANSS, total and subscales), Clinical Global Impression Scale – Severity (CGI-S), and Personal and Social Performance Scale (PSP). Exploratory evaluations included the Schizophrenia Quality of Life Scale-Revision 4 (SQLS-R4), Brief Assessment of Cognition in Schizophrenia (BACS), Healthcare Resource Utilization Questionnaire (HRUQ), and Wide Ranging Achievement Test 3 (WRAT3).

Safety: Safety evaluations included adverse events (AEs), clinical laboratory tests, electrocardiograms (ECGs), vital signs, physical examination, extrapyramidal symptom (EPS) rating scales (Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Simpson and Angus Rating Scale), and evaluation of the injection site.

Pharmacogenomics: An optional 10-mL blood sample was obtained at any time during the trial for those subjects who had given consent to participate in the genetic portion of the clinical study to allow for the analysis of genes hypothesized to be involved in paliperidone metabolism or response or in schizophrenia susceptibility or prognosis. 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: The primary efficacy variable was the time from randomization to recurrence during the DB phase. Subjects who met any of the predefined recurrence criteria were considered to have had a recurrence event; all other subjects were considered censored as of their last day of DB phase. The cumulative distribution function of the time to recurrence was estimated by the Kaplan-Meier method, time to recurrence was summarized, and treatments were compared using a 2-sided log-rank test. The estimate of the hazard ratio and its 95% confidence interval (CI) was based on Cox proportional hazard models with treatment as the only covariate. Additional predictors of the time to recurrence such as age group, sex, baseline body mass index (BMI) group, and geographic region were evaluated using Cox proportional hazard models to individually assess the effect of these covariates (including treatment and one covariate at a time). The overall significance level across treatment groups for all secondary analyses was 0.05 (2-sided) with no multiplicity adjustments. Analyses of DB data involving changes from baseline in secondary efficacy end points used the last observation carried forward (LOCF) approach. For each assessment time point, summary statistics were provided for each study phase on the PANSS total and subscale scores and changes from phase baseline to end point. Treatment comparison between paliperidone palmitate and placebo in the changes of PANSS total and subscale scores during the DB phase was performed using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline (DB) value as a covariate. For the CGI-S, PSP, and SQLS, at each assessment time point summary statistics were provided for each study phase on the scores and score changes from the baseline of each phase to end point. At each assessment time during the DB phase (except for DB baseline), p-values for between-treatment comparison were produced using an ANCOVA model on the change from baseline (and on the ranked data for CGI-S) with treatment and country as factors and baseline (DB) score as a covariate.

The 2-stage group-sequential design with 1 interim analysis and equal group sizes allowed for early stopping of the recurrence prevention phase in case of significant evidence of efficacy based upon the interim analysis. At the time of the 68th recurrence event (50% of the planned recurrence events), interim analysis was performed by the Independent Data Monitoring Committee (IDMC). The IDMC was to provide recommendations about stopping, modifying, or continuing the study based on ongoing safety monitoring and the interim efficacy analysis. The interim analyses (primary and sensitivity analyses) of the time-to-recurrence demonstrated a statistically significant difference in favor of paliperidone palmitate that exceeded the prespecified threshold for significance ($p=0.0106$), and the decision was made on 23 January 2007 to terminate the study per the IDMC recommendation. Since the study was terminated because of the significant results of the interim analysis, this analysis is considered the primary analysis as prespecified in the study protocol, and the analysis of the final efficacy data is considered confirmatory.

SYNOPSIS (CONTINUED)**SUMMARY - CONCLUSIONS**

EFFICACY RESULTS: Based on the interim analysis, paliperidone palmitate was superior to placebo ($p < 0.0001$) with regard to the primary efficacy end point of time to recurrence of symptoms of schizophrenia. This was confirmed in the final analysis ($p < 0.0001$), where the rate of recurrence was 48% (placebo) vs. 18% (paliperidone palmitate), and the median estimated time to a recurrence event was 172 days for subjects in the placebo group (not estimable for the paliperidone palmitate group because fewer than 25% of subjects experienced a recurrence event).

Table 1. Number of Subjects Experiencing Recurrence and Time to Recurrence During the DB Phase

Descriptive ^a	Paliperidone			Overall		
	Placebo	Palmitate	Total	Chisq	DF	P-value ^b
Primary Efficacy Analysis (Interim Analysis)						
Number of Assessed	156	156	312			
Number of Censored (%)	103 (66.0)	141 (90.4)	244 (78.2)			
Number of Events (%)	53 (34.0)	15 (9.6)	68 (21.8)			
25% Quantile (95% CI)	57.0 (49.0; 91.0)	NE	108.0 (83.0; 163.0)			
Median (95% CI)	163.0 (108.0; NE)	NE	NE			
75% Quantile (95% CI)	NE	NE	NE			
Statistical Test				29.411	1	<0.0001
Confirmatory Analysis (Final Analysis)						
Number of Assessed	203	205	408			
Number of Censored (%)	106 (52.2)	169 (82.4)	275 (67.4)			
Number of Events (%)	97 (47.8)	36 (17.6)	133 (32.6)			
25% Quantile (95% CI)	71.0 (57.0; 85.0)	NE (204.0; NE)	108.0 (85.0; 135.0)			
Median (95% CI)	172.0 (134.0; 227.0)	NE	NE (255.0; NE)			
75% Quantile (95% CI)	NE (255.0; NE)	NE	NE			
Statistical Test				48.632	1	<0.0001

^a Based on Kaplan-Meier product limit estimates.

^b Log-rank test.

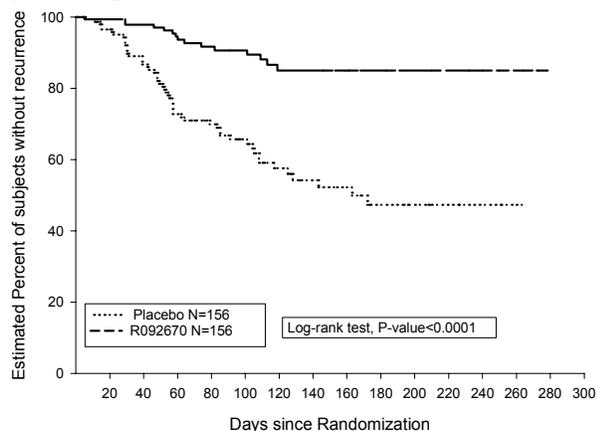
NE = these quantile values were not estimable since fewer than 25% of subjects in the paliperidone palmitate group and fewer than 75% of subjects in the placebo group experienced a recurrence.

A Kaplan-Meier plot (Figure 1) of the time to recurrence for primary efficacy analysis (interim analysis) shows that a higher proportion of subjects in the paliperidone palmitate group, compared to placebo remained recurrence free. Estimates of the treatment effect (based upon hazard ratio) in subjects treatment with paliperidone palmitate was similar regardless of the subjects' sex, geographic region, age, or baseline BMI assessed at the start of the DB phase.

During open-label treatment in the TR and MA phases, meaningful improvements in symptom control, compared to TR baseline, were observed in the all treated analysis set based on the decrease in PANSS total score (mean [SD], -8.7 [19.53]). Improvement was also shown based on the CGI-S scale for the intent-to-treat analysis set (those subjects who entered DB phase), in which 46% of subjects were rated by the investigator as 'mild', 'very mild', or 'not ill' at TR baseline, compared with 86% who received this rating at MA end point.

During the DB phase, the LOCF analysis of the change in PANSS total score from DB baseline showed that subjects who continued on paliperidone palmitate treatment remained relatively stable after an initial slight worsening immediately following randomization, whereas subjects in the placebo group showed significantly greater worsening (mean [SD] 11.1 [16.60] in the placebo group vs. 2.5 [12.16] in the paliperidone palmitate group, $p < 0.0001$). Between-group difference based on the ranks of the change from DB baseline in CGI-S was statistically significant ($p < 0.0001$). These findings are consistent with the higher percentage of subjects with a recurrence event and the higher (increased) PANSS total score at DB end point in the placebo group compared with the paliperidone palmitate group. A significantly greater mean decrease in PSP score from DB baseline was observed for the placebo group compared with the paliperidone palmitate group (-7.2 vs. -1.5; $p < 0.0001$). The 25% percentile of time to first ≥ 10 -point worsening in PSP on or before a recurrence was 169 days for the placebo group and 253 days for the paliperidone palmitate group (p -value=0.0014, log-rank test).

During the OLE phase, improvements from OLE baseline to end point in paliperidone-treated subjects were noted on the PANSS, PSP, and CGI-S assessments.

SYNOPSIS (CONTINUED)**Figure 1. Kaplan-Meier Plot of Time to Recurrence (Interim Analysis)**

SAFETY RESULTS: Treatment-emergent AEs reported most frequently ($\geq 5\%$) during the TR/MA phases were insomnia (15%), anxiety (10%), headache (9%), schizophrenia (7%), weight increased (6%), and nasopharyngitis (5%). During the DB phase, AEs that occurred most frequently were related to psychiatric disorders (26% and 14% in placebo and paliperidone palmitate groups, respectively). During the OLE phase, 56% of subject experienced treatment-emergent AEs. Injection site-related AEs occurred infrequently during the study and were generally mild in intensity. No unexpected events related to long-term exposure were identified that appear to be related to paliperidone palmitate.

Three subjects died during the TR/MA phases (1 suicide, 1 natural causes [most likely from a stroke, as reported by the investigator], and 1 accident). Two additional subjects died post-study (1 subject died due to accidental exposure 19 days after discontinuation from the MA phase and 47 days after the last injection of study drug and a second subject died due to 'heart attack' 10 days after discontinuation from the MA phase due to a serious suicide attempt and 42 days after the last injection of study drug).

No deaths were reported in the DB or OLE phases. Serious AEs were reported in 116 (14%) subjects during the TR/MA phases, and AEs resulted in study discontinuation for 52 (6%) subjects. During the DB phase, serious AEs were reported in 11 (5%) subjects in the paliperidone palmitate group and 26 (13%) subjects in the placebo group, and AEs resulted in study discontinuation in 3 subjects in the paliperidone palmitate group and 1 subject in the placebo group. During the OLE phase, 22 (6%) subjects had serious AEs and 6 (2%) subjects, all of whom had received placebo during the DB phase, discontinued due to AEs.

There were no reports of neuroleptic malignant syndrome. One subject experienced tardive dyskinesia (mild, non-serious) during the TR phase and 1 subject who had received placebo during the DB phase had tardive dyskinesia during the OLE phase. EPS-related AEs were reported for 9% of subjects during the TR/MA phases, 2% of placebo-treated and 6% of paliperidone palmitate-treated subjects during the DB phase, and 6% during the OLE phase. Results of EPS rating scales and use of anti-EPS medication were consistent with paliperidone palmitate treatment being associated with a low incidence of EPS-related AEs.

For most laboratory analytes, the incidence of treatment-emergent, markedly abnormal laboratory findings was low and suggested no between-group difference in incidence during DB phase. Mean prolactin levels increased from TR baseline to MA end point in both male (9.8 ng/mL) and female (25.3 ng/mL) subjects; these changes were shown to be reversible in subjects who received placebo during the DB phase (mean prolactin change from DB baseline to DB end point in the placebo group: -9.2 ng/mL for males and -16.6 ng/mL for females; in the paliperidone palmitate group: 3.7 ng/mL for males and 12.7 ng/mL for females). Similar percentages of male (48%) and female (49%) subjects had prolactin levels above the upper limit of laboratory normal, and the incidence of potentially prolactin-related AEs was 3% during the TR/MA phases. As expected, long-term exposure to paliperidone palmitate during the OLE phase was not associated with further increases in prolactin concentrations.

Mean increase in BMI from TR baseline to MA end point was mild (0.2 kg/m^2). The mean increase in body weight during the TR/MA phases was 0.7 kg, with abnormal weight increases ($\geq 7\%$) from TR baseline to MA end point noted in 12% of subjects. During the DB recurrence prevention phase, abnormal weight increases ($\geq 7\%$) from DB baseline to end point were noted in 6% of subjects in the paliperidone palmitate group compared with 3% in the placebo group. During the OLE phase, abnormal weight increases ($\geq 7\%$) relative to OLE baseline were noted in 13% of subjects, with the lowest incidence among subjects who received double-blind paliperidone palmitate. Long-term exposure to paliperidone palmitate during the OLE phase was associated with relatively small incremental weight gain.

Cardiovascular events including cardiac arrhythmias, orthostatic hypotension, and AEs suggestive of proarrhythmic potential were infrequent during the study. During transition/maintenance phases of the study, QT linear-derived correction (QTcLD) shifts from a normal average predose value to a prolonged maximum, post-transition value was recorded for 1

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subject and shifts from a normal average predose value to a borderline maximum post-transition value were recorded for 24 subjects based on QTcLD. During the DB phase, shift from a normal average predose value to a prolonged maximum value was recorded for 1 subject in the paliperidone palmitate treatment group. QTcLD values shifted from normal to borderline in 4 subjects in the placebo group and 7 subjects in the paliperidone palmitate group. For all phases combined (including OLE), only 2 subjects had QTcLD values above 480 ms (maximum value of 483 ms and 507 ms, both during the TR/MA phases), and no subject had a maximum increase of 60 ms or more from average predose QTcLD.

CONCLUSION: Treatment with paliperidone palmitate at doses between 25 to 100 mg eq. significantly delayed the time to recurrence of symptoms of schizophrenia after 24 weeks of maintained symptom stability. Because the primary use for paliperidone palmitate will be in the long-term treatment of subjects, these findings are particularly relevant and provide valuable guidance for practicing clinicians. Overall, findings from this study that also includes an optional 52-week OLE phase provide support that long-term treatment with paliperidone palmitate is efficacious, safe, and well tolerated.

Issue Date of the Clinical Study Report: 15 January 2009

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