SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Extended-Release ER OROS® paliperidone NAME OF ACTIVE INGREDIENT(S): paliperidone	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: R076477-SCH-305 CR004375

Title of Study: A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Extended Release OROS® Paliperidone (3, 9, and 15 mg/day) and Olanzapine (10 mg/day), With Open-Label Extension, in the Treatment of Subjects With Schizophrenia.

Coordinating Investigator: Robin Emsley, M.D. - Stikland Hospital, Research Centre, Belville, Cape Town, South Africa

Publication (Reference): None

Study Initiation/Completion Dates: 13 May 2004 to 24 May 2005	**Phase of development:** 3

Objectives: The primary objective of the double-blind phase of this study was to evaluate the efficacy and safety of 3 fixed dosages of ER OROS paliperidone (3, 9 and 15 mg/day) compared with placebo in subjects with schizophrenia. The efficacy response was measured by the change in the Positive and Negative Syndrome Scale (PANSS) total score from start of treatment to the end of the double-blind phase. Secondary objectives were to assess benefits in personal and social performance, global improvement in severity of illness, the benefits in patient-reported symptoms and well-being related to schizophrenia. Additional objectives were to assess the improvement to sleep associated with the use of ER OROS paliperidone compared with placebo, and to explore the dose-response relationship of ER OROS paliperidone, the relative efficacy of the ER OROS paliperidone groups versus the olanzapine group, the pharmacokinetics and the relationship between pharmacokinetics and efficacy (PANSS) and safety parameters (extrapyramidal symptoms [EPS], adverse events) of interest, and the genes/genotypes that may be related to the response or metabolism of ER OROS paliperidone. Safety of ER OROS paliperidone 3, 9, or 15 mg/day compared with placebo and olanzapine 10 mg/day, was assessed using adverse events, physical examinations, vital sign measurements, clinical laboratory evaluations, electrocardiograms (ECGs), and EPS rating scales.

Methodology: The randomized, double-blind, placebo- and active-controlled, parallel-group, dose-response study was conducted in 74 centers in the United States, Canada, Mexico, Eastern Europe (Bulgaria, Poland, Romania, Ukraine), Israel, Asia (Hong Kong, Malaysia, Republic of Korea, Singapore, Taiwan) and South Africa. Following a screening phase, subjects were randomized to receive placebo, ER OROS paliperidone 3, 9, or 15 mg, or olanzapine 10 mg in double-blind fashion for 6 weeks. The primary reason for inclusion of the olanzapine 10-mg treatment group in the study was to have a concurrent active control group to confirm that the study was adequate to detect a drug effect (i.e., assay sensitivity) in case the 3 ER OROS paliperidone treatment groups had failed to show efficacy.

Number of Subjects (planned and analyzed): 595 subjects (119 per treatment group) were planned for enrollment. 732 subjects were screened for the study, 618 subjects were randomly assigned to a treatment group (123 to placebo, 127 to 3 mg ER OROS paliperidone, 125 to 9 mg ER OROS paliperidone, 115 to 15 mg ER OROS paliperidone, and 128 to 10 mg olanzapine). 605 subjects were analyzed for efficacy (received study drug and had 1 postbaseline efficacy assessment), 614 subjects were analyzed for safety (received study drug).

Diagnosis and Main Criteria for Inclusion: Male or female patients 18 years of age or older and who met the DSM-IV criteria of schizophrenia for at least 1 year. Eligible subjects were experiencing active symptoms at the time of enrollment and had a PANSS total score between 70 and 120.

Test Product, Dose and Mode of Administration, Batch No.: ER OROS paliperidone one 3-mg capsule (batch numbers 03J01/F022, 03G09/F022, 03I10/F022, 04D13/F022, 04D05/F022) and 2 ER OROS matching placebo capsules (batch numbers 03F02/F125, 03J27/F027, 03G24/F027, 04B02/F027) (3-mg dosage group); ER OROS paliperidone one 9-mg capsule (03I23/F023, 03G14/F023, 03J13/F023, 04D26/F023, 04E04/F023) and 2 ER OROS matching placebo capsules (9-mg dosage group); or ER OROS paliperidone two 3-mg capsules and 1 ER OROS 9-mg capsule (15-mg dosage group) were administered orally once a day in the morning. Note: subjects in the ER OROS paliperidone 15-mg dose group received ER OROS paliperidone 12 mg from Days 1 through 7: ER OROS paliperidone one 3-mg capsule and one 9-mg capsule and one placebo capsule.

Reference Therapy, Dose and Mode of Administration, Batch No.: Olanzapine one 10-mg capsule (two 5-mg tablets overencapsulated into a single tablet; batch numbers 03F19/F292, 03G31/F291, 04C24/F292) and two olanzapine matching placebo capsules (batch numbers 03J20/F125, 04B09/F125, 04B16/F125) (olanzapine 10-mg group) and 3 olanzapine matching placebo capsules (placebo group) were administered orally once a day in the morning.

Duration of Treatment: Study drug was administered for 6 weeks.

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Criteria for Evaluation:

Efficacy: Key efficacy analyses were performed comparing results for each ER OROS paliperidone group with placebo. The criterion for the primary efficacy variable was the change from baseline in PANSS total score at the end of the double-blind phase (Day 43 or last postbaseline assessment). The secondary efficacy analyses included the change from baseline in the variable score at the end point (Day 43 or last postbaseline assessment): Personal and Social Performance Scale (PSP), Clinical Global Impression Scale – Severity (CGI-S), and Symptoms and Quality of Life in Schizophrenia Scale (SQLS). Other efficacy variables included the change from baseline to end point in sleep visual analog scale (VAS) and PANSS subscale scores, onset of therapeutic effect, and treatment responders. (An additional analysis compared the change from baseline in PANSS total scores for each ER OROS paliperidone group with the olanzapine group.)

Safety: Safety was based on the incidence of treatment-emergent adverse events and on changes from baseline in physical examinations, vital sign measurements, clinical laboratory tests, ECGs, and EPS scale scores.

Other Evaluations: Paliperidone and olanzapine plasma concentration data (sparse sampling) were obtained for a population pharmacokinetic analysis and pharmacokinetic/pharmacodynamic evaluations. Genotyping of *CYP2D6* was performed for a subset of subjects.

Statistical Methods: The change in PANSS total score from baseline to end point for each ER OROS paliperidone group was compared with placebo and between the ER OROS paliperidone 3-mg, 9-mg, and 15-mg groups by use of an analysis of covariance (ANCOVA) model with treatment and analysis center as factors and the baseline PANSS total score as a covariate (primary analysis). A similar analysis was performed for each of the PANSS factor scores, as described by Marder, and the PANSS subscale scores. For each ER OROS paliperidone group that was shown to be superior to placebo in the primary analysis, the comparison between this group and placebo was performed for PSP, CGI-S, and SQLS. Statistical comparisons between each ER OROS paliperidone group and placebo for the change from baseline in PSP scores (ANCOVA), CGI-S scores (ANCOVA on the ranks of change), and in SQLS, were performed using the unconditional randomization resampling algorithm to adjust for multiple testing. An additional analysis for the change from baseline to end point in PSP scores was performed using the Dunnett procedure to adjust for multiple comparisons. Statistical comparisons between each ER OROS paliperidone group and the placebo group for the change from baseline in sleep VAS scores using an ANCOVA model were performed. Onset of therapeutic effect was calculated as the first time point at which a change from baseline in PANSS total score in subjects treated with ER OROS paliperidone 3 mg, 9 mg, or 15 mg was significantly different (nominal significance level of 5%, 2-tailed), and remained different for the remainder of the study, from the change from baseline in PANSS total score in subjects treated with placebo. Responders were defined as subjects who show a 30% or more reduction from baseline in the PANSS total score at the last postbaseline assessment in the double-blind phase. Differences between each ER OROS paliperidone group and placebo were compared using a Cochran-Mantel-Haenszel test controlling for analysis center. (Also, an analysis of the change from baseline in the PANSS total scores comparing each ER OROS paliperidone group with olanzapine was performed using an ANCOVA model with treatment and analysis center as factors and with baseline as a covariate.)

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: The paliperidone plasma concentrations after administration of ER OROS paliperidone 3, 9 or 15 mg were generally within the expected concentration range. The average paliperidone plasma concentrations at predose, 1 to 2 hours postdose, and more than 4 hours post-dose (mean sampling time was about 4 hours) for the ER OROS paliperidone 15-mg group were 58.5, 53.2 and 48.2 ng/mL, respectively, on Day 15 (Visit 6) and 60.0, 59.7 and 57.9 ng/mL, respectively, on Day 36 (Visit 9), with no apparent fluctuation within a dosing interval and no accumulation of paliperidone over this period. The average plasma concentrations obtained after once daily administration of ER OROS paliperidone 3, 9 and or 15 mg appeared to be dose proportional.

The olanzapine plasma concentrations after administration of olanzapine 10 mg once daily were within ranges reported in the literature. Plasma concentrations of olanzapine at predose, 1 to 2 hours postdose, and more than 4 hours postdose were 18.5, 22.7 and 29.8 ng/mL, respectively, on Day 15 (Visit 6) and 18.3, 22.1 and 28.3 ng/mL, respectively, on Day 36 (Visit 9).

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EFFICACY RESULTS: ER OROS paliperidone, 3 mg, 9 mg, and 15 mg/day demonstrated significant improvement compared with placebo with regard to changes from baseline to end point in PANSS total score (primary efficacy variable). This finding was consistent with and complemented by statistically significant results for the secondary variables PSP, CGI-S, and all PANSS factor scores at all 3 doses of ER OROS paliperidone. The patient-rated SQLS showed a statistically significant improvement over placebo only at the 3-mg dose, although all doses of ER OROS paliperidone showed numerically greater improvements compared to placebo. Improvement in PANSS total score vs. placebo was first observed early with ER OROS paliperidone (within the first 4 days for all 3 doses); statistical superiority over placebo was maintained for the duration of the 6-week double-blind phase. The ER OROS paliperidone 15-mg group exhibited a statistically significantly greater mean decrease (improvement) in PANSS total scores than the ER OROS paliperidone 3-mg group; there was no significant difference in response between the ER OROS paliperidone 15-mg and 9-mg groups or the 9-mg and 3-mg groups. At end point, significantly more subjects in each ER OROS paliperidone group (40–53%) than in the placebo group (18%) demonstrated a 30% or greater reduction from baseline in PANSS total score (i.e., "treatment response"). Discontinuation rates due to lack of efficacy were lower in the ER OROS paliperidone groups compared with the placebo group. Improvement in quality of sleep VAS scores without exacerbation of daytime drowsiness was observed for all doses of ER OROS paliperidone.

		---------- ER OROS PAL ----------		
	Placebo (N=120)	3 mg (N=123)	9 mg (N=123)	15 mg (N=113)
PANSS total score (primary variable) (n)	120	123	123	112
Mean change (SD)	-2.8 (20.89)	-15.0 (19.61)*	-16.3 (21.81)*	-19.9 (18.41)*
PSP (n)	109	113	116	107
Mean change (SD)	-1.5 (15.82)	8.3 (17.11)*,#	7.6 (14.20)*,#	12.2 (15.65)*,#
CGI-S (n)	120	123	123	113
Median change (Range)	0.0 (-5;2)	-1.0 (-4;1)#	-1.0 (-4;2)#	-1.0 (-5;1)#
SQLS (n)	114	116	116	112
Mean change (SD)	-3.8 (13.40)	-7.4 (14.77)#	-6.7 (15.93)	-7.5 (16.45)
PANSS Factor Scores (n)	120	123	123	113
Mean change (SD)				
Positive symptoms	-2.1 (6.90)	-5.0 (6.89)†	-6.0 (7.74)†	-6.9 (6.87)†
Negative symptoms	-1.0 (5.52)	-3.8 (5.27)†	-3.9 (5.36)†	-4.2 (5.30)†
Disorganized thoughts	-0.2 (5.34)	-3.4 (5.06)†	-3.4 (5.47)†	-3.9 (4.46)†
Uncontrolled hostility/excitement	1.2 (4.68)	-1.1 (3.61)†	-1.2 (4.48)†	-2.3 (3.34)†
Anxiety/depression	-0.7 (3.46)	-1.8 (3.35)†	-1.9 (3.72)†	-2.6 (2.87)†
Quality of Sleep (n)	115	118	120	113
Mean change (SD)	3.6 (35.99)	9.0 (34.52)	12.3 (34.88)†	11.3 (33.17)
Daytime Drowsiness (n)	115	118	119	113
Mean change (SD)	-0.5 (29.69)	-2.9 (28.10)	-0.9 (33.85)	-3.8 (34.47)

***** Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using Dunnett's procedure to adjust for multiple comparisons.

# Denotes a statistically significant ($p<0.05$) improvement in score versus placebo using Unconditional Randomization Resampling Algorithm to adjust for multiple comparisons.

† Denotes a statistically significant ($p<0.05$) improvement with no adjustment for multiple comparisons.

A comparison between the olanzapine 10 mg group and the ER OROS paliperidone groups in terms of the primary efficacy variable showed no statistically significant between-group differences.

SAFETY RESULTS: ER OROS paliperidone 3 mg, 9 mg, or 15 mg/day was well tolerated by subjects with schizophrenia. There were no deaths in the study. The incidences of serious adverse events and adverse events resulting in discontinuation were similar across treatment groups and did not appear to be dose-related.

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		ER OROS PAL			Olanzapine
Treatment-emergent adverse events	Placebo (N=123) n (%)	3 mg (N=127) n (%)	9 mg (N=124) n (%)	15 mg (N=113) n (%)	10 mg (N=127) n (%)
Any event	74 (60)	91 (72)	94 (76)	87 (77)	92 (72)
Events related to study drug	52 (42)	62 (49)	74 (60)	56 (50)	62 (49)
Serious events	9 (7)	7 (6)	12 (10)	6 (5)	7 (6)
Events leading to study drug discontinuation	5 (4)	3 (2)	6 (5)	4 (4)	4 (3)

Of the more common adverse events, somnolence was reported more frequently by subjects who received olanzapine (17%) compared with other treatment groups (3-13%). The most common adverse events experienced by subjects in the ER OROS paliperidone groups were headache, insomnia, and tachycardia. The incidence and severity of EPS-related adverse events were generally comparable for the placebo and ER OROS paliperidone 3-mg group. There was a higher incidence of hypertonia, dystonia, and tremor in the ER OROS paliperidone 9-mg group than in the other treatment groups, and of extrapyramidal disorder and hyperkinesia in the ER OROS paliperidone 9-mg and 15-mg groups. One event of treatment-emergent tardive dyskinesia was reported in the ER OROS paliperidone 9-mg group; this event occurred on day 4 of the study and was considered doubtfully related to study medication by the investigator (the subject had a prior history of tardive dyskinesia and had recently discontinued clozapine treatment). Overall, there were few cases of severe or serious EPS-related events or of EPS-related events that resulted in discontinuation. Results of EPS rating scales, EPS-related adverse events, and anti-EPS medication use at the end of double-blind treatment were generally consistent, and indicate that the ER OROS paliperidone 3-mg group had rates similar to placebo, while the ER OROS paliperidone 9-mg group, and to some extent the 15-mg group, had higher rates of EPS. Isolated cases of suicide attempt occurred, with no clinically relevant differences between treatment groups (placebo: 2 subjects, ER OROS paliperidone 3 mg, 9 mg, and 15 mg: 2, 1, and 3 subjects, respectively; olanzapine: 2 subjects). There were no reports of neuroleptic malignant syndrome or cerebrovascular disorders or events among the study subjects.

For most laboratory analytes, the incidence of treatment-emergent markedly abnormal findings was low (≤3% of subjects per treatment group). There was a low incidence of adverse events related to abnormal laboratory findings (≤5% across treatment groups). More subjects in the olanzapine and ER OROS paliperidone 3-mg groups (2% each) had markedly elevated ALT values than the ER OROS paliperidone 15-mg group (1%) or the ER OROS paliperidone 9-mg or placebo groups (0%), consistent with a higher incidence in the olanzapine group of adverse events related to hepatic enzymes (1-5% in olanzapine vs 0-2% in other groups). The ER OROS paliperidone groups had slightly higher incidences of markedly low LDL (16-18%) than the placebo (14%) and olanzapine (4%) groups. The incidence of markedly low HDL was highest in the ER OROS paliperidone 15-mg and olanzapine groups (13-15%) and lowest in the ER OROS paliperidone 9-mg group (8%). More subjects in the placebo and olanzapine groups (3% each) than in the ER OROS paliperidone groups (0-1%) had markedly elevated levels of creatine kinase. Three subjects in the ER OROS paliperidone 9-mg or 15-mg groups had serious laboratory-related adverse events (2 were glucose-related, the third was 'water intoxication' associated with low potassium levels; 2 of these subjects were withdrawn). For subjects who received ER OROS paliperidone, mean increases from baseline in prolactin levels occurred that were greater in female than male subjects at all doses. Mean prolactin levels generally decreased after Day 15 in males, and after Day 36 in females in some of the treatment groups, without returning to the reference range by study end. Given the isolated reports of potentially prolactin-related adverse events (≤1% across active treatment groups), the increases in mean prolactin levels appear to be of limited immediate clinical relevance.

Based on a low incidence of adverse event reports, orthostatic changes in vital signs in the ER OROS paliperidone groups appeared to be of limited clinical relevance. The percentage of subjects with abnormally high pulse rates was higher in the ER OROS paliperidone groups than in the placebo or olanzapine groups, and generally increased with ER OROS paliperidone dose. This difference is consistent with a somewhat higher incidence of adverse events of tachycardia reported for subjects who received ER OROS paliperidone (9-14%) versus placebo (8%). There was, however, an inverse relationship between ER OROS paliperidone dose and incidence of tachycardia. Mean body weight increases were observed in all active treatment groups; mean percent increases were greatest among subjects who received olanzapine (3.4%), followed by ER OROS paliperidone 15 mg, 9 mg, and 3 mg (2.6%, 2.1%, and 1.1%, respectively).

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At assessment time points throughout the study, predominantly at 22 hours postdose on Days 4 and 8 and immediately predose on Days 15 and 36, small increases in QTcLD, QTcF, QTlc, and QTcB intervals from average predose were noted for paliperidone-treated subjects. This increase was highest with the 15-mg dose using all correction methods (maximal increase in QTcLD: 3.6 milliseconds [15 mg] compared with 2.4 milliseconds [placebo] on Day 43). The occurrence of increased QTcLD from baseline at 22 hours post dose on Days 4 and 8 may be explained by the relatively higher paliperidone plasma concentrations with a t_{max} at approximately 22 hours post dose. The incidence of subjects with normal QTcLD values at baseline and borderline or prolonged QTcLD values at end point showed no clinically relevant difference among treatments. The incidence of QTcLD increases from baseline of 30 to 60 msec was slightly greater for the ER OROS paliperidone 9-mg and 15-mg groups (11% and 12%, respectively) compared with the placebo and olanzapine groups (8% in each), but lower in the ER OROS paliperidone 3-mg group (5%). No subject had a postbaseline QTc interval ≥500 msec (using any correction method). One subject in the ER OROS paliperidone 3 mg group (Subject 500424) discontinued due to an ECG related adverse event ("ECG abnormality [ST-T]). Clinically significantly prolonged QTc intervals were to be reported as adverse events (preferred term: ECG abnormal specific). Overall, 13 subjects – 1 (1%) in the placebo group, 4 (3%) in the ER OROS 3-mg group, 2 (2%) in the ER OROS paliperidone 9-mg group, 4 (4%) in the ER OROS paliperidone 15-mg group, and 2 (2%) in the olanzapine group – had treatment-emergent adverse events related to prolonged QTc values. All subjects with these adverse events had QTcB values <500 msec.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: Graphical display of pharmacokinetic-pharmacodynamic relationships showed no apparent relationship between paliperidone plasma concentrations and any of the assessed safety parameters (AIMS, BARS, SAS total scores, and cardiovascular safety parameters: QTcLD) or their respective shifts from baseline.

CONCLUSIONS:

ER OROS paliperidone, administered at dosages of 3 mg, 9 mg, and 15 mg/day, was statistically superior to placebo in improving PANSS total scores at end point (primary efficacy variable) in this 6-week double-blind trial in subjects with schizophrenia. The treatment effect was observed at the first assessment on Day 4 in each of the ER OROS paliperidone dose groups (including the highest dose group, which was at that time receiving ER OROS paliperidone 12 mg/day). This finding was consistent with and complemented by statistically significant results at all doses for the secondary variables PSP, CGI-S, all PANSS factor scores, and the PANSS responder analysis. The patient-rated SQLS showed statistically significant differences in favor of paliperidone at only the 3-mg dose, although all doses of ER OROS paliperidone showed numerically greater improvements compared with placebo. Also noteworthy is the improvement in quality of sleep VAS scores without exacerbation of daytime drowsiness, which was observed for all doses of ER OROS paliperidone.

ER OROS paliperidone, administered at doses of 3 mg, 9 mg, and 15 mg per day for 6 weeks, was generally safe and well tolerated in subjects with schizophrenia. Several EPS-related adverse events were more commonly reported with the higher doses of ER OROS paliperidone; in the ER OROS paliperidone 3-mg group, the incidence and severity of most of these events were comparable to those in the placebo group. A dose-related increase in body weight was observed with ER OROS paliperidone. However, no clinically relevant effects on glucose or lipid metabolism were observed. There were few clinically relevant effects on ECG parameters: these effects included a slightly greater incidence of QTcLD increases from baseline of 30 to 60 milliseconds for the ER OROS paliperidone 9-mg and 15-mg groups than for the placebo group.

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