# SYNOPSIS

| NAME OF SPONSOR/COMPANY:<br>Johnson & Johnson Pharmaceutical Research & Development, L.L.C. | INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER | (FOR NATIONAL AUTHORITY USE ONLY) |
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| NAME OF FINISHED PRODUCT:<br>INVEGA®<br><br>NAME OF ACTIVE INGREDIENT(S):<br>paliperidone | Volume:<br><br>Page: | |

**Protocol No.:** CR003379

**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 (6, 9, and 12 mg/day) and Olanzapine (10 mg/day), With Open-Label Extension, in the Treatment of Subjects With Schizophrenia

**Coordinating Investigator:** Jaroslaw Strzelec, M.D., Ph.D. – Inventiva Biomedical and Sport Research, 95-080 Tuszyn, Poland

**Publication (Reference):** None

| **Study Initiation/Completion Dates:** 29 March 2004 to 25 January 2005 | **Phase of development:** 3 |
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**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 (6, 9, and 12 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 6, 9, or 12 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:** This randomized, double-blind, placebo- and active-controlled, parallel-group, dose-response study was conducted in Bulgaria, Croatia, Estonia, France, Greece, India, Netherlands, Poland, Russia, Spain, and Slovakia. Following a screening phase, subjects were randomized to receive placebo, ER OROS paliperidone 6, 9, or 12 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 were planned for enrollment. 680 subjects were screened for the study, 630 subjects were randomly assigned to a treatment group (127 to placebo, 123 to 6 mg ER OROS paliperidone, 122 to 9 mg ER OROS paliperidone, 130 to 12 mg ER OROS paliperidone, and 128 to 10 mg olanzapine). 628 subjects were analyzed for efficacy (received study drug and had at least 1 postbaseline efficacy assessment), 629 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 two 3-mg capsules (batch numbers 03G09/F022, 04C29/F022, 04D13/F022; 6 mg dosage group), ER OROS paliperidone one 9-mg capsule (batch numbers 03G14/F023, 04D26/F023), and one ER OROS paliperidone matching placebo capsule (batch numbers 03G24/F027, 04B02/F027) (9-mg dosage group), and ER OROS paliperidone one 3-mg and one 9-mg capsule (batch numbers 03G09/F022, 04C29/F022, 04D13/F022, 03G14/F023, 04D26/F023; 12 mg dosage group) were administered orally once a day in the morning.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Olanzapine 10-mg capsule (two 5-mg tablets overencapsulated into a single capsule; batch numbers 03F19/F292, 04C24/F292) and one placebo capsule (olanzapine 10 mg dosage group) or 2 placebo capsules (placebo group) were administered orally once a day in the morning (batch numbers 03G24/F027, 04B02/F027, 03F02/F125, 04B09/F125, 04B16/F125).

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

**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 6 mg, 9 mg, and 12 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), using Dunnett's procedure to adjust for multiple comparisons. 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 6 mg, 9 mg, or 12 mg was significantly different (nominal significance level of 5%, 2-tailed) and remained different for the remainder of the study, than 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.)

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**SUMMARY – CONCLUSIONS**

PHARMACOKINETIC RESULTS: For the 6 mg ER OROS paliperidone treatment group, mean paliperidone plasma concentrations at pre-dose, 1-2 hours post-dose, and more than 4 hours post-dose were 23.2, 23.3 and 22.0 ng/mL, respectively, at Visit 6 and 27.2, 26.2 and 25.3 ng/mL, respectively, at Visit 9. For the 9 mg ER OROS paliperidone treatment group, mean paliperidone plasma concentrations pre-dose, 1-2 hours post-dose, and more than 4 hours post-dose were 37.7, 36.4 and 35.0 ng/mL, respectively, at Visit 6 and 36.9, 35.6 and 34.7 ng/mL, respectively, at Visit 9. For the 12 mg ER OROS paliperidone treatment group, mean paliperidone plasma concentrations pre-dose, 1-2 hours post-dose, and more than 4 hours post-dose were 51.8, 50.9 and 49.4 ng/mL, respectively, at Visit 6 and 48.3, 46.4 and 44.9 ng/mL, respectively, at Visit 9. There was no apparent fluctuation of plasma concentrations within a dosing interval and no accumulation of paliperidone over a period of 6 weeks. The average plasma concentrations obtained after 6, 9 and 12 mg once-daily administration were dose proportional. Mean plasma concentrations of olanzapine at predose, 1 to 2 hours postdose and more than 4 hours postdose were 20.3, 25.6 and 31.5 ng/mL, respectively at Visit 6 and 20.8, 26.0 and 30.6 ng/mL , respectively at Visit 9.

EFFICACY RESULTS:

As shown below, ER OROS paliperidone, 6 mg, 9 mg, and 12 mg/day, demonstrated significant improvement compared to 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 results for the secondary efficacy variables, PSP, CGI-S, and PANSS factor scores. The patient-rated SQLS demonstrated significant improvement versus placebo at the 9 mg and 12 mg doses, although the effect appeared to vary across geographical regions. Improvement in PANSS total score vs. placebo was first observed early with ER OROS paliperidone (within the first 4 to 8 days); statistical superiority over placebo was maintained for the duration of the 6-week, double-blind phase. The ER OROS paliperidone 12 mg group exhibited a statistically significantly greater mean decrease (improvement) in PANSS total scores compared with the ER OROS paliperidone 9 mg group or 6 mg group; there was no notable difference in response between the ER OROS paliperidone 6 mg and 9 mg groups. At end point, significantly more subjects in each ER OROS paliperidone group (51% to 61%) than in the placebo group (30%) 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 to the placebo group. Improvement in quality of sleep VAS scores without exacerbation of daytime drowsiness was observed for all doses of ER OROS paliperidone.

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| | | ER OROS PAL | | |
|---|---|---|---|---|
| | Placebo (N=126) | 6 mg (N=123) | 9 mg (N=122) | 12 mg (N=129) |
| **PANSS total score (primary variable)** (n) | 126 | 123 | 122 | 129 |
| Mean change (SD) | -4.1 (23.16) | -17.9 (22.23)* | -17.2 (20.23)* | -23.3 (20.12)* |
| **PSP** (n) | 120 | 119 | 118 | 129 |
| Mean change (SD) | 0.5 (15.51) | 9.1 (15.52)*,# | 8.1 (14.46)*,# | 11.5 (15.98)*,# |
| **CGI-S** (n) | 126 | 122 | 122 | 129 |
| Median change (Range) | 0.0 (-4;2) | -1.0 (-4;2)# | -1.0 (-4;1)# | -1.0 (-5;1)# |
| **SQLS** (n) | 120 | 120 | 120 | 121 |
| Mean change (SD) | -4.9 (16.64) | -8.3 (14.75) | -12.9 (17.92)# | -13.4 (18.95)# |
| **PANSS Factor Scores** (n) | 126 | 123 | 122 | 129 |
| Mean change (SD) | | | | |
| **Positive symptoms** | -2.1 (6.98) | -6.6 (7.40)† | -6.2 (6.87)† | -8.2 (6.64)† |
| **Negative symptoms** | -1.0 (5.85) | -4.2 (6.17)† | -3.5 (5.43)† | -5.0 (5.98)† |
| **Disorganized thoughts** | -0.9 (5.70) | -3.5 (5.05)† | -3.1 (4.73)† | -4.6 (5.14)† |
| **Uncontrolled hostility/excitement** | 0.5 (4.48) | -1.4 (4.28)† | -1.8 (3.83)† | -2.4 (3.44)† |
| **Anxiety/depression** | -0.6 (3.97) | -2.1 (3.29)† | -2.6 (3.42)† | -3.0 (3.38)† |
| **Quality of Sleep** (n) | 119 | 121 | 120 | 126 |
| Mean change (SD) | 1.0 (35.49) | 13.5 (33.84)† | 10.5 (31.21)† | 12.2 (32.54)† |
| **Daytime Drowsiness** (n) | 119 | 121 | 120 | 126 |
| Mean change (SD) | -5.8 (30.26) | -2.4 (24.27) | -7.2 (30.73) | -6.4 (29.88) |

* 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.

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SAFETY RESULTS:

ER OROS paliperidone, 6 mg, 9 mg, or 12 mg/day, was well tolerated by subjects with schizophrenia. One death was reported in the olanzapine 10 mg group. The incidence of serious adverse events and adverse events resulting in discontinuation was low.

| | | ER OROS PAL | | | Olanzapine |
|---|---|---|---|---|---|
| | Placebo (N=126) | 6 mg (N=123) | 9 mg (N=122) | 12 mg (N=130) | 10 mg (N=128) |
| **Treatment-emergent adverse events** | n (%) | n (%) | n (%) | n (%) | n (%) |
| Any event | 79 ( 63) | 74 ( 60) | 77 ( 63) | 95 ( 73) | 81 ( 63) |
| Events related to study drug | 48 ( 38) | 52 ( 42) | 54 ( 44) | 69 ( 53) | 56 ( 44) |
| Serious events | 3 ( 2) | 5 ( 4) | 1 ( 1) | 6 ( 5) | 3 ( 2) |
| Events leading to study drug discontinuation | 8 ( 6) | 8 ( 7) | 4 ( 3) | 8 ( 6) | 9 ( 7) |

Of the more common adverse events, somnolence was reported more frequently by subjects who received olanzapine (14%) compared to other treatment groups (4% to 8%). A higher incidence of extrapyramidal disorder, hyperkinesia, hypertonia, dystonia, and dyskinesia was observed in the ER OROS paliperidone 9 mg and 12 mg groups compared to other treatment groups. The incidence of certain EPS-related adverse events in subjects treated with ER OROS paliperidone indicated a dose-response trend (extrapyramidal disorder: placebo: 1%, ER OROS paliperidone 6 mg: 3%, 9 mg: 7%, 12 mg:10%; hyperkinesia: placebo: 3%, ER OROS paliperidone 6 mg: 3%, 9 mg: 6%, 12 mg: 11%). Overall, there were few cases of severe EPS-related events or events that caused discontinuation. Isolated cases of suicide attempt occurred, with no clinically relevant differences between treatment groups (placebo: 2 subjects, ER OROS paliperidone 9 mg: 1 subject; olanzapine: 2 subjects) . There were no reports of glucose-related adverse events, neuroleptic malignant syndrome, or cerebrovascular disorders or events. No tardive dyskinesia was reported in subjects receiving active treatment. Based on adverse event reports, orthostatic changes in vital signs and elevations in serum prolactin in the ER OROS paliperidone groups were of limited clinical relevance.

For most laboratory analytes, the incidence of treatment-emergent, markedly abnormal laboratory findings was low (≤5% of subjects per treatment group); there was a low incidence of adverse events related to abnormal laboratory findings (≤4% in any treatment group). The olanzapine group had a higher incidence of markedly elevated ALT, cholesterol, and triglycerides compared to placebo or ER OROS paliperidone. Six subjects discontinued the study due to a liver and biliary system disorders adverse event (none were serious), including 1 subject in the placebo and each ER OROS paliperidone group (6 mg, 9 mg, and 12 mg), and 2 subjects in the olanzapine group. Also, 1 subject in the ER OROS paliperidone 6 mg group was discontinued from the study due to abdominal pain and vomiting and 2 days postdose experienced a serious adverse event of increased creatine phosphokinase and LDH values. For subjects who received ER OROS paliperidone, mean increases from baseline in prolactin levels were generally observed at Day 15; thereafter, mean prolactin levels generally decreased, but did not return to within the normal range by the end of the study. The percentage of subjects with abnormally high pulse rates was higher in the ER OROS paliperidone groups versus the placebo group; this was consistent with the incidence of adverse events of tachycardia. Mean body weight increases were observed in all active treatment groups; these increases were greatest among subjects who received olanzapine (2.1%), followed by ER OROS paliperidone 9 mg and 12 mg (0.9%), and were lowest in the ER OROS 6 mg group (0.5%); body weight decreased slightly in the placebo group (-0.9%).

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A small but statistically significant mean increase compared to placebo in QTc intervals with ER OROS paliperidone was noted on Day 4 and Day 8, mostly at 22 hours postdose, consistent with anticipated peak plasma levels. This increase was highest with the 12 mg dose (maximal increase in QTcLD: 7.5 msec [12 mg] compared to 1.8 msec [placebo]) on Day 8 at 22 hours postdose. QTcB increases were noted at all measured time points up to Day 8, consistent with observed increases in heart rate. Clinically significantly prolonged QTc values were to be reported as adverse events (preferred term: ECG abnormal specific). The incidence of these adverse events was 2-7% across treatment groups, highest in the ER OROS paliperidone 12 mg group. Two subjects were withdrawn from the study due to prolonged QTc values, including 1 in the placebo group and 1 in the ER OROS paliperidone 12 mg group (subject also had a treatment-emergent QTcB value ≥500 msec and QTc increase of >60 msec, using all 4 correction methods). In both cases, resolution of the prolonged QTc value occurred 2 to 8 days after the last dose of study drug.

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 doses of 6 mg, 9 mg, and 12 mg per day, was significantly more effective than 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 early with ER OROS paliperidone (within the first 4 to 8 days).

This finding was consistent with and complemented by statistically significant results for the secondary variables at all doses, including PSP, CGI-S, all PANSS factor scores (using Marder criteria), and the PANSS responder analysis. The patient-rated SQLS showed statistically significant differences in favor of paliperidone at the 9 and 12 mg doses, although the effect appeared to vary across geographical regions. 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 6 mg, 9 mg, and 12 mg per day for 6 weeks, was generally safe and well tolerated in subjects with schizophrenia. Tachycardia was more commonly reported with ER OROS paliperidone, and mean increases in prolactin levels were observed with paliperidone. However, little weight gain was noted and no clinically relevant effects on glucose and lipid metabolism were observed. A clinically relevant increase in the incidence of EPS-related adverse events was noted at the 9 and 12 mg per day doses. With the exception of increased heart rate and resulting increases in QTcB intervals, and small increases in QTcLD, QTcF, and QTlc intervals 22 hours postdose up to Day 8, no relevant effects on ECG parameters were observed.

Date of the report: 7 November 2005

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