SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	Paliperidone ER
Name of Active Ingredient(s)	Paliperidone

Protocol No.: R076477-SCH-4012

Title of Study: A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of a Fixed Dosage of 1.5 mg/day of Paliperidone Extended Release (ER) in the Treatment of Subjects With Schizophrenia

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Publication (Reference): None

Study Period: 21 September 2007 – 20 November 2008

Phase of Development: Phase 4

Objectives: The primary objective of this study was to evaluate the efficacy and safety of a fixed dosage of paliperidone ER (1.5 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 treatment phase.

The secondary objectives were to assess the following associated with the use of paliperidone ER (1.5 mg/day) compared with placebo: global improvement in severity of illness, the benefits to personal and social functioning, and improvement in subject-reported health status measured by the Medical Outcomes Study Short Form Health Survey-36 (MOS SF-36) and also the evaluation of the pharmacokinetics (PK) of paliperidone using a population PK approach.

Methods: This was a multicenter randomized, double-blind, placebo-controlled, parallel-group study, which consisted of a screening period (maximum 5 days, which included a 3- to 5-day washout of disallowed medications, if necessary); a 6-week double-blind treatment phase; and a poststudy visit (1 week after receiving the final study drug dose). At baseline (Day -1), the subjects were randomly assigned to 1 of 3 treatment groups to receive oral paliperidone ER 1.5 mg, paliperidone ER 6 mg, or placebo once daily for 6 weeks. At the time of randomization, subjects were to be hospitalized for a minimum of 8 days. A blood sample for pharmacogenomic research was collected from subjects who gave consent. Participation in pharmacogenomic research was optional.

Number of Subjects (planned and analyzed): A total of 201 subjects (67 per treatment group) from study centers in the United States, India, and Taiwan, were planned for and randomly assigned to the study (65 to placebo, 66 to paliperidone ER 1.5 mg, and 70 to paliperidone ER 6 mg). There was 1 randomly assigned subject who did not receive study medication. There was 1 randomly assigned, treated subject who did not have any postbaseline efficacy assessments. Thus, 200 subjects constituted the safety analysis set and 199 subjects constituted the ITT analysis set.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, 18 years of age or older, who were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) at least 1 year before screening; who were experiencing an acute episode with a PANSS total score at screening and at baseline between 70 and 120 were included.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone was supplied as oral capsules containing paliperidone ER 1.5 mg (Lot 07B12/F075, 07F29/F077) or 6 mg (Lot 06K06/F067, 07127/F067) tablets.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo tablets were supplied (Lot 06J16/F027).

Duration of Treatment: Subjects received paliperidone ER 1.5 mg, paliperidone ER 6 mg, or placebo tablets once daily for 6 weeks.

Criteria for Evaluation:

Pharmacokinetics: A sparse sampling procedure was followed. The procedure combined the PK information gathered from a few blood samples collected in this study with knowledge of the population PK analysis of paliperidone obtained in previous studies. The plasma concentration-time data collected was included in a population PK analysis.

Efficacy: The primary efficacy criterion was the change from baseline in PANSS total score from baseline to the end of the double-blind treatment phase (Week 6 or last postbaseline assessment). Secondary endpoints included changes from baseline to the end of the double-blind treatment phase (Week 6 or last postbaseline assessment) in Clinical Global Impression Severity (CGI-S), Personal and Social Performance Scale (PSP), and MOS SF-36. Other endpoints included onset of therapeutic effect, responder rate, change from baseline to end point in PANSS subscales and PANSS Marder scales. Longitudinal analysis of change from baseline of PANSS total score using observed data was performed to assess sensitivity of the primary analysis.

Safety: Safety was evaluated based on the change from baseline in physical examinations, vital sign measurements, electrocardiograms (ECGs), clinical laboratory testing (hematology, serum chemistry, and urinalysis), and monitoring for adverse events (AEs), assessment of extrapyramidal symptoms (EPS) using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Rating Scale (SAS).

Statistical Methods:

Sample Size Determination: Based on the pooled analysis of the 3 and 6 mg dose groups in Studies R076477-SCH-303, -SCH-304, and -SCH-305, it was observed that the mean change of PANSS total score from baseline was 11 points for the paliperidone ER 3 mg and the paliperidone ER 6 mg dose groups. Since there were no prior studies that tested the paliperidone ER 1.5 mg dose group, the difference of 11 points for this dose group was assumed to be the same as the difference for the previously tested 3 mg and 6 mg dose groups. Mean change of PANSS total score from baseline to Week 6 last-observation-carried-forward (LOCF) end point was assessed within an analysis of covariance (ANCOVA) framework. Since the 6 mg dose group was used for assay sensitivity only, adjustment for multiple comparisons was not made.

Given these assumptions, a sample size of 65 subjects per treatment group was considered enough to detect a significant treatment difference between the paliperidone ER 1.5 mg dose group and placebo group with a power of 87.5%. With an estimated drop-out rate of approximately 3%, the number of randomly assigned subjects was adjusted to 67 in each of the 3 treatment groups. Therefore, a total of approximately 201 subjects were to be randomly assigned to treatment groups in this study.

Primary endpoint: The primary efficacy endpoint was the change in PANSS total score from baseline to the end of the double-blind treatment phase. The change from baseline in PANSS total score from baseline to the end of the double-blind treatment phase was analyzed by using ANCOVA model. The LOCF method was used. The model included treatment and country as factors and baseline PANSS total score as a covariate. Treatment effects were estimated based on least-squares (LS) means of the difference. A test of significance between the paliperidone ER 1.5 mg dose group and placebo was carried out at a 5% level (2-tailed). Since the 6 mg dose group was used for assay sensitivity only, adjustment for multiplicity was

not made. A 2-sided 95% confidence interval was presented for the LS mean of the difference between the paliperidone ER 1.5 mg group and the placebo group.

Secondary endpoints: The CGI-S was analyzed using an ANCOVA model on the ranks of change from baseline with treatment and country as factors and baseline value (unranked) as a covariate. Other secondary efficacy variables, PSP and MOS SF-36, were also analyzed by using an ANCOVA model with treatment and country as factors and the respective baseline score as a covariate.

Other endpoints included:

Onset of Therapeutic Effect: Onset of therapeutic effect was calculated as the first time point at which the treatment groups (paliperidone ER 1.5 mg and placebo) were different (at the 2-sided 5% level of significance) and remain different thereafter until endpoint based on the change from baseline in the PANSS total score (LOCF).

Responder Rate: Responders were defined as those who show a 30% or more reduction from baseline in the PANSS total score at the end of 6 weeks or at the last postbaseline assessment in the double-blind phase. Differences between the paliperidone ER 1.5 mg treatment group and placebo were evaluated using the Cochran-Mantel-Haenszel test, controlling for country. Subjects randomly assigned to the paliperidone ER 6 mg treatment group were not included in the analysis.

PANSS Subscales and PANSS Marder Factors: Between-group comparisons of the change from baseline in PANSS score for PANSS subscales and PANSS Marder factors at each visit and at end point in the double-blind phase were analyzed using an ANCOVA model, controlling for country and baseline score.

Longitudinal Analysis of PANSS Total Score: To assess the sensitivity of the results, change from baseline in PANSS total score was explored using a repeated measures mixed effects model based on the observed data, with treatment, time, country, and a treatment-by-time interaction term as factors and baseline PANSS total score as a covariate.

Safety Analyses: Adverse events, clinical laboratory tests, ECG data, results of vital sign measurements, changes in weight or body mass index (BMI), and assessment of EPS symptoms were summarized using descriptive statistics or frequency tables, where applicable.

RESULTS:

STUDY DRUG EXPOSURE:

A total of 201 subjects were randomly assigned (65 to placebo, 66 to paliperidone ER 1.5 mg, and 70 to paliperidone ER 6 mg). There was 1 randomly assigned subject who did not receive study drug. There was 1 randomly assigned, treated subject who did not have any postbaseline efficacy assessments. Thus, 200 subjects constitute the safety analysis set and 199 subjects constitute the ITT analysis set.

The majority of ITT subjects were Asian (52%) or Black (34%), and 72% of the subjects were male. The mean age of all subjects was 39.5 years (range 18-65 years). A total of 111 (55%) randomly assigned subjects completed the study and 90 (45%) subjects discontinued the study prematurely. A total of 42 (21%) discontinued due to lack of efficacy, 19 (9%) withdrew consent, 14 (7%) discontinued due to an AE, 11 (5%) were lost to follow-up, and 4 (2%) discontinued due to other reasons.

The overall mean duration of hospitalization during the double-blind phase of the study was 10.6 days (a minimum of 8 days was required per the protocol). Duration of hospitalization was comparable across treatment groups.

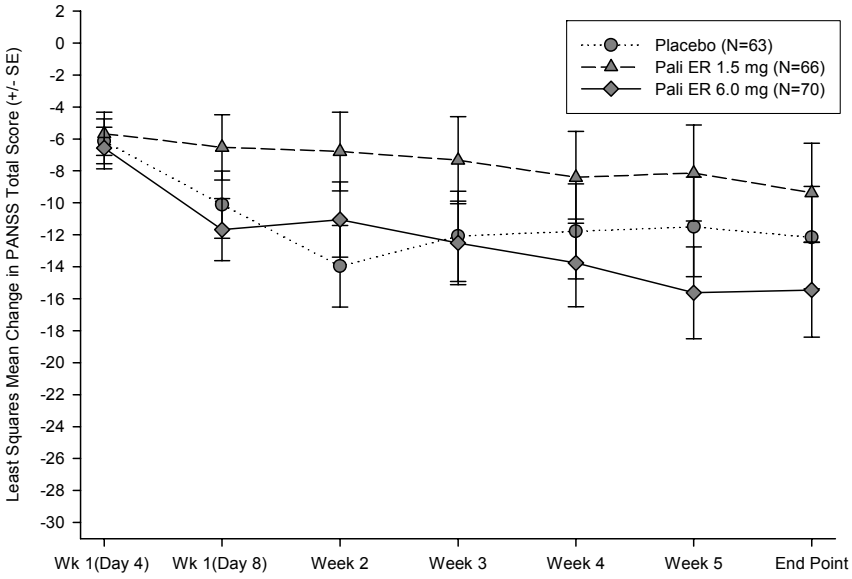
EFFICACY RESULTS

Primary Efficacy

Positive and Negative Syndrome Scale

The mean (SD) change from baseline to end point in PANSS total score was -11.7 (22.84), -8.9 (25.41), and -15.0 (26.02) in the placebo, paliperidone ER 1.5 mg, and paliperidone ER 6 mg groups, respectively. Based on the ITT LOCF analysis of the primary efficacy variable, the mean improvement in the placebo group was numerically higher than that in the paliperidone ER 1.5 mg group at end point. The difference between groups was not statistically significant (p=0.504). The LS mean difference for the paliperidone ER 1.5 mg group from placebo was +2.8 (95% confidence interval: [-5.47, 11.09]). Paliperidone ER 6 mg showed a numerically larger improvement compared to placebo at end point (LOCF). The LS mean difference from placebo was -3.3 (95% confidence interval: [-11.46, 4.90]) but the difference was not statistically significant (p=0.431).

Synopsis Figure 1: PANSS Total Score: Least-Squares Mean Change From Baseline Over Time (LOCF)
(Study R076477-SCH-4012: Intent-To-Treat Analysis Set)



Note: LS Means were estimated from ANCOVA model with factor(s) treatment (Placebo, Pali ER 1.5 mg, Pali ER 6 mg) and country, and baseline value as covariate (type III SS).

Secondary Efficacy

Clinical Global Impression-Severity (CGI-S) Scale

The median (range) change from baseline to end point for the CGI-S score was -1.0 (-2 to 2), 0.0 (-3 to 2), and -0.5 (-3 to 2) for the placebo, paliperidone ER 1.5 mg, and paliperidone ER 6 mg groups, respectively. The paliperidone ER 1.5 mg group was not statistically significantly different from placebo (p=0.626).

Personal and Social Performance (PSP) Scale

The mean (SD) change from baseline to end point for the PSP score was 1.6 (17.09) for placebo, 2.9 (14.37) for the paliperidone ER 1.5 mg group, and 5.7 (13.39) for the paliperidone ER 6 mg group. The paliperidone ER 1.5 mg group was not statistically significantly different from placebo (p=0.870).

MOS SF-36 Scale

The mean MOS SF-36 physical and mental component summary scores increased slightly (indicating improvement) from baseline to end point for the 3 treatment groups, with larger mean increases observed in the placebo group relative to the paliperidone ER 1.5 mg group.

Other Efficacy Results

Onset of Therapeutic Effect

Onset of therapeutic effect was assessed by determining the earliest time at which paliperidone ER demonstrated a statistically significant improvement over placebo. Based on the LS mean change from baseline to each visit (LOCF analysis) for the PANSS total score, paliperidone ER 1.5 mg showed a numerically lower improvement than placebo. The difference was significant only at Week 2.

Responder Rates

A treatment responder was defined as a subject with a 30% or greater reduction from baseline in PANSS total score during the double-blind phase. A higher proportion of subjects in the placebo group showed 20% or more reduction and 30% or more reduction from baseline in PANSS total score compared to paliperidone ER 1.5 mg. No statistically significant differences were noted.

PANSS Subscales and PANSS Marder Factors

For all of the 3 PANSS subscales and 5 PANSS Marder factors, the mean scores decreased (indicating improvement) from baseline to end point, with slightly larger mean decreases observed in the placebo group relative to the paliperidone ER 1.5 mg group; however, no statistically significant differences between the paliperidone ER 1.5 mg and placebo groups were noted.

Longitudinal Analysis of PANSS Total Score

The mixed effects model with unstructured variance-covariance matrix revealed a significant time effect ($p<0.0001$), a non-significant treatment effect ($p=0.431$), and a significant treatment-by-time interaction effect ($p=0.009$), indicating that the change from baseline in PANSS total score depended on time, and that the difference between treatments varied over time. Although PANSS total scores showed a mean decrease from baseline for all time points for the 3 treatment groups, placebo showed a greater decrease from baseline compared to paliperidone ER 1.5 mg at all time points except at Week 4 and Week 6. The greatest mean improvement was observed in the paliperidone ER 6 mg group at all time points but Week 2, where the greatest mean improvement was in the placebo group. These results corroborate those from the primary analysis.

Assay Sensitivity

Paliperidone ER 6 mg was used in the study for assay sensitivity. Although paliperidone ER 6 mg showed a numerically larger improvement compared to placebo using LOCF, no statistically significant differences were noted.

Efficacy Conclusions

- Based on the ITT last-observation-carried-forward (LOCF) analysis of the primary efficacy variable (change in PANSS total score from baseline to end point), the improvement in the paliperidone ER 1.5 mg group was not superior to placebo ($p=0.504$). The CGI-S and PSP scales, likewise, did not show a statistically significant difference between the placebo and paliperidone ER 1.5 mg groups.
- The placebo group showed a greater improvement than the paliperidone ER 1.5 mg group. Even if the placebo group showed the previously reported change from baseline (pooled results from Studies R076477-SCH-303, -SCH-304, and -SCH-305: mean [SD] -4.8 [21.95]) (ie, had there not been such a high placebo response), the 1.5 mg group would still not have been statistically significantly different from placebo. From this perspective, the 1.5 mg treatment group is not considered effective.

It has previously been demonstrated that both paliperidone ER 3 mg and 6 mg were significantly different from placebo. In the context of the current study, the results would suggest that the minimum effective dose is between 1.5 and 6 mg.

- Assay sensitivity could not be established in this study. This is in part due to a greater-than-expected mean improvement in the placebo group and the somewhat larger variability of the changes in PANSS total score observed in this study vs. pooled data from previous 3 studies. The mean (SD) improvement in the paliperidone ER 6 mg group (-15.0 [26.02]) was similar to that observed in pooled data from prior studies (mean change -16.9 [20.7]).
- Across the 3 countries participating in this study, the magnitude of improvement showed some differences but there was no evidence of a treatment-by-country interaction.

SAFETY RESULTS

No deaths were reported during the study. Approximately 11% of subjects in the placebo and paliperidone ER 1.5 mg groups experienced SAEs, higher than the incidence of SAEs in the paliperidone ER 6 mg group (7%). All SAEs in this study were psychiatric in nature. The incidence of treatment-emergent adverse events (TEAEs) leading to discontinuation of study medication was lower in the paliperidone ER 6 mg (3%) group than in the placebo group (8%) and the paliperidone ER 1.5 mg group (11%). The most common TEAE leading to discontinuation in both the placebo and paliperidone ER 1.5 mg groups, psychotic disorder, accounts for the high incidence in these groups when compared with the paliperidone ER 6 mg group.

Overall, TEAEs occurred at similar rates among the paliperidone ER groups (64% and 69% for the paliperidone ER 1.5 and 6 mg groups, respectively) and the placebo group (73%). This was also the case for the events considered by the investigators to be at least possibly related to study drug (30% and 44% for 1.5 and 6 mg groups, respectively, and 39% for placebo).

The most commonly reported (≥10%) TEAEs were headache and psychotic disorder in the placebo group; insomnia in the paliperidone ER 1.5 mg group; and headache, insomnia, and tremor in the paliperidone ER 6 mg group. Other notable TEAEs were schizophrenia (1.6% in the placebo group, 7.6% in the paliperidone ER 1.5 mg group, and 5.7% in the paliperidone ER 6 mg group) and psychotic disorder (14.1%, 7.6%, and 4.3% in the respective groups).

The percentages of subjects who experienced EPS-related AEs were higher in the paliperidone ER 6 mg group compared with those in the placebo and paliperidone ER 1.5 mg groups. The highest incidence was for tremor (10% in the paliperidone ER 6 mg group vs. 3% in the other 2 groups). Tardive dyskinesia, dystonia, oculogyric crisis, and trismus occurred only in the paliperidone ER 6 mg group.

The incidence of subjects with treatment-emergent orthostatic hypotension at any time during the double-blind treatment phase was higher in the paliperidone ER 6 mg group (10%) compared with those in the placebo group (5%) and paliperidone ER 1.5 mg group (3%). In addition, the incidence of abnormally high increases in pulse rate and in diastolic blood pressure was highest in the paliperidone ER 6 mg group; however, these differences were not significant.

One subject in each of the treatment groups had a normal average predose and a maximum postdose ECG value in the range of greater than 450 to 480 ms for the following 3 QTc parameters: QTcLD, QTcF, and QTcL. Three subjects in the placebo group and 1 subject in the paliperidone ER 6 mg group had a maximum postdose value in the range of greater than 450 to 480 ms and a normal average predose value for the QTcB parameter. Additionally, 1 subject in the paliperidone ER 6 mg group showed a maximum QTcB postdose value in the range of greater than 480 to 500 ms with a normal average predose value. No subject in the study had a QTc value greater than 500 ms after baseline. Maximum increases from baseline greater than 60 ms were observed for 1 subject in the paliperidone ER 6 mg group for each of the QT correction methods.

The mean percent weight changes from baseline at end point were +0.7%, +2.5%, and +0.7% in the placebo, the paliperidone ER 1.5 mg, and the paliperidone ER 6 mg group, respectively. Although the mean

percent change was highest in the paliperidone ER 1.5 mg group, the percent of subjects with a weight increase of 7% or more from baseline to end point was similar across treatment groups.

There was a larger mean increase from baseline at end point in prolactin levels in male and female subjects randomly assigned to the 2 paliperidone ER groups compared with those in the placebo group, with the largest mean increase seen in the 6 mg group. No potentially prolactin-related AEs were reported.

Safety Conclusions

- Overall, safety and tolerability findings were consistent with those previously observed in schizophrenia studies, and no new safety signals emerged from this study.
- The pattern of events reported for paliperidone ER during this 6-week double-blind study was similar to that previously observed in the Phase 3 studies in schizophrenia. No deaths were reported during the study.
- The finding that the rate of discontinuations due to AEs was numerically higher in both the placebo group (7.8%) and paliperidone ER 1.5 mg group (10.6%) than in the paliperidone ER 6 mg group (2.9%), coupled with the observation that psychotic disorder, the most frequent TEAE leading to discontinuation, was reported as the reason for discontinuation with similar frequencies in the placebo (6.3%) and paliperidone ER 1.5 mg (6.1%) groups, corroborates the primary efficacy observations. Further, the frequency of SAEs was higher in the placebo and the paliperidone ER 1.5 mg groups than in the paliperidone ER 6 mg group, with all of the SAEs being psychiatric events consistent with the underlying disease state.
- Based on mean changes from baseline to end point and the incidence of treatment-emergent markedly abnormal laboratory test values and AEs related to abnormal laboratory analyte findings, the effects of paliperidone ER on the results of chemistry and hematology laboratory tests did not show clinically relevant differences from those of placebo, with the exception of mean prolactin levels.

STUDY LIMITATIONS: There were no study limitations

CONCLUSION: This study, designed to determine the minimum effective dose of paliperidone ER, did not demonstrate efficacy of paliperidone ER at daily doses of 1.5 and 6 mg in the treatment of schizophrenia. The primary efficacy endpoint analysis is supported by the secondary endpoint analyses, as well as by the pattern of AEs and discontinuations. No firm conclusions can be drawn from these results because of the markedly high placebo response rate observed in the primary efficacy measurement.