SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: 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-1010

Title of Study: A Double-Blind, Placebo-Controlled, Randomized Study Evaluating the Effect of ER OROS® Paliperidone Compared with Placebo on Sleep Architecture in Subjects with Schizophrenia

Coordinating Investigator: Jean-Paul Macher, M.D. - ███████████████████████████ France

Publication (Reference): none

Studied Period (years): Clinical Conduct: 01 March 2005 - 18 August 2005 Sample Analysis: 26 August 2005 - 29 August 2005	**Phase of development:** 2a

Objectives: The primary objective of this study was to evaluate the change in the sleep architecture of subjects with schizophrenia and schizophrenia-related insomnia, treated with either 9 mg extended-release (ER) OROS paliperidone or placebo. Polysomnograph measurements were used in the assessment. The correlation between changes in the Positive and Negative Syndrome Scale (PANSS) scores and the changes in polysomnographic parameters from baseline to the end of the study were evaluated. The secondary objectives of the study were to assess the safety, tolerability, and pharmacokinetics (PK) of ER OROS paliperidone and to explore the relationship between the PK and pharmacodynamics (PD) of paliperidone.

Methodology: This was a multicenter, double-blind, randomized, placebo-controlled study in subjects with schizophrenia and schizophrenia-related insomnia. The study design incorporated a screening period lasting up to 14 days, a washout phase of up to 7 days (except where less time was needed to wash out prohibited medications) and 3 baseline days. All subjects received placebo on Days -2 and -1. Polysomnograms (PSGs) were recorded on all 3 baseline days to acclimate subjects to PSG procedures, for screening purposes, and to establish baseline values. The double-blind phase lasted 15 days. Subjects were hospitalized beginning on Day -3 until the completion of the study on Day 15 (Subjects could be kept in the hospital during the washout period, and hospitalization could be prolonged beyond the end of the study, if the investigator judged this to be necessary to accomplish washout safely or to stabilize the subject).

Number of Subjects (planned and analyzed): Planned: 30 subjects (paliperidone group, 15: placebo group, 15). Analyzed: 42 subjects (42 subjects for safety, 17 subjects for PK, 36 subjects for PD).

Diagnosis and Main Criteria for Inclusion: Eligible subjects were men and women aged 18 through 45 years, with a DSM-IV diagnosis of schizophrenia accompanied by schizophrenia-related insomnia, an apnea/hypopnea index of <10, a periodic leg movement (PLM) score with an arousal index of <10 for the PSG on Day–2, and meeting all other inclusion criteria for the study. Subjects were to weigh ≥50 kg (≥110 lbs), with a BMI ≥18 and ≤35 kg/m^2. Female subjects were to be postmenopausal for at least 2 years, surgically sterile, or practice an effective method of birth control.

Test Product, Dose and Mode of Administration, Batch No.: ER OROS paliperidone 9 mg capsules; oral administration on Days 1-14, Batch Nos. 04D26/F023 and 04E04/F023.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo capsules; oral administration on Days 1-14, Batch No. 04B02/F027.

Duration of Treatment: Fourteen days with double blind study medication.

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Criteria for Evaluation:

Pharmacokinetics: Venous blood samples for PK evaluations were taken predose on Days 3, 6, 9, 10, 12, 13, and 14; and after administration of drug at 2, 4, 6, 9, 12, and 24 hours on Day 10. Blood was collected 24 hours after drug administration on Day 14. The following PK parameters were estimated for paliperidone: predose plasma concentration ($C_{predose,Dx}$), observed maximum plasma concentration over a dosing interval at steady state ($C_{max,ss}$), observed minimum plasma concentration over a dosing interval at steady state ($C_{min,ss}$), time to reach the maximum plasma concentration at steady state ($t_{max,ss}$), area under the plasma concentration-time curve from zero to time 24 hours over a dosing interval at steady-state ($AUC_{24h,ss}$), average plasma concentration at steady-state, ($C_{avg,ss}$), and plasma concentration fluctuation index (peak/trough variation or FI). All PK parameters, with the exception of $C_{predose,Dx}$, were estimated from the plasma concentration data of Day 10 only. Steady-state was assessed graphically.

Pharmacodynamics: The PSGs were administered on Days −3 to −1 and on Days 13 and 14 and were used for pharmacodynamic sleep measurements, including but not limited to: Stage 2, Stage 3, and Stage 4 sleep, slow wave sleep (SWS), total rapid eye movement (REM) time, REM latency, total REM activity, total sleep time, latency to onset and persistent sleep, sleep efficiency index, number of microarousals and awakenings, and duration of time awake following sleep onset. The Leeds Sleep Evaluation Questionnaire (LSEQ) was administered and evaluated daily. Efficacy measures included the PANSS and the Clinical Global Impression Scale-Severity (CGI-S).

Safety: Evaluations included adverse events, vital signs, physical examinations, laboratory results including pregnancy test, and review of concomitant therapies. The following were also used to assess safety: Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and the Simpson Angus Scale (SAS).

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for the plasma concentrations of paliperidone at each sampling time and for the derived PK parameters. Graphical presentations were also done.

Pharmacodynamics: The PSGs were used for pharmacodynamic sleep measurements (see above). For each parameter scored, the average of the 2 measurements obtained on Days -2 and -1 was taken as the baseline value. If either of these 2 observations was missing, the assessment on the single study day available (either Day −2 or -1) was to be used as the baseline value. When available, the last 2 measurements obtained at the end of the double-blind period (generally on Days 13 and 14) were averaged to obtain the post-treatment endpoint value. If only 1 post-baseline PSG evaluation was available at the end of double-blind period, that value was used as the end point observation. An analysis of variance (ANOVA) model was used for the change from baseline in all of the PSG variables with the treatment (paliperidone, placebo) as a fixed effect. The statistical comparison of the changes from baseline at end point between treatment groups was performed by the 2-sided 90% confidence intervals approach, without adjustment for multiple confidence intervals. Correlations among 3 PSG variables (total sleep time, sleep efficiency index, and SWS duration) and the PANSS total score, in terms of change from baseline at end point, were calculated using the Pearson's correlation coefficient. Descriptive statistics per treatment and time point were used to summarize all sleep-related variables, including LSEQ scores, and their changes from baseline.

Efficacy: For PANSS scores (and subscores), shifts from baseline were calculated for all items. Descriptive statistics were calculated by treatment and time point. The CGI-S scores were summarized with incidence tables by treatment and time point.

Pharmacokinetic/Pharmacodynamic relationships: The PK/PD relationships were explored graphically by plotting $AUC_{24h,ss}$ (on Day 10) versus the following PSG parameters: number of microarousals during total sleep time, latency to sleep onset and persistent sleep, sleep efficiency index, total sleep time, duration of time awake after sleep onset, REM latency, REM sleep duration, and REM activity.

Safety: The incidences of adverse events, including those that were serious, lead to discontinuation, or were of clinical interest, were summarized for each treatment group by body system and preferred term. For each treatment group, the clinical laboratory results and vital signs were summarized using descriptive statistics and listed for each subject at each measurement time point. Medical history abnormalities and concomitant therapies were listed. Changes from baseline for the AIMS, BARS, and SAS evaluations were summarized by treatment group and time point using descriptive statistics.

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SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: Steady-state plasma concentrations of paliperidone were achieved within 3 to 6 days of once-daily dosing of 9 mg ER OROS paliperidone. The mean predose paliperidone plasma concentration on Day 6 was 38.5 ng/mL and 36.9 ng/mL at the day of PSG assessments (Day 14 and 15). The mean $C_{predose,Dx}$ of paliperidone on Day 10 was 31.7 ng/mL. After 10 days of once-daily administration of 9 mg ER OROS paliperidone, a low mean FI of 43.4% at steady state was observed. The mean total exposure ($AUC_{24h,ss}$) and $C_{avg,ss}$ over the dosing interval were 882 ng.h/mL and 36.7 ng/mL, respectively, while the mean $C_{max,ss}$ was 46.5 ng/mL.

PHARMACODYNAMIC RESULTS: The treatment groups were well matched at baseline in terms of sleep parameters. Although not clinically relevant, a few numerical imbalances were noted in the mean baseline values including, an increased Stage 2, REM, and total sleep duration as well as REM activity and density in the placebo group as compared with the ER OROS paliperidone group. On the other hand, the mean Stage 4 sleep duration and proportion, as well as latency to sleep onset, persistent sleep, and REM sleep were longer in the ER OROS paliperidone group. These findings were generally not considered clinically relevant. The PSG results are shown below and indicate that ER OROS paliperidone improved sleep architecture and sleep continuity. No clinically relevant effect on REM sleep was observed.

Sleep parameter[a]	Placebo (N=19)	ER OROS Paliperidone 9 mg (N=17)	Mean Difference	
Sleep duration (minutes)				
Stage 1	+1.4 (2.17)	-10.5 (4.02)	-11.9 (4.44)	*
Stage 2	-15.3 (11.07)	+35.4 (14.00)	+50.7 (17.67)	*
Stage 3	-1.9 (2.30)	+2.4 (2.85)	+4.2 (3.63)	
Stage 4	+2.4 (5.01)	-6.2 (6.55)	-8.6 (8.15)	
REM	-10.9 (6.41)	+7.4 (6.75)	+18.3 (9.31)	*
Slow wave (Stage 3 and 4)	+0.5 (6.01)	-3.9 (7.47)	-4.4 (9.50)	
Sleep proportion (%)[b]				
Stage 1	+0.6 (0.48)	-2.7 (0.89)	-3.3 (0.98)	*
Stage 2	-2.1 (2.22)	+4.9 (2.80)	+7.0 (3.54)	*
Stage 3	-0.4 (0.54)	+0.3 (0.62)	+0.7 (0.82)	
Stage 4	+0.7 (1.11)	-2.6 (2.32)	-3.2 (2.49)	
REM	-2.3 (1.37)	+1.0 (1.59)	+3.3 (2.09)	
Slow wave (Stage 3 and 4)	+0.3 (1.33)	-2.3 (2.50)	-2.6 (2.74)	
Other REM sleep parameters				
Latency to REM sleep (minutes)	+30.1 (10.75)	+13.6 (14.83)	-16.5 (18.05)	
REM sleep density (no. REM/hour)	-62.0 (36.23)	+4.1 (19.85)	+66.1 (42.70)	
Sleep continuity				
Total sleep time (minutes)	-24.4 (17.89)	+28.5 (15.62)	+52.8 (24.01)	*
Sleep period time (minutes)	-17.0 (11.19)	+24.7 (15.40)	+41.7 (18.75)	*
Latency to sleep onset (minutes)	+12.8 (8.53)	-22.5 (12.67)	-35.2 (14.99)	*
Latency to persistent sleep (minutes)	+14.9 (10.84)	-26.1 (15.63)	-41.0 (18.70)	*
Sleep efficiency index (%)	-5.0 (3.71)	+6.0 (3.28)	+11.0 (5.00)	*
Awakenings after sleep onset (no.)	+0.3 (2.66)	-6.7 (2.83)	-7.0 (3.88)	*

[a] Results are presented as mean (SE). [b] Sleep proportion values are relative to sleep period time.
* Statistically significant difference between groups for the mean changes (ER OROS paliperidone - placebo) at 10% level.

ER OROS paliperidone increased the subjective LSEQ sleep quality (+2.4 mm), ease of awakening from sleep (+9.5 mm), and behavior following wakefulness scores (+1.9 mm) over placebo at endpoint but the between-group differences were not statistically significant. The association between change in PANSS scores and change in total sleep time, sleep efficiency index, and SWS duration was evaluated. The magnitude of the linear correlation coefficients was variable and generally small.

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PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: There is no relationship between steady-state $AUC_{24h,ss}$ values and selected PSG parameters (REM sleep duration, REM activity, REM latency, total sleep time, latency to sleep onset and persistent sleep, sleep efficiency index, number of microarousals during total sleep time, and duration of time awake after sleep onset).

EFFICACY RESULTS: The PANSS total mean scores were low at baseline and decreased by 7.8 points from baseline to end point, indicating improvement in the severity of neuropsychiatric symptoms, in the ER OROS paliperidone group. There was a smaller mean decrease (-1.2 points) in the placebo group. Based on CGI-S scores, a slight improvement of ER OROS paliperidone over placebo treatment was observed at endpoint.

SAFETY RESULTS: The most commonly reported adverse events, each occurring in 2 subjects, were dystonia, extrapyramidal disorder, headache, and oculogyric crisis in the ER OROS paliperidone group and hyperkinesia, psychosis, somnolence, and nausea in the placebo group. Most of the observed adverse events were mild to moderate in severity. Among the EPS-related adverse events, a higher incidence of extrapyramidal disorder, dystonia oculogyric crisis, and dyskinesia was observed in the ER OROS paliperidone groups compared with placebo. These findings were supported by separate evaluations using the AIMS, BARS, and SAS instruments. There were generally no noteworthy changes for laboratory indices or vital sign measurements.

CONCLUSIONS: The results from polysomnographic and subjective sleep evaluations showed that treatment with ER OROS paliperidone 9 mg per day over a 14-day period results in improved sleep architecture, and sleep continuity. No clinically relevant effect on REM sleep was observed. Steady-state concentrations of paliperidone were achieved within 3 to 6 days after initiation of ER OROS paliperidone dosing. Oral administration of ER OROS paliperidone 9 mg once daily was well tolerated and provided benefit in the treatment of insomnia related to schizophrenia.

Date of the report: 3 November 2005