SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Paliperidone NAME OF ACTIVE INGREDIENT(S): Paliperidone		
Protocol No.: R076477-SCH-1014 CR011056 **Title of Study:** A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating QT/QTc Intervals Following Administration of Extended-Release Paliperidone and Quetiapine in Subjects With Schizophrenia or Schizoaffective Disorder		
Coordinating Investigator: L. Beckett, M.D. – IPS Research Company, Oklahoma City, OK, USA		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 14 February 2006 to 20 June 2006.		**Phase of development:** 1
Objectives: The primary objective of this study was to determine whether the effect on QT interval corrected for heart rate using the population specified linear derived method (QTcLD) at steady state is comparable between 12 mg paliperidone extended-release (ER) once daily and that of 400-mg quetiapine administered twice daily. The secondary objectives were to explore the relationship between the pharmacokinetics of paliperidone ER and electrocardiogram (ECG) parameters of interest and to explore the cardiovascular safety and tolerability of 18-mg paliperidone ER at steady state. The safety and tolerability of all treatments were evaluated.		
Methodology: This multicenter, placebo- and positive-controlled, randomized study consisted of 3 phases – a screening phase of up to 5 days, a 6-day placebo washout phase, and a treatment phase that included 1-day of open-label moxifloxacin treatment (Day 1), 10 days of double-blind treatment (Days 2 to 11), and end of study evaluations (Day 12). On Day 1, all subjects received open-label treatment with a single dose of 400-mg moxifloxacin administered in the morning. Moxifloxacin was used to establish assay sensitivity on the QTc interval. Subjects were then randomly assigned to receive double-blind treatment with placebo, paliperidone ER, or quetiapine on Days 2 to 11. Two doses of paliperidone ER were studied: 12 mg/day that is the maximum recommended dose and 18 mg/day that is a supratherapeutic dose (50% above the maximum recommended). Subjects randomly assigned to paliperidone ER were administered 12 mg on Days 2 to 6, 15 mg on Day 7, and 18 mg on Days 8 to 11. Subjects randomly assigned to quetiapine received 100 mg bid on Day 2, 200 mg bid on Day 3, 300 mg bid on Day 4, and 400 mg bid on Days 5 to 11. During the double-blind phase, in order to preserve the blind, all subjects across the treatment groups received an equal number of identical capsules – 2 capsules twice daily (morning and evening intake). In order to standardize the dosing relationship with respect to food intake, subjects received double-blind study drug 30 minutes after having a standardized breakfast on Days 2 to 11. Serial time matched 12-lead ECG triplicate readings were recorded on Days -2, -1, 6, and 11 (predose and 1, 1.5, 2.5, 3.5, 4.5, 6, and 12 hours postdose) as well as Day 1 (predose, 1, 1.5, 2.5, 3.5 hours postdose) and Days 7 and 12 (23.5 hours postdose).		
Number of Subjects (planned and analyzed): A sufficient number of subjects were planned to be enrolled to ensure that at least 100 subjects (40 subjects in each active treatment group and 20 in the placebo group) completed the predose ECG and pharmacokinetic assessments on Day 7. A total of 110 subjects were randomly assigned to treatment, 109 subjects were included in the safety analysis set, 96 subjects were included in the primary pharmacodynamic analysis set, and 91 subjects were included in the secondary pharmacodynamic analysis set.		
Diagnosis and Main Criteria for Inclusion: Men and women, between 18 and 50 years of age (inclusive), with stable symptoms and having a diagnosis of schizophrenia or schizoaffective disorder as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria with a normal 12-lead ECG at screening, a body mass index between 18 and 35 kg/m^2 (inclusive) and a body weight of at least 50 kg were enrolled in the study.		
Test Product, Dose and Mode of Administration, Batch No.: Paliperidone 6 mg and 9 mg ER tablets (overencapsulated) (batch/lot nos: 05F02/F061 and 05A10/F023); Paliperidone ER capsules were administered orally once daily: 12 mg (2 x 6 mg) on Days 2 to 6; 15 mg (9 mg and 6 mg) on Day 7, and 18 mg (2 x 9 mg) on Days 8 to 11. Subjects randomly assigned to paliperidone ER received 2 paliperidone ER capsules in the morning and 2 matching placebo capsules in the evening.		

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Reference Therapy, Dose and Mode of Administration, Batch No.: Assay sensitivity: A single moxifloxacin 400 mg tablet (batch/lot no: 5400CL8) was administered on Day 1 (open-label).

Active control: Quetiapine 100 mg and 200 mg tablets (overencapsulated) (batch/lot nos: 05K10/F272 and 05K14/F273); Subjects randomized to quetiapine received 1 quetiapine 100 mg capsule plus 1 placebo capsule administered bid on Day 2; one 200 mg capsule plus 1 placebo capsule bid on Day 3; one 100 mg and 200 mg bid capsules on Day 4; and two 200 mg capsules bid on Days 5 to 11.

Placebo to match paliperidone ER and quetiapine (batch/lot no: 05F03/F027). Placebo capsules were administered once daily for 6 days during the open-label placebo washout phase. During the double-blind phase, subjects randomly assigned to placebo received 2 placebo capsules twice daily on Days 2 to 11.

Duration of Treatment: 1 day of open-label moxifloxacin (Day 1), 10 days of double-blind treatment (Days 2 to 11) with placebo, paliperidone ER, or quetiapine, and end of study evaluations (Day 12).

Criteria for Evaluation:

Pharmacokinetics: Concentrations of paliperidone (R076477) and quetiapine in plasma were determined. Based on the individual plasma concentration-time data, the following pharmacokinetic parameters were estimated for paliperidone and quetiapine: $C_{predose,\ Dx}$; C_{min}; C_{max}; t_{max}; AUC_{τ}; $C_{avg,ss}$ and FI.

Pharmacodynamics: The ECG parameters evaluated included QT and heart rate corrected QT (QTc), RR, PR interval, QRS interval, T- and U-wave morphologies. The primary method for calculation of heart rate corrected QT interval was QTcLD. The QTcLD method was considered most appropriate as it incorporates all of the drug-free QT/RR interval data of the study in the linear modelling to derive the study-specific correction formula. For completeness, QT was also corrected for heart rate using the traditional formulae of Fridericia (QTcF) and Bazett (QTcB).

Safety: Evaluations included adverse events, concomitant medications, clinical laboratory tests (hematology, chemistry, and urinalysis), vital sign measurements, physical examination, extrapyramidal symptoms (EPS) rating scales, and the Clinical Global Impression-Severity (CGI-S).

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for the plasma concentrations at each sampling time and pharmacokinetic parameters of paliperidone and quetiapine.

Pharmacodynamics: The primary comparison of interest was the Days 6-7 on-treatment changes from baseline in QT interval corrected for heart rate using the linear derived method (ΔQTcLD) between once daily paliperidone ER 12 mg and quetiapine 400 mg twice daily at individual's observed t_{max}.

For each treatment group and by sex, QTc changes from baseline were summarized for the following categories - between 30-60 ms and >60 ms, and the absolute QTc interval prolongation was summarized for QTc intervals >450 ms, >480 ms, and >500 ms.

Pharmacokinetics/Pharmacodynamics: The relationships between ECG parameters were evaluated using graphical techniques. The relationship of drug concentration with the QT-interval was limited to correlations with QTcLD, being the primary correction method used in the statistical evaluation.

Safety: The incidence of adverse events was summarized for each treatment group (placebo, paliperidone ER 12 up to 18 mg, quetiapine, and moxifloxacin) as well as by paliperidone ER dose (12 mg and 15 or 18 mg). Descriptive statistics were provided for the other safety parameters for each treatment group.

Analysis Sets: The analyses of ECG parameters are presented for the primary and secondary pharmacodynamic analysis sets. The primary pharmacodynamic analysis set included 96 subjects who received the double-blind study medication they were randomized to, completed predose ECG and pharmacokinetic assessments on Day 7, and did not deviate from the protocol by taking excluded concomitant medications during the double-blind period or significantly deviate from the protocol defined treatment between Days 2 and 6 (inclusive). The secondary pharmacodynamic analysis set included 91 subjects who received the double-blind study medication they were

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randomized to, completed all study evaluations until Day 12, and did not deviate from the protocol by taking excluded concomitant medications during the double-blind period or significantly deviate from the protocol defined treatment between Days 2 and 11 (inclusive). The categorical analyses of QTc interval data and other safety summaries included 109 subjects who were randomly assigned to treatment and received at least 1 dose of study medication in the double-blind period, i.e., the safety analysis set.

SUMMARY – CONCLUSIONS

PHARMACODYNAMIC RESULTS: The primary comparison of interest was the change from baseline in QTcLD between once daily paliperidone ER 12 mg and quetiapine 400 mg twice daily at individual's observed t_{max} on Days 6-7 (steady state). At steady state the least squares mean change from baseline in QTcLD at each individual's observed t_{max} was 1.1 ms for paliperidone ER 12 mg and 6.1 ms for quetiapine. Given that the mean difference in QTcLD between paliperidone ER 12 mg and quetiapine was estimated to be 5.1 ms lower for paliperidone ER 12 mg with the upper limit of the 2-sided 90% CI [-9.2, -0.9] not exceeding 10 ms, noninferiority of once daily paliperidone ER 12 mg compared to quetiapine 400 mg twice daily is concluded.

A similar comparison was performed between a supratherapeutic dose of paliperidone ER (18 mg) and quetiapine 400 mg twice daily. At steady state, the mean change from baseline in QTcLD at individual's observed t_{max} was 3.7 ms for paliperidone ER 18 mg and 6.0 ms for quetiapine, and the mean difference in QTcLD between paliperidone ER 18 mg and quetiapine was estimated to be 2.3 ms lower (90% CI [-6.8, 2.3]) for paliperidone ER 18 mg. The upper limit of the 2-sided 90% confidence interval was <10 ms.

Assay sensitivity was established by evaluating the change in QTc using a single dose of moxifloxacin 400 mg. At 1 hour postdose, the least squares mean difference in QTcLD between moxifloxacin on Day 1 and baseline placebo was estimated to be 4.1 ms (90% CI [2.7, 5.5]).

At steady state, the maximum difference (4 hours 30 minutes postdose) in mean QTcLD change from baseline between paliperidone ER 12 mg and concurrent placebo was estimated to be 10.2 ms (90% CI [5.0, 15.5]), and between quetiapine and concurrent placebo, the maximum difference (2 hour 30 minutes postdose) was estimated to be 8.1 ms (90% CI [3.8, 12.5]).

At steady state, the maximum difference (4 hours 30 minutes postdose) in mean QTcLD change from baseline between paliperidone ER 18 mg and concurrent placebo was estimated to be 7.6 ms (90% CI [3.2, 11.9]), and between quetiapine and concurrent placebo, the maximum difference (2 hours 30 minutes postdose) was estimated to be 5.4 ms (90% CI [0.5, 10.2]).

No subjects in the paliperidone ER, quetiapine, or concurrent placebo groups had a QTcLD increase >60 ms. No subjects across the treatment groups had a QTcLD interval >480 ms at any time during the study, while 1 female subject in the paliperidone ER group had at least 1 observation of a QTcLD interval >450 ms on Days 11 and 12.

PHARMACOKINETIC RESULTS:

Paliperidone: On Days 6 and 11, paliperidone was at steady state. On Days 6 and 11, the mean (SD) C_{max} of 34.6 (16.2) ng/mL and 54.0 (27.6) ng/mL, respectively, was achieved between 22 to 36 hours after dosing. On average, a 1.5 times higher exposure (based on C_{max} and AUC_{τ}) was observed when comparing 18 with 12 mg paliperidone ER. A low mean fluctuation index on Days 6 and 11 was observed (59.9 and 45.9%, respectively).

Quetiapine: On Days 6 and 11, quetiapine was at steady state. On Days 6 and 11, the mean (SD) C_{max} of 1183 (370) ng/mL and 1262 (512) ng/mL, respectively, were achieved at a mean t_{max} of approximately 2.40 hours postdose at both days. The mean fluctuation index at steady state was 191 and 215% on Days 6 and 11, respectively.

PHARMACOKINETIC/PHARMACODYNAMIC RESULTS:

The observed trend between the mean change from baseline QTcLD versus mean paliperidone plasma concentration for 12 mg (Day 6) and 18 mg (Day 11) paliperidone ER at each time point of measurement suggests a possible correlation between plasma exposure and effect.

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SAFETY RESULTS: There were no deaths during the study. Three subjects experienced a serious treatment-emergent adverse event, including 1 in the placebo group, 1 in the paliperidone ER group, and 1 in the quetiapine group. Four subjects discontinued the study due to an adverse event, including 2 in the paliperidone ER group and 2 in the quetiapine group. No subjects discontinued the study due to a serious adverse event.

Paliperidone ER: The most commonly reported adverse events (≥10%) in paliperidone ER-treated (12 up to 18 mg) subjects were headache (23%), somnolence (23%), tachycardia (11%), akathisia (11%), dizziness (11%), and sedation (11%). The treatment-emergent adverse events reported in subjects receiving paliperidone ER were consistent with previous paliperidone studies.

Quetiapine: The most commonly reported adverse events (≥10%) in quetiapine-treated subjects were somnolence (35%), dry mouth (30%), tachycardia (19%), sedation (16%), headache (14%), orthostatic hypotension (14%), sinus tachycardia (12%), dyspepsia (12%), and dizziness (12%).

The most commonly reported adverse events (≥10%) in placebo-treated subjects were somnolence (18%) and headache (14%). There were no adverse event reported in ≥10% of moxifloxacin-treated subjects on Day 1; the most common adverse event was headache (2%).

Across the treatment groups, no adverse events were reported in terms suggestive of proarrhythmic potential as defined in the International Conference on Harmonisation (ICH) E14 guidance (i.e., syncope, seizure, ventricular tachycardia, ventricular fibrillation and flutter, torsades de pointes, and adverse events consistent with sudden death).

More subjects in the quetiapine (14%) group than in the paliperidone ER (5%) group (12 up to 18 mg) experienced at least 1 incidence of orthostatic hypotension during the study, while no subjects in the placebo group experienced these changes. As assessed by orthostatic changes in pulse rate and blood pressure, treatment-emergent orthostatic hypotension occurred in more subjects in the quetiapine group (30%) than in the paliperidone ER (12 up to 18 mg) group (11%), while no subjects in the placebo group experienced these changes. Three subjects in the quetiapine group and no subjects in the paliperidone ER group (12 up to 18 mg) with at least 1 observed incidence of treatment-emergent orthostatic hypotension changes in pulse rate and blood pressure had orthostatic hypotension reported as an adverse event, suggesting that these findings are of limited clinical relevance.

Akathisia was the most frequently reported EPS-related adverse event and occurred in 11% of paliperidone ER-treated subjects (1 in the 12 mg group and 4 in the 15 or 18 mg group) and 7% of quetiapine-treated subjects. Results of EPS rating scale did not reveal a change in either the incidence or severity of movement disorders. Benztropine was allowed for the treatment of EPS and was taken by 16% of paliperidone ER-treated (12 up to 18 mg) subjects and 9% of quetiapine-treated subjects. As EPS-related adverse events occur usually at treatment initiation, most of these events were reported during the treatment with paliperidone ER 12 mg (Days 2 to 6) and appropriately treated with anti-EPS medication at that time.

There were no clinically noteworthy changes in supine systolic and diastolic blood pressure measurements, or body temperature. More subjects had hepatic enzyme abnormalities in the quetiapine group than in the paliperidone ER treatment group (12 up to 18 mg). Across all treatment groups, there was an increase in body weight from the screening visit (1.9 kg for paliperidone ER [12 up to 18 mg], 2.3 kg for quetiapine, and 0.9 kg for placebo).

CONCLUSION:

Paliperidone ER at the maximum recommended dose of 12 mg/day was shown to be noninferior to quetiapine 400 mg twice daily (morning and evening intake) with respect to QTcLD prolongation in subjects with schizophrenia. The QTcLD prolongation observed with paliperidone at a supratherapeutic dose of 18 mg was less than quetiapine 400 mg twice daily. However, these data also indicate that both doses of paliperidone ER, 12 mg and 18 mg, and quetiapine 400 mg twice daily were associated with QTcLD prolongation compared to concurrent placebo. The clinical relevance of these small QTcLD increases is limited.

Taken together, results of the current study continue to support the cardiovascular safety of the ER formulation of paliperidone at the maximum recommended dose of 12 mg/day and a dose up to 50% above this recommendation.

Date of the report: 4 December 2006

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