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-1009 CR004201 **Title of Study:** A Placebo- and Positive-Controlled, Randomized Study Evaluating QT and QTc Intervals Following Administration of Immediate-Release Paliperidone in Subjects with Schizophrenia or Schizoaffective Disorder		
Coordinating Investigator: Howard A. Hassman, D.O., CNS Research Institute P.C., Clementon, New Jersey, USA		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 2 February 2005 to 26 May 2005.		**Phase of development:** 1
Objectives: The primary objective of this study was to assess the cardiovascular safety of paliperidone in subjects with schizophrenia or schizoaffective disorder, with particular attention to the length of the QT/QTc interval. Other electrocardiogram (ECG) parameters, such as QRS and PR intervals, were also measured and reviewed. The secondary objectives of the study were to explore the relationship between the pharmacokinetics of paliperidone and ECG parameters of interest, as well as to explore the safety and tolerability of paliperidone.		
Methodology: This multicenter, placebo- and positive-controlled, randomized study consisted of 3 periods – a screening period of up to 14 days (including a 5-day washout period), a double-blind period of 10 days (including the treatment phase [Days 1 to 8] and the posttreatment phase [Days 9 and 10]), and an end-of-study evaluation. Eligible subjects were randomly assigned to treatment with either paliperidone or moxifloxacin. Subjects randomly assigned to receive paliperidone were administered placebo on Day 1, paliperidone 4 mg on Day 2, paliperidone 6 mg on Day 3, and paliperidone 8 mg on Days 4 through 8. Subjects assigned to receive moxifloxacin were administered placebo on Days 1 through 7 and moxifloxacin 400 mg on Day 8. The moxifloxacin treatment group provided a concurrent active control to confirm that the study was adequate to detect a drug effect (i.e., assay sensitivity) on QTc interval. Baseline ECGs were recorded on the last day of the washout period (Day -1). Serial time matched 12-lead ECG triplicate readings were recorded on Days 1, 2, 3, 4, 5 (predose), 8, 9, and 10.		
Number of Subjects (planned and analyzed): Approximately 125 subjects were planned to be enrolled to ensure that at least 100 subjects (50 subjects in each treatment group, with at least 10 women in each group) completed the study. A total of 141 subjects were randomly assigned to treatment; 141 subjects were included in the safety analysis set, 102 subjects were included in the pharmacodynamic analysis set.		
Diagnosis and Main Criteria for Inclusion: Men and women, 18 to 50 years of age, with a diagnosis of schizophrenia or schizoaffective disorder as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria and no exacerbation of psychosis for at least 3 months before screening were eligible. Subjects had a normal 12-lead ECG, including normal sinus rhythm (heart rate between 50 and 100 bpm), QTcB interval ≤430 ms for men and ≤450 ms for women, QRS interval <110 ms, and PR interval <200 ms.		
Test Product, Dose and Mode of Administration, Batch No.: Immediate release (IR) paliperidone 2 mg capsules (batch/lot nos: 04J25/F052 and 05B02/F052). Paliperidone capsules were administered orally once daily: 4 mg on Day 2, 6 mg on Day 3, and 8 mg on Days 4 through 8.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Active control: a single oral dose of overencapsulated moxifloxacin 400 mg tablet (batch/lot nos: 04H04/F302 and 05B01/F302) was administered on Day 8. Placebo to match paliperidone (batch/lot nos: 04J18/F051 and 04L20/F051). Placebo to match moxifloxacin (batch/lot nos: 04H02/F301 and 04L21/F301).		
Duration of Treatment: 8 days		

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Criteria for Evaluation:

Pharmacokinetics: The following plasma paliperidone parameters were estimated: $C_{predose,\ Dx}$; C_{min}; C_{max}; t_{max}; AUC_{24h}; $C_{avg,ss}$; FI; λ_z; and $t_{1/2,\lambda z}$. Achievement of steady state was explored graphically by plotting the predose plasma concentrations on Days 4, 5, 6, 7, and 8.

Pharmacodynamics: 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), Sagie (QTlc), and Bazett (QTcB).

Safety: Evaluations included adverse events, clinical laboratory tests (hematology, chemistry, and urinalysis), vital sign measurements (supine blood pressure, pulse, and oral temperature), and physical examination.

Statistical Methods:

Pharmacokinetics: Descriptive statistics were calculated for the sampling times relative to dosing, the plasma concentrations of paliperidone at each sampling time, and the pharmacokinetic parameters.

Pharmacodynamics: The primary ECG variable was the difference in day-averaged QTcLD between IR paliperidone 8 mg at steady state (Day 8) and placebo (Day 1). Since administration of IR paliperidone 8-mg dose produces supratherapeutic plasma concentrations, it was of interest to examine the other day-differences with placebo on matching time points within the paliperidone arm. QTc changes relative to time-matched placebo (Day 1) measurements were summarized for QTc interval increase from baseline between 30-60 ms, and >60 ms. Absolute QTc interval prolongation was summarized for QTc intervals >450 ms, >480 ms, and >500 ms.

Pharmacokinetics/Pharmacodynamics: The potential relationship between plasma paliperidone concentration and change in QTcLD interval was examined graphically for i) QTcLD at each time point vs corresponding plasma concentration, ii) maximum QTcLD vs the corresponding plasma concentration, and iii) QTcLD, t_{max} against the corresponding C_{max}.

Safety: The incidence of adverse events was summarized for each treatment. Descriptive statistics were provided for the other safety parameters.

Analysis Sets: The primary and secondary analyses of ECG parameters are presented for the pharmacodynamic analysis set, which included 102 subjects who were randomly assigned to trial treatment, received at least 1 dose of double-blind study medication, completed the study through the ECG assessments on Days 9 and 10, and had plasma paliperidone concentrations consistent with appropriate administration of study drug. The categorical analyses of QTc interval data and other safety summaries included all 141 subjects who were randomly assigned to trial treatment and received at least 1 dose of study medication, i.e., the safety analysis set.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS: After administration of a single dose of 4 mg IR paliperidone on Day 2, the mean (SD) C_{max} of 35.2 (14.9) ng/mL was achieved approximately 2 hours postdose. Steady state was reached on Day 6, i.e., on the third day of dosing 8 mg IR paliperidone. On Day 8, mean C_{min} was 34.6 (18.4) ng/mL, mean C_{max} was 113 (43.3) ng/mL, and the mean FI was 128% (30.9); mean t_{max} was 2.15 hours, ranging from 0.52 to 6.08 hours postdose. Mean values for AUC_{24h} on Days 2 and 8 were 437 (198) and 1,531 (647) ng.h/mL. On Day 8, intersubject variability (CV%) was 50.4% for predose concentrations, 38.4% for C_{max}, and 42.2% for AUC_{24h}. Mean terminal half-life was 23.2 hours (range 10.6-51.1 hours). The pharmacokinetic results confirm that, as expected, administration of repeated doses of 8 mg IR paliperidone provided Day 8 plasma concentrations (mean [SD] C_{max}=113 [43.3] ng/mL) higher than those associated with the highest dosage of ER OROS paliperidone (multiple 15 mg doses: mean [SD] C_{max}=57 [30.1] ng/mL) used in clinical development.

PHARMACODYNAMIC RESULTS: The primary ECG variable was the difference in day-averaged QTcLD between IR paliperidone 8 mg at steady state (Day 8) and placebo (Day 1). On Day 8 of IR paliperidone treatment, the least squares mean (LSM [SE]) difference in QTcLD versus Day 1 (placebo) was estimated to be 5.5 (1.09) ms; the 90% confidence limits were 3.66 and 7.25 ms. Since the upper limit of the 90% confidence interval (7.25 ms) was below the predefined limit of 10.0 ms, the mean effect of IR paliperidone 8 mg at steady-state (Day 8) on QTcLD was considered to be no worse than that of placebo (Day 1).

Since the IR paliperidone 8-mg dose produced supratherapeutic plasma concentrations, the other day-differences with placebo were evaluated on matching time points within the paliperidone arm. The upper limit of the 90% CI remained below 10.0 ms for all time points, with the exception of the 1.5-hour observations on Days 2 (11.98 ms) and 4 (12.31 ms), and the 1 to 3-hour observations on Day 8 (≤13.62 ms); Days 2 and 4 were the first days of administration of the 4-mg and 8-mg doses of IR paliperidone. In this study, t_{max} was about 2 hours, both on Day 2 (single dose 4 mg) and on Day 8 (steady state 8 mg).

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PHARMACODYNAMIC RESULTS (continued): None of the subjects in either the IR paliperidone or moxifloxacin treatment group had a QTcLD increase >60 ms. Nineteen (26%) of 72 subjects in the IR paliperidone group and 12 (17%) of 69 subjects in the moxifloxacin group had a 30-60 ms increase in QTcLD. No subject in either treatment group had a QTcLD, QTcF, or QTlc interval ≥450 ms at any time during the study.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: The relationships between plasma paliperidone concentration and change in QTcLD and between plasma paliperidone concentration and change in heart rate were examined. An increasing effect is observed on QTcLD, change from baseline QTcLD, heart rate and change from baseline with increasing concentrations of paliperidone after dosing with 4 to 8 mg paliperidone. However, no correlation was observed between different measures of plasma concentration and these effects. The results suggest that the effects of paliperidone on QTcLD and heart rate are complex, and can not be fully described by plasma concentrations alone. Other factors such as daily variation in each measure (placebo effect) and physiological adaptation of the body to compensate for the effects induced by paliperidone should be considered. An example of the latter is that while mean concentrations at Day 8 between 1.5 and 4 hours remain at 100 ng/mL, mean values of change from baseline QTcLD decrease after that time point from about 10 to about 4 ms.

SAFETY RESULTS:

The most commonly reported adverse events in IR paliperidone-treated subjects were anxiety (22%), somnolence (14%), insomnia (13%), and dizziness (13%). After administration of a single dose of moxifloxacin, the most commonly reported adverse events were anxiety (10%), somnolence (5%), insomnia (5%), and headache (5%).

In the IR paliperidone treatment group, no adverse events were reported in terms suggestive of proarrhythmic potential as defined in the ICH E14 guidance (e.g., syncope, seizure, ventricular tachycardia, ventricular fibrillation and flutter, torsade de pointes, and adverse events consistent with sudden death) during the study. In the moxifloxacin treatment group, syncope of moderate intensity after receiving a single dose of moxifloxacin 400 mg on Day 8 was the only adverse event suggestive of proarrhythmic potential. After initiation of IR paliperidone, the most common cardiovascular or heart rate and rhythm-related adverse events were tachycardia reported in 4 (6%) of 69 subjects and palpitation, prolonged QT, abnormal ECG, and abnormal ECG, specific, each reported in 2 (3%) of 69 subjects. Most of the cardiovascular or heart rate and rhythm-related adverse events were mild or moderate in intensity and considered by the investigator to be at least possibly related to study drug. None of the cardiovascular or heart rate and rhythm-related adverse events in IR paliperidone-treated subjects were serious. One IR paliperidone-treated subject discontinued from the study due to tachycardia and an abnormal ECG.

After administration of a single oral dose of moxifloxacin 400 mg on Day 8, the only cardiovascular or heart rate and rhythm-related adverse event occurring in more than 1 subject was ECG abnormal specific (2 [3%] of 62 subjects; investigator's verbatim: "P terminally negative in v1"). Most cardiovascular adverse events in moxifloxacin-treated subject were moderate in intensity and considered by the investigator to be possibly related to study drug. There were no serious cardiovascular adverse events reported among moxifloxacin-treated subjects and no moxifloxacin-treated subject discontinued from the study due to a cardiovascular adverse event.

There were no deaths during the study. Three subjects had 1 or more serious adverse events, 2 in the paliperidone group (dystonia [n=1] and extrapyramidal disorder and dyspnea [n=1]) and 1 in the moxifloxacin group (anxiety). The serious adverse events in paliperidone-treated subjects resulted in discontinuation from the study. Other adverse events resulting in discontinuation from the study were hyperkinesia (n=1), dystonia and hypertonia (n=1), tachycardia and abnormal ECG (n=1), bradykinesia (n=1), and tetany (n=1) in the paliperidone treatment group and paresthesia (n=1) in a placebo-treated subject assigned to receive moxifloxacin. There were no clinically noteworthy changes in clinical laboratory analyte values, supine systolic and diastolic blood pressure measurements, or body temperature.

CONCLUSION:

In subjects with schizophrenia or schizoaffective disorder, was associated with a modest increase in QTcLD interval. For the primary ECG variable, difference in day-averaged QTcLD between IR paliperidone 8 mg at steady state (Day 8) and placebo (Day 1), the LSM (SE) difference was 5.5 (1.09) ms; the 90% confidence limits were 3.66 and 7.25 ms. Since the upper limit of the 90% confidence interval was below the predefined limit of 10.0 ms, the mean effect of IR paliperidone 8 mg at steady-state on QTcLD was considered no worse than that of placebo. Time-matched mean differences in QTcLD between IR paliperidone and placebo were examined for each study day and ECG measurement time point. The upper limit of the 90% confidence interval remained below 10.0 ms for all time points, with the exception of the 1.5-hour observations on Days 2 and 4, and between 1 and 3 hours on Day 8; the maximum LSM difference in QTcLD from placebo of 10.9 (90% confidence interval: 8.24 to 13.62) ms occurred 1.5 hours after administration of 8 mg IR paliperidone on Day 8. Administration of 8 mg IR paliperidone resulted in a maximum plasma concentration approximately twice as high as that observed with the highest (15 mg) dose of ER OROS paliperidone used in clinical development.

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CONCLUSION (continued):

The pharmacokinetic/pharmacodynamic analysis suggests that the effects of paliperidone on QTcLD are complex and cannot be explained by plasma concentrations alone. Although plasma concentrations measured around C_{max} coincide with the maximum effect on QTcLD change from baseline, the pharmacokinetic/pharmacodynamic relationship seems to be more complex. Other factors such as daily variation in each measure (placebo effect) and physiological adaptation of the body to compensate for the effects induced by paliperidone should be considered.

The safety profile of IR paliperidone 4 to 8 mg once daily for 7 days was consistent with its expected safety profile based on its pharmacologic activity as a serotonin-dopamine antagonist, with no unexpected or unusual safety issues. In IR paliperidone-treated subjects, no adverse events were reported in terms suggestive of proarrhythmic potential as defined in the ICH E14 guidance (i.e., syncope, seizure, ventricular tachycardia, ventricular fibrillation and flutter, torsade de pointes, and adverse events consistent with sudden death).

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