SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Not available NAME OF ACTIVE INGREDIENT(S): Paliperidone/R076477	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: Protocol R076477-SIV-101, CR004267 **Title of Study:** Open-Label Positron Emission Tomography (PET) Study of Central D_2-Receptor Occupancy in Healthy Subjects Following a Single Oral Dose of OROS Paliperidone		
Principal Investigator: Prof. Lars Farde, M.D. – Institute of Clinical Neuroscience, Section of Psychiatry, Karolinska Hospital, Stockholm; Sweden		
Publication (Reference): None		
Studied Period (years): Clinical Conduct: 28 March 2003 - 06 June 2003 Sample Analysis: 16 June 2003 - 19 June 2003		**Phase of development:** 1
Objectives: To estimate the relationship of D_2-receptor occupancy to plasma concentration and to help predict a suitable dose range of OROS paliperidone for subsequent clinical studies in subjects with schizophrenia. The safety of the single oral doses of OROS paliperidone was also documented.		
Methodology: This is a single-center, single-dose, open-label, Phase-1 Positron Emission Tomography (PET) study in 4 healthy subjects, 2 men and 2 women. After screening, healthy eligible subjects were hospitalized in the study unit from study Day 2 to Day 4. On Day 1 (the day before hospitalization), subjects entered the study unit from 5:00 p.m. to 8:00 p.m. for baseline prolactin blood sampling and sedation assessment. Each subject had a control magnetic resonance imaging (at screening) and 3 PET measurements using the radioligand [^{11}]C raclopride to measure central D_2-receptor occupancy in the putamen. Blood samples to measure plasma concentrations of paliperidone, using a liquid chromatography coupled to mass spectrometry/mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 0.10 ng/mL, were collected immediately before and at scheduled time points after dose administration on Day 2, and immediately before, halfway through, and immediately after the PET-2 and PET-3 measurements. Serum prolactin levels were also measured immediately before and at several scheduled time points after dose administration, and immediately before and after each PET measurement. At scheduled time points, supine and standing blood pressures, pulse, sensorium changes, temperature, and degree of sedation were recorded, subjects were questioned about adverse events, and they were evaluated for extrapyramidal symptoms (EPS). Adverse events were recorded and followed throughout the study.		
Number of Subjects (planned and analyzed): 4 healthy adult subjects		
Diagnosis and Main Criteria for Inclusion: between the ages of 20 and 45 years, inclusive, healthy based on a detailed screening medical history, physical examination, toxicology (drug & alcohol) screen, and clinical laboratory and cardiovascular evaluations.		
Test Product, Dose and Mode of Administration, Batch No.: Single oral dose (6 mg) of OROS paliperidone, administered as 3 extended-release (ER) tablets (2-mg), Batch: MV0214352 (ALZA Code Number: 0012828)		
Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable		
Duration of Treatment: 1 single dose		

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Criteria for Evaluation:

Pharmacokinetics: Based on the individual plasma paliperidone concentration-time data and using the actual sampling times, the following pharmacokinetic parameters of paliperidone were determined: C_{max}, t_{max}, $t_{1/2term}$, λ_z, AUC_∞, and AUC_{48h}.

Pharmacodynamics: D_2-receptor occupancy was measured using PET; 3 PET measurements were performed, a baseline PET before drug intake to determine the untreated D_2 binding, a second PET at the time of predicted peak plasma concentration (22 hours), and a third PET 46 hours after the study drug was given. Dopamine D_2-receptor occupancy was analyzed using the simplified reference tissue model approach.

Based on the individual serum prolactin concentration-time data (actual concentrations and change from baseline) using the actual sampling times, the following pharmacodynamic parameters of prolactin were determined: C_{max}, t_{max}, AUC_{48h}, AUC_{24h}, AUC_{24-48h}.

Safety: Safety was monitored using clinical laboratory testing, physical examination, vital-signs and electrocardiogram measurements, orthostatic intolerance assessments, EPS ratings (Simpson and Angus and Barnes Akathisia Rating Scales), and sedation assessments. Adverse events were recorded throughout the study and followed until resolution or stabilization.

Statistical Methods:

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

Pharmacodynamics: Descriptive statistics were calculated for the serum concentrations of prolactin (actual concentrations and change from baseline) at each sampling time and for its pharmacodynamic parameters.

Pharmacokinetics/Pharmacodynamics: or relationships of paliperidone plasma concentration to D_2-receptor occupancy. D_2-receptor occupancy was plotted versus individual plasma concentrations. From the derived relationship, the suitable dose range corresponding to 70% to 80% receptor occupancy was predicted.

Safety: The incidence, relationship to therapy, and severity of adverse events were summarized. Changes in clinical laboratory tests and vital signs were assessed by descriptive statistics. The number of subjects with pulse or blood pressure values outside the normal range was tabulated. Results of sedation and orthostatic intolerance assessments using Visual Analog Scale (VAS) were summarized descriptively by time point. Results of physical examination, electrocardiograms (ECG), and EPS ratings were listed.

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SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

Peak concentrations of paliperidone were attained at 24.1 hours postdose (median value). The individual peak plasma concentration of paliperidone ranged from 7.73 to 16.5 ng/mL.

PHARMACODYNAMIC RESULTS:

Positron Emission Tomography (PET) Measurements:

The data show that after single oral administration of 6 mg ER OROS paliperidone, the D_2-receptor occupancy increased to circa 66% (mean, n=4) at 22 hours postdose and decreased to 52% (mean, n=4) after 46 hours postdose. The D_2-occupancy values ranged from 40% to 79% (n=8).

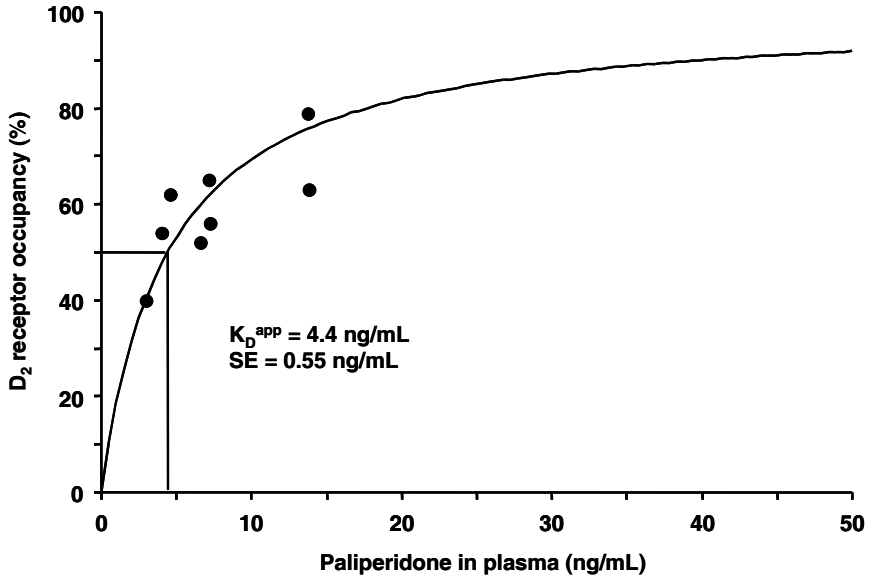
Prolactin:

The prolactin concentrations show a steep increase with a maximum reached at 5 hours after dosing on Day 1, both for the actual values and the change from baseline. This peak does not coincide with the maximum paliperidone concentrations, which are reached at circa 24 hours.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

The saturation hyperbolic model was fitted to the data to describe the D_2-receptor binding from 0 concentration to full saturation (see section 3.11.2.2). The calculated dissociation constant (K_D^{app}) value was 4.4 ng/mL (Figure 1). The corresponding optimal plasma concentration (corresponding to 70-80% D_2-receptor occupancy) can be estimated to be between 10 and 17 ng/mL.

Figure 1: D_2 occupancy versus paliperidone plasma concentration



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SAFETY RESULTS:

Adverse Events:

All subjects reported adverse events during the study. Adverse events reported by more than 1 subject were fatigue and dizziness. The majority of the adverse events were considered by the investigator to be mild or moderate in severity and related to study drug. Only 1 adverse event (somnolence) was rated as severe. There were no deaths and no serious adverse events reported during the study, and no subjects withdrew from the study due to an adverse event.

Clinical Laboratory Evaluation:

There were no clinically relevant changes in mean values for serum chemistry, hematology, and urinalysis laboratory results, and there were no subjects with clinically relevant abnormalities.

Other Safety Observations:

Apart from an increase in pulse, there were no clinically meaningful changes in physical examination findings (including body temperature and weight), ECG measurements, and EPS ratings. Although all subjects had symptoms of orthostatic hypotension, none of the subjects had to lie down and VAS scores revealed no severe or bothersome orthostatic symptoms. Furthermore, sedative activity was noted in all subjects as determined by the sedation VAS scores and the sedation questionnaire score, with the worst level of alertness being 'somewhat foggy, let down' (i.e., score 4 on a scale ranging from 1 meaning feeling active, vital, alert, or wide awake, to 7, meaning no longer fighting sleep, sleep onset soon; having dream-like thoughts).

CONCLUSION:

The study results show that a 6-mg ER OROS paliperidone dose corresponded to an average D_2-receptor occupancy of 66% when peak plasma levels were reached. The optimal plasma concentration range, corresponding to 70-80% D_2-receptor occupancy, was 10 to 17 ng/mL with a K_D^{app} equal to 4.4 ng/mL. A suitable dose range corresponding to 70-80% D_2-receptor occupancy was predicted to be 4.5 to 9 mg.

A single 6 mg dose of ER OROS paliperidone administered under fasted condition was safe and generally well-tolerated by healthy subjects.

Date of the report: 19 August 2004

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