SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	INVEGA® Tablets
Name of Active Ingredient	Paliperidone

Protocol No.: R076477-BIM-1003

Title of Study: An Open-Label, Drug-Drug Interaction Study between Steady-State Valproic Acid and Single-Dose Paliperidone Extended-Release in Healthy Men

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Publication (Reference): None

Study Period: 16 January 2009 to 15 February 2009. Database Lock date: 11 March 2009

Phase of Development: 1

Objectives: The primary objective of this study was to evaluate the effect of valproic acid (VPA) at steady-state on the pharmacokinetics (PK) of a single dose of orally administered INVEGA® (paliperidone) extended release (ER). The secondary objective was to evaluate the effect of a single 12-mg dose of paliperidone ER on the steady-state PK of VPA.

The safety and tolerability of the 12-mg tablet of paliperidone ER administered with and without Depakote® ER (divalproex sodium ER) to healthy men was also assessed.

Methods: This was an open-label, single-center, 2-treatment, single-sequence study in healthy men. The study consisted of a screening phase (within 21 days before the first study drug administration), an open-label treatment phase consisting of 2 consecutive treatment periods, and end-of-study evaluations upon completion of all the study procedures in the open-label treatment phase or at early withdrawal.

Subjects who satisfied the enrollment criteria at screening reported to the study center no later than 6 PM on Day -1 for baseline assessments, and remained in the study center for the entire duration of the open-label treatment phase, ie, until the last study assessment on Day 19.

All subjects received each of the following 2 treatments in a fixed sequential order:

- Treatment A: a single dose of 1 tablet of paliperidone ER 12 mg on Day 1;
- Treatment B: 2 tablets of divalproex sodium ER 500 mg once daily from Day 5 to 18 and a single dose of 1 tablet of paliperidone ER 12 mg on Day 15.

The maximum duration of the study for each subject was 40 days (including the screening phase).

Number of Subjects (planned and analyzed): Planned: Twenty-four (24) subjects were to be enrolled to ensure that at least 16 subjects completed the study. Analyzed: Of the 24 subjects enrolled in the study, 23 completed the study. All subjects received at least 1 dose of plaiperidone ER and were analyzed for safety. Twenty-three subjects were analyzed for PK. One subject was excluded from inferential statistics, as the PK profile of Day 1 only was available.

Diagnosis and Main Criteria for Inclusion: Healthy men, between 18 and 55 years of age, inclusive, with a body mass index (BMI; weight [kg]/height [m^2]) of 18 to 30 kg/m^2, inclusive, and a supine blood pressure between 90 and 140 mmHg systolic, inclusive, and 50 and 90 mmHg diastolic, inclusive were included.

Test Product, Dose and Mode of Administration, Batch No.:

Paliperidone ER (batch number: 7AG1026-X) was supplied as a dark yellow 12-mg capsule shaped tablet with the following approximate dimensions: length 11 mm, diameter 5 mm. There were 2 orifices approximately 0.64 mm in diameter on one end of the tablet.

Commercially available divalproex sodium ER was supplied as a gray ovaloid tablet with the Abbott corporate logo and code. Each tablet contained divalproex sodium equivalent to 500 mg of VPA.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not Applicable.

Duration of Treatment: The study drugs were administered as follows: a single dose of 1 tablet of paliperidone ER 12 mg on Day 1 and 2 tablets of divalproex sodium ER 500 mg once daily from Days 5 to 18 and a single dose of 1 tablet of paliperidone ER 12 mg on Day 15.

Criteria for Evaluation: Blood and urine samples were collected for PK and safety, as described below.

Pharmacokinetics: For the determination of plasma concentrations of paliperidone, venous blood samples (4 mL each) were taken within 2 hours before and at serial time points (up to 96 hours) after dosing with paliperidone ER. Additional venous blood samples (4 mL each) for the determination of VPA plasma concentrations were collected predose on Days 12 to 16 and 19, to confirm compliance and achievement of steady-state, and at serial time points on Days 14 and 15, to document plasma concentrations of VPA with and without administration of paliperidone ER.

Concentrations of paliperidone and VPA in plasma were determined using validated liquid chromatography coupled to tandem mass spectrometry methods, with target limits of quantification of 0.1 ng/mL and 5 µg/mL, respectively. Based on the individual plasma concentration-time data, using the actual sampling times, the following PK parameters of paliperidone were estimated for each of the treatments: maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (t_{max}), area under the plasma concentration-time curve from time 0 to time the last quantifiable concentrations (AUC_{last}), area under the plasma concentration-time curve from time 0 to infinite time (AUC_{∞}), calculated as the sum of AUC_{last} and $C_{last}/\lambda z$, in which C_{last} is the last observed quantifiable concentrations, percentage of AUC_{∞} obtained by extrapolation ($\%AUC_{\infty,ex}$), first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve (λz), and elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda z$ ($t_{1/2}$). The achievement of steady-state of VPA was explored graphically by plotting the trough plasma concentrations. The following PK parameters of VPA were estimated on Days 14 and 15: trough plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose (C_{trough}), maximum plasma concentration during a dosing interval ($C_{max,ss}$), time to reach the maximum plasma concentration ($t_{max,ss}$), area under the plasma concentration-time curve during a dosing interval (τ) (AUC_{τ}).

Safety: Safety and tolerability were evaluated by assessment of adverse events, clinical laboratory tests (hematology, chemistry, and urinalysis), vital sign measurements (pulse, blood pressure, and oral temperature), physical examination, and 12-lead electrocardiograms (ECGs) (RR, PR, QRS, QT, and QT corrected intervals, according to Fridericia [QTcF] and Bazett [QTcB]).

Statistical Methods:

Sample size determination: Based on a previous bioequivalence study (R076477-SCH-1017), the intrasubject coefficient of variation for AUCs and C_{max} of paliperidone was estimated to be less than or equal to 30% in healthy subjects. Using an estimate of 30% for intrasubject coefficient of variation, a sample size of 16 subjects was considered sufficient for the point estimate of the mean ratio of PK parameters of paliperidone with and without coadministration of divalproex sodium ER to fall within 83% to 121% of the true value with 90% confidence.

Based on a previous study (DORI-NOS-1003), the intrasubject coefficient of variation for AUCs and C_{max} of VPA after administration of divalproex sodium immediate release was estimated to be less than or equal to 10% in healthy subjects. The intrasubject variability for divalproex sodium ER was expected to be higher

as an ER formulation could exhibit inherently more variable PK compared with the immediate release formulation because of its incomplete absorption. Assuming an intrasubject variability of 15% for AUCs and C_{max} of VPA after divalproex sodium ER administration, a sample size of 16 subjects was considered sufficient for the point estimate of the mean ratio of PK parameters of VPA with and without coadministration of paliperidone ER to fall within 91% to 110% of the true value with 90% confidence.

To allow for a drop-out rate of about 30%, 24 subjects were to be enrolled in the study.

Pharmacokinetics: Individual subject, mean and median paliperidone and VPA concentration-time profiles were plotted. Paliperidone and VPA plasma concentration data at each time point, and paliperidone and VPA PK parameters, were summarized with mean, median, minimum, maximum, standard deviation (SD), and coefficient of variation.

The primary PK parameters of interest for evaluating the effect of VPA on paliperidone were AUC_{last}, AUC_{∞}, and C_{max} of paliperidone. The PK parameters were log-transformed before analysis. Only the data from subjects who completed the study were included in the statistical analysis. If 1 of the PK parameters of interest was not estimable for a given subject in 1 or more periods, the subject's data was not included in the statistical analysis of that particular PK parameter.

A mixed-effect model was fit to the data with the logarithm of 1 of the paliperidone PK parameters of interest as the dependent variable, treatment (with coadministration of divalproex sodium ER [Day 15] and without coadministration of divalproex sodium ER [Day 1]) as a fixed effect, and subject as a random effect. Using the estimated least-squares means and intrasubject variance from the mixed-effects model, the 90% confidence interval (CI) for the difference in means on the log scale between the 2 treatments (with coadministration of divalproex sodium ER [Day 15] and without coadministration of divalproex sodium ER [Day 1]) was constructed. The 90% CI for the log-scale data was retransformed using the anti-logarithm to obtain the 90% CI for the ratio of the geometric means of AUC_{last}, AUC_{∞}, and C_{max} with and without coadministration of divalproex sodium ER.

To evaluate the effect of paliperidone ER on the steady-state PK of VPA, similar mixed-effects modeling was performed using the VPA PK parameters of interest as a dependent variable, treatment (with coadministration of paliperidone ER [Day 15] and without coadministration of paliperidone ER [Day 14]) as fixed effect, and subject as a random effect.

Safety: The safety of paliperidone ER and its coadministration with divalproex sodium ER was evaluated from signing of informed consent through posttreatment follow-up by examining incidence, severity, relationship to study medication, and type of adverse events; changes in clinical laboratory results; physical examination and vital signs measurements; concomitant medication/therapy; and 12-lead ECGs. Data were summarized using descriptive statistics.

RESULTS:

Twenty-three of the 24 subjects enrolled in the study completed the study. One subject withdrew consent by choice and was discontinued.

Subjects were healthy males and the majority of the subjects were black (63%). The median age of the subjects was 40 years and the median BMI was 25.1 kg/m^2.

PHARMACOKINETIC RESULTS: Paliperidone PK parameters were available for 24 subjects after administration of paliperidone ER alone and for 23 subjects after coadministration of paliperidone ER and divalproex sodium ER. Overall, paliperidone peak plasma concentrations and AUC values were approximately 50% higher after coadministration of paliperidone ER with divalproex sodium ER than after administration of paliperidone ER alone. Median time to peak paliperidone plasma concentration and mean terminal elimination half-life were around 24 hours for both treatments.

Summary of Pharmacokinetic Parameters (Mean ± SD) of Paliperidone
(Study R076477-BIM-1003: Pharmacokinetic Analysis Set)

Treatment	C_{max} (ng/mL)	AUC_{last} (ng*h/mL)	AUC_{∞} (ng*h/mL)	$t_{1/2}$ (h)
Paliperidone Alone (N=24)	13.2 ± 5.60	493 ± 204	536 ± 224	23.5 ± 4.4
Paliperidone + VPA (N=23)	19.6 ± 10.4	727 ± 366	803 ± 413	24.0 ± 3.9

VPA=divalproex sodium ER

Summary of Analysis of Variance by Treatment for Pharmacokinetic Parameters of Paliperidone
(Study R076477-BIM-1003: Pharmacokinetic Analysis Set)

Parameter	N	Intra-subject CV (%)	Geomean Pali + VPA	Geomean Pali Alone	Ratio (%)	90% Confidence Interval (%)
C_{max} (ng/mL)	23	29.33	17.70	11.68	151.48	130.57 – 175.74
AUC_{last} (ng*h/mL)	23	26.91	657.39	438.07	150.06	130.95 – 171.97
AUC_{inf} (ng*h/mL)	23	27.14	721.73	475.41	151.81	132.32 – 174.18

Ratio= ratio of geometric means (Paliperidone +VPA/Paliperidone Alone).
VPA=divalproex sodium ER.

Summary of Analysis of Variance by Treatment for Pharmacokinetic Parameters of VPA
(Study R076477-BIM-1003: Pharmacokinetic Analysis Set)

Parameter	N	Intra-subject CV (%)	Geomean Pali + VPA	Geomean VPA Alone	Ratio (%)	90% Confidence Interval (%)
$C_{max,ss}$	23	7.15	82.50	80.01	103.11	99.44 – 106.91
AUC_{τ}	23	6.41	1693.92	1663.34	101.84	98.59 – 105.20

Ratio= ratio of geometric means (Paliperidone +VPA/VPA Alone).
VPA=divalproex sodium ER.

The effect of VPA on paliperidone was evaluated using a mixed effects model. Divalproex sodium ER increased the oral bioavailibility of paliperidone by an estimated 51% (C_{max}) and 50% to 52% (AUCs).

Valproic acid steady-state concentrations were similar after divalproex sodium ER administered alone and after coadministration with paliperidone ER. The treatment ratios for $C_{max,ss}$ and AUC_{τ} were close to 100%. The 90% CIs for geometric mean ratios of AUC_{τ} and $C_{max,ss}$ fell within 80% and 125%.

SAFETY RESULTS:

There were no deaths or serious or severe adverse events during the study. There were no discontinuations due to adverse events.

The number of subjects with adverse events was higher during treatment with paliperidone ER (79%) than during treatment with the divalproex sodium ER (43%) and paliperidone ER + divalproex sodium ER (35%). The most frequently reported adverse events in subjects receiving paliperidone ER were headache (29%) and dizziness (17%). Somnolence (22%) was the most frequently reported adverse event in subjects receiving divalproex sodium ER.

The majority of the adverse events were considered mild by the investigator. The subjects had a higher incidence of moderate adverse events during treatment with paliperidone ER than during treatment with divalproex sodium ER or paliperidone ER + divalproex sodium ER. The majority of the adverse events were considered doubtfully, possibly, or not related to the study drug by the investigator. Subjects had a higher incidence of adverse events that were considered possibly related to the study drug by the investigator during treatment with paliperidone ER than during treatment with divalproex sodium ER or paliperidone ER + divalproex sodium ER.

Other observations included 1 subject with an adverse event of mild palpitations that resolved spontaneously on the same day and 1 subject with an adverse event of mild left testicular pain that was noted as persistent.

There were no clinically significant changes in the laboratory test findings, vital signs, and ECGs.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION:

- Although paliperidone exposure was increased after coadministration with divalproex sodium ER tablets, there was no evidence that this significantly altered the safety profile.
- Individual plasma concentration-time profiles of subjects with the highest treatment ratio for oral bioavailability parameters of paliperidone ER suggest that a prolonged absorption time, possibly due to a delay in gastric emptying or another cause for slowing of the transit in the upper gastrointestinal tract, might have caused the increase in exposure.
- `A single 12-mg dose of paliperidone ER had no effect on the steady-state pharmacokinetics of VPA when coadministered with two 500 mg divalproex sodium ER tablets once daily.
- Paliperidone ER administered alone as a single 12-mg dose and when coadministered with two 500 mg divalproex sodium ER tablets was well tolerated by healthy subjects, and no new safety concern was identified.

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