SYNOPSIS

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

Protocol No.: R076477-BIM-1004

Title of Study: An Open-Label, Drug-Drug Interaction Study to Evaluate the Effect of Paliperidone Extended-Release ER on the Steady-State Pharmacokinetics of Valproic Acid in Clinically Stable Subjects with Schizophrenia, Bipolar I Disorder or Schizoaffective Disorder

Principal Investigator: Donald Garcia Jr., MD, FutureSearch Trials, Austin, TX; USA

Publication (Reference): None

Study Period: 10 February 2009 to 22 April 2009. Database Lock date: 02 June 2009.

Phase of Development: 1

Objectives: The primary objective of this study was to assess the potential effect of multiple doses of INVEGA® (paliperidone) extended release (ER) tablets on the steady-state pharmacokinetics (PK) of valproic acid (VPA).

The safety and tolerability of paliperidone ER coadministered with Depakote® ER (divalproex sodium ER) in clinically stable subjects with schizophrenia, bipolar I disorder, or schizoaffective disorder were also assessed.

Methods: This was an open-label, single-sequence, PK drug-drug interaction study of oral paliperidone ER coadministered with oral divalproex sodium ER in clinically stable subjects with schizophrenia, bipolar I disorder, or schizoaffective disorder who were on valproate therapy. The study consisted of a screening period of up to 21 days, a 13-day open-label treatment phase consisting of 2 consecutive treatment periods, and a post-treatment phase that included end-of-study (EOS) procedures on Day 13 or at the time of early withdrawal and a follow-up visit 1 week after the EOS (or early withdrawal) procedures.

Subjects who satisfied the enrollment criteria at screening reported to the study center no later than 6:00 p.m. on Day -1 for baseline assessments, and remained confined to the study center until all scheduled study assessments and evaluations were completed on Day 13. At a minimum, and at the discretion of the investigator, subjects were to be in the study center from the evening of Day 6 to the morning of Day 8, and from the evening of Day 11 to the morning of Day 13.

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

- Treatment A: divalproex sodium ER once daily on Days 1 to 7;
- Treatment B: divalproex sodium ER once daily together with 1 tablet of 12 mg paliperidone ER once daily on Days 8 to 12.

The number of tablets and daily dose of divalproex sodium ER varied amongst subjects depending on their prescreening therapeutic dose, but were to remain unchanged throughout the open-label treatment phase.

The maximum study duration for each subject was 41 days (including the screening phase and follow-up visit).

Number of Subjects (planned and analyzed): Planned: Approximately 16 male or female subjects were to be enrolled to ensure that at least 12 subjects completed the study. Analyzed: Of the 17 subjects enrolled in the study, 14 completed the study. All subjects who received at least 1 dose of study drug were analyzed for safety. Thirteen subjects were analyzed for PK and inferential statistics. One subject was excluded, as the subject did not fast for 10 hours before intake of divalproex sodium on Day 7.

Diagnosis and Main Criteria for Inclusion: Male or female subjects with a diagnosis of schizophrenia, bipolar I disorder, or schizoaffective disorder; between 18 and 65 years of age, inclusive; body mass index (BMI) between 18 and 35 kg/m^2, inclusive, and a body weight of not less than 50 kg; and with no psychiatric hospitalizations or changes in treatment with mood stabilizers, antipsychotics, or antimanic agents for at least 1 month prior to screening were included. The subjects' Clinical Global Impression of Severity of Illness (CGI-S) score was to be 3 or less at screening and baseline (Day -1).

Subjects were to be taking valproate (either VPA, sodium valproate, or divalproex sodium) for a minimum of 4 weeks prior to screening, with a stable therapeutic dose for a minimum of 2 weeks, and were to have therapeutic blood concentrations at screening (trough plasma/serum concentration above 50 µg/mL). Subjects, who were taking divalproex sodium ER once daily, continued this dose and regimen. Subjects on a different formulation and/or on a different dosing regimen (eg, twice daily) were switched to a once-daily regimen of divalproex sodium ER on Day 1, at a comparable daily dose (approximately 25 to 60 mg/kg/day) in line with the US Prescribing Information of Depakote ER.

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.

Commercially available divalproex sodium ER was supplied as a gray ovaloid oral tablet with the Abbott corporate logo and code. Each tablet contained divalproex sodium equivalent to 250 or 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: divalproex sodium ER (dose depended on the prescreening therapeutic dose) once daily on Days 1 to 7 and divalproex sodium ER once daily together with 1 tablet of 12 mg paliperidone ER once daily on Days 8 to 12.

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

Pharmacokinetics: Venous blood samples (3 mL each) were collected from all subjects for the determination of:

- Plasma concentrations of VPA predose on Days 4 to 12 and regularly during the 24-hour interval after drug administration on Days 7 and 12.
- Plasma concentrations of paliperidone before each daily paliperidone ER administration (Days 8 to 12) and 24 hours after the last administration of paliperidone ER on Day 12 (ie, in the morning of Day 13).

Concentrations of VPA and paliperidone in plasma were determined using validated liquid chromatography coupled to tandem mass spectrometry methods, with target limits of quantification of 2 µg/mL and 0.1 ng/mL, respectively. For all subjects, based on the individual plasma drug concentration versus time data on Days 7 and 12, using actual sampling times, the following steady state plasma PK parameters of VPA were determined: maximum plasma concentration during a dosing interval ($C_{max,ss}$); time to reach the maximum plasma concentration ($t_{max,ss}$); trough plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose (C_{trough}); area under the plasma concentration-time curve during a dosing interval (τ) (AUC_{τ}); average plasma concentration at steady state ($C_{avg,ss}$); and total clearance of drug after extravascular administration (CL/F). The achievement of steady state of VPA and paliperidone was explored graphically by plotting the trough plasma concentrations.

Safety: Safety and tolerability were evaluated by assessment of adverse events, clinical laboratory tests (hematology, serum chemistry, urinalysis, pregnancy testing, serology, urine drug screen, and alcohol breath test), vital signs (blood pressure, pulse, respiratory rate, temperature [tympanic]), physical

examination, 12-lead electrocardiograms (ECGs) (RR, PR, QRS, QT, and QT corrected intervals, according to Fridericia [QTcF] and Bazett [QTcB]) and CGI-S scores.

Statistical Methods:

Sample Size Determination: Based on a previous study, DORI-NOS-1003, the intrasubject coefficient of variation for area under the plasma concentration-time curve (AUC) and maximum plasma concentration (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 and 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 to clinically stable subjects with schizophrenia, bipolar I disorder, or schizoaffective disorder, a sample size of 12 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 89% to 112% of the true value with 90% confidence.

Approximately 16 subjects were to be enrolled to ensure that at least 12 subjects completed the study. Dropouts were to be replaced if the number of subjects who were expected to complete the study fell below 12.

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

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

A mixed effects model was fit to the data with the logarithm of one of the VPA PK parameters of interest as the dependent variable and treatment (with coadministration of paliperidone ER [Day 12] and without coadministration of paliperidone ER [Day 7]) as a fixed effect and subject as a random effect. Using the estimated least-square 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 paliperidone ER [Day 12] and without coadministration of paliperidone ER [Day 7]) was constructed. The 90% CI for the log-scale data was retransformed using anti-logarithm to obtain 90% CI for the ratio of the geometric means of AUC_{τ} and $C_{max,ss}$ with and without coadministration of paliperidone ER.

Safety: The safety of the paliperidone ER administration in combination with divalproex sodium ER was evaluated from the signing of informed consent through post-treatment follow-up by examining incidence, severity, relationship to study medication, and type of adverse events; changes in clinical laboratory results; ECG parameters; vital signs measurements; physical examination; CGI-S scores; and concomitant medication/therapy. Data were summarized using descriptive statistics.

RESULTS:

Fourteen of the 17 subjects enrolled in the study completed the study. Three subjects were withdrawn from the study, 1 subject each due to an adverse event, withdrawal of consent, and other reason.

The majority of subjects were white and male, and all but 3 subjects had a diagnosis of bipolar 1 disorder. The median age of the subjects was 39 years and the median BMI was 29.2 kg/m^2.

PHARMACOKINETIC RESULTS: Valproic acid PK parameters were available for 13 subjects after administration of divalproex sodium ER alone and after administration of divalproex sodium ER plus paliperidone ER. Plasma VPA steady-state concentrations were similar after administering divalproex sodium ER alone and after coadministration with paliperidone ER. Mean AUC_{τ} and $C_{max,ss}$ values were similar for both treatments.

Summary of Pharmacokinetic Parameters (Mean ± SD) of VPA
(Study R076477-BIM-1004: Pharmacokinetic Analysis Set)

Treatment	$C_{max,ss}$ (µg/mL)	AUCτ (µg*h/mL)
VPA Alone (N=13)	84.3 ± 25.2	1637 ± 531
VPA + Paliperidone (N=13)	80.8 ± 19.3	1597 ± 501

VPA=divalproex sodium ER

Summary of Analysis of Variance by Treatment for Pharmacokinetic Parameters of VPA
(Study R076477-BIM-1004: Pharmacokinetic Analysis Set)

Parameter	N	Intra-subject CV (%)	Geometric mean VPA + Pali	Geometric mean VPA Alone	Ratio (%)	90% Confidence Interval (%)
$C_{max,ss}$	13	8.65	78.06	80.01	97.56	91.84 – 103.64
AUC_{τ}	13	8.20	1495.54	1533.95	97.50	92.06 – 103.25

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

The effect of paliperidone on VPA was evaluated using a mixed effects model. The VPA treatment ratios for $C_{max,ss}$ and AUC_{τ} were close to 100%. The 90% confidence intervals for geometric mean ratios of AUC_{τ} and $C_{max,ss}$ fell within 80 and 125%.

SAFETY RESULTS:

There were no deaths during the study. One subject had a serious adverse event of blood creatinine increased and one subject discontinued due to a nonserious adverse event of akathisia. The serious adverse event of blood creatinine increased was based on an isolated laboratory finding, without clinical signs of acute renal impairment, and was considered by the laboratory to have likely been recorded in error. Despite the lack of remedial action, a normal creatinine value similar to baseline was recorded at a follow-up visit.

The number of subjects with adverse events was higher during treatment with paliperidone ER plus divalproex sodium ER (63%) than during treatment with divalproex sodium ER alone (18%). The most frequently reported adverse events by preferred term were sedation (19%), weight increased (19%), and somnolence (13%) in subjects receiving paliperidone ER plus divalproex sodium ER.

The majority of the adverse events were considered mild or moderate in severity by the investigator. All the adverse events reported during treatment with divalproex sodium ER alone were considered to be moderate in severity. Two adverse events were reported as severe during treatment with paliperidone ER plus divalproex sodium ER (musculoskeletal stiffness and blood creatinine increased [as noted above]). The majority of adverse events were considered not related or doubtfully related to the study drug by the investigator. Three subjects experienced adverse events considered very likely related to the study drug; akathisia, tongue paralysis, and somnolence (1 subject each). Adverse events experienced by subjects receiving only divalproex sodium ER were considered not related to the study drug by the investigator. Four subjects experienced adverse events that were noted as persisting; ie, weight increased (3 subjects) and heart rate increased (1 subject).

No subject had an increase in body weight of 7% or greater, and the mean change from baseline in body weight was 1.6 kg (2.43). Three subjects had markedly abnormal laboratory values; ie, high creatinine (reported as a serious adverse event [as noted above]), high potassium, and low chloride (1 subject each). Two subjects had QTcB and QTcF values greater than 450 ms. There were no other clinically noteworthy changes in the laboratory test findings, vital signs, or ECGs.

STUDY LIMITATIONS: The fixed sequential study design does not allow for a distinction between the effect of continued treatment with divalproex sodium ER and the addition of paliperidone ER in the evaluation of adverse events.

CONCLUSION:

Repeated administration of 12 mg paliperidone ER had no effect on the steady-state PK of VPA when coadministered with divalproex sodium ER tablets once daily.

While no new safety concerns were identified for paliperidone ER and divalproex sodium ER separately during this study, the rate of treatment-emergent adverse events increased after paliperidone ER was introduced to subjects who received divalproex sodium ER.

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