SYNOPSIS

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Name of Sponsor/Company	Ortho-McNeil Janssen Scientific Affairs, LLC
Name of Finished Product	INVEGA™
Name of Active Ingredient(s)	paliperidone

Protocol No.: R076477-SCH-4013, CR014347

Title of Study: A blinded-initiation study of medication satisfaction in subjects with schizophrenia treated with paliperidone ER after suboptimal response to oral risperidone

EudraCT Number: 2007 004482-18

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Publication (Reference): Not applicable.

Study Period: 03 October 2007 to 18 July 2008; Database lock occurred on 27 August 2008.

Phase of Development: 4

Objectives: The primary objective of this study was to assess the observed change in the Medication Satisfaction Questionnaire (MSQ) score, from baseline to the Week 6 end point, when paliperidone ER (6 to 12 mg/day) had been administered for at least 4 weeks to subjects with schizophrenia who were suboptimally responsive to oral risperidone 4 or 6 mg/day. The secondary objectives were to explore efficacy and safety outcomes in subjects treated with paliperidone ER for up to 6 weeks.

Methods: This was an international, multicenter (9 centers in Argentina, 5 in Colombia, 5 in Czech Republic, 5 in Slovakia, 8 in Ukraine, and 15 centers in the US), 6-week, prospective study designed to evaluate subject-assessed medication satisfaction after at least 4 weeks of paliperidone ER treatment in patients who were considered suboptimally responsive to oral risperidone. Outpatients with an established diagnosis of schizophrenia, who were receiving oral risperidone treatment (given at a stable dosage of either 4 mg or 6 mg/day for at least 4 weeks immediately prior to study entry) and who reported dissatisfaction with their current medication, were randomized in a blinded fashion, in a 1:1 ratio to either an immediate or a delayed initiation of paliperidone ER. A total of 201 subjects were randomized; 100 subjects were assigned to an immediate initiation and 101 subjects to a delayed initiation of paliperidone ER. Those assigned to an immediate initiation received paliperidone ER for a total of 6 weeks; those assigned to a delayed initiation continued their baseline dose of risperidone (4 mg or 6 mg/day) for 2 weeks and then received paliperidone ER beginning on Day 15 and continuing for 4 weeks. Flexibly dose of paliperidone ER was initiated at 6 mg/day up to 12 mg/day in 3 mg increments. Measures of efficacy and safety were assessed at visits scheduled weekly for the first 4 weeks and then at Week 6.

Number of Subjects (planned and analyzed): Planned: 150 subjects, 75 subjects per cohort.
Randomized: 201 subjects (Immediate Initiation 100 subjects; Delayed Initiation: 101 subjects). Analyzed for safety: 197 subjects (Immediate Initiation 98 subjects; Delayed Initiation: 99 subjects). Analyzed for efficacy: 191 subjects (Immediate Initiation: 95 subjects; Delayed Initiation: 96 subjects).

Diagnosis and Main Criteria for Inclusion: Subjects had to be diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorder, fourth edition (DSM-IV) (paranoid type, disorganized

type, undifferentiated type, or residual type). Subjects had to receive oral risperidone 4 or 6 mg/day for at least 4 weeks immediately before randomization and be considered suboptimally responsive according three main criteria:

1) Subjects had to have scores of at least 4 (moderate) on three or more of the following Positive and Negative Syndrome Scale (PANSS) symptoms: G4 Tension, G9 Unusual thought content, P1 Delusion, P3 Hallucinatory behavior, P4 Excitement, P5 Grandiosity, P6 Suspiciousness/persecution at screening and baseline visits.
2) Subjects had to have reported dissatisfaction with current medication as measured by a score ≤3 on item 14 on the Treatment Satisfaction Questionnaire for Medication (TSQM) at screening and baseline visits.
3) Subjects had to have an aspect of disease management, which in the investigator's opinion could potentially benefit from a change in antipsychotic medication.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER (3 and 6 mg tablets to make up 6-, 9-, and 12-mg doses) and risperidone (4 and 6 mg tablets to make up 4- and 6-mg doses) over-encapsulated in identical capsules, along with matching placebo capsules. Capsules were to be administered orally with water. Batch No.: 07E18/F066 and 07E22/F066 (paliperidone ER 3 mg); 07F08/F067 and 07I27/F067 (paliperidone ER 6 mg); 07A09/F149 and 07I18/F149 (risperidone 4 mg); 07F20/F155 (risperidone 6 mg); 06J16/F027 (placebo).

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

Duration of Treatment: 6 weeks.

Criteria for Evaluation:

Primary Efficacy Variable/Primary Time Point: The primary efficacy variable for this study was change from baseline in the MSQ score for all subjects combined at Week 6 last observation carried forward (LOCF) study end point.

Secondary Efficacy Variables: MSQ scores at each time point and by dichotomized categories (Dissatisfied MSQ score 1-4 [extremely dissatisfied – neither dissatisfied nor satisfied] and Satisfied MSQ score 5-7 [somewhat satisfied – extremely satisfied]) for each randomized group over time; TSQM; PANSS; Clinical Global Impressions Scale Severity (CGI-S); Pittsburgh Sleep Quality Index (PSQI); modified Covi Anxiety Scale (m-COVI), and Short Form-36 Health Survey (SF-36).

Safety Variables: Adverse events (AE), laboratory parameters, vital signs, physical examination, electrocardiograms (ECGs), Extrapyramidal Symptom Rating Scale – Abbreviated (ESRS-A), Abnormal Involuntary Movement scale (AIMS), Barnes Akathisia Rating Scale (BAS), Simpson-Angus Rating Scale (SAS), and selected items from the Udvalg for Kliniske Undersogelser (UKU) scale.

Statistical Methods: Sample size for this study was based on potential changes in the MSQ scores within subjects from baseline to endpoint using a one-sample paired t-test. The Intent-to-Treat (ITT) analysis set was defined as all randomized subjects who received at least one dose of study drug and had some follow-up efficacy data. Within-cohort comparisons were made using the paired t-test. Between-cohort comparisons involving the change scores were performed using the analysis of covariance (ANCOVA) with separate terms in the model for treatment and baseline characteristics such as country and MSQ, effectiveness TSQM score, side effects TSQM score, and convenience TSQM score as covariates. Descriptive statistics for the change scores in MSQ (n, mean, median, minimum and maximum) were also provided. Responses on the MSQ were dichotomized as Satisfied and Dissatisfied and the proportion of subjects with dichotomized responses on the MSQ scale was calculated at the study endpoint and compared between cohorts using a Fisher's exact test. For efficacy variables with missing values after randomization, the LOCF method of imputation was applied.

The Safety analysis set included all randomized subjects who received at least one dose of study drug and had some post-baseline safety data. Treatment emergent AEs (TEAEs), laboratory analyte values, vital sign

measurements, physical examinations, and ECG findings were summarized. Descriptive statistics at each visit and the changes from baseline for clinical laboratory tests, ECG results, ESRS-A, AIMS, BAS, SAS and selected items from the UKU were summarized.

RESULTS:

- A total of 201 subjects were randomly assigned in a 1:1 ratio to either to the Immediate Initiation group (n=100) and Delayed Initiation group (n=101). The majority of the Safety analysis set (n=197) was male (56.3%) and 66.0% was White. The mean age was 40.6 years, ranging from 19 to 80 years old. The baseline MSQ mean (SD) score was 2.7 (0.8).

- At baseline, the mean (SD) dose of risperidone was 4.28 (0.9) mg/day. During the trial the mean modal dose of paliperidone ER was 6.6 (1.5) mg/day for the Immediate Initiation and Delayed Initiation groups combined.

EFFICACY:

- The primary efficacy analysis showed a statistically significant increase (improvement) in MSQ score at the Week 6 (LOCF) end point (p-value<0.001). The mean (SD) change in MSQ score from baseline to the Week 6 end point was 2.4 (1.4) for the Immediate Initiation and Delayed Initiation groups combined.

- Analyses of MSQ scores from baseline to each time point (Week 2, 4, 6, and Week 6 [LOCF] end point) for both the Immediate Initiation and the Delayed Initiation groups, showed statistically significant increases with all within group comparisons p-values<0.001. The categorical summary of the MSQ score showed similar results.

- Overall, at the Week 6 (LOCF) end point, 82.7% of subjects in both groups combined had a MSQ score in the satisfied category. At study endpoint the distribution of the MSQ categories were similar in the Immediate and Delayed Initiation groups (p=0.125; both groups on paliperidone ER at this time point). For the dichotomized MSQ categories at Week 2, a higher percentage of subjects receiving paliperidone ER (Immediate Initiation group) reported “satisfaction”, 67.7%, compared with 45.3% of subjects who were still receiving risperidone at Week 2 (Delayed Initiation group) (p-value=0.002).

- The mean (SD) change from baseline in the Global TSQM score for the Immediate Initiation and Delayed Initiation groups combined at the Week 6 (LOCF) end point was 28.3 (23.1), p-value<0.001. Similar p-values (<0.001) were observed in all TSQM sub-scale scores (Effectiveness, Side Effects, and Convenience).

- The mean (SD) change from baseline in the total PANSS score to the Week 6 (LOCF) end point was -12.9 (13.1) p-value<0.001 for the Immediate Initiation and Delayed Initiation groups combined. At study end point, changes were observed in all PANSS factors (Positive, Negative, Disorganized Thoughts, Uncontrolled Hostility/ Excitement, Anxiety/Depression; all p values <0.001).

- Significant improvement from baseline was observed for the CGI-S score at Week 6 (LOCF) end point, (mean [SD] change: -0.8 [0.9]; p-value<0.001)

- For the SF-36, the observed mean (SD) changes from baseline to Week 6 (LOCF) end point for the physical composite score and mental composite scores were 1.5 (7.5); p-value= 0.009 and 7.0 (10.4); p-value<0.001, respectively. For all 8 domain scores, the scores increased from baseline to Week 6 and Week 6 (LOCF) end point, with p-values ≤0.029.

- The mean global PSQI score and the mean 7 domain scores decreased (improved) from baseline to Week 6 and Week 6 (LOCF) end point, with p-values<0.05 overall at all time points.

- The mean modified COVI total global score and the mean item scores for verbal report, behavior, somatic symptoms, decreased (improved) from baseline to the Week 6 (LOCF) end point p-value<0.001.

SAFETY:

- Overall, a total of 53.3% subjects experienced a TEAE. A slightly lower percentage of subjects experienced at least 1 TEAE in the Immediate Initiation group (50.0%) compared with the Delayed Initiation group (56.6%).

- The most frequently reported TEAEs included: insomnia (9.1%), constipation (7.6%), headache (7.6%), and somnolence (6.6%).

- Three percent of subjects experienced at least 1 TEAE considered severe and 3.6% of subjects experienced at least 1 TEAE considered very likely related to study medication.

- A total of 4.1% of subjects discontinued the study due to AE; no subject experienced a TEAE that led to temporary stop of study medication. Overall, the most common AE leading to discontinuation was schizophrenia (5 subjects, 2.5%). The other events leading to discontinuation (acute pancreatitis, suicidal ideation, and COPD) were each reported for 1 subject.

- A total of 3.6% of subjects experienced at least 1 SAE; no SAE resulted in death. In the Immediate Initiation group, 2 subjects each experienced 1 SAE of schizophrenia; 1 subject experienced acute pancreatitis and chronic obstructive pulmonary disease (COPD). In the Delayed Initiation group, 4 subjects experienced SAEs of schizophrenia. For 2 of the subjects the event occurred during the risperidone period and for 2 subjects the event occurred during the paliperidone ER period.

- Laboratory findings, vital signs, physical examinations, and ECG evaluations did not raise any safety concerns.

- Analysis of ESRS-A scores showed a significant improvement at the Week 6 (LOCF) end point compared to baseline in the following ESRS-A scores: Parkinsonism: mean change (SD) -0.6 (2.5), p-value=0.001, akathisia: mean change (SD) -0.3 (0.9), p-value<0.001, and dyskinesia: mean change (SD) -0.1 (0.6), p-value=0.010 overall for the 2 groups combined.

CONCLUSION: In this prospective study, schizophrenia subjects who were suboptimally responsive to risperidone reported improved medication satisfaction after 4 or 6 weeks of treatment with paliperidone ER. Paliperidone ER (6 to 12 mg) administered for up to 6 weeks was safe and well tolerated.

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