SYNOPSIS

Name of sponsor: Xian-Janssen Pharmaceutical Ltd Name of Test Drug: Paliperidone ER Active Ingredient of Test Drug: Paliperidone		

Protocol No.: PALIOROSSCH3011

Title of Study: A Randomized, 6-Week Double-Blind, Parallel Study to Evaluate the Efficacy and the Safety of Flexible Doses of Extended Release OROS® Paliperidone Compared with Olanzapine in the Treatment of Patients With Schizophrenia

Principle Investigator: Prof. Shu Liang, Peking University Institute of Mental Health

Publication (Reference): none

Study Initiation/Completion Dates: 3 July 2006 to 8 Dec 2006	**Phase of development: 3**

Objectives: The primary objective was to evaluate the efficacy and safety of flexible dosages of Extended Release (ER) OROS® paliperidone (3-12 mg/day) as compared with flexible dosages of Olanzapine (5-15 mg) in subjects with symptomatic schizophrenia.

The primary efficacy response was measured by the change in the PANSS total score from baseline to the end of treatment. The secondary efficacy responses were to: (1) Assess the changes in CGI-S associated with the use of ER OROS paliperidone compared with Olanzapine; (2) Assess the changes of PSP from baseline to the end of the treatment; (3) Assess the responder rate of ER OROS paliperidone; (4) Assess the effect of schizophrenia by means of change in PANSS subscales according to Marder factor scores; (5) Evaluation of the improvement in sleep associated with the use of ER OROS paliperidone.

Methodology: This was a randomized, double-blind, active-controlled, flexible-dose, parallel group, multicenter study. The study consisted of a screening phase, a double-blind treatment phase (6 weeks) and a safety follow-up phase (1 week).

The subjects in this study were randomized to 1 of 2 treatment groups to receive ER OROS paliperidone or Olanzapine once daily for the 6-week double-blind treatment phase. Randomization occurred in a ratio of 1 (ER OROS paliperidone) to 1 (Olanzapine). Subjects were to be hospitalized at least 14 days after entry. Those who received ER OROS paliperidone started at a dosage of 6 mg taken daily, dose could be titrated up by 3mg/day every 7 days, or down rapidly based on the balance of efficacy and safety/tolerability assessed by the investigator. After the initial 14 days, dose could be flexible within 3-12mg/day. Those who received olanzapine started at a dosage of 5mg taken daily, dose could be titrated up by 5mg/day every 7 days, or down rapidly based on the balance of efficacy and safety/tolerability assessed by the investigator. After the initial 7 days, dose could be flexible within 5-15mg/day.

Efficacy parameters included PANSS score, CGI-S, PSP and VAS score per assessment visit. The primary efficacy was the change in PANSS from baseline to the last post-randomization assessment. The secondary efficacy responses were the changes of the following scales from baseline at end point: CGI-S; PSP responder rate, PANSS factor scale; sleep VAS. Safety assessments included the adverse events, changes in physical examination, vital signs, laboratory tests at pretreatment and post treatment.

Number of Subjects (Planned and analyzed): It was planned to enroll approximately 344 subjects in the study, to ensure at least 258 subjects completed the study per protocol.

Diagnosis and Main Criteria for Inclusion: Subjects with the age of 18-65 years, met the criteria indicated in DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) (DSM-IV) for schizophrenia (295.10, 295.20, 295.30, 295.60, 295.90) with a PANSS total score between 60 and 120 (inclusive) at screening and baseline were enrolled in the study. Subject must have provided their informed consent before any trial-related procedures. Subject must be hospitalized for at least 14 days after enrollment.

SYNOPSIS (CONTINUED)

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER was manufactured by ALZA Corporation US. The dose strength is 3mg/tablet. To maintain blinding, all tablets were over-encapsulated. The study drug should be stored at 15-25^{o}C and avoid humidity. The manufacturing batch number of paliperidone ER was 05I21/F022, packing batch number was 347428. The placebo manufacturing batch number was 06B21/F027.

Reference Therapy, Dose and Mode of Administration, Batch No.: Olanzapine was manufactured by Eli Lilly England. The dosage strength was 5mg/tablet. To maintain blinded, all drugs were encapsulated. The drug should be stored at 15-25^{o}C and avoid humidity. The manufacturing batch number was 06B01/F318, packing batch number was 347428.

The administration of study drugs: a flexible dosage was designed in the study. The dosage range of paliperidone ER was 3-12 mg/day, and olanzapine was 5-15 mg/day. The study drug was orally administered once daily. Subject was recommended to take study drugs in the morning to ensure there were sufficient time for paliperidone ER to be released during the 24 hours. Study drugs could not be chewed, divided, solved or crashed.

Date & Visits	Paliperidone ER (mg/day)	Olanzapine (mg/day)
Baseline	6	5
End of Week 1	3-9	5-10
End of Week 2	3-12	5-15
End of Week 4	3-12	5-15
End of Week 6	3-12	5-15

Note: Investigators should base their decisions regarding dosage adjustments on maximizing the efficacy of the drug and minimizing the side effects.

Duration of Treatment:

The double-blind treatment duration was 6 weeks.

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was change in PANSS total score from baseline at double-blind end point (week 6 or last post-baseline efficacy assessment). Secondary efficacy endpoints included the following scales at each assessment time point: PSP, CGI-S, sleep VAS and PANSS factor score and PANSS reduction rate.

Safety:

The following safety parameters were assessed at screening (baseline) and end point: adverse events/serious adverse events, clinical laboratory tests (hematology, serum biochemisty, urinanalysis?, and serum prolactin, insulin glycosylated hemoglobin), vital sign measurements, body weight, ECG, EPS-related scales (SAS, BARS, AIMS) and physical examination.

Statistical Methods:

The efficacy analysis set in the study included ITT set and PP set. ITT set is the primary analysis set, results from PP set are to support the conclusion made from ITT set.

Demographic and baseline characteristics are descriptively summarized in all randomized subjects. [Andreas: Is this applicable to the synopsis?]The analysis of variance model is used to test the non-inferiority in primary efficacy endpoint between the two treatments. The significant level was 0.05. A LOCF method is used for missing data.

Adverse events are summarized according to body system and preferred term. The causality and severity of the adverse events between treatments judged by investigators are also summarized. Subjects' withdrawal from study due to adverse events and all the serious adverse events are also provided descriptively. Clinical laboratory analyses values, vital sign measurements, ECG data, and EPS rating scale results during the trial are summarized. A listing of subjects with any laboratory results outside the reference ranges are also provided.

SYNOPSIS (CONTINUED)

Summary-Conclusion

Efficacy Results: A flexible dose of 3-12 mg/day paliperidone ER for the treatment of schizophrenia for 6 weeks was evaluated in comparison with active control of olanzapine at a dose of 5-15 mg/day. The result shows that PANSS total score in paliperidone ER group was reduced from baseline of 83.38 ± 12.64 to 51.04 ± 16.10 at end point, total reduction is 32.33 ± 17.08; PANSS total score in olanzapine group reduced from baseline 85.55 ± 13.26 to 51.48 ±15.53 at end point, total reduction is 34.08 ± 17.40. The difference between two groups is not statistical significant (p=0.369), indicating paliperidone ER can significantly improve PANSS total score (primary efficacy endpoint) and that the efficacy of paliperidone ER in this study is non-inferior to olanzapine.

Secondary efficacy variables are further supporting the efficacy of paliperidone ER in subjects with schizophrenia. When assessed by CGI-S, both paliperidone ER and olanzapine treatment markedly improved the severity of condition, only few subjects were judged at end point by investigators as "markedly" or "severely" ill. In addition, both paliperidone ER and olanzapine can improve the functioning of the subject using PSP scale.

When assessed by using ≥ 30% and ≥ 50% response rates, both paliperidone ER and olanzapine groups had similar rates, with ≥ 30% response rate in paliperidone ER and olanzapine groups being 85% and 88%, respectively, while ≥ 50% response rates were 71% and 69%, respectively. The improvements in PANSS factor scores were also marked in the two treatment arms. In addition, both paliperidone ER and olanzapine treatment improved subjects' quality of sleep and daytime drowsiness. The treatment effect was similar.

In general, the results of the efficacy evaluations indicate that paliperidone ER administered at flexible doses of 3-12mg/day for 6 weeks was non-inferior to olanzapine administered at flexible doses of 5-15 mg/day.

Safety Results: : As shown in the table below, treatment-emergent adverse events occurred with a frequency of 85% in the paliperidone ER and 72% in the olanzapine group during the double-blind phase of 6 weeks. At least possibly related treatment-emergent adverse events were reported in 68% in the paliperidone ER and 62% in the olanzapine group.

Table 1: Summary of adverse events
(PALIOROSSCH3011: safety analysis set)

	Paliperidone ER (N=141)	Olanzapine (N=145)	Total (N=288)
All adverse events	122 (85%)	105 (72%)	227 (79%)
Possibly related adverse events	97 (68%)	90 (62%)	187 (65%)
Death	0 (0%)	0 (0%)	0 (0%)
Serious adverse events	2 (1%)	0 (0%)	2 (1%)
Pregnancy	0 (0%)	1 (1%)	1 (<1%)
With AE leading to permanent stop	5 (3.5%)	3 (2.1%)	8 (2.8%)

Possibly related AE: the causality is judged by investigators as possible, probable and likely related

Treatment-emergent adverse events that occurred more commonly (≥ 5% of subjects) in any treatment group were extrapyramidal symptoms, akathisia, dizziness, insomnia, somnolence, anxiety, constipation, abnormal liver enzymes, tachycardia, and upper respiratory tract infection.

Of the treatment-emergent adverse events that occurred in ≥ 5% of the subjects in any treatment group, the following were more common (i.e. group differences of ≥ 3%) in the paliperidone ER group: extrapyramidal symptoms, dizziness, insomnia, anxiety, tachycardia and upper respiratory tract infection.

Of the treatment-emergent adverse events that occurred in ≥ 5% of the subjects in any treatment group, the following were more common (i.e. group differences of ≥ 3%) in the olanzapine group: somnolence and abnormal liver enzymes.

Most treatment emergent adverse events were mild or moderate in severity and possibly or probably related to the respective study drug. There were no deaths in the study. During the study, serious treatment-emergent adverse events were reported for 2 (1%) subjects in the paliperidone ER group and 0 (0%) subjects in the olanzapine group. One pregnancy (1%) was reported in the olanzapine group. A total of 8 (2.8%) subjects discontinued the study drug due to adverse events: 5 (3.5%) in the paliperidone ER group and 3 (2.1%) in the olanzapine group.

SYNOPSIS (CONTINUED)

There was a low incidence (0% in the paliperidone ER and 2.8% in the olanzapine group) of treatment-emergent glucose-related adverse events during the study. A total of 5 (3.5%) subjects in the paliperidone ER group experienced potentially prolactin-related adverse events during the study compared to 0 (0%) subjects in the olanzapine group. Except for higher insulin levels and increased liver enzymes in the olanzapine group there were no notable mean changes from baseline to endpoint in hematology or urinalysis parameters. The mean increases in body weight in the paliperidone ER group was 2.99 kg compared to 3.60 kg with olanzapine. At study endpoint, weight increases from baseline of ≥ 7% were more common among subjects in the olanzapine group (37.8%) than the paliperidone ER (28.1%) group.

Conclusions: The change from baseline in PANSS total score at the 6-week endpoint indicates that paliperidone ER has an efficacy similar to that of olanzapine in the treatment of schizophrenia. The results of secondary efficacy endpoints (responder rates, CGI-S, PSP, sleep VAS) also support this conclusion. The statistical analyses indicate that there was no statistically significant difference in these efficacy parameters between the two treatments.

The 6-week study results show that paliperidone ER is safe and well tolerated. The type of adverse events observed in this study was consistent with those reported in previous studies. The incidence of metabolic parameters (incl. weight gain, blood glucose and lipids) and abnormal liver function tests in the paliperidone ER group was lower than in the olanzapine group.

This non-inferiority study comparing paliperidone ER with olanzapine for the treatment of schizophrenia demonstrates that paliperidone ER in the recommended dose range of 3-12mg/day is safe, well tolerated and effective in subjects with schizophrenia.

The overall findings of this 6-week phase III flexible-dose study conducted in China are in line with previous studies using fixed-dose designs in schizophrenia patients (paliperidone ER, INVEGA®) US prescribing information http://www.invega.com/invega/prescribing.html; Fowler et al. 2008).

In the present flexible dose study, at the end of treatment approximately 85.0% subjects on paliperidone ER received the maximal daily dose of 9-12 mg, and 90.1% subjects on olanzapine received the maximal daily dose of 10-15 mg. The double-blind, flexible dose study design and the 5 mg starting dose for olanzapine most likely explain why most patients where titrated up, since the usual therapeutic dose range for olanzapine targets doses above 10 mg daily. This, combined with the overall good tolerability during the study duration, encouraged uptitration of most patients and also led to the relatively high daily dose levels of paliperidone ER due to the double-blinded study design and the 6 mg starting dose in the paliperidone ER arm.

From previous studies, the recommended dose of paliperidone ER is 6 mg once daily with no requirement for initial dose titration. Some patients may benefit from higher doses, up to 12 mg/day, and for some patients, a lower dose of 3 mg/day may be sufficient. Paliperidone ER 3 mg and 6 mg once daily were associated with EPS-related measures at placebo level whereas a dose-related increase has been observed for the 9 mg and 12 mg doses (US prescribing information).

References:

Fowler JA, Bettinger TL, Argo TR. Paliperidone extended-release tablets for the acute and maintenance treatment of schizophrenia. Clin Ther. 2008 Feb;30(2):231-48.

US prescribing information INVEGA® February 2008 http://www.invega.com/invega/prescribing.html

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