1. Synopsis

Sponsor name: Janssen Pharmaceutical K.K.	Summary table of clinical trial Relevant part in application dossiers Volume No.: Page:	(For official use)
Product name: Paliperidone		
Active ingredient name: Paliperidone		

Protocol No: JNS007ER-JPN-S31 CR012625
Study Title: A Placebo-Controlled Double-Blind Comparative Study of JNS007ER in Patients with Schizophrenia

Investigators:
A total of 65 investigators including Toshinari Odawara (see Appendix 16.1.4a)

Investigator Site:
A total of 65 medical institutions including Psychiatric Center of Yokohama City University Medical Center (see Appendix 16.1.4a)

Published papers: None

Study period: Date of informed consent obtained from the first subject: July 11, 2006 Date of final observation in the last subject: November 20, 2007	Clinical phase: Phase III Study type: Confirmation study

Objectives:
Paliperidone ER 6 mg was orally administered to patients with schizophrenia once daily for 6 weeks to assess the efficacy in a placebo-controlled, double-blind, parallel-group comparison study. Secondarily, the safety of paliperidone ER 6 mg/day was assessed. The primary endpoint for efficacy was the change in total PANSS score from the baseline at the final assesment.

Study design:
This study was a multicenter, randomized, fixed-dose, placebo-controlled, double-blind, parallel-group comparison study to assess the efficacy of paliperidone ER in patients with schizophrenia. For subjects who had given their own written consent to participating in the study, after being confirmed about the eligibility in screening tests, they were randomly assigned to the paliperidone group, placebo group, or olanzapine group. The subjects were orally administered once daily, in principle, after breakfast for 6 weeks from the day of baseline assessment in a double-blind condition.
As the primary assessment for efficacy, the amount of change in the Positive and Negative Syndrome Scale (PANSS) total score from baseline to endpoint was made an indicator. Secondarily, PANSS subscale scores and Clinical Global Impression-Severity (CGI-S) were made indicators. As for safety, adverse events (subjective symptoms/ objective findings), height, blood pressure, pulse rate, body temperature, body weight, ECG test (12-lead), laboratory test, pregnancy test, and Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) were assessed.

Number of subjects (at planning and at analysis):

	Placebo group	Paliperidone group	Olanzapine group	Total
At planning				
Target number of registered subjects:	141	141	47	329
Number of subjects analyzed for efficacy (FAS):	133	133	45	311
At analysis				
Number of registered subjects:	138	136	47	321
Number of subjects analyzed for efficacy (FAS):	138	134	46	318
Number of subjects analyzed for safety:	138	134	47	319

<table>
<tr><td>Sponsor name:
Janssen Pharmaceutical K.K.</td><td rowspan="3">Summary table of clinical trial
Relevant part in application dossiers
Volume No.:

Page:</td><td rowspan="3">(For official use)</td></tr>
<tr><td>Product name:
To be determined.</td></tr>
<tr><td>Active ingredient name:
Paliperidone</td></tr>
<tr><td colspan="3">Diagnosis and Major Inclusion Criteria:
1. Patients who have given their own consent in writing to participate in the study.
2. Patients diagnosed with schizophrenia according to the diagnostic criteria of DSM-IV (295.30, 295.10, 295.20, 295.90, 295.60).
3. Patients who have acute symptoms of schizophrenia.
4. Patients at least 20 years of age at the time of informed consent.</td></tr>
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Study Drugs, Dosage and Administration, Manufacturing Codes

1. Study drugs, manufacturing codes

Drug Type		Mfg. code	Lot number
Paliperidone ER 3mg tablets	Phase III tab.	03FF	06D17/F064
	Marketed tab.	12FK	06I07/F065
Placebo tablets	Phase III tab.	03FF	06D12/F063
	Marketed tab.	12FK	06I01/F073 06I04/F073
Olanzapine 2.5mg tablets	Marketed tab.	03FF	06D25/F319
		12FK	06I12/F319

The tablets were individually encapsulated to make indistinguishable in appearance as shown below.

For the paliperidone group: One Paliperidone ER 3mg tablet was put in one capsule.
For the placebo group: One placebo tablet was put in one capsule.
For the olanzapine group: Two olanzapine 2.5mg tablets were put in one capsule.

2. Dosage and Administration

The following doses were orally administered to subjects once daily after breakfast, in principle. Drug treatment on the initial day of study drug treatment was given to subjects after the first meal after the baseline assessment.

Paliperidone group: 2 capsules (Two paliperidone ER 3mg x 2tablets)
Placebo group: 2 capsules (Two placebo tablets)
Olanzapine group: 2 capsules (Oolanzapine 2.5mg x 4tablets)

Study period:

Double-blind period (study drug treatment period) 6 weeks, follow-up period 1 week,
Total: 7 weeks

The follow-up period was set up only for subjects who were not transferred to the continuously conducted long-term study.

Assessment items:

1. Subject characteristics
2. Medical history
3. Status of prior therapies and concomitant therapies.
4. Status of treatment with the study drugs
5. Efficacy: PANSS, CGI-S
6. Safety: Adverse events (subjective symptoms/ objective findings), height, blood pressure, pulse rate, body temperature, body weight, ECG tests (12-lead), laboratory tests, pregnancy test, DIEPSS

Major statistical methods:

1. Populations analyzed

As populations to be analyzed for efficacy, a full analysis set (FAS) and a per-protocol set (PPS) were set up, and the FAS was defined as a primary population analyzed. For safety, a safety analysis set was set up.

2. Subject characteristics

For age, gender, body weight, disease type, and duration of disease, etc. at screening period, a frequency tabulation or caluculation of descriptive statistics were conducted according to the property of data. For continuous variables, 2-sample t-test was conducted. For ordinal categorical variables, the Wilcoxon rank-sum test was conducted. As for nominal variables, chi-square tests were conducted. At a 15% level of significance, it was considered that no imbalance was observed between the placebo group and paliperidone group.

3. Efficacy

a. Primary endpoint

The change in total PANSS score from baseline at the final assessment was adopted as a primary endpoint. The period of endpoint (at 6 weeks in LOCF data) was considered a primary assessment period.

Primary analysis

· The change in total PANSS score from baseline at the endpoint (LOCF data). The change in total PANSS score from baseline at the endpoint, using data of the placebo group and paliperidone group, ANCOVA was conducted adopting treatment group as a factor, and total PANSS score at baseline as a covariate. The difference in least square mean between the paliperidone group and placebo group and the 95% confidence interval were calculated to conduct comparison tests between the treatment groups.

Secondary analyses

· Comparison with the placebo group by assessment period

Using data of the placebo group and paliperidone group, an analysis of the total PANSS score and the change from baseline was conducted by assessment time, same as the primary analysis.

· Comparison with the olanzapine group by assessment period

Using data of the olanzapine group and paliperidone group, an analysis of the total PANSS score and the change from baseline was conducted by assessment time, same as the primary analysis. No comparison test between the treatment groups was conducted.

· Analysis in PPS

An analysis in PPS was conducted similarly to the primary analysis and the comparison by assessment time.

b. Secondary endpoints

· Proportion of responders

The number and proportion of subjects with a exceeding 30% or 20% improvement in total PANSS score from baseline at the endpoint and at each assessment time were calculated by treatment group, and the placebo group and paliperidone group were compared using the Fisher's exact test.

· PANSS subscale scores

Descriptive statistics of the score change from baseline at the endpoint and at each assessment time were calculated by treatment group to compare the treatment groups.

· CGI-S

The frequency tabulations for at the endpoint and at each assessment time were conducted by treatment group. The score was regarded as a continuous quantity, and descriptive statistics of the score change from baseline were calculated by treatment group to conduct a comparison test between treatment groups.

4. Safety

· Adverse events

Adverse events that newly occurred after the study drug treatment and those that worsened after the study drug treatment (Treatment-Emergent Signs and Symptoms; TESS) were analyzed. The tabulation was conducted based on the System Organ Class (SOC) and Preferred Terms (PT) in MedDRA/J. The number of subjects with events, the incidence, and the number of events were tabulated by treatment group. The tabulation was also conducted by severity and by causal relationship. Adverse reactions, serious adverse events, prolactin-related adverse events, extrapyramidal symptom-related adverse events, and those resulting in discontinuation of treatment were tabulated as well.

· Laboratory tests, body weight, blood pressure, pulse rate, body temperature, and ECG tests.

For quantitative items, descriptive statistics of measured values and changes from baseline in each assessment time were calculated by treatment group. For qualitative items, a frequency tabulation at each assessment time was conducted. For items with a standard range, a cross tabulation between before and after treatment was conducted. For prolactin level, a cross-tabulation between before and after treatment by gender was also conducted. For QT-corrected intervals, OtcB, QTcF, QTlc and QTcLD were calculated using parameter values measured by the ECG reading physician, and a classified tabulation was conducted for QT-corrected values and changes from baseline.

· DIEPSS

In each item, a frequency tabulation of scores was conducted by treatment group at each assessment time. For the placebo group and paliperidone group, a comparison between the treatment groups was conducted using the Wilcoxon rank-sum test. For total score, descriptive statistics of score changes from baseline at each assessment time were calculated by treatment group. For the placebo group and paliperidone group, ANCOVA was conducted adopting treatment group as a factor and baseline score as a covariate to conduct a comparison test between the treatment groups.

5. Level of significance

Two-tailed tests were conducted at the 5% significance level and one-tailed tests were conducted at the 2.5% significance level unless otherwise stated.

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Active ingredient name: Paliperidone		

Summary/Conclusions:

Efficacy results

Of 321 subjects registered in this study, 2 subjects of the paliperidone group and 1 subject of the olanzapine group were excluded (a total of 3 subjects). The remaining 318 subjects (placebo group 138 subjects, paliperidone group 134 subjects, and olanzapine group 46 subjects) were considered a primary population analyzed for efficacy, FAS.

In demographic and other standard value characteristics at baseline, no imbalance was observed between the placebo group and paliperidone group in any item except the duration of disease.

In the primary analysis of the change in total PANSS score from baseline at the endpoint, the difference [95% confidence interval] in least square mean between the paliperidone group and placebo group calculated from an ANCOVA model adopting treatment group as a factor and total PANSS score at baseline as a covariate was -12.7 [-17.16; -8.25], and statistically significant difference was observed ($p<0.0001$). That is, the primary objective, the superiority of the paliperidone group to the placebo group was confirmed.

The comparison of total PANSS score at each assessment time revealed a larger decrease in score of the paliperidone group at any assessment time ($p<0.05$) at 1 week to at 6 weeks after the start of treatment, compared with the placebo group, and at 1 week the efficacy of paliperidone ER was suggested. The difference between the treatment groups became larger as the time passed.

In the comparison of the change in total PANSS score from baseline at the endpoint between the paliperidone group and olanzapine group, the difference [95% confidence interval] in least square mean between the two groups calculated similarly to the primary analysis was 0.4 [-5.63; 6.41].

In the comparison of PANSS subscale scores, the paliperidone group showed larger decreases in every subscale scores compared with the placebo group ($p<0.05$).

With regard to PANSS responders at the endpoint, the proportions of 30% responders in the placebo group and paliperidone group were 9.4% (13/138) and 25.4% (34/134), respectively, and the proportion was higher in the paliperidone group ($p=0.0007$).

In the distribution of CGI-S assessment, the number of subjects in the placebo group assessed as “None” to “Moderate” decreased from 90 to 68, and the number of subjects assessed as “Slightly severe” to “Most severe” increased from 48 to 70. In the paliperidone group, the number of subjects assessed as “None” to “Moderate” increased from 85 to 95, and the number of subjects assessed as “Slightly severe” to “Most severe” decreased from 49 to 39. The CGI-S assessment was scorized and tabulated. As a result, the paliperidone group showed a larger decrease in CGI-S score at any assessment time after 1week, compared with the placebo group.

The proportion of discontinued subjects due to insufficient efficacy was 46.4% (64/138) in the placebo group and 23.9% (32/134) in the paliperidone group, and the paliperidone group showed a lower percentage.

The proportion of subjects who received a rescue treatment (lorazepam or diazepam) during the double-blind period was 37.7% (52/138) in the placebo group and 29.9% (40/134) in the paliperidone group, and the paliperidone group showed a lower percentage.

The analysis results in PPS were revealed to be supporting the results of the primary analysis in FAS.

As a result of the analysis of stratified subgroups with different characteristic factors such as demographic standard values, etc., almost a steady efficacy was considered to be expected in the subgroups, although it was difficult to assess the efficacy of paliperidone ER in some population due to the small number of subjects.

Safety results

Of the registered subjects, the population analyzed for safety in this study was 319 subjects (placebo group 138 subjects, paliperidone group 134 subjects, and olanzapine group 47 subjects) who were randomized and treated with the study drug at least once. Since the number of subjects in

the olanzapine group was approximately 1/3 of the paliperidone group, it was difficult to directly compare the assessment items, but descriptive statistics were calculated to conduct an inspective comparison.

The mean total dose ±SD of the study drug in the paliperidone group was 203.5 ±80.2 mg, and the median and range were 258.0 mg (12-264 mg), and the mean duration ±SD of the study drug treatment was 33.9 ±13.4 days, and the median and range were 43.0 days (2-44 days).

The incidence of adverse events in the double-blind period was 81.2% (259/319) overall. The details were 79.7% (110/138) 253 events in the placebo group, 81.3% (109/134) 271 events in the paliperidone group, and 85.1% (40/47) and 115 events in the olanzapine group. The incidence of adverse reactions was 69.6% (96/138) 179 events in the placebo group, 71.6% (96/134) 182 events in the paliperidone group, and 78.7% (37/47) 94 events in the olanzapine group.

In the follow-up period overall, 22 adverse events in 19 subjects occurred.

As a result of the tabulation of adverse events by SOC, adverse events with ≥ 10% incidences in the paliperidone group were laboratory tests abnormalities 31.3% (42/134), psychiatric disorders 27.6% (37/134), gastrointestinal disorders 23.1% (31/134), infections and infestations 19.4% (26/134) and nervous system disorders 19.4% (26/134). Of these events, the events that showed higher incidences in the paliperidone group than in the placebo group were laboratory tests abnormalities, gastrointestinal disorders, infections and infestations, and nervous system disorders, and those with higher incidences in the paliperidone group than in the olanzapine group were infections and infestations, and gastrointestinal disorders. The incidences of psychiatric disorders, nervous system disorders, and laboratory tests abnormalities were lower in the paliperidone group than in the olanzapine group.

Adverse events with ≥ 5% incidences in the paliperidone group were schizophrenia 16.4% (22/134) 22 events, insomnia 11.2% (15/134) 15 events, nasopharyngitis 10.4% (14/134) 15 events, constipation 8.2% (11/134) 11 events, extrapyramidal disorders 7.5% (10/134) 10 events, blood triglyceride increased 6.7% (9/134) 12 events, blood creatine phosphokinase increased 6.7% (9/134) 9 events, body weight increased 6.0% (8/134) 8 events, and hepatic function abnormal 5.2% (7/134) 7 events. Of these events, adverse events except schizophrenia showed higher incidences in the paliperidone group than in the placebo group. The events that showed higher incidences in the paliperidone group than in the olanzapine group were insomnia, nasopharyngitis, extrapyramidal disorders, blood triglyceride increased, blood creatine phosphokinase increased, and hepatic function abnormal. The incidences of schizophrenia, constipation and body weight increased were lower in the paliperidone group than in the olanzapine group.

Death was observed in 1 subject of the paliperidone group. This event was a death due to suicide (adverse event name: schizophrenia; description in CRF: exacervation of schizophrenia) that occurred on day 31 after the start of study drug treatment (29 days after the last drug administration).

The incidences of serious adverse events including the death were 0.7% (1/138) 1 event (schizophrenia) in the placebo group, 3.0% (4/134) 4 events (schizophrenia in 3 subjects, pneumonia in 1 subject) in the paliperidone group, and 4.3% (2/47) 2 events (schizophrenia in 1 subject, mood alterations in 1 subject) in the olanzapine group. All the serious adverse events were psychiatric disorders related to exacervation of schizophrenia, except for 1 subject with pneumonia in the paliperidone group. All the serious adverse events were confirmed to have recovered, except for the one case of death.

The incidences of adverse events resulting in discontinuation of treatment were 38.4% (53/138) 53 events in the placebo group, 9.0% (12/134) 12 events in the paliperidone group, and 23.4% (11/47) 12 events in the olanzapine group, and the percentage was lowest in the paliperidone group. Most of the adverse events resulting in discontinuation of treatment were the underlying disease – schizophrenia, and the incidences were 33.3% (46/138) 46 events in the placebo group, 6.0%

(8/134) 8 events in the paliperidone group, and 14.9% (7/47) 7 events in the olanzapine group.

The incidences of extrapyramidal symptom-related adverse events were 8.0% (11/138) 12 events in the placebo group, 17.2% (23/134) 24 events in the paliperidone group, and 10.6% (5/47) 5 events in the olanzapine group. The incidence was highest in the paliperidone group.

As adverse events presumed to be prolactin-related ones, 1 event (metrorrhagia) occurred in 0.7% (1/138) of the placebo group and 1 event (galactorhroea) occurred in 0.7% (1/134) of the paliperidone group. Blood prolactin levels listed by gender were examined for the mean change from baseline. As a result, both men and women in the placebo group and olanzapine group showed a decrease at every assessment time, whereas the men and women in the paliperidone group showed an increase at every assessment time.

The incidences of blood glucose-related adverse events were 5.1% (7/138) 8 events in the placebo group, 4.5% (6/134) 6 events in the paliperidone group, and 6.4% (3/47) 3 events in the olanzapine group.

Adverse events suggesting the possible induction of arrhythmia occurred in 0.7% (1/138) 1 event in the placebo group, 3.7% (5/134) 5 events in the paliperidone group, and 10.6% (5/47) 6 events in the olanzapine group.

In the paliperidone group, there were no incidences of neuroleptic malignant syndrome (a significant adverse reaction generally observed in association with antipsychotic treatment), tardive dyskinesia, diabetes mellitus, convulsion disorder such as epilepsy, cerebrovascular disorder, ileus paralytic, syndrome of inappropriate ADH secretion, or rhabdomyolysis. Orthostatic hypotension was observed only in 0.7% (1/138) of the placebo group, and was not observed in the paliperidone group.

Adverse events related to body weight increased or lipid metabolism in the paliperidone group were blood triglyceride increased in 6.7% (9/134), body weight increased in 6.0% (8/134), hyperphagia and blood cholesterol increased in 1.5% (2/134) each, and hyperlipidaemia in 0.7% (1/134). Such events in the placebo group were blood cholesterol increased in 1.4% (2/138) and increased appetite in 0.7% (1/138). In the olanzapine group, the events were body weight increased in 10.6% (5/47), blood triglyceride increased in 6.4% (3/47), increased appetite in 4.3% (2/47), and hyperlipidaemia and hypertriglyceridaemia in 2.1% (1/47) each.

Paliperidone ER is a product containing insoluble ingredients, and the insoluble ingredients are excreted in feces as they are. Even though adverse events related to gastrointestinal obstruction were not observed in this study.

In the assessment of laboratory test values, clinically significant changes were not observed in any item in the hematological examination, blood chemical examination or urinalysis, except for prolactin.

In the assessment of blood pressure, pulse rate and body temperature on fluctuations of the mean change from baseline, a decrease in blood pressure in the paliperidone group and olanzapine group, and a decrease in pulse rate in the placebo group were observed, but these were not clinically significant ones.

In the assessment of body weight on fluctuations of the mean change from baseline, body weight decreased with time in the placebo group, but it increased at 4 weeks and 6 weeks in the paliperidone group. In the olanzapine group, body weight showed an increase with time. A frequency tabulation of change rate of body weight was conducted. As a result, the proportion of subjects with > 7% increase in body weight at 6 week compared with baseline was 0% (0/55) in the placebo group, 10.1% (9/89) in the paliperidone group, and 21.9% (7/32) in the olanzapine group, and those with > 7% increase were observed in the paliperidone group and olanzapine group.

In the assessment of ECG findings, clinically significant findings were not observed in the paliperidone group. When the mean change in QTc from baseline was assessed, no change suggesting prolongation QTc was observed in the paliperidone group. As a QTc-related adverse event, one event of electrocardiogram QT corrected interval prolonged was observed in 1 subject of

the paliperidone group, but the recovery of the event was confirmed and its severity was mild and it was not serious.

Conclusions

From the results described above, the efficacy of paliperidone ER 6 mg/day in schizophrenia patients was confirmed. The safety of paliperidone ER 6 mg/day continuously administered once daily for 6 weeks was no big difference from the safety characteristics of paliperidone ER supposed from the past domestic or overseas clinical studies of the drug, and it was confirmed that there was no clinically serious problem.

Date of reporting: April 17, 2008 (date of the medical adviser's signature)

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