Synopsis

Sponsor name: Janssen Pharmaceutical K.K.	Study summary table Corresponding section in application data Volume number: Page:	(Space for reviewing authorities)
Brand name: (To be determined)		
Active ingredient name: Risperidone		

Study title:
A parallel-group comparative open-label study of long-acting injectible Risperidone versus Risperidone tablets in patients with Schizophrenia.

Investigators:
A total of 56 investigators including Ichiro Kusumi

Investigator Sites:
A total of 56 medical institutions in Japan including Department of Psychiatry/Neurology, Hokkaido University Hospital

Publications: None

Study period: Obtained date of first patient's consent: June 11, 2004 Completed date of last patient's observation: April 27, 2006	**Clinical phase:** Phase III
	Study type: Verification study

Objectives:
To evaluate the efficacy and safety of R064766LAI (hereinafter referred to as RIS-LAI) in patients with schizophrenia in an open-label parallel-group comparison study using risperidone tablets (hereinafter referred to as RIS-Tab) as a control.

Study methods:
RIS-LAI at 25-50 mg was administered to gluteal muscle in patients every 2 weeks for 24 weeks (a total of 12 doses). RIS-Tab at 2-6 mg/day in divided two doses was orally administered for 24 weeks. For efficacy, the non-inferiority of the RIS-LAI group to RIS-Tab group was verified using the change from baseline in total score of positive and negative syndrome scale (PANSS) at the final evaluation as an indicator. As for safety, the safety (subjective symptoms/objective findings, physical examination, ECG examination, laboratory examinations, injection site reaction, drug-induced extrapyramidal symptoms scale [DIEPSS], and adverse events) in the RIS-LAI group was compared with that in the RIS-Tab group.

Sample size (at planning and at analysis):
At planning: 200 patients (RIS-LAI group: 150, RIS-Tab group: 50)
At analysis: total number of randomized patients: 205 (RIS-LAI group: 153, RIS-Tab group: 52)
Efficacy analysis set (FAS): 198 patients
Per-protocol set (PPS): 167 patients
Safety analysis set (SAS): 198 patients

Diagnosis and major criteria for enrollment of patients:
Patients who met all of the following inclusion criteria and none of the exclusion criteria were enrolled in this study.

1. Patients diagnosed with schizophrenia according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (295.30, 295.10, 295.20, 295.90, 295.60).
2. Patients who are taking antipsychotics at a risperidone-equivalent dose up to 6 mg/day for 28 days before the date of informed consent with no change in the dosage and administration (except for medications used on an as-needed basis).
3. Patients with a total PANSS score of ≥ 60 to < 120.
4. Patients who are at least 20 years of age on the day of informed consent.
5. Both inpatients and outpatients are acceptable (patient's discharge during the study period is

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allowed.)

6. Patients who can give their own consent in writing to participate in the study. (If it is objectively considered difficult to obtain the patient's own consent, it is allowed to obtain consent of the patient's representative.

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Investigational drug, dosage and administration, lot numbers:

Investigational drug (study drug code): RIS-LAI (R064766LAI)

1. Dosage Form/Description
   Injection (3 formulations of RIS-LAI 25, 37.5 and 50 mg)
   One vial containing risperidone 25, 37.5 or 50 mg.
   One syringe containing 2 mL of solution for suspending.
2. Dosage and administration
   Patients received a total of 12 injections of RIS-LAI in the deep gluteal muscle (alternately in the right or left region) biweekly.
   Treatment was started at an initial dose of 25 mg followed by dose escalation or dose reduction by 12.5 mg up to 50 mg.
   However, no change in dosage was to be made at week 18 or later.
   According to the rule of dose escalation, dose escalation was conducted after treatment at the same dose was repeated at least twice. Dose reduction was allowed if the investigator or subinvestigator considered it necessary.
3. Lot numbers
   RIS-LAI 25 mg: 10CD
   RIS-LAI 37.5 mg: 11CH
   RIS-LAI 50 mg: 12CI
   Solution for suspending RIS-LAI: 13CK

Control drug (study drug code): RIS-Tab

1. Dosage Form/Description
   Tablets
   White film-coated tablets with a score line in the center, containing risperidone 1 mg per tablet
2. Dosage and administration
   RIS-Tab was orally administered twice a day for 24 weeks.
   The initial dose was 2 mg/day followed by dose escalation or dose reduction by 2 mg up to 6 mg/day.
   However, no change in dosage was to be made at week 18 or later.
   According to the rule of dose escalation, dose escalation was conducted after treatment at the same dose was repeated at least twice. Dose reduction was allowed if the investigator or subinvestigator considered it necessary.
3. Lot numbers
   RIS-Tab: 40CK

Treatment period (study period):

1. RIS-LAI group
   Observation period: 24 weeks (treatment at 25-50 mg every 2 weeks)
   Follow-up period: 6 weeks
   Total: 30 weeks
2. RIS-Tab group
   Observation period: 24 weeks (treatment at 2-6 mg/day in divided two doses)
   Follow-up period: 1 weeks
   Total: 25 weeks

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Endpoints:

Efficacy

1. Primary endpoint
   - Change from baseline in total PANSS score
2. Secondary endpoint
   - Change from baseline in PANSS subscale score
   - Change in clinician's global impression in change (CGI-C)

Safety

Adverse events, subjective symptoms/objective findings, physical examination, laboratory examinations, ECG examination, injection site reaction, DIEPSS

Statistical methods:

Analysis sets

1. Full analysis set (FAS)

It is considered a population of patients randomized in this study except the following patients.
- Patients who have not been treated with the investigational drug.
- Patients whose efficacy evaluation after treatment with the investigational drug was not conducted at all.

2. Per-protocol set (PPS)

It is considered a population of patients in FAS except the following patients.
- Patients who did not meet a major inclusion criterion or met a major exclusion criterion.
- Patients whose treatment compliance is not good.
- Patients who had a significant protocol violation concerning concomitant medications.

3. Safety set

It is considered a population of patients randomized in this study except the following patients.
- Patients who have not been treated with the investigational drug.

Patient characteristics

For patient's age at screening, gender, body weight, disease type and duration of disease, etc., tabulation and tests were conducted according to the property of data to confirm the balance between treatment groups using a 15% significance level as a reference.

Status of investigational treatment

For final dose of the investigational drug and most frequent dose after dose fixation, descriptive statistics were calculated. Cross-tabulations of the dose of prior antipsychotics (risperidone-equivalent dose) and the final dose and most frequent dose of the investigational drug were conducted.

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Statistical methods: (continued)

Efficacy

1. Analysis sets

FAS was considered a primary analysis set for efficacy. In selection of the primary analysis set, it is required to determine this considering the principle that biases should be minimized and an increase in type I error should be avoided. In this study, due to the difference in formulation characteristics between RIS-LAI and RIS-Tab, adoption criteria (e.g., treatment status) must be provided in PPS for each treatment group, and biases may be caused in a comparison between treatment groups. Therefore, FAS was used as a primary analysis set. For the primary endpoint, an analysis in PPS was conducted as a secondary analysis.

2. Primary endpoint

Total PANSS score was considered a primary endpoint. The timing of the primary endpoint was to be at the time of final evaluation (when the final evaluation was conducted in each patient).

a. Primary analysis

In FAS, descriptive statistics were calculated for change from baseline in total PANSS score at final evaluation. The 95% confidence interval of the mean difference between treatment groups (RIS-LAI group – RIS-Tab group) was calculated using analysis of covariance (ANCOVA) model with treatment group as a factor and with baseline total PANSS score serving as the covariate in order to confirm that the upper limit of confidence interval did not exceed 7.

b. Secondary analyses

• Inter-group comparison and intra-group comparison

In FAS, descriptive statistics were calculated for change from baseline in each evaluation time, and a comparison between treatment groups was conducted using a similar ANCOVA model as in the primary analysis. Intra-group comparison (score at each evaluation time and baseline score were compared) was conducted using the paired *t*-test.

• ANCOVA

ANCOVA for change from baseline at the final evaluation was conducted in FAS with treatment group and baseline total PANSS score serving as covariates and with patient characteristics having biases between treatment groups as a factor.

• Analysis over time

In FAS, an analysis of repeated measurement data was conducted using marginal models with treatment group and time and interaction between treatment group and time as factors and with baseline total PANSS score serving as the covariate, and with a structure of variance-covariance matrix as compound symmetry, and a comparison between treatment groups was conducted for fluctuations of change in total PANSS score over the observation period.

• Analysis in PPS

In PPS, the analyses described in the item of primary analysis were conducted.

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Statistical methods:

Efficacy (continued)

3. Secondary endpoints

a. PANSS subscale score

Positive syndrome score, negative syndrome score, general psychopathology score, and BPRS score

In FAS, descriptive statistics were calculated for change from baseline in PANSS subscale score at the final evaluation time and at each evaluation time, and a comparison between treatment groups was conducted using ANCOVA models with treatment group as a factor and with baseline score serving as the covariate. Intra-group comparison (score at each evaluation time and baseline score were compared) was conducted using the paired *t*-test.

b. CGI-C

In FAS, classified tabulation was conducted at the final evaluation time and at each evaluation time, and a comparison between treatment groups was conducted using the Wilcoxon rank-sum test.

Safety

1. Analysis sets

For safety endpoints, an analysis was conducted in the safety set.

2. Endpoints

Adverse events, subjective symptoms/objective findings, physical examination values, laboratory examination values, ECG examination values, injection site reaction, DIEPSS

3. Analysis methods

a. In adverse events, tabulation of the number of patients with events and the incidence was conducted by item. Tabulation by severity and causality was also conducted.

b. In physical examination values, laboratory examination values, ECG examination values and injection site reaction, classified tabulation was conducted or descriptive statistics were calculated according to the property of data.

c. For injection site reaction, classified tabulation was conducted by evaluation time.

d. For each item of DIEPSS, classified tabulation of score was conducted by evaluation time, and a comparison with baseline was conducted using the Wilcoxon signed-rank test. For score at each evaluation time and worst score during observation period, descriptive statistics of change from baseline in score were calculated, and a comparison between treatment groups was conducted using the Wilcoxon rank-sum test.

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Summary – Conclusion:

Efficacy results

The primary endpoint – difference of change from baseline (least square mean) in total PANSS score between treatment groups (RIS-LAI group – RIS-Tab group) at final evaluation and the 95% confidence interval were -0.3 (-5.35; 4.82). The upper limit of confidence interval was below 7 which was set as a limit value for the non-inferiority, and the non-inferiority of the RIS-LAI group to the RIS-Tab group was verified.

The percentage of patients with a ≥ 20% decrease from baseline in total PANSS score was 38.8% (57/147 patients) in the RIS-LAI group and 43.1% (22/51) in the RIS-Tab group at week 24. Both treatment groups showed a ≥ 20% decrease in approximately 40% of patients.

In CGI-C at the final evaluation, patients judged as "No change" or better were 83.7% (123/147 patients) in the RIS-LAI group and 86.3% (44/51) in the RIS-Tab group, and both groups showed similar results. The results supported the primary evaluation results suggesting that "treatment with RIS-LAI is not inferior to treatment with RIS-Tab".

In order to assess the relationship between the dose of prior antipsychotics and the maintenance dose of RIS-LAI in switching of prior antipsychotics to RIS-LAI, the most frequent dose after dose fixation of RIS-LAI (at week 18) was tabulated by dose of prior antipsychotics ([≤ 2 mg], [> 2 mg , ≤ 4 mg], [> 4 mg]). As a result, the percentage of patients whose most frequent dose was 25 mg was highest in all of the prior antipsychotic categories. The most frequent dose was 25 mg in approximately 70% of the patients in categories of ([≤ 2 mg] and [> 2 mg , ≤ 4 mg] and approximately 40% of them in the category of [> 4 mg]). Approximately 60% of the patients (66/115) resulting in having a dose fixation period (at week 18 or later) were treated at 25 mg irrespective of the dose of prior antipsychotics. In the tabulation results of the most frequent dose by treatment status of prior antipsychotics (risperidone as single agent, single agent of an antipsychotic other than risperidone, multi-agent therapy), the percentage of patients treated at 25 mg was highest in any treatment status.

Safety results

The percentage of patients who had any adverse event during the study period was 93.2% (137/147) in the RIS-LAI group and 96.1% (49/51) in the RIS-Tab group, and the both groups showed similar results.

The incidences of adverse events that occurred at a frequency of ≥ 10% in either RIS-LAI group or RIS-Tab group were: blood prolactin increased 32.0% (47/147) and 49.0% (25/51); insomnia 36.1% (53/147) and 35.3% (18/51); nasopharyngitis 16.3% (24/147) and 25.5% (13/51); weight increased 12.9% (19/147) and 11.8% (6/51); constipation 10.2% (15/147) and 13.7% (7/51); psychiatric symptoms 10.2% (15/147) and 9.8% (5/51); and blood triglycerides increased 10.2% (15/147) and 5.9% (3/51), respectively.

There was no death during the study period.

The incidences of serious adverse events reported during the study period were 11.6% in the RIS-LAI group (17/147; 22 events) and 5.9% in the RIS-Tab group (3/51; 3 events). In the system organ class (SOC), adverse events categorized into "mental disorder" occurred most frequently, and these events occurred in 8.8% of the RIS-LAI group (13/147; 15 events) and 5.9% of the RIS-Tab group (3/51; 3 events).

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The percentage of patients resulting in discontinuation of treatment due to "worsening of psychiatric symptoms" was 12.2% (18/147) in the RIS-LAI group and 9.8% (5/51) in the RIS-Tab group. The RIS-LAI group tended to show a higher percentage of discontinuation in patients whose risperidone-equivalent antipsychotic dose was high. In tabulation results of discontinued patients by treatment status of prior antipsychotics, the percentage of patients treated with "risperidone as single agent" was highest. Regarding the time of discontinuation, there were many patients in the RIS-LAI group who were discontinued early after dose escalation in the titration stage of dose adjustment. Particularly, discontinued patients were often observed transiently from at week 3 when treatment with prior antipsychotics was discontinued. On the other hand, no clear tendency in the time of discontinuation was observed in the RIS-Tab group.

The incidence of "extrapyramidal symptom-related adverse events" and the severity of events were lower in the RIS-LAI group compared with the RIS-Tab group. Similarly the percentage of patients treated with a concomitant antiparkinsonian agent at 4 weeks after initial investigational treatment was lower in the RIS-LAI group. The results suggest that RIS-LAI reduces the risk of the onset of "extrapyramidal symptom-related adverse events" compared with RIS-Tab, and the risk of adverse events observed in concomitant use of antiparkinsonian agents as well.

The incidence of "prolactin-related adverse events" was 34.0% (50/147) in the RIS-LAI group and 51.0% (26/51) in the RIS-Tab group. "Blood prolactin increased" occurred most often in both groups, but the incidence was low in the events being associated with clinically abnormal findings. Regarding "blood glucose-related adverse events", the incidence was low in either group, and there were no events being associated with clinically abnormal findings.

As for "injection site reaction-related adverse events", the incidence was 13.6% (20/147) in the RIS-LAI group. The "injection site reaction" that occurred with a highest incidence was more often observed at the early stage of the study (weeks 0-4). The duration of adverse events was short in most events and "recovery" was confirmed within 1 month in all the patients except 2 patients.

Conclusion

The non-inferiority of RIS-LAI to RIS-Tab in the primary efficacy endpoint – change from baseline in total PANSS score at the final evaluation was confirmed in this study. In addition, RIS-LAI was indicated to improve psychiatric symptoms in schizophrenia patients irrespective of treatment status of prior antipsychotics and the dosage. The overall safety was similar between RIS-LAI and RIS-Tab, and the tolerability of RIS-LAI was confirmed to be comparable to that of RIS-Tab. Regarding "adverse events related to extrapyramidal symptoms", it was confirmed that the risk was reduced with RIS-LAI treatment.

Treatment with RIS-LAI 25 mg could maintain the efficacy of prior antipsychotics in most patients irrespective of the dose of prior antipsychotics, but part of patients required dose escalation of RIS-LAI to maintain the efficacy. Since there was a discontinued patient due to worsening of psychiatric symptoms during the dose adjustment period of RIS-LAI, the use of an antipsychotic such as oral risperidone or a psychotropic agent should be considered in the stage of dose adjustment of RIS-LAI.

Date of report: November 30, 2006

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