Synopsis

Sponsor name: Janssen Pharmaceutical K.K.	Summary Table of Study Relevant place in NDA materials	(For official purpose)
Product name: RISPERDAL® CONSTA®	Volume number:	
Active ingredient name: Risperidone	Page:	

Protocol No.: CR003262

Study Title: Multiple-dosing study of long acting injectable of risperidone in schizophrenic patients

Medical Advisor: Kohei Yagi (Visiting Professor, Keio University School of Medicine)

Investigators: Naoyuki Shinoda and other 8 physicians.

Investigator Site: Dept. of Psychiatry/Neurology, Chiba University Hospital and other 8 medical institutions.

Publications: Unpublished.

Study period: Date of obtaining informed consent from first subject (himself/herself): November 13, 2002 Date of last observation in last subject：October 14, 2003	Clinical phase: Phase I/II

Objectives:

To assess the pharmacokinetics and safety in schizophrenic patients after multiple intramuscular (IM) dose administration of R064766LAI 25, 37.5 or 50mg every 2 weeks, 6 injections in total. Secondarily, the efficacy will also be assessed.

Study methods:

Schizophrenic patients who meet the inclusion criteria and do not meet any of the exclusion criteria will be randomly assigned to any one of the dose groups (25, 37.5 or 50 mg) at registration. Each intramuscular injection will be administered alternately in the right and left gluteal every 2 weeks, 6 injections in total.

Sample Size:

Target sample size: 8 subjects per dose group, 24 subjects in total.

Number of treated subjects: 28 subjects (number of subjects analyzed for safety and efficacy: 28, number of subjects analyzed for pharmacokinetics: 27)

Diagnosis and Major Criteria for Entry:

Inclusion Criteria

(1) Patients diagnosed with schizophrenia according to the DSM-IV criteria.

(2) Patients with a total Positive and Negative Syndrome Scale (PANSS) score of 60 to <120 at screening.

(3) Patients at least 20 years of age and younger than 65 years of age on the date of informed consent.

(4) Both inpatients and outpatients are acceptable (change in the status is allowed).

(5) Patients who can give their own consent or their legal representative's consent in writing to participating in the study after being given a sufficient explanation about the study.

Sponsor name: Janssen Pharmaceutical K.K.	Summary Table of Study Relevant place in NDA materials	(For official purpose)
Product name: RISPERDAL® CONSTA®	Volume number:	
Active ingredient name: Risperidone	Page:	

Exclusion Criteria

(1) Patients diagnosed to have a mental disease other than schizophrenia according to the DSM-IV criteria.

(2) Patients with Parkinson's disease.

(3) Patients judged to be ineligible as subjects in the study due to worsening or worsening tendency of the psychiatric symptoms.

(4) Patients with a convulsive disease such as epilepsy or a history of the disease.

(5) Patients with a history of neuroleptic malignant syndrome or physical exhaustion associated with dehydration or malnutrition, etc.

(6) Patients with a complication or history of diabetes, and patients with risk factors of diabetes such as hyperglycemia or obesity, etc (e.g. $HbA_{1c} \geq 5.9\%$).

(7) Patients with a bleeding tendency.

(8) Patients with hepatic impairment [T-Bil ≥3.0mg/dL; AST (GOT), ALT (GPT), ALP ≥ 2.5-fold the upper limit of reference range at the institution], renal impairment (BUN ≥25 mg/dL, creatinine ≥ 2 mg/dL), or cardiovascular disorders (e.g., QTc: ≥450 msec).

(9) Pregnant women, breast-feeding women, or patients who may be pregnant, and patients who wish pregnancy during the study period.

(10) Patients who had blood collection (blood donation) exceeding 200 mL within 30 days before the date of informed consent, or exceeding 400 mL within 90 days.

(11) Patients who received another sustained-release antipsychotic (depot agent) within 60 days before the initiation of the study.

(12) Patients whose experience of risperidone treatment cannot be confirmed.

(13) Patients corresponding to contraindications of Risperdal®.

①Patients in coma.

②Patients under the strong influence of CNS depressants such as barbiturates.

③Patients receiving epinephrine treatment.

④Patients with hypersensitivity to ingredients of the product.

(14) Patients with drug allergy or drug hypersensitivity.

(15) Patients who participated in another clinical study within 90 days before the date of informed consent.

(16) Other patients judged ineligible as subjects in the study by the investigator or subinvestigator.

Investigational product, Dose regimen, manufacturing code:

R064766LAI 25mg : contains risperidone 25 mg per vial; manufacturing code 06BH

Sponsor name: Janssen Pharmaceutical K.K.	Summary Table of Study Relevant place in NDA materials	(For official purpose)
Product name: RISPERDAL® CONSTA®	Volume number:	
Active ingredient name: Risperidone	Page:	

R064766LAI 37.5mg : contains risperidone 37.5 mg per vial; manufacturing code 07BH

R064766LAI 50mg : contains risperidone 50 mg per vial; manufacturing code 08BH

Diluent: contains 2 mL per syringe; manufacturing code 09AI

R064766LAI suspension solution will be prepared immediately before treatment, and promptly after that, the injection will be administered alternately in the right and left gluteal muscle, every 2 weeks.

Treatment period:

R064766LAI treatment period: 10 weeks (6 administrations at 2-week intervals)

Follow-up period: 8 weeks

Total: 18 weeks

Evaluation Criteria:

Primary endpoint

Pharmacokinetics (dose relationship in steady state):

After multiple intramuscular dose administration of R064766LAI 25, 37.5 or 50mg every 2 weeks, 6 times, plasma concentration of unchangedrisperidone, metabolite 9-OH-risperidone and active moiety (sum of risperidone and 9-OH-risperidone) in steady state will be assessed.

Safety:

Safety after R064766LAI treatment [adverse events, subjective symptoms/objective findings, laboratory examinations, physical examination, ECG examination, injection site reaction, Drug Induced Extrapyramidal Symptoms Scale (DIEPSS)] will be assessed.

Secondary endpoints

Pharmacokinetics (plasma drug concentration profiles):

The pharmacokinetics (e.g., lag time, elimination half-life) after initial treatment with R064766LAI to 18 weeks (Day 127) will be assessed.

Efficacy:

The efficacy of R064766LAI will be assessed using PANSS and Clinical Global Impression (CGI).

Statistical methods:

Pharmacokinetics

(1) The following analyses will be conducted based on actual measurement values of plasma risperidone and 9-OH-risperidone concentrations, as well as the active moiety concentration.

[After initial treatment to 18 weeks (Days 1-127)]

Basic statistics [mean, standard deviation and median] at each interval of blood sampling and the elimination half-life will be calculated.

[Treatment interval (10 to 12 weeks after initial treatment) after the 6th treatment expected to be steady state.]

[C_{max}, C_{min}, $C_{ss\,av}$, t_{max}, $AUC_{(10w \rightarrow 12w)}$] will be calculated.

(2) Dose relationship in steady state

The regression analysis will be conducted for the dose relationship in C_{max}, $C_{ss\,av}$ and $AUC_{(10w \rightarrow 12w)}$ at treatment interval (10 to 12 weeks after initial treatment) after the 6th treatment expected to be steady state.

(3) Plasma drug concentration profiles

Pharmacokinetic characteristics (e.g., lag time, elimination half-life) in multiple dose administration of R064766LAI will be assessed from plasma risperidone, 9-OH-risperidone and active moiety concentration profiles.

Safety

(1) Adverse events

The number of subjects with events and the incidence will be tabulated for each adverse event item. The tabulation by severity and causal relationship will also be conducted.

(2) DIEPSS

The classified tabulation of score in each item will be conducted by assessment time. For score of each assessment time and worst score after R064766LAI treatment, descriptive statistics of score change from baseline will be calculated.

(3) Physical examination, ECG examination, laboratory examinations, injection site reaction

The classified tabulation will be conducted or descriptive statistics will be calculated for each assessment time according to the property of data.

(4) Additional treatment with antiparkinsonian agent

The percentage of subjects given additional treatment with an antiparkinsonian agent after investigational treatment and the percentage of subjects with dose escalation of antiparkinsonian agent after investigational treatment will be calculated.

Efficacy

(1) PANSS

For total score, positive symptom scale score, negative symptom scale score, general psychopathology scale score, and Brief Psychiatric Rating Scale (BPRS) score, descriptive statistics of change from baseline will be calculated at the final assessment (time when final assessment was conducted before 12 weeks after initial treatment in each subject) for each

assessment time.

(2) CGI-C

The classified tabulation will be conducted at final assessment time and for each assessment time.

(3) Additional treatment with antipsychotics

The number of subjects given additional treatment with an antipsychotic agent and the percentage will be calculated, and descriptive statistics of the number of treatment days will be calculated.

Summary ― Conclusion:

Results of pharmacokinetics

When R064766LAI at 25, 37.5 or 50 mg was given to schizophrenic patients every 2 weeks, 6 times by multiple intramuscular dose administration, plasma concentration reached the steady state at 6 weeks after initial treatment (4th treatment). The determination coefficients R^2 of C_{max}, $AUC_{(10w\rightarrow12w)}$ and $C_{ss\ av}$ were 0.3576, 0.3004 and 0.3007 (the significance of correlation was p=0.0013, p=0.0037 and p=0.0037, respectively). The y-intercept of regression formula was not significantly different from 0 (p=0.8431, p=0.5362 and p=0.5366, respectively), and the dose relationship in C_{max}, $AUC_{(10w\rightarrow12w)}$ and $C_{ss\ av}$ of plasma active moiety in steady state was suggested at the dose range from 25 to 50 mg.

Results of safety

At least one adverse event was observed in 27 of 28 subjects treated with the investigational product, but no dose dependence in the incidence was observed and no difference in the events was observed across dose groups. No adverse event specific to the drug was observed with the exception of injection site reactions, and they were almost similar to the adverse events observed with oral risperidone. In the ECG examination, physical examination and laboratory examinations, no clinically significant problem was observed. During this study, no serious adverse events were observed.

Results of efficacy

Compared with baseline, the mean total PANSS score in the time of steady state decreased in all the dose groups. When the oral antipsychotic agent was switched to R064766LAI, the efficacy of the prior medication was maintained or an improving tendency of the symptoms was observed.

Conclusion

With regard to the primary objective in this study, after multiple dose administration of R064766LAI at 25, 37.5 or 50 mg, the dose relationship was observed in plasma drug concentration in steady state. The safety and tolerability up to 50 mg were confirmed. For efficacy, the secondary objective, the efficacy of oral antipsychotic used as prior medication was maintained or an improving tendency of the symptoms was observed.

Sponsor name: Janssen Pharmaceutical K.K.	Summary Table of Study Relevant place in NDA materials	(For official purpose)
Product name: RISPERDAL® CONSTA®	Volume number:	
Active ingredient name: Risperidone	Page:	
Date of report: September 26, 2006		

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.