Synopsis

Sponsor: Janssen Pharmaceutical K.K	Summery tables of each study Individual study table referring to part of the Dossier Volume: Page:	(For National Authority use only)
Finished Product: RISPERDAL®tablet		
Active Ingredient: Risperidone(JK6476)		
Title of Study: Double-blind, placebo-controlled clinical trial of JK6476 (risperidone) in patients with hallucinations and delusions associated with Alzheimer's disease		
Investigators: Total of 53 including Yoshiyuki Tamura, Asahikawa Medical College Hospital		
Study Centers: Total of 53 including Asahikawa Medical College Hospital		
Published Literature: None		
Study Period: Date of First Informed Consent: December 23, 2001 Date of Final Observation: March 11, 2003 (terminated early)		Phase of Development: Phase III

Objectives:

1) Efficacy

Primary objective:

To confirm efficacy by comparing the difference in the score before and after treatment with the formulation administered in the double-blind period of the study in the risperidone group and the placebo group using the BEHAVE-AD psychotic symptom cluster score as the primary endpoint.

Secondary objectives:

- To compare change in BEHAVE-AD cluster scores and total score with the placebo.
- To compare changes in the CMAI aggressiveness and non-aggressiveness item scores with the placebo.
- To compare changes in the CGI-C with the placebo.

2) Safety

To compare symptoms and clinical signs and the results of physical examination, laboratory tests, electrocardiography, DIEPSS, N-ADL, and MMSE with the placebo.

Methodology (Study Design):

Multicenter, placebo-controlled, randomized, double-blind, parallel-group comparative study

No. of Subjects (planned and analyzed):

296 subjects planned; 30 subjects were analyzed for efficacy and safety.

Diagnosis (Subjects), main inclusion criteria :

(1) Subjects are diagnosed as having Alzheimer's disease according to the DSM-IV.
(2) Subjects have a score not greater than 23 according to the MMSE.
(3) Subjects have a BEHAVE-AD psychotic score of 2 or greater for any item in the psychotic cluster (Items 1-12).
(4) Subjects in whom hallucination or delusion is observed after the onset of the symptoms of dementia at least 28 days prior to the day of the screening.
(5) In- or out-patients with one caregiver who is able to observe the patient's symptoms throughout the trial and the patient's hospitalization status will not be changed throughout the trial.
(6) Subjects are ambulatory with or without assistance.
(7) The legally acceptable representative gave written IC for participation in the trial with full understanding of the content of the trial.

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Trial drug: JK 6476 (risperidone) tablet (0.25 mg tablet)

Control drug: placebo

Doses, Method of Administration and Administration Period:

Risperidone was supplied as 0.5 mg tablets. Administration was performed orally.

Dosing regimen:

(1) Run-in (single blind) period (1 week):
One tablet twice a day in the morning and evening (2 tablets/day)

(2) Double-blind period (8 weeks):
The dose was given in a flexible dose regimen of 0.5 – 2.0 mg daily in 2 doses. The dose for all subjects was to be titrated to at least 0.5 mg daily.

Reference therapy: None

Criteria for evaluation:

Efficacy
- BEHAVE-AD
- CMAI
- CGI

Safety
- Physiological examinations
- Subjective symptoms/objective findings (AEs)
- ECG
- Laboratory tests (hematology, blood biochemistry, urinalysis)
- Extrapyramidal symptoms (DIEPSS)
- Daily living activities (N-ADL)
- MMSE

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Statistical Method:

Efficacy (Primary)

Absolute change in the BEHAVE-AD psychotic symptom cluster score (from baseline to the final evaluation time) was compared between the groups by *t*-test. The 95% confidence interval for the difference in the mean between the groups was shown along with the p value.

Efficacy (Secondary)

The BEHAVE-AD (total, cluster scores, and global rating) and CMAI (total and aggression and non-aggression scores) results were compared between the groups by *t*-test. The CGI-C results were classified and tabulated and compared between groups using Wilcoxon's rank sum test.

Safety

The number of patients with adverse events and the incidence of adverse events were tabulated by item. The scores for each DIEPSS item were classified and tabulated and compared with baseline using Wilcoxon's signed rank test. Basic statistics were calculated for the scores at each evaluation time and absolute change in the score from the worst score baseline in the double-blind period and compared between treatment groups using Wilcoxon's rank sum test. For the physical examination values, laboratory values (quantitative values), electrocardiography values, MMSE, and N-ADL (scores for each item and total score for 5 items), basic statistics were calculated for each evaluation time, and the results were compared with baseline (screening time in the case of MMSE) by paired *t*-test.

Summary:

Summary of patient baseline characteristics

Thirty patients were included in the double-blind period. The mean age of these patients was 76.8 years in the placebo group and 78.7 years in the risperidone group. Most were women, with women making up approximately 77% of patients in both groups. The mean MMSE score at baseline was 15.8 in the placebo group and 15.0 in the risperidone group. The mean length of time since onset of dementia was 3.14 years in the placebo group and 5.01 years in the risperidone group. There were no clinically significant differences between the two groups.

The mean BEHAVE-AD psychotic symptom cluster score at baseline differed slightly between the placebo group (6.2) and the risperidone group (4.9).

Efficacy results

Given that this study was terminated early and few subjects completed the study, no definitive conclusions regarding efficacy can be drawn from these results.

The mean absolute change in the BEHAVE-AD psychotic symptom cluster score from baseline did not differ between the two groups (placebo group: -1.4; risperidone group: -1.3).

Descriptive Statistics for BEHAVE-AD Psychotic Symptom Cluster Score

ITT analysis set

Evaluation time	Placebo group					Risperidone group					Difference between treatment groups in absolute change from baseline	
	Number of patients	Observed score		Absolute change from baseline		Number of patients	Observed score		Absolute change from baseline			
		Mean	SE	Mean	SE		Mean	SE	Mean	SE	Mean (95% confidence interval)	p value[a]
Baseline	17	6.2	1.1			13	4.9	0.7				
After 1 wk	17	4.7	1.1	-1.5	0.4	12	3.9	0.8	-0.5	0.5	1.0 (-0.3, 2.3)	0.1181
After 2 wk	17	4.6	1.0	-1.6	0.5	13	4.2	0.9	-0.7	0.6	0.9 (-0.7, 2.5)	0.2630
After 4 wk	16	3.9	0.8	-2.4	0.8	11	4.5	1.2	-0.7	0.7	1.7 (-0.7, 4.1)	0.1554
After 8 wk	14	5.0	1.2	-1.6	0.6	9	4.3	1.2	-1.1	0.7	0.5 (-1.4, 2.5)	0.5821
All final evaluation	17	4.9	1.0	-1.4	0.6	13	3.6	1.0	-1.3	0.6	0.0 (-1.7, 1.8)	0.9584

a: Comparison between treatment groups by-*t* -test

Safety results

The incidence of adverse events during the double-blind period was 64.7% (11/17 patients) in the placebo group and 84.6% (11/13 patients) in the risperidone group.
Serious adverse events occurred in 1 patient in the risperidone group and consisted of loss of consciousness. This occurred on treatment day 31 in the double-blind period and resolved on the same day. There was a “possible” causal relationship.
Events believed to be related to extrapyramidal symptoms consisted of extrapyramidal disorders, tremor, and muscle rigidity and occurred in 0/3, 2/0, and 1/1 patients in the placebo group/risperidone group. Total number of patients who experienced extrapyramidal symptoms was 3/17 (17.6%) in the placebo and 4/13 (30.8%) in the risperidone group.
Apart from pyrexia seen in 3 patients in the risperidone group only, for which a causal relationship was ruled out, all other adverse events occurred in only 1 or 2 patients and the difference could not be investigated.
Apart from one patient in the placebo group who was withdrawn due to QTc prolongation on electrocardiograms, no other patients had clinically problematic findings on laboratory tests, physical examination, or electrocardiography.

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Conclusions:

Due to the small number of subjects , no definitive conclusions regarding efficacy can be drawn based on the data collected during this study.
Investigation of safety showed that loss of consciousness was reported as SAE in 1 patient in the risperidone group. Incidence of extrapyramidal symptoms in the risperidone group (30.8%) was higher than that of placebo group (17.6%). Pyrexia, which occurred in 3 of the 13 patients in the risperidone group only. Even though only data from a small number of subjects was available, safety results were comparable to those observed in other studies with risperidone.

Report date: October 15, 2005

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