SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: RISPERDAL® NAME OF ACTIVE INGREDIENT(S): Risperidone (R064766)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: RIS-USA-232 **Title of Study:** Efficacy and Safety of a Flexible Dose of Risperidone Versus Placebo in the Treatment of Psychosis of Alzheimer's Disease		
Principal Investigator: [redacted] M.D. - [redacted] USA		
Publication (Reference): None		
Study Initiation/Completion Dates: 21 Dec 2000 - 27 Jan 2003		**Phase of development:** 3b
Objectives: The primary objective was to compare the efficacy of risperidone and placebo in the treatment of psychosis of Alzheimer's disease (PAD) using as co-primary endpoints the change from baseline in the score for the psychosis subscale of the Behavior Pathology in Alzheimer's disease Rating Scale (BEHAVE-AD) and the Clinical Global Impression of Change (CGI-C). Secondary objectives were 1) to compare the efficacy of risperidone and placebo using the change from baseline in the other subscale scores and the total score of the BEHAVE-AD, and 2) to evaluate and compare the safety and tolerability of risperidone and placebo as assessed by adverse events, extrapyramidal symptoms (EPS) evaluated using the Simpson and Angus Rating Scale (SARS) and the Abnormal Involuntary Movement Scale (AIMS), clinical laboratory tests, vital signs, and ECGs.		
Methodology: This was a randomized, double-blind, placebo-controlled, multicenter study consisting of 2 phases. During the 7-day run-in phase, antipsychotic medication was discontinued. Subjects were then randomly assigned to receive either placebo or risperidone during the 8-week, double-blind treatment phase.		
Number of Subjects (planned and analyzed): The planned sample size was 230 subjects per group. Of the 560 subjects who entered the study, 87 failed screening and were not randomized. The remaining 473 subjects (238 in the placebo group and 235 in the risperidone group) were randomized and treated. This intent-to-treat (ITT) analysis set was used as the basis for the safety analysis. The modified ITT (MITT) analysis set included all subjects who were psychotic at both screening and baseline. The primary efficacy analysis set included 416 subjects (214 in the placebo group and 202 in the risperidone group) from the MITT set who were enrolled at study centers that complied with the principles of Good Clinical Practice (GCP) (MITT-EXCL analysis set).		
Diagnosis and Main Criteria for Inclusion: Men and women, at least 55 years old, were eligible for this study if they had a diagnosis of dementia of the Alzheimer's type with or without a vascular component, a score of 2 or more on any item of the BEHAVE-AD psychosis subscale at screening, and a Mini-Mental State Examination (MMSE) score of 5 to 23. Subjects had to be residents of nursing homes or long-term care facilities and had to be deemed in need of treatment with an atypical antipsychotic medication.		
Test Product, Dose and Mode of Administration, Batch No.: Risperidone was supplied as 0.25 mg tablets (Batch numbers 00F28/F70 and 01C27/F070) and 0.50 mg tablets (Batch numbers 00F29/F9, 00C23/F09, and 00F29/F09). Oral risperidone was given in a flexible dose regimen of 1 to 1.5 mg daily in 2 doses. The dose for all subjects was to be titrated to at least 1 mg daily.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo tablets (Batch numbers 00F27/F7, 00C22/F7, and 01E21/F007) were identical to the risperidone tablets in appearance, taste, smell, and formulation, except for the absence of risperidone. The dose and titration for placebo were identical to those for risperidone.		
Duration of Treatment: 8 weeks		

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Criteria for Evaluation:

Efficacy: Different and independent raters evaluated the subjects using the BEHAVE-AD and the CGI scale at baseline and Weeks 1, 2, 3, 4, 6, and 8 of the double-blind treatment phase.

Safety: Safety parameters included adverse events, clinical laboratory tests, vital signs, ECGs, body weight, body mass index (BMI), and 2 scales for assessing EPS: the SARS and the AIMS.

Statistical Methods:

Efficacy

Change from baseline in BEHAVE-AD psychosis subscale score, BEHAVE-AD total score and subscale scores at every time point	Analysis of covariance (ANCOVA) model including treatment group and pooled investigator as factors and baseline score as a covariate. The difference in least squares mean (LS Means) between risperidone and placebo groups was used in comparing efficacy between treatment groups. Within-group comparisons with paired t-test.
CGI-C Score	Van Elteren test controlling for pooled investigator.
Change from baseline in BEHAVE-AD psychosis subscale score at Weeks 1, 2, 4, and 8	Longitudinal analysis using a mixed effects model.
Onset of maintained CGI improvement	Cochran-Mantel-Haenszel (CMH) test controlling for pooled investigator.

Safety

Adverse events	Number and percent of subjects with adverse event by treatment group.
Time to first occurrence of selected adverse events	Kaplan-Meier product limit estimator, Gehan's generalized Wilcoxon test for between-treatment group comparisons.
Change from baseline in vital signs, body weight, ECG, SARS, AIMS, and laboratory parameters	Descriptive statistics (N and percent of subjects exceeding predefined limits, mean, and SD) were estimated for each treatment group. Van Elteren test controlling for pooled investigator was used for between-treatment group comparisons. Within-group comparisons were made with the Wilcoxon signed-rank test. Distributions of subjects according to predefined criteria for abnormal values were compared using a CMH test controlling for pooled investigator.

SUMMARY:

Seventy-five percent of the subjects in each group completed the 8-week treatment phase. The percentages of subjects who discontinued treatment for different reasons were comparable in the 2 treatment groups.

The mean age of the ITT subjects was 83.3 years. Most were women (77.0%) and Caucasian (80.1%). The mean CGI-S score at baseline was 3.3 in both the placebo and risperidone groups, and the mean MMSE score was 13.2 in both groups. Most subjects (88.2%) had a diagnosis of Alzheimer's type dementia without a vascular component. The mean time since the onset of dementia was 4.2 years, and the mean time since the onset of psychosis was 1.5 years. The mean duration of the current institutionalization was 1.3 years.

The mean mode dose during double-blind treatment was 1.09 mg/day for the risperidone group, and the equivalent of 1.18 mg/day for the placebo group.

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EFFICACY RESULTS: The results of the co-primary efficacy variables showed no statistically significant differences between risperidone and placebo in the BEHAVE-AD psychosis subscale score or the CGI-C score at endpoint.

BEHAVE-AD Score Psychosis Subscale Score at Endpoint - MITT-EXCL Analysis Set

	--------Placebo--------		----------Risperidone----------	
	N	Mean (SD)	N	Mean (SD)
Baseline	214	8.2 (4.85)	202	7.6 (4.10)
Endpoint	212	5.7 (5.51)	201	4.7 (4.62)
Change from baseline to endpoint				
Mean	212	-2.5 (3.91)	201	-2.9 (3.91)
LS mean	212	-2.3 (3.55)	201	-2.9 (3.55)
Difference from placebo in LS mean (95% CI)				-0.6 (-1.25, 0.14)
P value[a]				0.118

[a] From ANCOVA model including treatment and pooled investigator as factors, and baseline score as covariate.

CGI-C Scores at Endpoint - MITT-EXCL Analysis Set

	Placebo (N=213)	Risperidone (N=201)	P value[a]
Marked worsening	9 (4.2%)	8 (4.0%)	
Moderate worsening	9 (4.2%)	12 (6.0%)	
Minimal worsening	12 (5.6%)	11 (5.5%)	
No change	64 (30.0%)	38 (18.9%)	
Minimal improvement	46 (21.6%)	67 (33.3%)	
Moderate improvement	49 (23.0%)	50 (24.9%)	
Marked improvement	24 (11.3%)	15 (7.5%)	0.416

[a] From Van Elteren test controlling for pooled investigator.

Based on the table above, 34.3% of the subjects in the placebo group and 32.3% of those in the risperidone group showed moderate or marked improvement at endpoint. Minimal, moderate, or marked improvement occurred in 55.9% and 65.7% of subjects, respectively. Approximately the same percentages of subjects (14.1% and 15.4%, respectively) showed worsening.

There were no clinically meaningful differences between the groups at endpoint for the BEHAVE-AD total score or remaining BEHAVE-AD subscale scores. There was no statistically significant difference between the groups in the time to onset of maintained improvement as assessed by the CGI-C.

There was evidence from subgroup analyses that risperidone was more effective than placebo in subjects with more severe dementia disease at baseline, i.e., those with baseline MMSE scores of 5 to 9. In this subgroup, the mean change from baseline in the BEHAVE-AD psychosis subscale score was -4.1 in the risperidone group and -2.2 in the placebo group (p=0.069). In addition, the distribution of CGI-C scores at endpoint was significantly different between risperidone and placebo (p=0.024), with 68.4% of the subjects in the risperidone group and 41.9% of those in the placebo group showing minimal, moderate, or marked improvement.

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SAFETY RESULTS: Treatment-emergent adverse events (TEAEs) occurred in 63.9% of the subjects in the placebo group and 74.5% of the subjects in the risperidone group. The type and frequency of TEAEs were similar in the 2 groups, except that somnolence occurred in proportionately more subjects in the risperidone group (16.2%) than the placebo group (4.6%). Most TEAEs in both groups were judged by the investigators to be unrelated or of doubtful relationship to study medication. Most TEAEs were mild or moderate and occurred at a fairly steady rate over time. The noticeable exception was psychiatric events, such as somnolence and insomnia, which occurred at higher rates during the first 2 weeks of the study, particularly in the risperidone group. The percentage of subjects who discontinued treatment due to adverse events was similar in the placebo (10.1%) and risperidone (10.6%) groups. The TEAEs most commonly leading to discontinuation in the risperidone group were somnolence (5 subjects) and hypertonia (3 subjects). The incidence of serious TEAEs was similar in the placebo group (13.0%) and the risperidone group (14.0%). The most common serious TEAE was urinary tract infection, which occurred in 6 subjects in the placebo group and 8 subjects in the risperidone group. TEAEs led to the deaths of 6 (2.5%) subjects in the placebo group and 9 (3.8%) subjects in the risperidone group either during or within 30 days after the study.

Adverse events considered to be of particular interest in this study are summarized in the next table. The risperidone group reported slightly higher incidences of certain TEAEs that were categorized as cerebrovascular, vascular, and cardiac-related events, compared with the placebo group. The occurrences of serious events of these types, and of deaths related to these types of TEAEs, were also somewhat higher in the risperidone group.

The incidence of EPS-related events was higher in the risperidone group than in the placebo group (8.5% versus 3.4%). No subject experienced tardive dyskinesia. None of the EPS-related events were serious or rated severe, and no subject in the risperidone group received anti-EPS medication during the study. Proportionately more subjects in the risperidone group than in the placebo group had increases (worsening) in total SARS scores at endpoint, however, whereas proportionately more subjects in the placebo group had decreases (improvement) in total SARS scores ($p=0.005$). The distribution of subjects according to the change in AIMS total score at endpoint was similar in the 2 treatment groups ($p=0.905$), with more than 75% of the subjects in each group showing no change from baseline.

There was no apparent difference between the groups in the rate of glucose-related TEAEs. As already noted, somnolence occurred more frequently in the risperidone group than in the placebo group. Only 1 subject had a serious TEAE of somnolence, but this subject was in the placebo group.

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SAFETY RESULTS (continued):

Treatment-Emergent AEs of Interest - ITT Analysis Set

		Placebo (N=238) n (%)	Risperidone (N=235) n (%)
Cerebrovascular	Any[a]	1 (0.4)	4 (1.7)
	Serious[b]	1 (0.4)	3 (1.3)
	Died[b]	0 (0)	1 (0.4)
Vascular[c]	Any[a]	1 (0.4)	7 (3.0)
	Serious[b]	4 (1.7)	6 (2.6)
	Died[b]	1 (0.4)	2 (0.9)
Cardiac-related	Any[a]	15 (6.3)	24 (10.2)
	Serious[b]	8 (3.4)	16 (6.8)
	Died[b]	1 (0.4)	5 (2.1)
Edema-related	Any[a]	11 (4.6)	12 (5.1)
	Serious[b]	0 (0)	0 (..0)
	Died[b]	0 (0)	0 (0)
EPS-related	Any[a]	8 (3.4)	20 (8.5)
	Serious[b]	0 (0)	0 (0)
	Died[b]	0 (0)	0 (0)
Glucose-related	Any[a]	5 (2.1)	4 (1.7)
	Serious[b]	1 (0.4)	1 (0.4)
	Died[b]	0 (0)	0 (0)
Somnolence	Any[a]	11 (4.6)	38 (16.2)
	Serious[b]	1 (0.4)	0 (0)
	Died[b]	0 (0)	0 (0)

[a] Includes events occurring during treatment or within 4 days after last dose of study medication.
[b] Includes events occurring during treatment or within 30 days after last dose of study medication.
[c] Includes all cerebrovascular TEAEs and 1 type of cardiac-related TEAE (myocardial infarction). Subjects with those events are counted in both categories.

Mean values for prolactin increased during treatment in the risperidone group but not in the placebo group. Nearly all (95%) subjects in the risperidone group had at least 1 prolactin value above the upper limit of the normal range. However, no subject had any TEAEs that were potentially related to prolactin elevations. The only other notable effect of risperidone on laboratory results was related to glucose. Although mean values for glucose did not change appreciably in either group, a slightly higher percentage of subjects in the risperidone group (27%) than in the placebo group (19%) had abnormally high glucose values sometime during the study. However, elevated glucose levels in both groups may suggest that some samples could have been obtained under non-fasting conditions rather than under fasting conditions, as specified by the protocol.

Risperidone had no unexpected, clinically relevant effect on vital signs, weight, BMI, or ECGs. As expected, a slight increase in mean heart rate was noted in the risperidone group but not in the placebo group.

CONCLUSIONS:

The results of this study failed to show a statistically significant difference between risperidone and placebo in the treatment of PAD, based on the 2 prospectively specified primary endpoints, BEHAVE-AD psychosis subscale score and CGI-C. The pattern of adverse events associated with risperidone in this study was similar to that found in previous studies with risperidone in dementia.

Date of the report: 26 February 2004