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-INT-24—**Psychosis in Alzheimer's disease (PAD) analysis**

Title of Study: Risperidone in the treatment of behavioral disturbances in demented patients: an international, multicenter, placebo-controlled, double-blind, parallel-group trial using haloperidol as internal reference

Note: information specific to the current analysis of the PAD subpopulation is presented in bold.

Principal Investigator: Multicenter trial

Publication (Reference): Publications based on the trial are in Appendix 1.6

Study Initiation/Completion Dates: 20 March 1995 - 9 December 1996 | **Phase of development:** 3

Objectives: The primary objective of the original trial was to determine the efficacy profile of risperidone compared with that of placebo in patients with dementia and behavioral disturbances. Haloperidol was used as internal reference to prove the validity of the trial design with respect to efficacy. Secondary objectives were to evaluate and compare the extrapyramidal symptom (EPS) profile of risperidone with that of placebo and haloperidol; to evaluate and compare the general safety and tolerability of risperidone with placebo and haloperidol; and to document the concentrations of risperidone and the active moiety of risperidone plus 9-OH-risperidone.

The objective of the current analysis was to compare the efficacy of risperidone and placebo in the treatment of patients with PAD. Haloperidol was also compared with placebo; no comparison was performed between risperidone and haloperidol with respect to efficacy. The change from baseline in the Behavior Pathology in the Alzheimer's Disease Rating Scale (BEHAVE-AD) psychosis subscale score and the Clinical Global Impression of Change (CGI-C) were co-primary endpoints.

Methodology: This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter, international trial with 3 treatment groups (risperidone, haloperidol, and placebo) conducted in patients with dementia and behavioral disturbances. After a maximum 1-week single-blind placebo-washout period, during which antipsychotic medication was discontinued, patients were randomized to double-blind treatment with placebo, risperidone, or haloperidol for 12 weeks.

The current clinical trial report presents efficacy data relevant to the PAD subpopulation. Demographic, background, pharmacokinetic, and safety data are presented for the original trial population of patients with dementia and behavioral disturbances.

Number of Subjects (planned and analyzed): The planned sample size in the original trial was 342 (114 per treatment group), and 344 patients were randomized and treated (114 placebo, 115 risperidone, and 115 haloperidol). This intent-to-treat (ITT) analysis set was used as the basis for the safety analyses and secondary efficacy analyses.

The primary efficacy analysis set included the 142 patients (44 placebo, 52 risperidone, and 46 haloperidol) with PAD (the PAD analysis set).

Diagnosis and Main Criteria for Inclusion: In the original trial, men or women at least 55 years old were eligible if they had dementia of the Alzheimer's type with or without a vascular component, or vascular dementia, and had behavioral disturbances, a score of 4 or more on the Functional Assessment Staging (FAST), a score of 23 or lower on the Mini-Mental State Examination (MMSE), a BEHAVE-AD total score of at least 8, and a BEHAVE-AD global rating of at least 1. Patients were to be institutionalized.

The criteria for selecting patients with PAD were derived from the diagnostic criteria of Jeste and Finkel: PAD patients had Alzheimer's disease or mixed dementia and a score of at least 2 on any item of the BEHAVE-AD psychosis subscale (delusion and hallucination items) at both screening and baseline.

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Test Product, Dose and Mode of Administration, Batch No.: Risperidone was supplied as a 1-mg/mL oral solution (Batch number 94D26/164). Oral risperidone was administered twice daily as flexible doses of 0.5 to 4.0 mg/day. The dose for all patients could be titrated upwards or downwards during the trial depending on individual patient response, and was to begin at 0.5 mg/day at the start of double-blind treatment.

Reference Therapy, Dose and Mode of Administration, Batch No.: Oral haloperidol was supplied as a 1-mg/mL oral solution (Batch number 94J19/F84), and was administered using the same dose and titration regimen as for risperidone.

Placebo was administered as oral tablets (Batch number 93D29/F7) during the wash-out phase. During the double-blind phase, oral placebo solution (Batch number 94J20/F71) was administered using the same dose and titration regimen as for risperidone.

Duration of Treatment: 12 weeks

Criteria for Evaluation:

Pharmacokinetics: Plasma concentrations of risperidone and the active moiety (risperidone and 9-OH-risperidone) were determined by radioimmunoassays. The quantification limits were 0.10 ng/ml (risperidone) and 0.20 ng/ml (the active moiety).

Efficacy: All efficacy parameters, with the exception of CGI-C, were to be evaluated at screening and baseline. Postbaseline evaluations of the BEHAVE-AD and CGI were scheduled for all visits; postbaseline evaluations of the Cohen-Mansfield Agitation Inventory (CMAI) were scheduled for Weeks 2, 4, 6, 8, 10, and 12; and postbaseline evaluations of the MMSE and FAST were scheduled for Week 12 only.

Safety: Safety parameters included adverse events, the Extrapyramidal Symptom Rating Scale (ESRS), clinical laboratory tests, electrocardiograms (ECGs), vital signs, body weight, and physical examinations. **The MMSE was included as a safety variable in the current presentation of trial results (ITT analysis set).**

Statistical Methods:

Pharmacokinetics

ITT analysis, Kruskal Wallis analysis of variance, Mann-Whitney U-test, Wilcoxon matched-pairs signed-ranks test, Analysis of covariance (ANCOVA), Van Elteren test, Shapiro-Wilk test, Cochran-Mantel-Haenszel test.

Efficacy parameters (original ITT analysis) versus plasma concentrations of risperidone, 9-OH-risperidone and the active moiety were evaluated by Mann-Whitney U-test or linear regression. Safety parameters (sedation scores, ESRS total and Parkinsonism score) versus plasma concentrations of risperidone, 9-OH-risperidone and the active moiety were evaluated by Kruskal-Wallis test and linear regression.

Efficacy

The co-primary endpoints in the PAD analysis were the change from baseline to Week 12 LOCF/endpoint in the BEHAVE-AD psychosis subscale score and the distribution of CGI-C results at Week 12 LOCF/endpoint. Analyses based on the PAD analysis set were performed for the following efficacy variables: the change from baseline at every prescribed timepoint for each subscale of the BEHAVE-AD and CMAI, and for CGI-C and CGI-S scores based on both observed and LOCF data. The secondary efficacy variable FAST was not reanalyzed for the PAD subpopulation.

The primary efficacy comparison in this trial was between risperidone and placebo, and the comparison between haloperidol and placebo was provided for completeness. There was no comparison between risperidone and placebo, and no adjustment for multiplicity.

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Efficacy (continued)	
Change from baseline in BEHAVE-AD psychosis subscale score	**ANCOVA model including treatment group and investigator as factors and baseline score as a covariate. Treatment effects were assessed by using the means and least-squares means (LSMeans) and the between-treatment differences in LSMeans (with the 95% confidence intervals) derived from the ANCOVA model.**
CGI-C Score	**Cochran-Mantel-Haenszel (CMH) statistic using modified ridit scores (the Van Elteren test) controlling for investigator/study site.**
Secondary efficacy variables	**Statistical analysis methods similar to the analysis of the primary efficacy variables.**
Safety	
Adverse events	Number and percent of patients with adverse events by treatment group.
Clinical laboratory tests	Descriptive statistics and pre- versus on-treatment and posttreatment cross-tabulations. Clinically significant (pathological) values were also determined.
ESRS	Descriptive statistics and maximum score were determined by treatment group. Treatment differences in ESRS subscale scores and parkinsonism items were analyzed using an ANCOVA model.
Vital signs, ECGs, and body weight	Descriptive statistics were determined by treatment group. Clinically significant changes were also determined.
MMSE	Change from baseline in the MMSE total score was analyzed using a similar ANCOVA model as in the analysis of the BEHAVE-AD psychosis subscale score primary efficacy variable.

SUBJECT INFORMATION

Overall, 65% of patients in the placebo group, 59% of patients in the risperidone group, and 70% of patients in the haloperidol group completed the 12-week treatment phase. Adverse events led to the discontinuation of 14% of placebo patients, 22% of risperidone patients, and 17% of haloperidol patients.

In the ITT analysis set, 56% of patients were female, and the median age was 81 years (overall range 56 to 97 years). At trial entry, Alzheimer's disease without a vascular component was diagnosed in the majority of patients (in 68% of all patients). The treatment groups were comparable for all baseline and demographic characteristics.

In the PAD analysis set, 60% of all patients were female. The median age in the placebo group was 81.0 years (range 66 to 97) and the median age in the risperidone group was 80.5 years (range 69 to 97 years). At trial entry, Alzheimer's disease without a vascular component was diagnosed in 90% of all patients. The baseline mean BEHAVE-AD psychosis subscale score was 6.4 in placebo patients and 6.0 in risperidone patients.

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PHARMACOKINETIC RESULTS: The overall median plasma concentrations (range) during the double-blind treatment period were 1.58 ng/ml (NQ–30.2) for risperidone, 7.13 ng/ml (NQ–56.9) for 9-hydroxy-risperidone and 9.16 ng/ml (NQ–62.4) for the active moiety. In ITT patients, 9-OH-risperidone and active moiety plasma levels correlated inversely with the creatinine clearance. The median active moiety level was 18% higher in patients with creatinine clearance <50 mL/min/1.73 m² as compared to that in patients with a higher clearance. No effect (p>0.05) of the 7 most common co-medications on the drug plasma concentrations and the risperidone/active moiety ratio was observed.

EFFICACY RESULTS: In PAD patients, neither of the co-primary efficacy variables demonstrated a statistically significant difference between risperidone and placebo.

BEHAVE-AD Psychosis Subscale Score at Week 12 LOCF/Endpoint – PAD Analysis Set

		Mean (SD)			Comparison with Placebo		
Treatment	N	Baseline	Week 12 LOCF/ Endpoint	Change	LSMean Change (SD)	Diff. in LSM Change (95%CI)	p-value
Placebo	44	6.4 (3.33)	3.9 (3.88)	-2.5 (3.84)	-2.9 (3.07)	-	-
Risperidone	52	6.0 (3.16)	3.7 (3.35)	-2.4 (3.71)	-2.9 (3.07)	-0.0 (-1.3, 1.2)	0.971
Haloperidol	46	6.6 (3.64)	2.8 (2.92)	-3.8 (3.34)	-4.2 (3.07)	-1.3 (-2.6, -0.0)	0.042

N: Number of patients with both baseline and postbaseline timepoint measurements.

LSMean change (SD): LSMean change and pooled SD based on ANCOVA model.

CI: Confidence interval.

p-value: Comparison with placebo based on ANCOVA model with treatment, investigator as factors, and baseline value as covariate.

CGI-C Scores at Week 12 LOCF/Endpoint - PAD Analysis Set

		Worsening			No	Improvement			
		Marked	Moderate	Minimal	Change	Minimal	Moderate	Marked	
Treatment	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	p-value
Placebo	44	3 (6.8)	4 (9.1)	3 (6.8)	11 (25.0)	12 (27.3)	10 (22.7)	1 (2.3)	-
Risperidone	52	0 (0.0)	8 (15.4)	3 (5.8)	8 (15.4)	16 (30.8)	16 (30.8)	1 (1.9)	0.473
Haloperidol	46	0 (0.0)	4 (8.7)	5 (10.9)	3 (6.5)	12 (26.1)	16 (34.8)	6 (13.0)	0.043

p-value: Van Elteren test controlling for investigator.

SAFETY RESULTS: Safety findings are presented for the original trial population described in the RIS-INT-24 clinical trial protocol (the ITT analysis set).

Adverse Events (AEs) in >10 Patients in Any Treatment Group - ITT Analysis Set

(N = number of patients with data)	Placebo (N = 114)	Risperidone (N = 115)	Haloperidol (N = 115)
Most frequently reported AE (with onset during double-blind phase):			
Fall	13 (11.4)	17 (14.8)	16 (13.9)
Agitation	12 (10.5)	14 (12.2)	13 (11.3)
Somnolence	5 (4.4)	14 (12.2)	21 (18.3)
Injury	13 (11.4)	13 (11.3)	14 (12.2)
Purpura	12 (10.5)	6 (5.2)	3 (2.6)
No. (%) with one or more AE	83 (72.8)	88 (76.5)	92 (80.0)
No. (%) of deaths	5 (4.4)	2 (1.7)	6 (5.2)
No. (%) with one or more serious AE	8 (7.0)	13 (11.3)	14 (12.2)
No. (%) treatment stopped due to AE	16 (14.0)	23 (20.0)	20 (17.4)
No. (%) with EPS-like AE	12 (10.5)	17 (14.8)	25 (21.7)

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SAFETY RESULTS (continued)

Extrapyramidal symptoms:

(N = number of patients with data)	Placebo (N = 114)		Risperidone (N = 115)		Haloperidol (N = 115)	
	Mean score at BL	LSMean max. shift from BL	Mean score at BL	LSMean max. shift from BL	Mean score at BL	LSMean max. shift from BL
ESRS total	8.6	+2.6	9.1	+3.0	10.7	+4.6 #
Parkinsonism	7.0	+1.4 +	7.5	+2.6	8.8	+3.6
Dystonia	0.2	+0.2	0.2	+0.1	0.2	+0.2
Dyskinesia	1.3	+1.4 @	1.4	+0.6	1.6	+1.2
Sedation (1=none, 7= extremely severe)	Mean score at BL 1.3	Mean shift at endpoint +0.1	Mean score at BL 1.3	Mean shift at endpoint +0.5 *	Mean score at BL 1.4	Mean shift at endpoint +0.5

BL: baseline.
+ p <0.1 ANCOVA versus risperidone; idem Van Elteren test.
# p = 0.055, ANCOVA versus risperidone, p = 0.06 Van Elteren test.
@ p = 0.06 ANCOVA *vs.* risperidone, p >0.1 Van Elteren test.
* p <0.05 versus placebo Van Elteren test.

Clinical laboratory parameters: No consistent changes or clinically relevant abnormalities in laboratory tests.
Blood pressure and heart rate: No consistent changes or clinically relevant abnormalities in blood pressure or heart rate.
Body weight: Mean change at endpoint was -0.3 kg under risperidone, -1.2 kg under haloperidol (p <0.01 Wilcoxon intra-group comparison) and -0.9 kg under placebo (p <0.05, Wilcoxon).
ECGs: No consistent changes or clinically relevant abnormalities in ECG parameters.
MMSE: Risperidone appeared to have a statistically significantly greater effect on cognition compared with placebo based on the change in MMSE total score from baseline to endpoint. However, the difference between treatments was not statistically significant based on the observed data at Week 12.

Pharmacokinetic/pharmacodynamic correlations: No apparent pharmacokinetic/pharmacodynamic correlations were found between the efficacy and safety parameters and the plasma concentrations of risperidone, 9-hydroxy-risperidone, and the active moiety in the original trial population.

CONCLUSION: **In a post-hoc analysis of the subpopulation of patients with PAD (44 placebo and 52 risperidone patients), the results of this trial failed to show a statistically significant difference between risperidone and placebo in the treatment of PAD, based on the 2 prospectively specified primary endpoints, the BEHAVE-AD psychosis subscale score and the CGI-C.** The safety results of this trial were consistent with extensive safety data on risperidone derived from clinical and postmarketing experience in patients with dementia.

Date of the report: 29 March 2004