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-63—**Psychosis in Alzheimer's disease (PAD) analysis**

Title of Study: A randomized, double-blind, placebo controlled study of risperidone for treatment of behavioral disturbances in patients with dementia

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: 31 July 1995 - 7 March 1997 | **Phase of development:** 3

Objectives: The primary objective of the original trial was to evaluate the safety and efficacy of risperidone in the treatment of behavioral disturbances associated with dementia.

The objective of the current analysis was to compare the efficacy of risperidone (0.5, 1.0, or 2.0 mg/day) and placebo in the treatment of patients with PAD. 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 trial conducted in patients with dementia at long-term inpatient care facilities in the United States. After a maximum 1-week single-blind placebo-washout period, during which antipsychotic medication was discontinued, patients were randomized to double-blind treatment with risperidone (0.5, 1.0, or 2.0 mg/day) or placebo for 12 weeks.

The current clinical trial report presents efficacy data relevant to the PAD subpopulation. 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 596, and 625 patients were actually randomized and treated (163 placebo, 149 risperidone 0.5 mg/day, 148 risperidone 1.0 mg/day, and 165 risperidone 2.0 mg/day). This intent-to-treat (ITT) analysis set was used as the basis for the safety analyses and secondary efficacy analyses. Pharmacokinetic analyses were performed for the original trial population and for trial sites that complied with the principles of GCP.

The primary efficacy analysis set included the 290 patients (75 placebo, 71 risperidone 0.5 mg/day, 65 risperidone 1.0 mg/day, and 79 risperidone 2.0 mg/day) with PAD who were enrolled at trial sites that complied with the principles of GCP (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, 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 had to be residents of psychiatric hospitals, nursing homes, or other long-term care facilities for at least 1 month.

The criteria for determining 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.

SYNOPSIS (CONTINUED)

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)

Test Product, Dose and Mode of Administration, Batch No.: Risperidone was supplied as 0.25-mg (Batch numbers 94K24/F70, 95E03/F70, and 96F03/F70), 0.5-mg (Batch numbers 93K02/F9, 95E04/F9, and 95I12/F9), and 1.0-mg (Batch numbers 93L08/F5 and 96D15/F5) tablets. Oral risperidone was administered twice daily as fixed doses of 0.5, 1.0, or 2.0 mg/day. For patients randomized to 1.0 or 2.0 mg/day, the dose was titrated upwards in increments of no more than 0.5 mg/day every 2 days, in double-blind fashion, during the first week of double-blind treatment.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo tablets (Batch number 93D29/F7) were identical to the risperidone tablets in appearance and formulation, except for the absence of risperidone. The dose and titration for placebo were identical to those for risperidone.

Duration of Treatment: 12 weeks

Criteria for Evaluation:

Pharmacokinetics: Plasma samples for the determination of risperidone and 9-OH-risperidone were obtained at Weeks 4, 8, and 12. The assays were performed using radioimmunoassay procedures.

Efficacy: All efficacy parameters, with the exception of CGI-C, were to be evaluated at baseline. The BEHAVE-AD, CGI, Cohen-Mansfield Agitation Inventory (CMAI), and Physical Self-Maintenance Scale (PSMS) were to be evaluated at all postbaseline visits during the double-blind treatment phase, and the MMSE and FAST test were to be evaluated at Week 12 only.

Safety: Safety parameters included adverse events, the Extrapyramidal Symptom Rating Scale (ESRS), clinical laboratory tests, vital signs (including body weight), electrocardiograms (ECGs), use of concomitant lorazepam, and use of concomitant medication to treat extrapyramidal symptoms (EPS). **The MMSE was included as a safety variable in the current presentation of trial results (ITT analysis set).**

Statistical Methods:

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-Severity (CGI-S) scores based on both observed and LOCF data. The secondary efficacy variables FAST and PSMS were not reanalyzed for the PAD subpopulation.

A protocol-predefined multiplicity adjustment method (Holm's testing procedure) was applied to the evaluation of the treatment effect between each risperidone dose group and placebo.

Change from baseline in BEHAVE-AD psychosis subscale score	**Analysis of covariance (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 (i.e., the Van Elteren test) controlling for investigator/study site. Percent of CGI-C responders (marked or moderate improvement).**
Secondary efficacy variables	**Statistical analysis methods similar to the analysis of the primary efficacy variables.**

SYNOPSIS (CONTINUED)

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)

Safety	
Adverse events	Number and percent of patients with adverse events by treatment group. Between-treatment comparisons of frequencies by body class were performed using the CMH test controlling for investigator.
Clinical laboratory tests	Descriptive statistics and pre- versus on-treatment and posttreatment cross-tabulations. Clinically significant (pathological) values were also determined.
ESRS, vital signs, and ECGs	Descriptive statistics were determined by treatment group. The analysis of changes from baseline used an analysis of variance (ANOVA) model including treatment, investigator, and treatment-by-investigator interaction terms. Clinically significant changes were determined for vital signs and ECGs.
MMSE	Change from baseline in the total MMSE score was analyzed using a similar ANCOVA model as in the analysis of the BEHAVE-AD psychosis subscale score primary efficacy variable.
Concomitant medication (EPS or lorazepam)	Number and percent of patients who used any EPS medication or lorazepam during double-blind treatment. Between-treatment comparisons of frequencies by body class were performed using the CMH test controlling for investigator.
Pharmacokinetics	
Plasma concentrations, pharmacokinetic-pharmacodynamic correlations	Similar methods to those used in the original clinical trial report. Plasma concentration data were reanalyzed for the original trial population excluding patients from the GCP non-compliant center.

SUBJECT INFORMATION:

Overall, 69.6% of all patients (73.0% in the placebo group, 78.5% in the risperidone 0.5-mg/day group, 69.6% in the risperidone 1.0-mg/day group, and 58.2% in the risperidone 2.0-mg/day group) completed the 12-week treatment phase. Adverse events led to a higher percentage of patients discontinuing treatment in the risperidone 2.0-mg/day than other groups: 12.3% in the placebo group, 8.1% in the risperidone 0.5-mg/day group, 16.2% in the risperidone 1.0-mg/day group, and 24.2% in the risperidone 2.0-mg/day group.

In the ITT analysis set, 32% of patients were male, and the median ages in each treatment group ranged from 82 to 84 years (overall range 58 to 105 years). At trial entry, Alzheimer's disease without a vascular component was diagnosed in the majority of patients: 73% of all patients had Alzheimer's disease, 16% had vascular dementia, and 11% had mixed dementia.

In the PAD analysis set, 23% of patients were male, and the median ages in each treatment group ranged from 83 to 85 years (overall range 58 to 105 years). At trial entry, Alzheimer's disease without a vascular component was diagnosed in the majority of patients: 88% of all PAD patients had Alzheimer's disease and 12% had mixed dementia.

PHARMACOKINETICS: Findings were similar to those presented in the original clinical trial report. The exclusion of the GCP non-compliant trial center did not notably affect the results.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.		
NAME OF FINISHED PRODUCT: RISPERDAL®	Volume:	
NAME OF ACTIVE INGREDIENT(S): Risperidone (R064766)	Page:	

EFFICACY RESULTS: In PAD patients, risperidone 1.0 mg/day demonstrated statistically significant superiority compared with placebo in both co-primary efficacy variables. The differences between the 0.5-mg/day or 2.0-mg/day risperidone group and the placebo group were not statistically significant.

BEHAVE-AD Psychosis Subscale Score at Week 12 LOCF/Endpoint – PAD Analysis Set Excluding GCP Non-Compliant Site

		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	73	7.7 (4.29)	5.0 (5.41)	-2.7 (4.69)	-2.8 (3.66)	-	-
RIS 0.5 mg/day	71	7.1 (3.34)	4.5 (4.15)	-2.5 (4.40)	-3.1 (3.66)	-0.2 (-1.5, 1.0)	0.729
RIS 1.0 mg/day	65	7.8 (3.68)	3.7 (3.64)	-4.2 (4.20)	-4.7 (3.66)	-1.9 (-3.2, -0.6)	0.004*
RIS 2.0 mg/day	79	6.8 (3.16)	3.5 (3.17)	-3.3 (3.86)	-4.0 (3.66)	-1.2 (-2.4, 0.0)	0.056

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

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

CI: confidence interval.

*** Based on Holm's testing procedure, the smallest p-value was evaluated at the 0.0167 significance level.**

CGI-C Scores at Week 12 LOCF/Endpoint- PAD Analysis Set Excluding GCP Non-Compliant Site

		Worsening			No Change	Improvement			
		Marked	Moderate	Minimal		Minimal	Moderate	Marked	
Treatment	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	p-value
Placebo	74	0 (0.0)	8 (10.8)	7 (9.5)	21 (28.4)	16 (21.6)	13 (17.6)	9 (12.2)	-
RIS 0.5 mg/day	71	2 (2.8)	5 (7.0)	4 (5.6)	18 (25.4)	22 (31.0)	13 (18.3)	7 (9.9)	0.517
RIS 1.0 mg/day	65	0 (0.0)	4 (6.2)	4 (6.2)	8 (12.3)	21 (32.3)	19 (29.2)	9 (13.8)	0.003*
RIS 2.0 mg/day	79	2 (2.5)	5 (6.3)	7 (8.9)	9 (11.4)	24 (30.4)	22 (27.8)	10 (12.7)	0.072

p-value: Van Elteren test controlling for investigator.

*** Based on Holm's testing procedure, the smallest p-value was evaluated at the 0.0167 significance level.**

SAFETY RESULTS: Safety findings are presented for the original trial population described in the RIS-USA-63 clinical trial protocol (the ITT analysis set).

Adverse Events in >10% of Patients in Any One Treatment Group - ITT Analysis Set

Adverse events	Placebo (N=163)	Risperidone 0.5 mg/day (N=149)	Risperidone 1.0 mg/day (N=148)	Risperidone 2.0 mg/day (N=165)
No. of patients (%) with ≥1 AE	138 (84.7%)	125 (83.9)	121 (81.8)	146 (88.5)
Most common AEs (>10% of patients in any one group)				
Injury	61 (37.4)	49 (32.9)	42 (28.4)	52 (31.5)
Edema peripheral	9 (5.5)	24 (16.1)	19 (12.8)	30 (18.2)
Fever	12 (7.4)	15 (10.1)	11 (7.4)	24 (14.5)
Pain	13 (8.0)	12 (8.1)	4 (2.7)	17 (10.3)
Somnolence	13 (8.0)	15 (10.1)	25 (16.9)	46 (27.9)
Agitation	17 (10.4)	11 (7.4)	8 (5.4)	14 (8.5)
Extrapyramidal disorder	12 (7.4)	10 (6.7)	19 (12.8)	35 (21.2)
Rhinitis	9 (5.5)	7 (4.7)	9 (6.1)	17 (10.3)
Coughing	13 (8.0)	16 (10.7)	8 (5.4)	14 (8.5)
Upper respiratory tract infection	6 (3.7)	15 (10.1)	11 (7.4)	9 (5.5)
Fall	33 (20.2)	24 (16.1)	19 (12.8)	41 (24.8)
Urinary tract infection	21 (12.9)	24 (16.1)	19 (12.8)	35 (21.2)
Purpura	19 (11.7)	25 (16.8)	18 (12.2)	17 (10.3)

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: RISPERDAL®	Volume:	
NAME OF ACTIVE INGREDIENT(S): Risperidone (R064766)	Page:	

SAFETY RESULTS (continued)

	Placebo (N=163)	Risperidone 0.5 mg/day (N=149)	Risperidone 1.0 mg/day (N=148)	Risperidone 2.0 mg/day (N=165)
No. (%) of patients with ≥1 serious AE	19 (11.7)	14 (9.4)	20 (13.5)	27 (16.4)
No. (%) of deaths	5 (3.1)	6 (4.0)	13 (8.8)	6 (3.6)
Number (%) of dropouts for AEs	21 (12.9)	13 (8.7)	25 (16.9)	42 (25.5)
Number (%) of patients with ≥1 EPS-like AEs	12 (7.4)	10 (6.7)	19 (12.8)	35 (21.2)

Extrapyramidal Symptom Rating Scale (ESRS)

	Placebo (N=163)		Risperidone 0.5 mg/day (N=149)		Risperidone 1.0 mg/day (N=148)		Risperidone 2.0 mg/day (N=165)	
	Mean at BL	Maximum shift from BL	Mean at BL	Maximum shift from BL	Mean at BL	Maximum shift from BL	Mean at BL	Maximum shift from BL
ESRS total	11.45	3.45	12.31	2.77	12.20	3.28	11.05	4.68
Parkinsonism	9.60	2.68	10.59	2.40	10.14	3.20	9.39	4.61[a]
Dystonia	0.12	0.14	0.21	0.10	0.24	0.06	0.33	0.04
Dyskinesia	1.73	1.22	1.50	0.79	1.82	0.55[b]	1.33	0.55[b]

BL: baseline.
Higher scores imply worsening condition.
[a] $p < 0.05$ with placebo having lower scores. P-values for pairwise comparisons are from two-way ANOVA with interactions.
[b] $p < 0.05$ with risperidone having lower scores.

Vital signs: no consistent changes or clinically relevant abnormalities in blood pressure or heart rate were observed.
ECG: no consistent changes or clinically relevant abnormalities in ECG parameters were observed.
Body weight at endpoint: the mean change at endpoint was -0.01 lbs for placebo, +1.60 lbs for risperidone 0.5 mg/day ($p<0.05$ compared with placebo, two-way ANOVA with interactions), +0.83 lbs for risperidone 1.0 mg/day, and +0.82 lbs for risperidone 2.0 mg/day.
Laboratory parameters: no consistent changes or clinically relevant abnormalities in laboratory parameters were observed.
MMSE: Risperidone 1.0 mg/day produced greater changes in cognition compared with placebo, as shown by the change from baseline in MMSE total score. These changes were of a small magnitude, consistent with fluctuations often observed in such patients, and appeared not to be clinically significant.

CONCLUSION: In a post-hoc analysis of the subpopulation of patients with PAD (75 placebo, 71 risperidone 0.5 mg/day, 65 risperidone 1.0 mg/day, and 79 risperidone 2.0 mg/day patients), risperidone 1.0 mg/day demonstrated statistically significant superiority compared with placebo in the co-primary efficacy variables, the BEHAVE-AD psychosis subscale score and the CGI-C. The results of this trial failed to show a statistically significant difference between risperidone 0.5 or 2.0 mg/day and placebo in the treatment of psychosis measured by the co-primary variables. The pattern of safety findings associated with risperidone in this trial was similar to that shown in previous trials of risperidone in patients with dementia.

Date of the report: 8 April 2004