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-AUS-5—**Psychosis in Alzheimer's disease (PAD) analysis** **Title of Study:** Risperidone in the treatment of behavioral and psychological symptoms in dementia: a multicenter, double-blind, placebo-controlled, parallel-group trial **Note: information specific to the current analysis of the PAD subpopulation is presented in bold.**		
Principal Investigator: [redacted] MB BS, FRACP, FRANZCP, MD; [redacted] Australia		
Publication (Reference): Listed in Appendix 1.6.		
Study Initiation/Completion Dates: 25 February 1998 - 7 February 2001		**Phase of development:** 3B
Objectives: The primary objectives of the original trial were: 1) to compare the efficacy of risperidone versus placebo in treating Behavioral and Psychological Symptoms in Dementia (BPSD), specifically agitation, aggression, and psychosis; 2) To evaluate and compare the safety and tolerability of risperidone versus placebo in this subject population; and 3) to evaluate nursing burden and health care resource use for subjects with manifestations of BPSD who were treated with risperidone or placebo in the 12-week trial. **The objective of the current analysis was to compare the efficacy of risperidone and placebo in the treatment of subjects 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, placebo-controlled, parallel-group, multicenter trial conducted in subjects with BPSD in a nursing home environment in Australia or New Zealand. After a maximum 1-week single-blind placebo-washout period, during which antipsychotic medication was discontinued, subjects were randomized to treatment with double-blind risperidone or placebo for 12 weeks. **The current clinical trial report presents efficacy data relevant to the PAD subpopulation. Safety data are presented for the original trial population of subjects with BPSD. Quality of life/general resource use data were not reanalyzed and are not included in the current clinical trial report.**		
Number of Subjects (planned and analyzed): The planned sample size in the original trial was 342, and 337 subjects were randomized and treated (170 placebo and 167 risperidone). This intent-to-treat (ITT) analysis set was used as the basis for the safety analyses and the secondary efficacy analyses. **The primary efficacy analysis set included the 93 subjects (47 placebo and 46 risperidone) 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 with vascular dementia, and with 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), and one of the following scores on the Cohen Mansfield Agitation Index (CMAI) disruptive form: a frequency score of at least 4 on at least one aggressive item, a frequency score of 3 on at least two aggressive items, a frequency score of 2 on at least three aggressive items, or two aggressive items occurring at a frequency of 2 and one at a frequency of 3. Subjects had to be living in a nursing home environment. **The criteria for selecting subjects with PAD were derived from the diagnostic criteria of Jeste and Finkel: PAD subjects 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 numbers 96C19/383, 96C22/384, 96I24/321, and 99A18/672). Oral risperidone was administered twice daily as flexible doses of 0.5 to 2.0 mg/day. The dose for all subjects could be titrated upwards or downwards during the trial depending on individual subject response, and was to begin at 0.5 mg/day on the first day of double-blind treatment.

Reference Therapy, Dose and Mode of Administration, Batch No.: Oral placebo solution (Batch numbers 96J01/F71, 97A24/F71, and 98L16/F71) was identical to risperidone 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: 12 weeks

Criteria for Evaluation:

Efficacy: All efficacy parameters, with the exception of CGI-C, were to be evaluated at screening, and the BEHAVE-AD, CMAI, and the CGI-Severity (CGI-S) were also evaluated at baseline. Evaluations of the CGI were scheduled at all postbaseline visits during the double-blind treatment phase; postbaseline evaluations of the BEHAVE-AD and CMAI were scheduled for Weeks 4, 8, and 12; and postbaseline evaluations of the Mini-Mental State Examination (MMSE) and FAST were scheduled for Week 12 only.

Safety: Safety parameters included adverse events, the Extrapyramidal Symptom Rating Scale (ESRS), clinical laboratory tests, vital signs, body weight, and physical examination. **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-S scores based on both observed and LOCF data. The secondary efficacy variable FAST was not reanalyzed for the PAD subpopulation.

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.**

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Safety	
Adverse events	Number and percent of subjects with adverse events by treatment group. Between-group comparisons for subjects who died were performed using a Gehan's Generalized Wilcoxon test controlling for investigator.
Concomitant medications	The number of subjects requiring extrapyramidal symptom (EPS) medication during treatment was compared using the CMH test controlling for center. Time to first re-administration of antiparkinson medication was determined and estimated using the Kaplan-Meier product-limit method and treatment groups compared via a Generalized Wilcoxon test. The same methods were applied to the administration of benzodiazepines.
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 data were assessed using an ANCOVA controlling for treatment, baseline score (as covariate), and investigator.
Vital signs	Descriptive statistics were determined by treatment group. Between-group comparisons were performed at screening using analysis of variance and at endpoint using ANCOVA. Clinically significant changes were also determined.
MMSE	Changes from screening were analyzed using the van Elteren test controlling for investigator.

SUBJECT INFORMATION

Overall, 67.1% of subjects in the placebo group and 73.1% of subjects in the risperidone group completed the 12-week treatment phase. Adverse events led to a lower percentage of subjects discontinuing treatment in the placebo than risperidone group (8.2% versus 13.2%).

In the ITT analysis set, 71% of subjects were female, and the median age in each treatment group was 84 years (overall range 56 to 100 years). At trial entry, Alzheimer's disease without a vascular component was diagnosed in the majority of subjects (in 62% of placebo and 59% of risperidone subjects).

In the PAD analysis set, 85% of subjects were female, and the median age in each treatment group was 84 years (overall range 61 to 97 years). At trial entry, Alzheimer's disease without a vascular component was diagnosed in the majority of subjects (in 85% of placebo and 80% of risperidone subjects). The baseline mean BEHAVE-AD psychosis subscale score was 9.4 in placebo subjects and 9.7 in risperidone subjects.

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EFFICACY RESULTS: In PAD subjects, risperidone demonstrated statistically significant superiority compared with placebo in both co-primary efficacy variables.

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	46	9.3 (5.82)	6.0 (5.74)	-3.3 (6.78)	-3.4 (4.58)	-	-
Risperidone	44	9.3 (5.68)	4.2 (4.15)	-5.2 (5.38)	-5.5 (4.58)	-2.1 (-4.2, -0.1)	0.039

N: Number of subjects 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 Excluding GCP Non-Compliant Site

		Worsening			No	Improvement			
		Marked	Moderate	Minimal	Change	Minimal	Moderate	Marked	
Treatment	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	p-value
Placebo	47	0 (0.0)	5 (10.6)	10 (21.3)	13 (27.7)	7 (14.9)	9 (19.1)	3 (6.4)	--
Risperidone	46	0 (0.0)	1 (2.2)	2 (4.3)	5 (10.9)	11 (23.9)	21 (45.7)	6 (13.0)	<0.001

p-value: Van Elteren test controlling for investigator.

SAFETY RESULTS: Safety findings are presented for the original population described in the RIS-AUS-5 clinical trial protocol (the ITT analysis set).

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

(N = number of subjects with data)	Placebo (N = 170)	Risperidone (N = 167)
Adverse events (AE)		
Most frequently reported AE:		
Injury	63 (37.1)	60 (35.9)
Somnolence	43 (25.3)	61 (36.5)
Fall	46 (27.1)	42 (25.1)
Agitation	42 (24.7)	33 (19.8)
Urinary tract infection	25 (14.7)	39 (23.4)
Purpura	27 (15.9)	30 (18.0)
Constipation	26 (15.3)	19 (11.4)
Conjunctivitis	18 (10.6)	20 (12.0)
Skin disorder	16 (9.4)	18 (10.8)
Aggressive reaction	18 (10.6)	9 (5.4)
Diarrhea	22 (12.9)	5 (3.0)
No. (%) with one or more AE	157 (92.4)	157 (94.0)
No. (%) of deaths	5 (2.9)	6 (3.6)
No. (%) with one or more serious AE	12 (7.1)	25 (15.0)
No. (%) treatment stopped due to AE	14 (8.2)	22 (13.2)
No. (%) with cerebrovascular disorder	3 (1.8)	15 (9.0)
No. (%) with EPS-like AE	27 (15.9)	39 (23.4)

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SAFETY RESULTS (continued)

Extrapyramidal Symptom Rating Scale (ESRS) - ITT Analysis Set

	Placebo (N = 170)		Risperidone (N = 167)		
	Mean (SE) at baseline	Change at endpoint (SE)	Mean (SE) at baseline	Change at endpoint (SE)	p-value
Total ESRS	4.9 (0.49)	0.5 (0.48)	4.5 (0.40)	0.7 (0.35)	0.407
Bucco-linguo-masticatory factor	0.9 (0.17)	-0.1 (0.17)	1.0 (0.18)	-0.0 (0.17)	0.440
Parkinsonism/dystonia total	10.4 (0.54)	-0.7 (0.42)	11.0 (0.59)	1.6 (0.47)	<0.001
Parkinsonism total score	10.2 (0.52)	-0.6 (0.40)	10.7 (0.56)	1.5 (0.45)	<0.001

SE: standard error.

Clinical laboratory parameters: There were no consistent or clinically significant changes in blood chemistry or hematology.

Blood pressure: Mean systolic blood pressure decreased significantly ($p = 0.002$) from screening at endpoint in the risperidone group, i.e., by 5.1 mmHg. There was no significant change in the placebo group. The difference between the groups approached statistical significance ($p = 0.079$). Mean diastolic blood pressure did not change significantly from screening at endpoint in either group, and there was no significant difference between the groups.

Heart rate: Mean pulse rate did not change significantly from screening at endpoint in either group, and there was no significant difference between the groups.

Body weight: Decreases from screening in weight and body mass index were statistically significant ($p < 0.001$) in the placebo group (decreases in the risperidone group were not statistically significant), resulting in significant ($p < 0.05$) differences between the placebo and risperidone groups at endpoint. However, these changes were not considered to be of clinical importance.

MMSE: Risperidone had no negative effect on cognitive function when compared with placebo, as measured by MMSE total scores.

CONCLUSION: **In a post-hoc analysis of the subpopulation of subjects with PAD (47 placebo and 46 risperidone subjects), risperidone demonstrated statistically significant superiority compared with placebo in the co-primary efficacy variables BEHAVE-AD psychosis subscale score and the CGI-C.** The pattern of safety findings associated with risperidone in this trial was similar to that shown in previous trials of risperidone in subjects with dementia.

Date of the report: 24 March 2004