SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, a division of Janssen Pharmaceutica N.V. NAME OF FINISHED PRODUCT: RISPERDAL® tablet 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-83

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]; Israel

Publication (Reference): None

Study Initiation/Cutoff Dates: 11 July 2001 – 27 September 2001 (terminated early)	**Phase of development:** 3b

Objectives:

The primary objective of the study was:
- to compare the efficacy of risperidone versus placebo in the treatment of psychosis of Alzheimer's Disease (AD): both the change from baseline in the BEHAVE-AD psychosis cluster score and the Clinical Global Impression of Change (CGI-C) were employed as primary end points.

The secondary objectives of the study were:
- to compare the efficacy of risperidone versus placebo based on the change from baseline of the total score and the scores on the other subscales of the BEHAVE-AD; and
- to evaluate and compare the safety and tolerability of risperidone versus placebo in this population as assessed by adverse events, including EPS, clinical laboratory tests, vital signs, and ECGs during this 8-week study.

Since the study was terminated early, the objectives are no longer applicable.

Methodology: This was a randomized, double-blind, placebo-controlled, multicenter study, which was conducted internationally and consisted of 2 phases. All eligible subjects first participated in a single-blind, placebo-controlled run-in phase of 7 days. In this phase, any currently unallowable medication was tapered or discontinued as per protocol. Afterwards, subjects were randomized to placebo or risperidone. The double-blind treatment phase then started. Risperidone was given in a flexible dose regimen of 1 to 1.5 mg daily in a twice daily regimen. All subjects were titrated to at least a 1-mg daily dose. Therefore, the minimum dose was set at 1 mg daily, to be increased to 1.5 mg daily as a maximum dose if, in the investigator's opinion, the treatment at the lower dose of 1 mg had not yet shown the optimal effect. Subjects remained institutionalized for the duration of the double-blind treatment phase. Subjects were monitored for their psychosis and other behavioral signs and symptoms, using the BEHAVE-AD. An assessment of global benefit was to be made at regular times using the CGI-C. Both the BEHAVE-AD and the CGI-C were to be completed by different and independent raters. Safety and tolerability evaluations included adverse event monitoring (including extrapyramidal symptoms), standard clinical laboratory evaluations (hematology, biochemistry, and urinalysis), vital sign and ECG measurements, and physical examinations.

Number of Subjects (planned and analyzed): 408 subjects planned; 18 subjects were analyzed for efficacy and safety.

Diagnosis and Main Criteria for Inclusion: Men and women, ≥55 years of age, with AD and clear symptoms of psychosis (and otherwise healthy) residing in nursing homes or other long-term care facilities and from whom the appropriate informed consent had been obtained.

Test Product, Dose and Mode of Administration, Batch No.: Risperidone 0.25-mg tablets, 1 to 1.5 mg daily in 2 dosages (i.e., 2 to 3 tablets b.i.d.), Batch No.: 00F28/F70, 01B06/F070.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo tablets, 1 to 1.5 mg daily in 2 dosages (i.e., 2 to 3 tablets b.i.d.), Batch No.: 00F27/F07, 01B05/F007, 00C12/F7, 00B16/F07.

Duration of Treatment: Each subject was to receive risperidone or matching placebo tablets (b.i.d.) for a period of 8 weeks.

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Criteria for Evaluation:

Efficacy Evaluations:

BEHAVE-AD Psychosis Cluster Score was to be completed by a trained rater at screening; baseline; and at Visits 3, 4, 6, and 8.

CGI-C was assessed at all visits from Visit 3 onwards (before the clinical evaluation and adverse event assessments).

Secondary Parameters (Total and Other Subscales of the BEHAVE-AD) were to be completed by a trained rater at screening; baseline; and at Visits 3, 4, 6, and 8.

Safety Evaluations:

Adverse Events were reported between the first and last administration of study medication in the double-blind treatment phase.

Extrapyramidal Symptoms were assessed using both the AIMS and the SARS. The global rater was to score both scales at baseline, Visits 6, and Visit 8.

Clinical Laboratory Tests: Blood samples for biochemistry and hematology and a random urine sample for urinalysis (optional) were to be taken at screening (potentially to be repeated before randomization), Visit 6, and Visit 8.

Vital Signs were to be performed at screening and baseline before 9.00 a.m. and at all other visits prior to the morning intake of the study medication. The subject first had to be in the supine position for 5 minutes. Subsequently, the subject had to stand for 2 minutes. Both in the supine and standing position, systolic and diastolic blood pressure had to be measured. The radial pulse rate was to be recorded during a full 60 seconds.

A physical examination was to be conducted at screening and repeated at Visit 8. Body weight was to be measured at screening, baseline, and at Visits 6 and 8.

An ECG was to be recorded in the morning before 9.00 a.m. at screening and baseline, and before drug dosage at Visits 6 and 8.

SUMMARY – CONCLUSIONS

DEMOGRAPHICS RESULTS: The 18 subjects enrolled in the study ranged in age from 76 to 94 years. Overall, the majority of the subjects were women; the placebo group and the risperidone group comprised 5 (63%) and 8 (80%) women. All subjects were white, with the exception of 1 Hispanic subject included in the risperidone group. There were no clinically meaningful differences between the 2 treatment groups with respect to these demographic parameters.

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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 change from baseline in the BEHAVE AD psychotic symptom subtotal at end point was +0.6 in the placebo group and -2.4 in the risperidone group. Bearing in mind that higher scores indicate severe symptoms, there was a slight improvement in the risperidone group compared with placebo. Also, the mean baseline value in the risperidone group was (slightly) higher compared with the placebo group.

BEHAVE-AD Psychosis Score – Descriptive Statistics
(Study RIS-INT-83: ITT Analysis Set)

	Placebo (N=8)		Risperidone (N=10)	
	n	Mean (SD)	n	Mean (SD)
Baseline	8	6.6 (3.29)	10	7.6 (3.41)
Week 1	8	6.4 (4.00)	10	5.3 (3.71)
Week 2	7	7.4 (4.12)	8	6.4 (5.04)
Week 4	5	5.4 (4.28)	4	6.8 (4.99)
Week 8	1	10.0	1	8.0
End point	8	7.3 (4.46)	10	5.2 (4.13)
Change from baseline	8	+0.6 (4.84)	10	-2.4 (5.58)

At baseline, the CGI-S score was similar in the 2 treatment groups. In both treatment groups, the majority (70% and 75%) of the subjects had either moderate or marked CGI-S scores at baseline. At end point, the percentage of subjects with a minimal to marked improvement was 40% in the risperidone group and 25% in the placebo group.

Summary of CGI Score
(Study RIS-INT-83: ITT Analysis Set)

	Placebo (N=8)		Risperidone (N=10)	
	n	%	n	%
Baseline				
Mild	0	0.0	1	10.0
Moderate	3	37.5	5	50.0
Marked	3	37.5	2	20.0
Severe	2	25.0	1	10.0
Extremely severe	0	0.0	1	10.0
End point				
Marked worsening	1	12.5	2	20.0
Moderate worsening	2	25.0	0	0.0
Minimal worsening	0	0.0	0	0.0
No change	3	37.5	4	40.0
Minimal improvement	1	12.5	3	30.0
Moderate improvement	1	12.5	0	0.0
Marked improvement	0	0.0	1	10.0

Secondary efficacy parameters were not analyzed because the study was terminated early.

SYNOPSIS (CONTINUED)

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SAFETY RESULTS:

Overall, 13 (72%) subjects reported at least 1 adverse event. The proportion of subjects with adverse events was similar for each treatment group (75% of the subjects in the placebo group and 70% of the subjects in the risperidone group). The majority of adverse events were considered mild or moderate and unrelated or doubtfully related to the study drug. One subject in each treatment group had serious adverse events; the risperidone-treated subject had cerebral hemorrhage during the study and the placebo-treated subject had neoplasm NOS and aggravated psychosis after the study. The subject included in the risperidone treatment group discontinued the study because of this serious adverse event (cerebral hemorrhage). The other subject, randomized to the placebo treatment group, died due to progression of pulmonary cancer several days after he was excluded from the study. Two other risperidone-treated subjects were prematurely withdrawn from the study due to adverse events. These adverse events were confusion, fall, and gait abnormal in 1 subject and extrapyramidal disorder and abnormal lab values in the other subject. No clinically meaningful changes in the safety findings were found in the few subjects examined in this study.

CONCLUSION:

Due to the small number of subjects, no definitive conclusions regarding efficacy can be drawn based on the data collected during this study. Even though only data from a small numbers of subjects was available, safety results were comparable to those observed in other studies with risperidone.

Date of the report: 12 December 2003