SYNOPSIS

Trial identification and protocol summary

Company: Janssen Research Foundation **Finished product**: RISPERDAL® **Active ingredient**: Risperidone (R064,766)		
Title: An open-label, long-term study of risperidone for treatment of behavioral disturbances in patients with dementia		**Trial No**.: RIS-USA-70 **Clinical phase**: III
Investigator: Multicenter	**Country**: USA	
Reference: JRF, Clinical Research Report RIS-USA-70, 16 October, 1998 N137141		
Trial period: Start: 20 Nov 95 End: 06 April 98	**No. of investigators**: 34 **No. of patients**: 330	
Indication/objectives: The primary objective of this trial was to evaluate the safety and tolerability of risperidone in demented patients when treated for up to 12 months.		
Trial design: This was an open-label, long-term multicenter trial conducted in patients with dementia for up to 12 months. Ideally, patients began open-label risperidone treatment on the last visit of the preceding study, RIS-USA-63. Treatment began with 0.25 mg b.i.d. in divided doses and was titrated to an optimal dose.		
Patient selection: • Inclusion criteria: - Patients who completed the preceding double-blind trial, RIS-USA-63. - Patients who enrolled in the extension study within two weeks of completing the final visit - of the RIS-USA-63 trial. - Patients signed informed consent prior to trial entry. - Patients were male or female, ≥55 years of age. - Patients had a diagnosis of dementia of the Alzheimer's type (AD), vascular dementia (VD), or mixed (AD and VD), as defined by *Diagnostic & Statistical Manual, 4th* Edition (DSM-IV). - Patients had a score of at least 4 on the Functional Assessment Staging (FAST) and a score ≤23 on the Mini-Mental State Examination (MMSE). Patients had the following Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) scores: total score of at least 8 and global rating of at least 1 (i.e., mildly troubling to the caregiver or dangerous to the patient). - Patients resided in a state psychiatric hospital, nursing home, or other long-term care facility for at least one month. • Exclusion criteria: - Patients who prematurely discontinued from the RIS-USA-63 for any reason, - Patients with untreated reversible causes of dementia (e.g., conditions when treated, cognitive deficits improved).		
- Patients with general medical or neurological conditions that diminish cognition, including but not limited to: untreated vitamin deficiency, severe hepatic or renal dysfunction, electrolyte imbalance, sepsis syndrome, hypo- or hyperglycemia, untreated hypothyroidism, normal pressure hydrocephalus, previous brain trauma, brain tumor, mental retardation, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or neurosyphilis.		
- Patients with a diagnosis of dementia related to infection with human immunodeficiency virus, as defined by DSM-IV.		
- Patients with a diagnosis of substance-induced persistent dementia, as defined by DSM-IV.		
- Patients with a diagnosis of delirium or amnestic disorder, as defined by DSM-IV.		
- Patients with psychiatric disorders that could have accounted for the observed psychotic disturbances (e.g., a diagnosis of schizophrenia, schizoaffective disorder, or delusional disorder or patients with a diagnosis of affective disorder with current clinically determined depression or mania).		
- Patients with a history of hypersensitivity to risperidone.		
- Patients with a history of neuroleptic malignant syndrome.		
- Patients with a seizure disorder.		
• Exclusion criteria (continued)		

- Patients diagnosed with carcinoma in the past five years, except for treated skin cancer. - Patients with malignant melanoma were excluded.	
- Patients who had received concomitant medications (other than over-the-counter medications or antibiotics) for less than 30 days. Doses of concomitant medications should have been stable for 30 days. Minor variations (up to 25%) in the dose of the concomitant medication were permitted.	
- Patients who had received a depot neuroleptic injection within one treatment cycle of screening.	
- Patients who were expected to continue treatment with antipsychotics, antidepressants, lithium, carbamazepine, and/or valproic acid during the trial.	
- Patients who had received Cognex® or Hydergine®, and were not willing to discontinue its use during the trial period.	
- Patients with clinically significant laboratory or electrocardiogram (ECG) findings.	
- Patients exhibiting behaviors which could have directly endangered the patients' lives or the life of another person, or patients, who in the opinion of the investigator, were at risk of carrying out such behavior.	
- Patients who had received an investigational drug or participated in an investigational trial within 30 days prior to entry into the trial.	
Treatment	
Form - dosing route	Matching tablets - oral
Medication	Risperidone 0.25 mg / Risperidone 0.5 mg / Risperidone 1.0 mg
Batch number	95E03/F70, 96F03/F70 / 97G02/F9, 97B24/F9, 97B24/F9, 95I18/F9, 93K02/F9, 95E04/F9, 95C28/F9, 93A19/F9 / 93L08/F5, 96E20/F5, 97G01/F5
Dosage	Divided doses in the morning and at bedtime; treatment began with 0.25 mg b.i.d. and was titrated to an optimal dose.
Duration of treatment	Up to 12 months
Duration of trial	12 months
Disallowed medication	Antipsychotics, lithium, carbamazepine, valproic acid, antidepressants, Cognex® and Hydergine® or other investigational drugs.

Assessments	Visit						
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Efficacy: Primary: BEHAVE-AD	X	X	X	X	X	X	X
Secondary: CGI,	X	X	X	X	X	X	X
CGI-C,		X	X	X	X	X	X
PSMS	X	X	X	X	X	X	X
Safety: ESRS	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X
Laboratory tests	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X
ECG	X		X		X		X
Concurrent Medications	X	X	X	X	X	X	X
Statistical methods	Intent-to-treat analysis; paired t-tests, Wilcoxin sign-rank test.						

CGI = Clinical Global Impression, CGI-C = Clinical Global Impression-Change, PSMS = Physical Self-Maintenance Scale, and ESRS = Extrapyramidal Symptom Rating Scale.

Main features of the patient sample and summary of the results

Baseline characteristics - patient disposition		Risperidone N(%)
Number of patients entered (M/F)		104/226
Age: Mean (range), yrs		82.5(60-99)
Dropouts - Total number:		197
Reason:	Adverse event	87
	Chose to discontinue	34
	Administrative reason	16
	Other reason	19
	Ineligible	2
	Intercurrent illness*	10
	Abnormal lab results*	8
	Poor compliance	5
	Inadequate response	15
	Lost to follow-up	1

* Data included in counts of adverse events.

Mean Change from Baseline (DB & OL) at Endpoint in BEHAVE-AD Subscale Scores

	Placebo N=86,DB* N=85,OL*	Ris 0.5mg N=77, DB* N=77, OL*	Ris 1mg N=74, DB* N=73, OL*	Ris 2mg N=76, DB* N=76, OL*	All risp N=227,DB* N=226, OL*	Total N=313,DB* N=311, OL*
Total Score Mean Change (DB baseline)	-7.94	-7.75	-7.76	-8.61	-8.04	-8.01
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Mean Change (OL Baseline)	-3.19	-2.08	-1.08	0.53	-0.88	-1.51
p-value	<0.001	0.003	0.135	0.527	0.042	<0.001
Psychotic Symptoms Mean Change (DB)	-2.73	-2.69	-2.89	-2.92	-2.83	-2.81
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Mean Change (OL)	-1.00	-0.55	-0.53	0.47	-0.20	-0.42
P-value	0.009	0.072	0.061	0.158	0.266	0.012
Paranoid/Delusional Symptoms Mean Change (DB)	-2.06	-2.35	-2.41	-2.36	-2.37	-2.28
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Mean Change (OL)	-0.87	-0.52	-0.26	0.42	-0.12	-0.32
P-value	0.014	0.055	0.212	0.092	0.401	0.022
Hallucinations Mean Change (DB)	-0.67	-0.34	-0.49	-0.57	-0.46	-0.52
P-value	<0.001	<0.001	<0.001	<0.0102	<0.001	<0.001
Mean Change (OL)	-0.13	-0.03	-0.27	0.05	-0.08	-0.09
P-value	0.160	0.827	0.032	0.779	0.351	0.163

Mean Change from Baseline (DB & OL) at Endpoint in BEHAVE-AD Subscale Scores

	Placebo N=86,DB* N=85,OL*	Ris 0.5mg N=77, DB* N=77, OL*	Ris 1mg N=74, DB* N=73, OL*	Ris 2mg N=76, DB* N=76, OL*	All risp N=227,DB* N=226, OL*	Total N=313,DB* N=311, OL*
Activity Disturbances						
Mean Change (DB)	-1.14	-1.38	-1.11	-0.87	-1.12	-1.12
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Mean Change (OL)	-0.60	-0.45	-0.25	-0.14	-0.28	-0.37
P-value	0.001	0.001	0.217	0.479	0.007	<0.001
Aggressiveness						
Mean Change (DB)	-2.55	-2.44	-2.42	-2.91	-2.59	-2.58
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Mean Change (OL)	-1.59	-0.77	-0.40	0.38	-0.26	-0.62
P-value	<0.001	0.010	0.205	0.332	0.181	<0.001
Diurnal Rhythm Disturbances						
Mean Change (DB)	-0.33	-0.38	-0.39	-0.36	-0.37	-0.36
P-value	0.002	0.001	0.002	0.003	<0.001	<0.001
Mean Change (OL)	-0.04	-0.22	0.04	0.04	-0.05	-0.05
P-value	0.724	0.012	0.634	0.665	0.341	0.328
Affective Disturbances						
Mean Change (DB)	-0.23	-0.47	-0.09	-0.64	-0.41	-0.36
P-value	0.061	0.001	0.532	<0.001	<0.001	<0.001
Mean Change (OL)	0.08	-0.06	0.15	-0.16	-0.03	0.00
P-value	0.396	0.632	0.241	0.153	0.713	0.956
Anxiety/Phobia						
Mean Change (DB)	-0.97	-0.40	-0.85	-0.91	-0.72	-0.79
P-value	<0.001	0.020	<0.001	<0.001	<0.001	<0.001
Mean Change (OL)	-0.05	-0.03	-0.10	-0.07	-0.06	-0.06
P-value	0.645	0.895	0.506	0.679	0.523	0.445

p-value based on paired t test of no difference from baseline.

*DB: Number of patients with double blind (RIS-USA-63) assessments.

*OL: Number of patients with open-label (RIS-USA-70 assessments.

JRF--Trial RIS-USA-70

Summary Results at endpoint of persistent (emergent or improved) tardive dyskinesia (TD) compared with DB baseline by DB treatment-group designations

Presence of persistent TD	Placebo	RIS 0.5 mg	RIS 1 mg	RIS 2 mg	All Risperidone	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Endpoint Results for Patients with dyskinetic symptoms at DB baseline						
Absent	14 (78)	10 (77)	15 (94)	11 (92)	36 (88)	50 (85)
Present	4 (22)	3 (23)	1 (6)	1 (8)	5 (12)	9 (15)
Total	18	13	16	12	41	59
Endpoint Results for Patients without dyskinetic symptom at DB baseline						
Absent	66 (96)	62 (95)	57 (100)	64 (100)	183 (98)	249 (98)
Present	3 (4)	3 (5)	0	0	3 (2)	6 (2)
Total	69	65	57	64	186	255

Adverse events (AE) by decreasing order	Risperidone (N=330)
No. of patients (%) with ≥1 AE	310 (93.9)
Most common AEs (>10% of patients)	
• Injury	174 (52.7)
• Urinary tract infections	117 (35.5)
• Bodily fall	99 (30.0)
• Oedema peripheral	89 (27.0)
• Purpura	86 (26.1)
• Somnolence	84 (25.5)
• Fever	74 (22.4)
• Skin ulceration	71 (21.5)
• Coughing	68 (20.6)
• Upper resp. tract infec.	62 (18.8)
• Skin discoloration	60 (18.2)
• Pain	58 (17.6)
• Rhinitis	56 (17.0)
• Constipation	46 (13.9)
• Rash	46 (13.9)
• Diarrhea	45 (13.6)
• Weight decrease	44 (13.3)
• Vomiting	42 (12.7)
• Pneumonia	40 (12.1)
• Conjunctivitis	39 (11.8)
• Oedema	37 (11.2)
No. (%) of deaths No (%) of patients other SAE No (%) AE Discontinuations	29 (8.8) 113 (34) 87 (26)

Conclusions: Risperidone long-term treatment illustrated statistical improvement in psychotic and aggressive symptoms associated with dementia. Over the 12 months of the study, only 5% of the patients developed emergent, or worsened TD. Additionally, in those patients who had dyskinetic symptoms at baseline, 15% developed worsening symptoms by endpoint, and almost 50% of patients with TD showed improvement in their symptoms. In those who did not have dyskinetic symptoms, only 2% developed them during treatment. In this population of debilitated patients, few serious adverse events occurred that were related to risperidone, and there were no unexpected morbidities. Two patients developed elevated liver enzymes over the treatment course. Mean QTc change from baseline was 2.44 msec. Six patients with normal QTc intervals at baseline developed QTc intervals ≥500 msec at endpoint; one of these patients discontinued treatment because of this event. In summary, the improved efficacy results and the relatively low incidence of drug-related safety issues support the benefit/risk ratio of long-term treatment.