SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN PHARMACEUTICA N.V. **Finished product**: Risperdal® **Active ingredient**: Risperidone (R64766)		
Title: The safety and efficacy of risperidone versus placebo as adjunctive therapy to mood stabilizers in the treatment of the manic phase of bipolar disorder	**Trial No.**: RIS-INT-46 **Clinical phase**: III	
Investigator: [redacted] M.D.	**Countries**: Canada, Israel, Norway, South-Africa, Spain, United Kingdom	
Reference: JRF, Clinical Research Report RIS-INT-46, May 2000 (N 149541)		
Trial period: Start: 02 October 1997 End: 06 October 1999	**No. of investigators**: 15 **No. of patients entered**: 157 **No. of patients randomized**: 151 **No. of patients treated**: 150 **No. of patients entering open-label:** 124	
Indication / objectives: Bipolar disorder / double-blind assessment of the efficacy and safety of risperidone as adjunctive therapy to mood stabilizers in the treatment of the manic phase of bipolar disorder, and collection of additional safety and efficacy data during an 10-week open-label phase		
Trial design: DB phase: (3 weeks): double-blind, randomized parallel-group, placebo-controlled OL phase: (10 weeks): open risperidone treatment		

Patient selection:

- Inclusion criteria:
  - Age between 18 and 65 years (extremes included);
  - Patients hospitalized for mania with a minimum score, at Baseline, of 20 on the Young Mania Rating Scale (YMRS); Patients with concurrent symptoms of depression could be entered;
  - Patients diagnosed as suffering from Bipolar disorder as defined in the DSM-IV (296.4x, 296.6x);
  - Patients who had been receiving a mood stabilizer for a minimum of 2 weeks prior to screening; if the patient was not receiving a mood stabilizer, treatment had to be initiated prior to randomization;
  - Patients who were medically stable on the basis of a pretrial physical examination, medical history and electrocardiogram;
  - Patients had to be inpatients for a minimum of the first 4 days of double-blind treatment;
  - Patients had signed the informed consent form; or patient's relative, guardian or legal representative had signed the informed consent form; as per local Ethics Committee requirements;
  - Patients were randomized within 7 days after hospital admission.
- Exclusion criteria:
  - Other Axis I DSM-IV diagnosis other than nicotine or caffeine dependence;
  - Use of disallowed concomitant therapy;
  - History of alcohol or drug abuse or dependence, within 3 months before entry into the trial;
  - Seizure disorder requiring medication;
  - Patients with untreated hypothyroidism; patients with adequately treated thyroid insufficiency could be admitted;
  - Participation in an investigational drug trial within 30 days prior to the start of the trial;
  - Known sensitivity to risperidone, lithium, valproate or carbamazepine;
  - History of severe drug allergy or hypersensitivity;
  - History of neuroleptic malignant syndrome (NMS);
  - Use of clozapine within 30 days before entry into the trial;
  - Use of depot neuroleptics within one treatment cycle before entry into the trial;
  - Patients who, as judged by the investigator, were at imminent risk of causing injury to self or others, or causing significant damage to property;
  - Laboratory values outside the normal range;
  - Serious or unstable medical illnesses: liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, or metabolic disturbances, labile hypertension, poorly controlled diabetes mellitus;
  - Pregnancy or breast-feeding;
  - Woman of childbearing potential without adequate contraception (sterilization, abstinence, barrier, intrauterine device, oral contraceptives, intramuscular or subdermal administration of depot-progestagens).

Treatment		
Form - dosing route	matching tablets - oral	
Medication	Risperidone 1 mg	Placebo
Batch numbers	97A24/F5, 98C06/F5, 98A28/F5	95I11/F7
Daily dosage	DB phase: Day 1 & 2: 2 mg; Day 3 & 4: 1-4 mg; Day 5-21: 1 to 6 mg OL phase: 0 to 6 mg	
Duration of treatment	DB phase: three weeks double-blind treatment: risperidone or placebo OL phase: 10 weeks open-label risperidone treatment	
Duration of trial	13 weeks	
Disallowed medication	Antipsychotics other than the trial medication; Mood stabilizers other than lithium, valproate or carbamazepine; Benzodiazepines other than lorazepam, temazepam, flurazepam or oxazepam; After Day 7, no rescue medication for agitation was permitted; Antiparkinson medication was not permitted at Baseline, but could be used with OL treatment.	

Assessments DB phase	**Screen -3 to -1**	**Baseline Day 1**	**Day 3**	**Day 8**	**Day 15**	**Day 22**
Plasma concentration risperidone		X				X
Serum conc. mood stabilizer*	X	X	X	X	X	X
Efficacy						
• Primary variable: YMRS	X	X		X	X	X
• Secondary variables: CGI-C[1], BPRS[2], HAM-D[3]		X		X	X	X
Safety						
• Adverse events, ESRS[4]		X		X	X	X
• Clinical laboratory, ECG, physical examination	X					X
• Weight		X				X
• Vital signs	X	X		X	X	X

Assessments OL phase	**Day 7**	**Day 14**	**Day 28**	**Day 42**	**Day 56**	**Day 70**
Plasma concentration risperidone						X
Serum conc. mood stabilizer*						X
Efficacy:						
• YMRS, CGI-C, BPRS, HAM-D	X	X		X		X
Safety						
• ESRS, vital signs	X	X		X		X
• Adverse events	X	X	X	X	X	X
• ECG, lab, weight, phys. exam.						X

Statistical methods	Intent-to-treat analysis, ANCOVA, Van Elteren test, generalized Wilcoxon test, paired t-test, Wilcoxon matched-pairs signed-rank test, Cochran-Mantel-Haenszel test

* Additional samples could be taken if clinically indicated.

[1] CGI-C: Clinical Global Impression of Change.
[2] BPRS: Brief Psychiatric Rating Scale.
[3] HAMD: Hamilton Depression Rating Scale.
[4] ESRS: Extrapyramidal Symptom Rating Scale.

Main features of the patient sample and summary of the results

Baseline characteristics - patient disposition	**Placebo n = 75**	**Risperidone n = 75**
Number of patients randomized (M/F)	31/44	32/43
Age: median (min, max), yrs	42 (19, 65)	37 (20, 63)
Discontinuations -: Total, n (%)	27 (36.0)	34 (45.3)
reason* for discontinuation:		
• Adverse event	6 (8.0)	9 (12.0)
• Patient withdrew consent	7 (9.3)	3 (4.0)
• Other	4 (5.3)	6 (8.0)
• Patient noncompliant	6 (8.0)	2 (2.7)
• Insufficient response	2 (2.7)	5 (6.7)
• Patient lost to follow-up	2 (2.7)	4 (5.3)
• Patient ineligible to continue the trial	0 (0.0)	4 (5.3)
• Patient asymptomatic/cured	0 (0.0)	1 (1.3)

* not including patients who stopped treatment but continued having trial assessments

Pharmacokinetics: Plasma concentrations (ng/mL) of the active moiety (= sum of risperidone and 9-hydroxy-risperidone), risperidone and 9-hydroxy-risperidone at Baseline, End point of the double-blind phase and End point of the open-label phase of the trial (pooled for the three mood stabilizers).

	Time	**N**	**Mean ±S.D.**	**Median (min-max)**
Active Moiety	Baseline	17	NQ*	NQ
	End point DB	72	22.1 ±24.0	17.2 (NQ-111)
	End point OL	29	38.4 ±25.3	39.4 (0.25-108)
Risperidone	Baseline	17	NQ	NQ (NQ-80.4)
	End point DB	75	5.32 ±11.79	0.67 (NQ-69.6)
	End point OL	29	9.53 ±15.04	3.29 (0.13-71.0)
9-hydroxy-risperidone	Baseline	17	NQ	NQ (NQ-39.3)
	End point DB	72	16.5 ±16.9	14.0 (NQ-60.5)
	End point OL	29	28.9 ±20.6	30.9 (NQ-98.3)

*NQ : <0.20 ng/mL for active moiety and <0.10 ng/mL for risperidone.

Efficacy	**Placebo**			**Risperidone**		
	Mean ±S.E. Baseline score	Mean ±S.E. change from Baseline at Week 3	Mean ±S.E. change from Baseline at nd point DB	Mean ±S.E. Baseline score	Mean ±S.E. change from Baseline at Week 3	Mean ±S.E. change from Baseline at nd point DB
Primary variable: change from Baseline at End point DB on YMRS total score	n = 72 28.2 ±0.7	n = 33 -17.1 ±1.8	n = 72 -10.5 ±1.4	n = 69 29.3 ±0.7	n = 46 -19.9 ±1.4	n = 68 -14.5 ±1.5 ◊
Secondary variables • change fr. Baseline at Day 8 on YMRS total	-	*Week 1* n = 68 -6.7 ±1.0	-	-	*Week 1* n = 67 -10.2 ±1.1 *	-
• change from Baseline on YMRS total at End point of open phase	-	-	*End pt. open* n = 61 -24.3 ±1.2	-	-	*End pt. open* n = 62 -22.7 ±1.5
• BPRS Total score	34.1 ±0.8	-11.2 ±1.2	-4.8 ±1.1	36.4 ±1.0	-12.6 ±1.2	-10.1 ±1.1**
Anergia cluster	4.4 ±0.1	-0.4 ±0.2	-0.1 ±0.1	4.7 ±0.2	-0.2 ±0.2	-0.3 ±0.1
Activity cluster	7.3 ±0.2	-3.0 ±0.4	-1.5 ±0.3	7.5 ±0.3	-3.1 ±0.3	-2.4 ±0.3 ◊
Anxiety/depression cluster	6.0 ±0.2	-0.9 ±0.3	-0.1 ±0.2	6.2 ±0.3	-1.0 ±0.3	-0.8 ±0.3 ◊
Hostility cluster	6.0 ±0.3	-2.2 ±0.4	-0.6 ±0.4	6.7 ±0.4	-2.6 ±0.4	-2.1 ±0.4 *
Thought disturbances	10.4 ±0.4	-4.7 ±0.6	-2.6 ±0.5	11.3 ±0.4	-5.6 ±0.5	-4.5 ±0.5 *
• HAM-D total score	8.1 ±0.6	-5.1 ±0.7	-2.1 ±0.6	8.6 ±0.7	-5.0 ±0.8	-4.1 ±0.7
• Clinical Global Impression – Change from Baseline (CGI-C)	At End point DB, the CGI-C ratings in the RIS treatment group were significantly better than those of the PLA group (p = 0.022, Van Elteren test controlling for country).					
• Number of patients who discontinued early from DB phase	Twenty-five patients (33.3%) from the PLA group, and 15 (20.0%) from the RIS group discontinued the double-blind treatment early, and entered OL risperidone treatment.					
• Time to early discontinuation from DB phase	Twenty-five percent of the patients from the PLA group early discontinued the DB phase of the trial by Day 8, versus 25% of the patients from the RIS group by Day 13 (p = 0.043, generalized Wicoxon test).					
• No. of patient with ≥50% improvement on YMRS	At End point DB, 30 patients (41.7%) of the PLA group reached at least 50% improvement on the YMRS, compared with 40 patients (58.8%) in the RIS group (p = 0.045, CMH test).					
• Mean time to ≥30% improvement YMRS	The mean number of days it took to achieve an onset of therapeutic response (30% decrease from Baseline YMRS score) was 13.4 days in the PLA group, and 11.3 days in the RIS group (p = 0.082, generalized Wilcoxon test)					
• % of patients using rescue medication	The percentages of patients using rescue medication the double-blind phase of the trial were: lorazepam 62.7% PLA, 72.0% RIS; antiparkinson medication 8.0% PLA, 16.0% RIS, and antidepressants 2.7% PLA, and 1.3% RIS.					
• % of days on rescue medication	Lorazepam was used 57.8% of the time (trial days) by lorazepam-users in the placebo group, compared with 43.9% of the time by lorazepam-users in the risperidone group (p = 0.023, ANOVA). Antiparkinson medication was used 64.3% of the time (trial days) by the antiparkinson-users of the PLA group, compared with 48.7% of the time by the antiparkinson-users of the RIS group (p = 0.236, ANOVA).					

Differences with PLA using ANCOVA statistical model on change from Baseline, ◊ $p < 0.1$, * $p \leq 0.05$; **$p \leq 0.01$

EFFICACY (continued)					
• Serum concentration of mood-stabilizer treatment during DB	Time	Placebo		Risperidone	
		N	Mean ±S.E.	N	Mean ±S.E.
Lithium (mEq/L)	Baseline DB	41	0.55 ±0.04	37	0.55 ±0.05
	Day 3	36	0.64 ±0.05	31	0.56 ±0.04
	Week 1	37	0.70 ±0.04	38	0.61 ±0.03
	Week 2	26	0.76 ±0.05	35	0.61 ±0.04
	Week 3	19	0.75 ±0.07	27	0.63 ±0.04
Valproate (µg/mL)	Baseline DB	17	49.76 ±6.64	17	46.33 ±7.34
	Day 3	9	61.78 ±7.78	14	67.95 ±7.75
	Week 1	14	82.21 ±4.85	13	70.56 ±7.49
	Week 2	6	76.00 ±14.64	13	64.18 ±6.76
	Week 3	5	97.00 ±5.87	9	63.04 ±7.54
Carbamazepine µg/mL	Baseline DB	13	4.84 ±0.65	12	4.98 ±1.07
	Day 3	9	6.36 ±0.30	12	6.92 ±0.83
	Week 1	11	6.35 ±0.74	14	6.41 ±0.64
	Week 2	11	6.34 ±0.44	11	6.78 ±0.45
	Week 3	9	5.69 ±0.29	7	6.31 ±0.53
• Serum concentration of mood-stabilizer treatment during OL	Time	Placebo[1]		Risperidone	
		N	Mean ±S.E.	N	Mean ±S.E.
Lithium (mEq/L)	Week 1	9	0.71 ±0.05	11	0.63 ±0.05
	Week 2	6	0.70 ±0.09	3	0.53 ±0.09
	Week 4	2	0.59 ±0.02	6	0.70 ±0.10
	Week 6	2	0.60 ±0.00	4	0.70 ±0.13
	Week 8	2	0.73 ±0.23	3	0.88 ±0.06
	Week 10	22	0.79 ±0.05	20	0.74 ±0.05
Valproate (µg/mL)	Week 1	4	42.75 ±11.40	4	60.00 ±7.69
	Week 2	1	57.00	1	30.00
	Week 4	3	86.67 ±22.66	1	47.00
	Week 6	3	73.67 ±11.26	0	-
	Week 8	2	63.50 ±22.50	0	-
	Week 10	8	79.25 ±5.86	9	80.78 ±9.74
Carbamazepine µg/mL	Week 1	5	6.93 ±0.85	2	6.39 ±2.55
	Week 2	1	10.10	3	6.33 ±1.20
	Week 4	0	-	1	6.60
	Week 6	0	-	2	7.00 ±0.00
	Week 8	0	-	0	-
	Week 10	12	6.30 ±0.31	7	6.13 ±0.49

[1]: Patients were taking OL risperidone; they had taken placebo in the DB phase.

Safety (n = number of patients with data)	**Placebo** **(n = 75)**	**Risperidone** **(n = 75)**
Most commonly reported (>5%) adverse events (AEs) **during double-blind** treatment		
• Headache	7 (9.3)	7 (9.3)
• Insomnia	6 (8.0)	3 (4.0)
• Nausea	2 (2.7)	4 (5.3)
• Hyperkinesia	0	5 (6.7)
• Tremor	1 (1.3)	4 (5.3)
No. (%) with one or more AEs **during DB**	38 (50.7)	43 (57.3)
No. (%) with EPS-related AEs **during DB**	6 (8.0)	16 (21.3)
No. (%) of deaths **during DB**	0	0
No. (%) with one or more other serious AEs **during DB**	2 (2.7)	2 (2.7)
No. (%) treatment stopped due to AE **during DB**	4 (5.3)	1 (1.3)
Most commonly reported (>7%) adverse events (AEs) **during open-label** treatment	Placebo[1] (n = 61)	Risperidone (n = 63)
• Headache	4 (6.6)	10 (15.9)
• Somnolence	10 (16.4)	6 (9.5)
• Depression	3 (4.9)	6 (9.5)
• Extrapyramidal disorder	6 (9.8)	5 (7.9)
• Dizziness	4 (6.6)	5 (7.9)
• Diarrhoea	6 (9.8)	4 (6.3)
• Hypertonia	5 (8.2)	4 (6.3)
• Insomnia	5 (8.2)	3 (4.8)
No. (%) with at least one AE **during OL**	50 (82.0)	45 (71.4)
No. (%) with EPS-related AEs **during OL**	17 (27.9)	16 (25.4)
No. (%) of deaths **during OL**	0 (0.0)	0 (0.0)
No. (%) with one or more other serious AEs **during OL**	6 (9.8)	6 (9.5)
No. (%) treatment stopped due to AE **during OL**	3 (4.9)	8 (12.7)

ESRS	The level of EPS was low throughout the trial, no consistent changes were noted in ESRS scores. The only statistically significant difference between RIS and PLA ESRS scores was seen on the mean maximum change from Baseline DB during DB treatment on the CGI of parkinsonism (p=0.040, Van Elteren test).
Vital signs	There were no consistent changes or clinically relevant abnormalities in blood pressure or heart rate in the course of the trial (DB and OL).
Weight	Mean weight change at End point DB was +0.5 kg (n = 57) in the PLA group, and +1.7 kg (n = 60) in the RIS group (p = 0.012 ANOVA). At End point of the OL phase, there was a mean weight increase of +2.7 kg in the PLA group (now receiving RIS), and of +2.5 kg in the RIS group, compared to the weight reached at End point DB.
ECG	There were no consistent changes in ECG parameters. There were five patients (1 PLA, 4 RIS) with a prolonged QTcB value at Baseline, and one RIS patient with a prolonged QTcF value at Baseline. There were no prolonged or pathological QTcB or QTcF values in the RIS group in the DB or open phase of the trial. In the PLA group, there was one prolonged QTcB value at End point of DB, and one pathological QTcB and QTcF value at End point of the open phase. There were two patients with a QTcB and QTcF change of clear concern (>60 ms) under RIS (one during DB and one during open-label phase).
Laboratory safety	There were no consistent changes or clinically relevant abnormalities in the laboratory results.

[1]: Patients were taking OL risperidone; they had taken placebo in the DB phase.

Conclusions

The totality of the efficacy results of this trial leads to the conclusion that risperidone was shown to be superior to placebo as an adjunctive therapy to mood stabilizers in the treatment of manic episodes associated with Bipolar Disorder, even though risperidone was only marginally statistically significantly superior to placebo on the primary efficacy parameter. The efficacy shown on the primary variable was supported by the clinical benefit seen in the CGI ratings and the number of patients who showed therapeutic response on the YMRS.

A post hoc analysis on the primary efficacy parameter excluding the patients taking carbamazepine suggests that risperidone is significantly superior to placebo ($p = 0.053$) as adjunctive therapy to lithium or valproate.

Analyses of 3-week double-blind as well as 10-week open-label safety data provided no suggestion of a unique safety concern with the use of risperidone in patients with bipolar disorder suffering a manic or mixed episode.