SYNOPSIS

Trial Identification

Company: Johnson & Johnson Pharmaceutical Research and Development, L.L.C. **Finished product**: Risperdal® **Active ingredient**: Risperidone (R64766)		
Title: The Efficacy and Safety of Flexible Dosage Ranges of Risperidone vs Placebo in the Treatment of Manic or Mixed Episodes Associated With Bipolar I Disorder	**Trial No**.: RIS-IND-2 **Clinical phase**: III	
Investigator: Multicenter	**Country**: India	
Reference: J&JPRD, Clinical Study Report RIS-IND-2, 2002 (EDMS-PSDB-1813062: 3.0)		
Trial period: Start: 12 March 2001 End: 24 December 2001	**No. of investigators**: 8 **No. of subjects entered**: 324 **No. of subjects randomized**: 291	

Protocol Summary

Indication / Objectives: Mania or mixed episodes associated with Bipolar I disorder / double-blind assessment of the efficacy and safety of risperidone as monotherapy in 3 weeks of treatment of subjects during the manic phase of Bipolar I disorder, to determine an association between risperidone and improvement or worsening of comorbid depressive symptoms, to estimate onset of maintained anti-manic clinical response, and to explore possible relationships between plasma concentrations of the active moiety and efficacy and safety of risperidone.

Trial Design: This was a 3-week, randomized, double-blind, parallel-group, multicenter, placebo-controlled Phase 3 trial conducted in (initially) hospitalized subjects with Bipolar I disorder who were experiencing a manic or mixed episode (according to DSM-IV).

Main Selection Criteria:

Inclusion Criteria:

- Subjects must have been 18 years of age or older.
- Female subjects were either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (oral or parenteral hormonal contraceptives; intrauterine device; barrier and spermicide. Abstinence was not considered an acceptable method, except while the patient was hospitalized in a sex-segregated unit).
- Female subjects must have had a negative urine pregnancy test at screening and at baseline.
- Subjects or their legal representatives provided informed consent and signed an informed consent document prior to screening.
- Subjects must have met DSM-IV criteria for Bipolar I Disorder, Most Recent Episode Manic (296.4x) or Mixed (296.6x). Other Axis I and II disorders except those listed as exclusion criteria were allowable.
- Subjects were voluntarily hospitalized at the time of enrollment. The primary diagnosis prompting the hospital admission must have been the manic or mixed episode that satisfied the inclusion criterion above.
- Subjects had a history of at least one prior documented manic or mixed episode that required treatment. Such manic or mixed episodes must not have been “manic-like” episodes in that they must not have been caused by somatic antidepressant treatment.
- Subjects must have received a total score of at least 20 on the Young Mania Rating Scale (YMRS) at screening and at baseline.

Exclusion Criteria:

- Subjects met DSM-IV criteria for Schizoaffective Disorder.
- Subjects met DSM-IV criteria for rapid cycling.
- Subjects had a known or suspected borderline or antisocial personality disorder.
- Subjects had a known or suspected history of substance dependence (excluding nicotine and caffeine) according to DSM-IV criteria within the three months prior to screening.
- Subjects believed by the investigator to be at significant risk for suicidal or violent behavior during the course of the trial.
- Female subjects who were pregnant or nursing.
- Subjects had a known or suspected seizure disorder.
- Subjects had a known or suspected history of other serious, unstable illnesses must have been otherwise healthy on the basis of a physical examination, medical history, electrocardiogram, and the results of blood biochemistry, hematology, and urinalysis tests.
- Subjects were not to have been enrolled if their serum ALT or AST tests were greater than twice the upper limit of the central laboratory's reference range. Subjects were eligible for enrollment when the results of any other biochemistry, hematology, or urinalysis tests were not within the central laboratory's reference ranges only when the investigator judged the deviations not to be clinically noteworthy.
- Subjects had hypo- or hyperthyroidism unless stabilized on appropriate medication for at least 3 months prior to screening (a normal TSH was required prior to randomization).
- Subjects whose YMRS total score at baseline had decreased by more than 25% from their screening score.
- Subjects had received an antidepressant medication or electroconvulsive therapy within the 4 weeks prior to screening. Antidepressant medications include known antidepressants used for other indications (e.g., anxiety disorders, sleep disturbance, smoking cessation) as well as St. John's Wort.
- Subjects had a history of neuroleptic malignant syndrome (NMS) or similar encephalopathic syndrome.
- Subjects, by history, had received within 3 days prior to baseline, any psychotropic medication prohibited in the Concomitant Therapy section of the protocol. Exceptions were permitted for such subjects and they were allowed to be enrolled (no sooner than the following day and with the concurrence of the sponsor) when the investigator determined that their symptoms were much worse compared with screening.
- Subjects were receiving antiparkinsonian drugs or beta-adrenergic blockers at baseline.
- Subjects had received cocaine, phencyclidine, amphetamine, methylphenidate, pemoline, an opioid, or a hallucinogen within 3 days prior to baseline, as evidenced by history or as suggested by a positive urine drug screen (UDS).
- Subjects had been intoxicated with alcohol within 3 days prior to baseline, as evidenced by history or as suggested by a blood alcohol level (BAL) of greater than 100 mg/dL at screening. Exceptions were permitted for such subjects and they were allowed to enroll (no sooner than the following day and with the concurrence of the sponsor) if the investigator determined that their symptoms were much worse compared with screening.
- Subjects had received clozapine within 1 month prior to screening.
- Subjects had received a depot antipsychotic within one treatment cycle prior to screening.
- Subjects had a known or suspected history of hypersensitivity or intolerance to risperidone.
- Subjects had a history of a poor anti-manic response to an antipsychotic drug which was used as the sole anti-manic agent.
- Subjects had a known or suspected history of severe drug allergy or hypersensitivity.
- Subjects had previously participated in this trial.
- Subjects had participated in any investigational drug trial within 3 months prior to screening.
- Subjects had an anticipated life expectancy of 6 months or less.

Treatment		
Form – dosing route	Matching tablets – oral	
Medication	Placebo tablets	Risperidone tablets (1 mg)
Batch numbers	00B16/F07	99J05/F5
Dosage	Day 1: 3 mg; Day 2: 2-4 mg; Day 3: 1-5 mg; Days 4-21: 1-6 mg	
Duration of treatment	3 weeks double-blind placebo or risperidone treatment	
Duration of trial	3 weeks	
Disallowed medication	The following psychotropic drugs were not allowed within 3 days (at a minimum) prior to the baseline visit or during the trial except as indicated below. • Anticonvulsant drugs. • Antidepressant drugs/St. John's Wort (prohibited within 4 weeks of screening). • Anti-manic drugs. • Antipsychotics/neuroleptics, other than trial medication. • Cognition enhancers. • Dopamine-releasing or dopamine agonist drugs. • Lithium. • Sedatives/hypnotics/anxiolytics (lorazepam or diazepam was permitted except in 8 hours prior to behavioral assessments). Other drugs or herbal preparations used by the subject for a psychotropic effect (e.g., Gingko Biloba, kava kava).	

Assessments	Screening	Baseline		DB Wk 1		DB Wk 2	DB Wk 3
Day	-3 to -1	1	3	7	8	14	21
Plasma concentration of risperidone and 9-hydroxy-risperidone				X			X
Efficacy							
• Primary variable							
- YMRS	X	X	X	X		X	X
• Secondary variables							
- CGI-Severity		X	X	X	X	X	X
- GAS		X	X	X		X	X
- MADRS		X	X	X		X	X
- PANSS		X		X		X	X
Safety							
• Adverse events[a]			X	X	X	X	X
• Clinical laboratory	X	X					X
• ECG		X		X			X
• ESRS		X		X		X	X
• Vital signs[a]	X	X	X	X	X	X	X
• Body weight		X		X		X	X
• Physical exam	X						X
• SCID	X						

YMRS: Young Mania Rating Scale, CGI-Severity: Clinical Global Impression of Illness – severity item, GAS: Global Assessment Scale, MADRS: Montgomery Asberg Depression Rating Scale, PANSS: Positive and Negative Syndrome Scale, ECG: electrocardiogram, ESRS: Extrapyramidal Symptom Rating Scale, SCID: Structured Clinical Interview for DSM-IV.
a: measured/collected on every inpatient day

Variable	Statistical Methods
Efficacy	
Change from baseline in total YMRS, CGI-S, GAS, total PANSS, MADRS scores at every timepoint	ANCOVA model including treatment group, investigator, and baseline psychosis as factors and baseline value as a covariate. The difference in LSMeans between RIS and placebo groups was used in comparing between treatment groups in efficacy. Within-group comparisons paired t-test.
50% improvement in total YMRS score	CMH test controlling for investigator and psychosis for comparison between risperidone and placebo treatment groups.
Change from baseline in Total YMRS at Day 3, Weeks 1, 2, and 3	Longitudinal analysis using a mixed effects model
Onset of maintained response measured by total YMRS score	CMH test for row mean score difference, controlling for investigator and psychosis
Safety	
Adverse events	Number and % of patients with adverse event by treatment group
Change from baseline in vital signs, body weight, ECG, ESRS, and laboratory safety	Descriptive statistics (N and % of patients exceeding pre-defined limits, mean, and SE) were estimated for each treatment group. Ordered ridit score (Van Elteren) test controlling for investigator and psychotic features used for between treatment group comparisons. Within-group comparisons made with paired t-test or Wilcoxon signed-rank, as appropriate.
Pharmacokinetics	Descriptive statistics of the concentration of the active moiety, risperidone, and 9-hydroxy-risperidone at each time point by treatment group.

Main Features of the Subject Sample and Summary of the Results

Baseline characteristics - subject disposition	Placebo N = 144	Risperidone N = 146
Number of subjects treated (M/F)	81/63	100/46
Age: mean (SE), yrs	35.5 (1.04)	34.7 (0.98)
Age: median (min; max), yrs	32.0 (18; 65)	32.0 (18; 70)
BMI: mean (SE)	21.0 (0.34)	20.8 (0.34)
Discontinuation of treatment – total n (%)	42 (29.2)	16 (11.0)
Adverse event	3 (2.1)	5 (3.4)
Insufficient response	21 (14.6)	7 (4.8)
Other	2 (1.4)	2 (1.4)
Subject lost to follow-up	10 (6.9)	1 (0.7)
Subject withdrew consent	6 (4.2)	1 (0.7)
Trial medication[a]		
Mean (SE) number tablets per day	5.32 (0.06)	5.23 (0.06)
Mode (SE) number tablets per day	5.7 (0.07)	5.6 (0.08)

BMI: Body mass index
a: risperidone 1 tablet = 1 mg

Pharmacokinetics

Descriptive statistics of the plasma concentrations (ng/mL) of the active moiety, risperidone and 9-hydroxy-risperidone at each visit (normalized to a 4-mg dose)

Visit	N	Median time after last drug intake (min – max) (h)	Mean ± SD	Median (min – max)
Active moiety				
Week 1 predose	123	21.00 (14.00 – 26.50)	26.4 ± 17.9	22.8 (2.91 – 142)
Week 1 postdose	117	1.00 (0.50 – 3.00)	57.3 ± 33.7	51.9 (4.09 – 150)
Week 3 predose	121	19.72 (13.00 – 24.50)	34.4 ± 32.8	27.4 (0.65 – 295)
Risperidone				
Week 1 predose	123	21.00 (14.00 – 26.50)	5.51 ± 9.22	1.60 (NQ[a] – 55.2)
Week 1 postdose	117	1.00 (0.50 – 3.00)	28.2 ± 25.7	19.3 (0.47 – 115)
Week 3 predose	121	19.72 (13.00 – 24.50)	8.44 ± 24.48	1.81 (NQ – 185)
9-hydroxy-risperidone				
Week 1 predose	123	21.00 (14.00 – 26.50)	20.9 ± 13.3	19.0 (0.57 – 86.7)
Week 1 postdose	117	1.00 (0.50 – 3.00)	29.1 ± 15.4	26.7 (2.30 – 80.7)
Week 3 predose	121	19.72 (13.00 – 24.50)	25.9 ± 17.2	23.1 (0.65 – 111)

a: not quantifiable by the LC-MS/MS-method (<0.10 ng/mL)

Efficacy

Primary variable	
Change from baseline at Week 3 LOCF/endpoint in total YMRS score	
Placebo (N=142)	**Risperidone (N=144)**
-10.5 (1.30)	-22.7 (1.14) ***

Secondary variables				
Visit	**Placebo**		**Risperidone**	
Total YMRS score – Change from baseline at Day 3, Week 1, and Week 2				
	N	**Mean (SE)**	**N**	**Mean (SE)**
Day 3 LOCF	142	-4.4 (0.61)	144	-5.0 (0.48)
Week 1 LOCF	142	-8.1 (0.83)	144	-11.7 (0.83)***
Week 2 LOCF	142	-9.8 (1.14)	144	-18.6 (0.99)***
YMRS response rate (≥50% decrease from baseline)				
	N	**n (%)**	**N**	**n (%)**
Day 3 LOCF	142	5 (3.5)	144	5 (3.5)
Week 1 LOCF	142	24 (16.9)	144	36 (25.0)*
Week 2 LOCF	142	45 (31.7)	144	74 (51.4)***
Week 3 LOCF/Endpoint	142	51 (35.9)	144	105 (72.9)***
CGI-severity – Change from baseline				
	N	**Mean (SE)**	**N**	**Mean (SE)**
Day 3 LOCF	142	-0.3 (0.06)	143	-0.3 (0.05)
Week 1 LOCF	142	-0.6 (0.09)	143	-1.0 (0.08)***
Week 2 LOCF	142	-0.8 (0.12)	143	-1.6 (0.10)***
Week 3 LOCF/Endpoint	142	-0.9 (0.13)	143	-2.0 (0.12)***
GAS – Change from baseline				
	N	**Mean (SE)**	**N**	**Mean (SE)**
Day 3 LOCF	142	4.5 (0.70)	143	4.4 (0.60)
Week 1 LOCF	142	8.7 (1.09)	143	13.4 (1.08)***
Week 2 LOCF	142	10.5 (1.45)	143	20.5 (1.33)***
Week 3 LOCF/Endpoint	142	12.9 (1.71)	143	27.6 (1.60)***
PANSS – Change from baseline				
	N	**Mean (SE)**	**N**	**Mean (SE)**
Week 1 LOCF	138	-4.4 (0.68)	143	-7.6 (0.64)***
Week 2 LOCF	138	-5.4 (1.01)	143	-13.3 (0.89)***
Week 3 LOCF/Endpoint	138	-5.7 (1.16)	143	-15.4 (1.03)***
MADRS – Change from baseline				
	N	**Mean (SE)**	**N**	**Mean (SE)**
Day 3 LOCF	142	-1.2 (0.20)	143	-1.7 (0.23)**
Week 1 LOCF	142	-2.0 (0.28)	143	-2.9 (0.25)***
Week 2 LOCF	142	-2.3 (0.30)	143	-3.2 (0.30)***
Week 3 LOCF/Endpoint	142	-2.5 (0.32)	143	-3.2 (0.43)**
Onset of maintained YMRS response – n (%)				
	Placebo (N=142)		**Risperidone (N=144) *** **	
Day 3	3 (2.1)		4 (2.8)	
Week 1	12 (8.5)		27 (18.8)	
Week 2	21 (14.8)		39 (27.1)	

LOCF=last observation carried forward.

* p value <0.05, ** p value <0.01, *** p value <0.001 indicates significant difference between placebo and risperidone.

A negative change indicates a decrease from the baseline mean.

For all but GAS, a negative mean change indicates an improvement from baseline.

Safety (n = number of subjects with data)	**Placebo** **N = 144**	**Risperidone** **N = 146**
Most frequently reported (≥5%) adverse events (preferred term)		
• Extrapyramidal disorder	9 (6.3)	51 (34.9)
• Tremor	2 (1.4)	14 (9.6)
• Headache	4 (2.8)	8 (5.5)
• Insomnia	15 (10.4)	9 (6.2)
• Somnolence	4 (2.8)	8 (5.5)
No. (%) with one or more adverse event	69 (47.9)	94 (64.4)
No. (%) of deaths	0	0
No. (%) with one or more serious adverse event	3 (2.1)	4 (2.7)
No. (%) treatment stopped due to adverse event	3 (2.1)	5 (3.4)
No. (%) with EPS-related adverse event	11 (7.6)	66 (45.2)
No. (%) with glucose-related adverse event	0	2 (1.4%)
No. (%) with potentially prolactin-related adverse event	0	0

ESRS	• There was a statistically significant difference between the treatment groups in ESRS Parkinsonism/ Dystonia/ Dyskinesia total change from baseline to endpoint. The extent of the change for most of the patients who did change was small (1-5 points), and was consistent with EPS-related adverse events being mostly rated as mild in severity.
Vital signs	• There were no differences between treatment groups in vital signs.
Weight	• There were no clinically important weight changes with risperidone.
ECG	• There were no clinically meaningful differences in ECG parameters between treatment groups. • No patients in either treatment group had a QTc >500 ms, regardless of the correction used.
Clinical laboratory values	• There were no clinically important changes in mean laboratory values, except for increased prolactin in the risperidone group.

There were no unexpected adverse events. Of the EPS-related adverse events in the risperidone group, 59% were rated as mild and 33% were rated as moderate. There was one discontinuation in the risperidone group due to an EPS-related event, which was rated moderate in severity.

Conclusions

Risperidone with flexible doses of 1 to 6 mg/day was effective as monotherapy in the treatment of acute manic episodes associated with Bipolar I disorder over a 3-week period without induction of depression. This treatment was safe and generally well-tolerated; there were no unexpected adverse events.