SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (formerly Janssen Research Foundation) NAME OF FINISHED PRODUCT: RISPERDAL® NAME OF ACTIVE INGREDIENT(S): Risperidone	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: RIS-INT-69

Title of Study: The Efficacy and Safety of Flexible Dose Ranges of Risperidone vs Placebo or Haloperidol in the Treatment of Manic Episodes Associated with Bipolar I Disorder

Principal Investigator: [redacted], M.D., Ph.D. – [redacted], Russia

Publication (Reference): none

Study Initiation/Completion Dates: 14 January 2001/26 September 2002	**Phase of development:** 3

Objectives: The primary objective was to assess the antimanic efficacy of risperidone relative to placebo after 3 weeks of treatment in patients with bipolar I disorder, manic episode. Secondary objectives were to document maintenance of anti-manic efficacy of risperidone by comparison to haloperidol after 12 weeks of treatment, to estimate the onset of antimanic response, to determine change in comorbid depressive symptoms, to estimate the risk of switching to depression over 12 weeks, to assess the safety and tolerability of risperidone over 12 weeks, and to explore pharmacokinetic-response relationships.

Methodology: This was a randomized, double-blind, parallel-group, multicenter clinical trial consisting of a 3-week double-blind period, followed by 9 weeks of either double-blind or open-label treatment. Patients with a manic episode associated with bipolar I disorder were randomized to receive oral risperidone, oral haloperidol or placebo. Patients were stratified according to the presence or absence of psychotic features at baseline. Risperidone was dosed once daily and flexibly in a range of 1-6 mg/day and haloperidol was also dosed once daily and flexibly in a range of 2-12 mg/day to optimize each patient's level of efficacy and tolerability. After completing the 3-week double-blind period, patients could continue double-blind treatment for an additional 9 weeks (with placebo patients crossed over to risperidone), or enter a 9-week open label period of treatment with risperidone.

Number of Subjects (planned and analyzed): Planned enrollment: approximately 435 subjects; 438 subjects were randomized.

Diagnosis and Main Criteria for Inclusion: The target population was manic adults with a DSM-IV diagnosis of bipolar I disorder, most recent episode manic, with at least 1 prior manic or mixed episode. At screening and baseline, YMRS ≥20, at baseline MADRS ≤20. Main exclusion criteria were : DSM-IV diagnosis of schizoaffective disorder or rapid cycling, or substance dependence, a decrease of ≥25% in YMRS from screening to baseline, patients believed by the investigator to be at significant risk for suicidal or violent behavior during the trial, a history of neuroleptic malignant syndrome, receiving anti-EPS medications at baseline.

Test Product, Dose and Mode of Administration, Batch No.: Dosing throughout the trial was once daily in the evening with or without a meal.

Risperidone 1 mg capsules batch numbers: 00F22/F122, 01C12/F122; Risperidone 1 mg tablets batch numbers: 00C24/F05, 01C28/F005, 01C29/F05, 01B09/F005

Reference Therapy, Dose and Mode of Administration, Batch No.:

Placebo capsules batch numbers: 00F21/F120, 01C07/F120; Placebo tablets batch numbers: 00B16/F07, 01C26/F007;

Haloperidol 2 mg capsules batch numbers: 00F26/F093, 01E02/F093; Haloperidol 2 mg tablets batch numbers: 99J04/F56, 01D20/F056

Duration of Treatment: Treatment with double-blind placebo, risperidone or haloperidol for first 3 weeks, followed by 9-week maintenance period of treatment with haloperidol (double-blind only) or risperidone (double-blind or open label).

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: RISPERDAL® NAME OF ACTIVE INGREDIENT(S): risperidone	Volume: Page:	

Criteria for Evaluation:

Pharmacokinetics: Pre- and postdose samples at Week 3 and Week 12. Samples from risperidone-treated patients were analyzed to determine concentrations of risperidone and 9-hydroxy-risperidone.

Efficacy: Efficacy was assessed using YMRS, CGI-Severity, GAS, BPRS, MADRS. The primary efficacy parameter was the change in YMRS total score at the 3-week endpoint.

Safety: Adverse events, laboratory tests, vital signs measurement, ECG recordings, physical examinations, ESRS ratings.

Statistical Methods: Intent-to-treat (ITT) population was used for all analysis.

Efficacy: Change from baseline in total YMRS, CGI-S, GAS, BPRS, and MADRS at every time point and the 3- and 12-week end points: ANCOVA model including treatment group, country, and baseline psychosis as factors and baseline value as a covariate. For 3-weeks analysis, t-tests for pairwise comparisons of differences in least squares means between each active group and placebo. For 12-weeks analysis, 95% confidence interval of risperidone minus haloperidol difference. Within-group comparisons by paired t-test. Change over time also analyzed by a mixed effects model. 50% improvement in total YMRS score at every time point and the 3- and 12-week end points: number and % of patients with ≥50% improvement. For 3-weeks analysis, pairwise comparisons between each active group and placebo by CMH test controlling for country and baseline psychosis. Onset of maintained response during first 3 weeks: pairwise comparisons between each active group and placebo by CMH mean scores test controlling for country and baseline psychosis.

Safety: Adverse events: Number and % patients with adverse event by group. Change from baseline in vital signs, body weight, ECG, and ESRS: Descriptive statistics and % of patients exceeding pre-defined limits. Pairwise comparisons between each active group and placebo (3-weeks) and between risperidone and haloperidol (12-weeks) by CMH mean scores test using ordered ridit score (Van Elteren's test) controlling for country and baseline psychosis. Within-group comparisons by paired t-test or Wilcoxon signed-rank, as appropriate. Laboratory safety: descriptive statistics and % patients exceeding pre-defined limits.

Pharmacokinetics: Descriptive statistics of the concentration of the active moiety, risperidone, and 9-hydroxy-risperidone were provided for each sampled timepoint.

SUMMARY – CONCLUSIONS

DISPOSITION, BASELINE AND DEMOGRAPHIC CHARACTERISTICS

438 patients were randomized: 140 to placebo, 154 to risperidone, and 144 to haloperidol. Of the 119 patients in the placebo group who completed Part I, 73 continued double-blind treatment into Part II, and 42 entered Part III (open-label). Of the 137 completers of Part I in the risperidone group, 90 continued into Part II, and 43 entered Part III. Of the 130 completers in the haloperidol group, 64 entered Part II, and 61 entered Part III.

At baseline, there were no clinically meaningful differences between treatment groups in demographic variables. At baseline, there were no statistically significant or clinically meaningful differences between treatment groups in mean total YMRS, MADRS and BPRS or distribution of CGI-severity. At baseline, 33.1% of patients presented with psychotic features.

In the 3-week double-blind period, the median mode number of tablets per day was higher in the placebo group (6) than in the risperidone and haloperidol groups (4). The mean daily dose of risperidone was 3.9 mg. The mean daily dose of haloperidol was 7.5 mg. Over the 12-week double-blind period, the mean daily dose of risperidone was 3.9 mg and the mean daily dose of haloperidol was 7.1 mg.

PHARMACOKINETICS:

Pre- and postdose drug plasma concentrations at the end of the 3-week double-blind period were comparable to the pre- and postdose drug plasma concentrations at the end of the 12-week double-blind period and the end of the open-label period.

SYNOPSIS (CONTINUED)

EFFICACY RESULTS:

The acute anti-manic efficacy of risperidone was superior to placebo in the 3-week, placebo-controlled part of this trial. This effect was maintained over an additional 9 weeks of treatment, as shown by the comparison with haloperidol at the end of the 9-week double-blind maintenance period. LOCF data is presented below for double-blind treatment comparisons (placebo vs. risperidone at 3-week endpoint and risperidone vs. haloperidol at the 12-week endpoint). Efficacy data from patients who crossed over from placebo to double-blind risperidone treatment and patients who received open-label risperidone treatment are not shown in the table but are contained in the report.

Total YMRS Score Change from Baseline						
Endpoint	Placebo		Risperidone		Haloperidol	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
3-week (Primary)	**138**	**-9.4 (0.94)**	**153**	**-15.1 (0.84)*****	**144**	**-13.9 (0.85)*****
12-week			153	-20.7 (1.05)	144	-18.4 (1.00)
Between group difference with haloperidol in LS means (95% CI)				-1.5 (-394; 1.03)		
CGI-Severity Change from baseline						
3-week	138	-0.9 (0.11)	153	-1.4 (0.09)***	144	-1.3 (0.09)***
12-week			153	-2.1 (0.13)	144	-1.9 (0.12)
Between group difference with haloperidol in LS means (95% CI)				-0.2 (-0.47; 0.13)		
GAS Change from baseline						
3-week	130	10.3 (1.28)	147	17.1 (1.44)***	131	14.7 (1.40)***
12-week			149	25.4 (1.91)	134	21.0 (1.85)
Between group difference with haloperidol in LS means (95% CI)				3.1 (-1.3; 7.6)		
BPRS Change from baseline						
3-week	137	-4.2 (0.59)	152	-7.0 (0.59)***	144	-6.8 (0.56)**
12-week			152	-8.4 (0.71)	144	-8.1 (0.66)
Between group difference with haloperidol in LS means (95% CI)				-0.5 (-2.1; 1.1)		
MADRS Change from baseline						
3-week	138	-1.7 (0.38)	153	-3.3 (0.38)***	144	-2.7 (0.35)
12-week			153	-2.6 (0.57)	144	-2.3 (0.51)
Between group difference with haloperidol in LS means (95% CI)				-0.3 (-1.7; 1.1)		
YMRS Response Rate (>50% decrease from baseline)						
	N	n (%)	N	n (%)	N	n (%)
3-week	138	45 (32.6%)	153	74 (48.4%)$^{++}$	144	68 (47.2%)$^{+}$
12-week			153	103 (67.3%)	144	92 (63.9%)
12-week (of 3-week responders)			54[a]	53 (98.1%)	37[a]	37 (100%)

*p value<0.05; **p value<0.01; ***p value<0.001 for comparison with placebo based on ANCOVA model including treatment, country, psychosis as factors and baseline YMRS as covariate. $^{+}$p<0.05; $^{++}$p<0.001 for comparison with placebo based on CMH test controlling for country and psychosis.
[a]Number of 3-week responders who continued in double-blind.

SYNOPSIS (CONTINUED)

SAFETY RESULTS:

Risperidone was generally well-tolerated. There were few discontinuations due to adverse events.

Summary of Safety Data for Entire Trial

	PLACEBO (DB 3 weeks) (N=140)	RISPERIDONE (DB 12 weeks)[a] (N=227)	RISPERIDONE (OL 9 weeks)[b] (N=146)	HALOPERIDOL (DB 12 weeks) (N=144)
Total no. subjects with adverse events	75 (53.6%)	153 (67.4%)	84 (57.5%)	111 (77.1%)
No. (%) with one or more serious adverse event	3 (2.1%)	7 (3.1%)	8 (5.5%)	7 (4.9%)
No. (%) treatment stopped due to adverse event	7 (5.0%)	14 (6.2%)	8 (5.5%)	7 (4.9%)
No. (%) died	0	0	1 (0.6%)[c]	0

a: Includes 73 patients who first completed 3 weeks of placebo treatment (PLA DB/RIS DB).
b: Includes 42 patients who first completed 3 weeks of placebo treatment (PLA DB/RIS OL), 43 patients who first completed 3 weeks of double-blind risperidone treatment (RIS DB/RIS OL), and 61 patients who first received 3 weeks of double-blind haloperidol treatment (HAL DB/RIS OL).
c: The [redacted] patient in the HAL DB/RIS OL group died during open-label treatment with risperidone of a completed suicide attempt.

Adverse event information is provided in the tables below only for the 3-week and 12-week double-blind periods. The safety profile during the 9 week open-label period was similar to that observed in the 9-week double-blind maintence period. Details are in the report.

Adverse events during 3-week double-blind period

AE System Organ Class Adverse Event Preferred Term	PLACEBO (N=140) n (%)	RISPERIDONE (N=154) n (%)	HALOPERIDOL (N=144) n (%)
No. (%) with adverse events (≥5% in any treatment group)	75 (53.6)	93 (60.4)	111 (77.1)
Centr & periph nervous system disorders	36 (25.7)	59 (38.3)	96 (66.7)
Extrapyramidal disorder	12 (8.6)	26 (16.9)	58 (40.3)
Hyperkinesia	4 (2.9)	14 (9.1)	22 (15.3)
Headache	7 (5.0)	12 (7.8)	7 (4.9)
Tremor	8 (5.7)	10 (6.5)	16 (11.1)
Dizziness	8 (5.7)	9 (5.8)	7 (4.9)
Dystonia	1 (0.7)	7 (4.5)	10 (6.9)
Hypertonia	0	6 (3.9)	13 (9.0)
Bradykinesia	1 (0.7)	1 (0.6)	12 (8.3)
Psychiatric disorders	18 (12.9)	16 (10.4)	19 (13.2)
Insomnia	6 (4.3)	2 (1.3)	8 (5.6)
Total no.(%) subjects with any EPS-related AE	24 (17.1)	48 (31.2)	90 (62.5)
Total no. (%) subjects with any glucose-related AE	0	0	1 (0.7)
Total no. (%) subjects with any prolactin-related AE	0	4 (2.6)	0

Note: Adverse events reported any time during treatment or within 4 days of end of treatment are included. Incidence is based on the number of subjects, not the number of events.

SYNOPSIS (CONTINUED)

Adverse events in 12-week double-blind period			
	RISPERIDONE	HALOPERIDOL	PLA DB/RIS DB
AE System Organ Class Adverse Event Preferred Term	(N=154) n (%)[a]	(N=144) n (%)[a]	(N=73) n (%)[b]
No. (%) subjects with AEs with onset during 12-week DB period (≥5% in any treatment group)	109 (70.8)	120 (83.3)	44 (60.3)
Centr & periph nervous system disorders	74 (48.1)	102 (70.8)	33 (45.2)
Extrapyramidal disorder	37 (24.0)	62 (43.1)	21 (28.8)
Hyperkinesia	15 (9.7)	28 (19.4)	4 (5.5)
Headache	14 (9.1)	9 (6.3)	4 (5.5)
Tremor	12 (7.8)	19 (13.2)	
Dizziness	10 (6.5)	7 (4.9)	6 (8.2)
Hypertonia	8 (5.2)	15 (10.4)	
Dystonia	7 (4.5)	11 (7.6)	
Bradykinesia	2 (1.3)	13 (9.0)	
Psychiatric disorders	33 (21.4)	31 (21.5)	17 (23.3)
Somnolence	15 (9.7)	8 (5.6)	7 (9.6)
Depression	7 (4.5)	8 (5.6)	7 (9.6)
Insomnia	3 (1.9)	11 (7.6)	
Total no. subjects with any EPS-related AE	61 (39.6)	96 (66.7)	28 (38.4)
Total no. subjects with any glucose-related AE	0	1 (0.7)	0
Total no. subjects with any prolactin-related AE	6 (3.9)	2 (1.4)	0

Note: Adverse events reported any time during treatment or within 4 days of end of treatment are included.

Incidence is based on the number of subjects, not the number of events.

a: Includes data from 3-week double-blind period.

b: Data during 9 weeks of risperidone treatment.

The severity of most EPS-related adverse events in risperidone-treated patients was mild. There was a statistically significant difference between risperidone and haloperidol (in favor of risperidone) in the change from baseline in the total Parkinsonism/Dystonia/Dyskinesia score at 12-week endpoint.

There was no mean change in blood glucose levels from baseline to endpoint in the risperidone group. There was an increase in mean prolactin levels from baseline to endpoint in risperidone-treated patients, however the incidence of potentially prolactin-related adverse events was small. There were no clinically important findings from laboratory tests, vital signs, and ECG that were different from those reported in patients with schizophrenia.

Mean weight change from baseline to 12-week endpoint was 1.4 kg in the risperidone group and 0.8 kg in the haloperidol group.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

Grapical exploration of the pharmacokinetic/pharmacodynamic relationship showed no apparent relationship between predose active moiety plasma concentration and any of the assessed efficacy and safety parameters or their respective shifts from baseline.

CONCLUSION:

The acute anti-manic efficacy of risperidone in patients with bipolar I disorder was superior to placebo in the 3-week, placebo-controlled part of this trial. This effect was maintained over an additional 9 weeks of treatment, as documented by the similar antimanic efficacy of risperidone and the active comparator haloperidol at the end of the 9-week double-blind maintenance period. Maintenance of effect was further supported by responder analyses at 12 weeks of patients who had responded at 3 weeks.

Risperidone administered to patients with bipolar mania was safe and well-tolerated over a 3-week treatment period compared with placebo. In comparison to haloperidol over a 12-week period, risperidone was safe and well tolerated and induced less EPS. There were no unexpected adverse events or safety findings with risperidone that have not already been reported.

Date of the report: 12 May 2003