SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen-Cilag Ltd. 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-SCH-302

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Clinical Study of the Efficacy and Safety of Risperidone for the Treatment of Schizophrenia in Adolescents

Coordinating Investigator: [redacted] M.D., [redacted] USA

Publication (Reference): Not Applicable

Study Initiation/Completion Dates: 3 August 2004 to 27 December 2005	**Phase of development:** 3

Objectives: The primary objective of this study was to assess the antipsychotic efficacy of risperidone in treating adolescents with schizophrenia. Additional objectives were to assess the safety and tolerability of risperidone during 6 weeks of treatment and to determine the genes/genotypes that may be related to the response or metabolism of risperidone in adolescents with schizophrenia.

Methodology: This was a 6-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical study conducted at 23 sites in 4 countries. Subjects were randomly assigned to 1 of 3 treatment groups: oral placebo tablets; oral risperidone tablets 1 to 3 mg/day (dosage group A); or oral risperidone tablets 4 to 6 mg/day (dosage group B). The study comprised 2 phases: a screening phase (with a possible washout period) and a 6-week double-blind treatment phase. Study medication was to be titrated up to the assigned target dosage range by Day 7; the investigator then titrated the dosage to the maximum tolerated dosage within the target dosage range up to Day 14 to optimize efficacy while minimizing adverse effects. Subjects could be enrolled as inpatients or outpatients as clinically indicated. A subject was considered as having completed the study if they had completed all assessments at Week 6 (Visit 6) of the double-blind treatment phase.

Number of Subjects (planned and analyzed): Planned: 159 subjects; analyzed: 160 subjects.

Diagnosis and Main Criteria for Inclusion: Subjects aged 13 to 17 years with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of schizophrenia and suffering from an acute episode (Positive and Negative Syndrome Scale [PANSS] between 60 and 120, inclusive).

Test Product, Dose and Mode of Administration, Batch No.: Oral risperidone, 0.5 mg 03D25/F009, 04H27/F009; 1 mg 03D28/F005, 04I01/F005; 2 mg 03D29/F013, 04I14/F013; 3 mg 03C03/F040, 04I17/F040; 4 mg 03C04/F012, 04I23/F012.

Reference Therapy, Dose and Mode of Administration, Batch No.: Oral placebo, 03D23/F007 and 04J01/F007.

Duration of Treatment: 6 weeks

Criteria for Evaluation:

Efficacy: The primary efficacy measure was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at the Day 43 (6-week) end point. Secondary efficacy measures included (1) change from baseline at Visits 3, 4, and 5 (Days 8, 15, and 29) in total PANSS score; (2) change from baseline at each visit and at end point in PANSS subscale scores; (3) the number and percentage of subjects achieving a clinical response (at least 20% improvement compared with baseline at Visits 3, 4, and 5 [Days 8, 15, and 29] and at end point) on the total PANSS score; (4) change from baseline at end point in Clinical Global Impression – Severity (CGI-S) score; (5) Clinical Global Impression – Improvement (CGI-I) score at end point; and (6) change from baseline at end point in Children's Global Assessment Scale.

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Safety: Safety was assessed by adverse events; extrapyramidal symptom scales (Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Simpson Angus Scale); clinical laboratory testing (including hematology, serum chemistry, and urinalysis); body weight and height; and vital signs. Additional safety assessments, done at screening or baseline and at end point, included prolactin (blinded), luteinizing hormone, follicle-stimulating hormone, and testosterone measurements; physical examinations; Tanner staging; urine drug screening; and electrocardiograms. An Independent Data Monitoring Committee reviewed adverse event reports and laboratory findings throughout the study.

Statistical Methods: All statistical tests were interpreted at the 5% significance level (2-sided). The analysis set for both efficacy and safety was the intent-to-treat set, i.e., all randomized subjects who had at least 1 dose of study medication.

The primary efficacy measure was the change in total PANSS score from baseline to the Day 43 end point, i.e., the last post-baseline observation carried forward to the Day 43 end point. An analysis of covariance (ANCOVA) model was applied in the analysis of the primary efficacy variable, with treatment and country as factors and total PANSS score at baseline as the covariate. The primary comparison was between each of the risperidone dosage groups and placebo. A step-down testing procedure was applied to compare the difference in least squares means between each of the risperidone dosage groups and placebo sequentially. An ANCOVA was also performed for secondary variables: change from baseline in total PANSS at intermediate time points and for PANSS subscales, CGI-S, CGAS, and CGI-I (analysis of variance) at every time point and the Day 43 end point. Fisher's least significant difference test was used to obtain nominal unadjusted p-values for pairwise comparisons of least squares means between each active group and placebo. For total PANSS, change over time was also analyzed by a mixed effects model. The percent of subjects with ≥20% improvement in total PANSS score was analyzed with pairwise comparisons between each active group and placebo using the Cochran-Mantel-Haenszel test controlling for country.

Adverse events were summarized as the number and percentage of subjects with adverse events. Descriptive statistics were provided for change from baseline in laboratory determinations, vital signs, ECG, body weight, z-scores, and EPS scales. In addition, for all but EPS scales, the percentage of subjects exceeding predefined limits was provided.

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SUMMARY - CONCLUSIONS

EFFICACY RESULTS: A summary of changes from baseline to the Day 43 end point for the primary (total PANSS) and various secondary efficacy parameters is presented below (efficacy analysis set):

		Mean (SD)			Between-group comparison	
Parameter Treatment	N	Baseline	Endpoint (LOCF)	Change	Diff in LS Mean Changes (95% CI)	p value[a]
Total PANSS						
Placebo	54	93.2 (10.27)	84.4 (16.59)	-8.9 (16.11)	—	—
RIS 1-3 mg	54	95.4 (11.01)	74.1 (17.79)	-21.3 (19.61)	-12.0 (-17.95;-5.99)	<0.001
RIS 4-6 mg	50	93.0 (11.87)	71.8 (18.35)	-21.2 (18.29)	-12.8 (-18.83;-6.71)	<0.001
PANSS Positive Symptoms						
Placebo	54	26.8 (5.23)	23.8 (6.27)	-3.0 (6.31)	—	—
RIS 1-3 mg	54	26.5 (5.07)	20.2 (6.10)	-6.3 (6.53))	-3.6 (-5.64;-1.53)	<0.001
RIS 4-6 mg	50	25.7 (4.10)	19.2 (5.70)	-6.5 (5.38)	-4.1 (-6.20;-2.00)	<0.001
PANSS Negative Symptoms						
Placebo	54	23.0 (4.73)	21.1 (5.26)	-1.9 (4.34)	—	—
RIS 1-3 mg	54	24.1 (4.79)	18.7 (5.59)	-5.4 (6.07)	-3.2 (-4.83;-1.48)	<0.001
RIS 4-6 mg	50	23.7 (4.27)	18.8 (5.57)	-4.9 (4.87)	-2.8 (-4.47;-1.07)	0.002
CGI-S						
Placebo	54	4.6 (0.66)	4.2 (0.99)	-0.4 (0.81)	—	—
RIS 1-3 mg	54	4.7 (0.80)	3.5 (0.97)	-1.2 (0.97)	-0.7 (-1.06;-0.42)	<0.001
RIS 4-6 mg	50	4.5 (0.71)	3.3 (1.00)	-1.2 (1.12)	-0.8 (-1.17;-0.51)	<0.001
CGI-I						
Placebo	54	—	3.6 (1.22)	—	—	—
RIS 1-3 mg	54	—	2.8 (1.08)	—	-0.9 (-1.21; -0.36)	<0.001
RIS 4-6 mg	50	—	2.7 (1.24)	—	-0.8 (-1.28; -0.42)	<0.001
CGAS						
Placebo	52	42.2 (12.34)	50.1 (16.77)	7.9 (14.84)	—	—
RIS 1-3 mg	51	39.0 (12.74)	55.9 (15.37)	16.9 (15.95)	7.8 (2.25;13.27)	0.006
RIS 4-6 mg	48	41.9 (11.58)	60.7 (14.51)	18.9 (18.37)	10.8 (5.26;16.24)	<0.001

Note: For all parameters except CGAS, lower scores indicate more favorable condition or greater improvement.

[a] p value: Difference in least squares means from ANCOVA model with treatment and country as factors and baseline value (where measured) as covariate.

LOCF=last observation carried forward.

Statistical analysis of the mean change from baseline to Day 43 end point in the total PANSS score, the primary efficacy variable, indicated that risperidone was significantly more effective than placebo in the treatment of schizophrenia when administered at doses of 1 mg/day to 3 mg/day and at doses of 4 mg/day to 6 mg/day. Efficacy was comparable in both dose groups, with no additional benefit seen in the higher dose treatment group.

Statistically significant improvements on the total PANSS score was observed as early as Day 8 in the risperidone 4-6 mg treatment group and Day 15 in the 1-3 mg group.

Treatment with both dose ranges of risperidone was consistently more effective than placebo, as measured by change in total PANSS score from baseline to Day 43 end point, regardless of sex, race, occurrence of somnolence during treatment, hospitalization status at screening, and mode dose group during the fixed target dose segment.

These results were supported by statistically significant improvements at Day 43 end point in the risperidone 1-3 mg dose group and the risperidone 4-6 mg dose group in the following secondary efficacy measurements: CGI-S, CGI-I, CGAS, and the percentage of subjects with at least 20% improvement from baseline in total PANSS score.

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SAFETY RESULTS:

Overall, risperidone was well tolerated and the qualitative nature and frequency of side effects, both reported and measured, were similar to what has been noted in clinical trials in adults with schizophrenia.

There were no deaths in this study. Serious adverse events were reported by 2 subjects in the placebo group, compared with 1 subject in each of the risperidone groups (the event was psychosis in both risperidone-treated subjects). The rate of discontinuation from the study due to an adverse event was 4% in placebo subjects, 5% in the risperidone 1-3 mg group, and 8% in the risperidone 4-6 mg group.

The most common adverse events (reported by more than 10% of subjects) in the risperidone 1-3 mg group were somnolence, tremor, agitation, and headache, and in the risperidone 4-6 mg group were somnolence, extrapyramidal disorder, dizziness, and hypertonia.

EPS-related adverse events are consistent with the known pharmacodynamic effects of risperidone and occurred with greater frequency in the high-dose group.

Consistent with the known effect of risperidone on prolactin, an increase in prolactin levels from baseline to end point was observed. The mean increase was greater in the risperidone 4-6 mg dose group than the 1-3 mg dose group. There was a dose-dependent increase in the number of subjects who had on-therapy prolactin levels >100 ng/mL (all such subjects in the risperidone groups were female). None of these elevated prolactin values were associated with adverse events.

There were small decreases in mean fasting glucose levels from baseline to end point in the placebo group and risperidone 1-3 mg group, compared with an increase (0.30 mmol/L) in the risperidone 4-6 mg group. Two risperidone-treated subjects had post-baseline fasting glucose levels above 6.4 mmol/L. No elevated glucose values were associated with adverse events.

Mean weight increased by 0.12 kg in the placebo group, 1.3 kg in the risperidone 1-3 mg group, and 1.5 kg in the risperidone 4-6 mg group over the course of the 6-week trial. No subject in the risperidone-treated groups went from <85th BMI percentile at baseline to the ≥95th BMI percentile during the study.

One male subject had borderline abnormal values of QTcF and QTcLD at Day 44. There was no other QTc prolongation in the study, and no subject had increases from screening of >60 ms.

CONCLUSIONS:

Risperidone therapy, at dose ranges of 1-3 mg/day and 4-6 mg/day, was unequivocally superior to placebo in the treatment of adolescents with an acute exacerbation of schizophrenia. There was no meaningful difference in efficacy between the two risperidone treatment groups at end point.

Adolescents in this trial tolerated risperidone well in both dose ranges. The overall rate of adverse events was similar for the 1-3 mg and 4-6 mg dose groups, but the 4-6 mg dose group showed a higher incidence of extrapyramidal disorder, dizziness, and hypertonia compared with the lower dose group (1-3 mg). The safety profile and adverse events reported and observed in this trial were qualitatively similar to those seen in risperidone trials in adults with schizophrenia.

The overall benefit-risk profile of treatment with risperidone 1-3 mg/day in adolescents with schizophrenia may be better than with the higher dose range of 4-6 mg/day.

Date of the report: 6 December 2006