SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: RISPERDAL® NAME OF ACTIVE INGREDIENT(S): Risperidone (R064766)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CR003361 **Title of Study:** The Efficacy and Safety of Risperidone in the Treatment of Adolescents with Schizophrenia		
Coordinating Investigator: Miroslaw Dabkowski, M.D. – Odzial Psychiatri Dzieci, UL Curie-Sklodowskiej, Torun; Poland 87-100		
Publication (Reference): Not Applicable		
Study Initiation/Completion Dates: 24 April 2001 - 13 March 2006		**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 8 weeks of treatment, and to explore the pharmacokinetics and the pharmacokinetic relationship to efficacy and safety of risperidone in adolescents with schizophrenia.		
Methodology: This was an 8-week, randomized, double-blind, parallel-group, multicenter clinical study conducted at 41 sites in 8 countries. Subjects were randomly assigned to 1 of 2 treatment groups: – Risperidone low dose group: oral risperidone 0.15–0.6 mg/day for subjects weighing ≥50 kg or 0.003-0.012 mg/kg/day for subjects weighing <50 kg – Risperidone high dose: oral risperidone 1.5–6 mg/day for subjects weighing ≥ 50 kg or 0.03–0.12 mg/kg/day for subjects weighing <50 kg The study comprised 2 phases: a screening phase (with a possible washout period) and an 8-week double-blind treatment phase. Study medication was to be titrated up to the assigned target dosage range by Day 12. The investigator could then adjust the dosage to achieve the maximum tolerated dose within the target dosage range; however, the dose was to remain stable during the last 4 weeks of the double-blind phase. Subjects were required to be inpatients at the time of enrollment. Thereafter, a subject may have been transferred to a less restrictive form of treatment if his/her psychiatric condition was deemed adequately stabilized.		
Number of Subjects (planned and analyzed): Planned: 260 subjects: analyzed: 279 subjects in the intent-to-treat (ITT) analysis set (i.e., all randomized subjects who took at least 1 dose of study medication), 257 subjects in the modified ITT (MITT) analysis set (i.e., all subjects in the ITT analysis set with a diagnosis of schizophrenia and an age >12 years and ≤17 years at baseline), 255 subjects in the efficacy analysis set (i.e., MITT analysis set excluding 2 subjects due to GCP noncompliance), 188 subjects in the pharmacokinetic analyses, 144 subjects in the pharmacokinetic/pharmacodynamic analysis		
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.: Risperidone 1 mg/mL oral solution (for high-dose risperidone group), batch nos.: 4HB5L00, 02BB/143, 00D27/817; Risperidone 0.1 mg/mL oral solution (for risperidone low-dose group), batch nos.: 04K10/F118, 02DB/294, 02DB/296, 00J09/458		
Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable		
Duration of Treatment: 8 weeks		
Criteria for Evaluation: Pharmacokinetics: Blood samples were collected at Days 28 (pre- and postdose), and 56 (predose) for the determination of plasma concentrations of risperidone and 9-hydroxy-risperidone. Plasma concentrations of the active moiety were calculated by the summation of risperidone and 9-hydroxy-risperidone plasma concentrations.		

SYNOPSIS (CONTINUED)

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Criteria for Evaluation (continued):

Pharmacogenomics: A blood sample (up to 10 mL) was obtained during screening for genetic analysis in subjects who gave informed consent/assent for this part of the study

Efficacy: The primary efficacy measure was the change from baseline in the PANSS total score at the Day 56 (8-week) end point. Secondary efficacy measures included (1) change from baseline at Visits 3, 4, 5, and 6 (Days 7, 14, 28, and 42) 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 each visit and at end point on the total PANSS score); (4) change from baseline at each visit and at end point in Clinical Global Impression – Severity (CGI-S) score; and (5) Clinical Global Impression – Improvement (CGI-I) score at each postbaseline visit and at end point.

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, prolactin, and urinalysis); body weight and height; pregnancy testing; vital sign measurements; electrocardiograms (ECGs); urine drug screening; and physical examination and Tanner staging. A Data Safety Monitoring Board reviewed adverse event reports and laboratory findings throughout the study.

Pharmacokinetic/Pharmacodynamic Relationships: The relationship between the steady-state predose plasma concentrations of the active moiety (Day 56) and selected efficacy parameters (PANSS and CGI) and safety parameters (QTcLD and SAS) was explored graphically.

Statistical Methods: All statistical tests were interpreted at the 5% significance level (2-sided). Safety analyses were performed for the ITT and MITT (primary safety analysis set) analysis sets. Efficacy data were analyzed for the efficacy analysis set.

The primary efficacy measure was the change in total PANSS score from baseline to the 8-week end point, i.e., the last postbaseline observation carried forward (LOCF) to the 8-week 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 difference in least squares means between each of the risperidone dosage groups was estimated. An ANCOVA was also performed for secondary variables: change from baseline in total PANSS score at intermediate time points and for PANSS subscale scores, CGI-S, and CGI-I (analysis of variance) at every time point and the 8-week end point. For total PANSS score, change over time was analyzed using both LOCF and observed case data. The percent of subjects with ≥20% improvement in total PANSS score was analyzed with pairwise comparisons between risperidone dose groups using the Cochran-Mantel-Haenszel test controlling for country and diagnosis.

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 parameters, body weight, body mass index (BMI), z-scores, and EPS scales. For all but EPS scales, the percentage of patients exceeding predefined limits was provided.

Descriptive statistics and graphical presentation of the pharmacokinetic data were performed as was graphical exploration of pharmacokinetic/pharmacodynamic relationships. As both once-daily and twice-daily dosing were allowed, plasma concentrations following both dosing regimens were compared graphically and via descriptive statistics.

SUMMARY/CONCLUSIONS

PHARMACOKINETICS: Plasma concentrations increased with dose. Dosage-adjusted plasma concentrations were comparable between the 2 risperidone dose groups. For both risperidone dose groups, predose normalized plasma concentrations at steady-state (Day 28 versus Day 56) were comparable. Average dose-normalized and dose-adjusted (to 0.04 mg/kg/day) pre- and postdose plasma concentrations of the active moiety were 16.8 ± 11.7 ng/mL (Day 28 and Day 56 combined) and 33.5 ± 18.3 ng/mL (Day 56), respectively (risperidone dose groups and once-daily and twice-daily dosing regimens combined).

SYNOPSIS (CONTINUED)

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SUMMARY – CONCLUSIONS (continued)

EFFICACY RESULTS: A summary of changes from baseline to the Day 56 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						
RIS low-dose	131	93.3 (14.14)	80.8 (24.33)	-12.5 (20.32)		
RIS high-dose	124	96.4 (15.39)	72.8 (22.52)	-23.6 (22.83)	-10.3 (-15.53; -5.09)	<0.001
PANSS Positive Symptoms						
RIS low-dose	131	26.6 (5.16)	21.8 (7.27)	-4.8 (6.26)		
RIS high-dose	124	26.5 (5.16)	18.9 (6.54)	-7.6 (7.11)	-2.9 (-4.43; - 1.34)	<0.001
PANSS Negative Symptoms						
RIS low-dose	131	23.3 (6.61)	20.8 (8.04)	-2.5 (6.43)		
RIS high-dose	124	24.6 (7.54)	19.1 (6.80)	-5.5 (7.88)	-2.4 (-3.98; -0.82)	0.003
CGI-S						
RIS low-dose	131	4.9 (0.84)	4.1 (1.45)	-0.9 (1.22)		
RIS high-dose	124	5.1 (0.83)	3.6 (1.35)	-1.4 (1.23)	-0.6 (-0.89; -0.29)	<0.001
CGI-I						
RIS low-dose	131	---	3.2 (1.41)	---		
RIS high-dose	124	---	2.6 (1.28)	---	-0.6 (-0.91; -0.24)	<0.001

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

[a] p value: Comparison between RIS doses based on ANCOVA model with treatment and country as factors and baseline value (where measured) as covariate.

For the primary (change in total PANSS score from baseline to end point) and all of the secondary efficacy parameters displayed above, high-dose risperidone (1.5-6.0 mg/day) was statistically significantly more effective than low-dose risperidone (0.15-0.60 mg/day) for treatment of adolescents with schizophrenia. At Day 56, there was also a statistically significant difference between groups, indicating greater improvement in the risperidone high-dose group, in the PANSS subscales of uncontrolled hostility/excitement (p=0.002) and disorganized thoughts (p<0.001); the between-group difference in the anxiety/depression subscale did not achieve statistical significance (p=0.058). The 2 risperidone treatment groups separated showing statistically significant differences in the efficacy measurements as early as Day 7, and the separation was maintained at all subsequent time points.

The percentage of subjects with a ≥20% reduction from the baseline total PANSS score (i.e., improvement) at the Day 56 end point was statistically significantly higher in the risperidone high-dose group (72.6 %) than in the risperidone low-dose group (49.6 %, p<0.001; CMH test controlling for country).

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 adult subjects treated with risperidone for schizophrenia.

In the risperidone high-dose group (1.5-6.0 mg/day), 74.4% of subjects reported at least 1 adverse event versus 65.2% in the low-dose group (0.15-0.6 mg/day). The most common adverse events in subjects treated with low doses of risperidone were headache, insomnia, somnolence, and agitation. The most common adverse events in subjects who received high doses of risperidone were somnolence, weight increase, and hypertonia. Adverse events reported at an incidence that was at least 5% higher in the risperidone high-dose group versus the low-dose group included hypertonia, hyperkinesia, somnolence, tremor, and weight increase.

SYNOPSIS (CONTINUED)

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SAFETY RESULTS (continued):

There were no deaths in this study and similar, low percentages of subjects in the low- and high-dose risperidone groups experienced serious adverse events (3% and 4%, respectively) or discontinued due to adverse events (4.5% and 4.0%, respectively). Most of the serious adverse events represented a worsening of the subjects' underlying psychiatric condition (psychosis). There were no suicide attempts; suicidal ideation was reported as a serious adverse event for 1 subject and as a symptom of serious psychosis for another subject, both of whom received low-dose risperidone. One subject in the risperidone high-dose group became pregnant while receiving study drug; she was withdrawn from the study and subsequently delivered a healthy baby.

EPS-related adverse events are consistent with the known pharmacodynamic effects of risperidone and occurred with greater frequency in the high-dose group (32.8% versus 9.8% for the low-dose group). No tardive dyskinesia was reported.

No glucose-related adverse events, including new onset diabetes, were reported and no clinically important changes in glucose or insulin levels were observed during the study.

Consistent with the known effect of risperidone on prolactin, a dose-dependent mean increase in prolactin levels from baseline to end point was observed. In both treatment groups, the mean increases were greater in female versus male subjects. There was also a dose-dependent increase in the number of subjects who had on-therapy prolactin levels >100 ng/mL. A small number of subjects in each treatment group (2 subjects [1 male and 1 female] in the low-dose group and 7 [2 males and 5 females] in the high-dose group) experienced potentially prolactin-related adverse events; none of these adverse events was treatment limiting.

Mean weight increased by 1.7 kg in the low-dose risperidone group and 3.2 kg in the high-dose risperidone group in the 8-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 female subject (high-dose risperidone group) with a normal baseline value had a prolonged QTcLD (>470 ms) at Day 56. There was no other QTc prolongation (QTcF or QTcLD) in the study, and no subject had increases from screening of >60 ms.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: Graphical exploration of the pharmacokinetic/pharmacodynamic relationship showed no apparent relationship between predose active moiety plasma concentrations (Day 56) and the selected safety (QTcLD and SAS) or efficacy parameters (PANSS and CGI) or their respective shifts from baseline.

CONCLUSION:

- Risperidone treatment in the higher dose range of 1.5-6 mg/day (median mode dose = 4 mg/day) was unequivocally superior to lower doses of 0.15-0.6 mg/day (median mode dose = 0.4 mg/day) in adolescents with an acute exacerbation of schizophrenia.
- Adolescents in this trial tolerated risperidone well in both dose ranges. EPS-related adverse events and weight gain were more pronounced in subjects in the high-dose risperidone group.
- The safety profile and adverse events reported and observed in this trial were qualitatively similar to those seen in risperidone trials in schizophrenic adults.

Date of the report: 7 DECEMER 2006

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