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.: CR003364

Title of Study: The Efficacy and Safety of Risperidone in the Treatment of Adolescents with Schizophrenia: a Six-month Open-label Study

Coordinating Investigator: Miroslaw Dabkowski, M.D. Odzial Psychiatri Dzieci, UL Curie-Sklodowskiej, Torun; Poland 87-100

Publication (Reference): None.

Study Initiation/Completion Dates: 29 May 2001 to 28 March 2006 | **Phase of development:** 3

Objectives: The objectives of the study are to assess the efficacy and safety of risperidone in adolescents with schizophrenia over 6 months of treatment.

Methodology: This was a 6-month, open-label, multicenter clinical study conducted in 58 sites in 11 countries. Subjects who completed a minimum of 24 days of double-blind treatment in study RIS-USA-231 or RIS-SCH-302 or those who discontinued from study RIS-USA-231 or RIS-SCH-302 because of tolerability issues and were expected to benefit from a continuation of risperidone were considered for enrollment in this study. Subjects entering from study RIS-USA-231 received a single 0.01 mL/kg dose on Day 1, regardless of prior dose during the double-blind study. Subjects entering from study RIS-SCH-302 also received a single 0.5 mg dose on Day 1, regardless of the previous treatment. On each day after Day 1, the investigator increased the daily dose to a minimum dose of 2 mg/day by Day 7. Titration continued thereafter to the maximally tolerated dose within the 2 to 6 mg/day range, which was to be maintained for the remainder of the study. The maximal tolerated dose could be adjusted only in cases of emergent tolerability or efficacy issues. Subjects who could not be maintained at the minimum of 2 mg/day were to be withdrawn from the study. Subjects continued to receive open-label risperidone for 6 months or until early discontinuation.

The original protocol was amended (Amendment 3) to change the duration of treatment from 12 months to 6 months; thus, subjects enrolled before Amendment 3 may have been treated for up to 12 months. In addition, subjects with schizophreniform disorder and subjects between 2 and 18 years of age were initially allowed to enroll in study RIS-USA-231. Study RIS-USA-231 was amended to exclude subjects with schizophrenia disorder and to change the age range of eligible subjects from 2 to 18 years to 13 to 17 years.

Per-protocol, an analysis was planned after 100 subjects had been treated for at least 6 months at doses at or above the efficacious doses as determined in the double-blind, placebo-controlled study RIS-SCH-302. This current report summarizes the results of the analysis performed on data from subjects who completed or discontinued study RIS-USA-234 as of 31 March 2006. The protocol also allowed for subjects to directly enroll into study RIS-USA-234; however, no directly enrolling subjects had completed or discontinued as of 31 March 2006.

Number of Subjects (planned and analyzed): Planned: 100 subjects; 297 subjects were included in the intent-to-treat (ITT) analysis set (i.e., all enrolled subjects who took at least 1 dose of study medication)

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 with a PANSS score between 40 and 120, inclusive, at screening and baseline.

Test Product, Dose and Mode of Administration, Batch No.: Risperidone 0.5 mg tablet, batch nos.: 03D25/F009, 04H27/009, 04H27/F009; Risperidone 1 mg tablet, batch nos.: 03D28/F005, 04I01/F05, 04I01/F005, 04K03/F005; Risperidone 2 mg tablet, batch nos.: 03D29/F013, 04I14/F013; Risperidone 3 mg tablet, batch nos.: 03C03/F040, 04I17/F040; Risperidone 4 mg tablet, batch nos.: 04I23/F012; Risperidone 1 mg/mL oral solution, batch nos.: 00D27/817, 00H16/027, 02BB/143, 4HB5L00

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Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable

Duration of Treatment: At least 6 months.

Criteria for Evaluation:

Efficacy: Efficacy measures included 1) change from open-label baseline at each visit, at Month 6 end point and at overall end point in the total PANSS score and in the PANSS subscale scores; 2) the number and percentage of subjects achieving a clinical response (at least 20% improvement) compared with open-label baseline at each visit, at Month 6 end point and at overall end point on the total PANSS score; 3) change from open-label baseline at each visit, at Month 6 end point and at overall end point in CGI-S score; 4) CGI-I score at each visit, at Month 6 end point and at overall end point. For the completion of the CGI-I, improvement was compared with the baseline for this open-label study (RIS-USA-234); and 5) change from open-label baseline at Month 6 end point and at overall end point in C-GAS score.

Safety: Safety was assessed by adverse events; extrapyramidal symptom scales (Abnormal Involuntary Movement Scale, Barnes Akathisia rating scale, and Simpson Angus Scale); clinical laboratory tests (hematology, serum chemistry, prolactin, and urinalysis); body weight and height; pregnancy testing; vital sign measurements; ECGs; urine drug screening; physical examination, and Tanner staging.

Statistical Methods: Safety and efficacy analyses were performed for the ITT analysis set. All efficacy analyses included the change from baseline based on both the observed case (OC) and the last postbaseline observation carried forward (LOCF). The Month 6 endpoint and the overall endpoint were included in the efficacy summaries. No formal hypothesis testing was planned. Description statistics and graphical presentation of the efficacy data were performed. The means and mean changes from open-label baseline in the PANSS total score and each subscale score and the percent of subjects with clinical improvement of at least 20% from open-label baseline in the PANSS total score were provided at each time point, at the Month 6 end point and at end point (OL). For CGI-S, frequency counts and means and mean changes from open-label baseline were provided at each time point, at the Month 6 end point and at end point (OL). Cross-tabulations of the open-label baseline scores versus the Month 6 end point scores and versus the end point (OL) scores were generated. For CGI-I, frequency counts and means were provided at each time point, at the Month 6 end point and at end point (OL). The distribution of CGI-S and CGI-I scores were plotted over time. Plots were generated based on observed case and LOCF. For C-GAS, The means and mean changes from open-label baseline were provided.

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, electrocardiograms (ECGs) parameters, body weight, body mass index (BMI), z-scores, and EPS scales.

SUMMARY - CONCLUSIONS

STUDY POPULATION: A total of 297 subjects (293 with schizophrenia and 4 subjects with schizophreniform disorder) were enrolled and treated with risperidone: 41 subjects had received placebo in the previous double-blind study, RIS-SCH-302), and are included in the PLA/RIS group, and 256 subjects had received risperidone in 1 of 2 previous double-blind studies (74 subjects in study RIS-SCH-302 and 182 subjects in study RIS-USA-231) and are included in the RIS/RIS group.

Subjects were aged 7 to 17 years (median 16 years), including 11 subjects ≤12 years old who had previously participated in RIS-USA-231 (prior to an amendment changing the age limits). The majority of subjects were male (62%) and most were white (70%). The weight of the study population (median 58.7 kg) was relatively high for the subject's age, with most subjects (81%) weighing ≥50 kg.

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EFFICACY RESULTS: A summary of the changes from open-label baseline to Month 6 end point and open-label end point for the efficacy parameters is presented below:

		Mean (SD)		
Parameter Treatment	N	Open-label Baseline	Change Month 6 End Point (LOCF)	Change End Point (LOCF)
Total PANSS				
PLA/RIS	40	84.25 (17.311)	-24.43 (18.577)	-24.43 (18.577)
RIS/RIS	254	71.04 (19.409)	-9.83 (17.598)	-9.87 (18.476)
ALL RIS OL	294	72.83 (19.641)	-11.82 (18.397)	-11.85 (19.123)
PANSS Positive Symptoms				
PLA/RIS	40	23.48 (6.127)	-8.15 (6.762)	-8.15 (6.762)
RIS/RIS	254	18.97 (5.875)	-3.00 (5.466)	-2.87 (5.822)
ALL RIS OL	294	19.58 (6.099)	-3.70 (5.917)	-3.59 (6.216)
PANSS Negative Symptoms				
PLA/RIS	40	21.35 (5.691)	-5.38 (5.642)	-5.38 (5.642)
RIS/RIS	254	18.62 (6.559)	-2.78 (5.705)	-2.83 (5.852)
ALL RIS OL	294	18.99 (6.507)	-3.13 (5.757)	-3.18 (5.879)
CGI-S				
PLA/RIS	40	4.10 (0.982)	-1.38 (0.952)	-1.38 (0.952)
RIS/RIS	254	3.53 (1.185)	-0.59 (1.144)	-0.57 (1.210)
ALL RIS OL	294	3.61 (1.714)	-0.70 (1.150)	-0.68 (1.209)
CGI-I				
PLA/RIS	40	---	2.40 (0.982)	2.40 (0.982)
RIS/RIS	254	---	2.78 (1.400)	2.78 (1.443)
ALL RIS OL	294	---	2.73 (1.355)	2.73 (1.394)
C-GAS				
PLA/RIS	39	51.10 (16.701)	15.15 (13.802)	15.15 (13.802)
RIS/RIS	206	57.98 (15.153)	6.33 (14.435)[a]	6.71 (14.581)
ALL RIS OL	245	56.89 (15.579)	8.24 (14.721)[a]	8.06 (14.760)

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

[a] Most subjects enrolled before Amendment 3 had no postbaseline C-GAS assessments on or before Month 6; 141 subjects in the RIS/RIS group and 180 in the ALL RIS OL group were included in the analysis for the change in C-GAS from open-label baseline to Month 6 end point.

Risperidone administered at doses of 2 to 6 mg/day continued to show improvement and maintain improvement throughout the open-label extension study, as measured by mean change from open-label baseline to Month 6 end point and overall end point in the total PANSS score. The percentage of subjects with ≥20% reduction from the baseline total PANSS score (i.e., improvement) at the Month 6 endpoint was higher for subjects previously treated with placebo (82.5%) than for those previously treated with risperidone (55.9%). Similarly, the percentage of subjects with ≥20% reduction from the baseline total PANSS score at endpoint was higher for subjects previously treated with placebo (82.5%) than for those previously treated with risperidone (57.9%).

The improvement was largest during the first month of open-label treatment, and continued to increase during the following 6 to 12 months. The effect was observed in both groups of subjects who had been previously treated with placebo or with risperidone, with the former group showing a larger improvement.

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EFFICACY RESULTS (continued):

These results were confirmed by the analysis of other efficacy measures (PANSS positive subscale, PANSS negative subscale, PANSS other subscales, percent change in total PANSS score, CGI-severity, CGI-improvement and C-GAS).

SAFETY RESULTS:

Overall, risperidone was well tolerated and the qualitative nature of side effects, both reported and measured, were similar to what has been noted in adult schizophrenic subjects treated with risperidone.

There was 1 death (suicide) in the study. Serious adverse events were reported for 15% subjects. Psychosis, suicide attempt, aggressive reaction, depression, and injury were the only adverse event reported as serious for more than 2 subjects. The percentage of subjects who were withdrawn from the study because of adverse events was low (9%). Serious adverse events and adverse events leading to discontinuation of study drug were reported more often in subjects previously treated with risperidone than those previously treated with placebo.

Treatment-emergent adverse events were reported for 86% of subjects. The overall incidence of treatment-emergent adverse events was similar in subjects previously treated with placebo and those previously treated with risperidone. The most common adverse events were somnolence, headache, weight increase, hypertonia, insomnia, tremor, and psychosis.

There were 16 reports of suicide-related adverse events: 7 of these were suicidal ideation or thoughts with no suicide attempt and 9 were suicide attempts, one resulting in death.

EPS-related adverse events were reported for approximately one-third of subjects. The most common EPS-related adverse events were hypertonia, tremor, extrapyramidal disorder, and hyperkinesia. The majority of EPS-related events were mild or moderate in severity. There were no reports of tardive dyskinesia. Mean changes in EPS rating scales did not indicate any worsening in the severity of akathisia symptoms (BARS), Parkinsonism symptoms (SAS) or dyskinetic symptoms (AIMS) over the open-label treatment period.

Consistent with the known effect of risperidone on prolactin, an increase in mean prolactin levels was observed. The most pronounced increase was observed over the first month of treatment. Mean increases in prolactin were greater in female versus male subjects. Potentially prolactin-related adverse events were reported for 9% of subjects (27 of 297 subjects). The most common events of this type were hyperprolactinemia, lactation nonpuerperal in female subjects, and gynecomastia in male subjects. Nine subjects had potentially prolactin-related adverse events other than hyperprolactinemia. No subjects had an adverse event suggestive of delayed pubertal maturation.

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.

Somnolence was reported by approximately a quarter of all subjects. The incidence of fatigue was low (4%). Most occurrences of somnolence or fatigue had their onset during the first 2 weeks of treatment. The median duration of somnolence was 16 days, and the median duration of fatigue was 9.5 days.

Weight increase was reported as a treatment-emergent adverse event for 14% of subjects. The incidence of weight increase was similar in subjects previously treated with placebo (15%) and those previously treated with risperidone (14%).

Mean weight increased by 4.2 kg and mean height increased by 0.96 cm over the course of this 6-month study. One subject had an increase from a baseline BMI percentile of <85th to ≥95th at Month 6 end point, and 3 subjects had an increase from a baseline BMI percentile of <85th to ≥95th at open-label end point. Increases from baseline to Month 6 endpoint in mean height z-scores were smaller (0.03) than those for mean weight (0.23) and BMI z-scores (0.24).

There was a mean increase from baseline in leptin levels. The clinical importance of this change is difficult to assess because the regulation of leptin levels during childhood is poorly understood and no laboratory reference ranges have been established for leptin in this population. Changes in leptin were positively correlated with weight change.

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SAFETY RESULTS (continued):

There were no clinically meaningful changes from baseline to Month 6 open-label endpoint in mean ECG parameters and corrected QTc intervals (heart rate, PR, QRS, QT, RR, QTcF, QTcB, QTcLD QRS axis, QT dispersion, and RR interval). One subject had postbaseline prolonged QTcF and QTcLD interval values and another subject had postbaseline increases in QTcF and QTcLD intervals >60 ms, neither of which was reported as an adverse event.

As expected for an adolescent population, there was a shift from baseline toward greater developmental maturation in both male and female subjects, as measured by Tanner stage. Four subjects showed a 1-point decrease in Tanner stage during risperidone treatment. Patient profiles for these cases were reviewed, and there was no report in any of the cases of changes on physical examination supporting the reduction in Tanner Stage, and no correlation with specific changes in laboratory parameters.

CONCLUSION:

- In adolescents with schizophrenia, risperidone administered at doses of 2 to 6 mg/day continued to result in symptomatic improvement and maintain previously gained improvement throughout a 6-month, open-label extension study.
- Adolescents in this study tolerated risperidone in doses ranges of 2 to 6 mg/day, with very low rates of treatment discontinuation due to adverse events.
- The safety profile and adverse events reported and observed in this study were qualitatively similar to those seen in risperidone studies in adult schizophrenia patients.
- Results of this study confirm that risperidone is the first antipsychotic to demonstrate prolonged safety and efficacy in a population of severely impaired adolescent schizophrenic patients, a population for whom there is significant unmet medical need.

Date of the report: 7 December 2006

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