SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Risperdal®	Volume:	
NAME OF ACTIVE INGREDIENT(S): Risperidone (R064766)	Page:	

Protocol No.: RIS-USA-150 Part 1

Title of Study: A Double-Blind, Placebo-Controlled Study of Risperidone in Children and Adolescents With Autistic Disorder

Principal Investigator: ███████████ Ph.D, M.S.N.- ████████████████████ ████████████

Publication (Reference): Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. New England Journal of Medicine 2002; 347:314-321.

Study Initiation/Completion Dates:	Phase of development: 3
Start Date: 26 May 1999	
End Date: 18 April 2001	

Objectives: The primary objective of the study was to evaluate the efficacy and safety of risperidone compared to placebo in the treatment of children and adolescents with Autistic Disorder.

Methodology: This was a multicenter, randomized, 8-week double-blind, placebo-controlled, parallel group, flexible-dose study in children and adolescents between the ages of 5 and 17 years 2 months with Autistic Disorder.

Number of Subjects (planned and analyzed): At least 100 subjects were planned to be enrolled with a minimum of 20 to 25 subjects per center. One hundred and one subjects (49 and 52 subjects in the risperidone and placebo groups, respectively) were randomized and treated in the study. Ninety-five subjects were between 5 and 12 years and 6 subjects were >12 years of age.

Diagnosis and Main Criteria for Inclusion: The target population was males and females between the ages of 5 and 17 years 2 months ($\geq$ 15 kg body weight) with a DSM-IV diagnosis of Autistic Disorder. They had a mental age of at least 18 months as measured by the Weschler Intelligence test, Revised Leiter or Mullen test. Subjects had a Clinical Global Impression (CGI) score of at least 4 and a score of 18 or greater on the Irritability Scale of the Aberrant Behavior Scale (ABC). Subjects were in good physical health, could be on anticonvulsants for treatment of a seizure disorder if the dosage was stable for 4 weeks and seizure free for at least 6 months. Subject's parent, was able to give written informed consent.

Test Product, Dose and Mode of Administration, Batch No.: Dosing throughout the study was flexible starting with a single oral dose of 0.25mg or 0.5mg tablet taken at bedtime depending on the weight of the subject. On the Day 4 study medication was increased to a b.i.d dosing schedule. Subjects who weighed between 15 and 20 kg, had a starting dose of 0.25 mg/day and for those subjects $\geq$ 20 kg the starting dose was 0.5 mg/day For subjects weighing between $\geq$ 20 - $\leq$ 45 kg a maximum dose of 2.5 mg daily was administered, 1.0 mg in the morning and 1.5 mg at bedtime. For subjects weighing $\geq$ 45 kg their maximum dose was 3.5 mg daily, 1.5 mg in the morning and 2.0 mg at bedtime.

Risperidone 0.5 mg tablets batch numbers 97G02/F9, 99E18/F9; Risperidone 1 mg tablets batch numbers 97G01/F5;

SYNOPSIS (CONTINUED)

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Reference Therapy, Dose and Mode of Administration, Batch No.: Identical placebo 0 mg/day tablets batch number 95I11/F7

Duration of Treatment: 8 weeks

Criteria for Evaluation:

Pharmacokinetics: Not applicable

Efficacy: The co-primary efficacy parameters for this study are the change from baseline in Irritability subscale scores of ABC and CGI-C at end point.

The secondary efficacy parameters were defined as changes from baseline to end point as measured on the following scales:

1. ABC subscales – Lethargy/Social Withdrawal, Stereotypic Behavior, Hyperactivity/non-compliance, and Inappropriate speech.

2. CGI-S – clinical global impression of severity.

3. Vineland Maladaptive Behavior Domain.

4. ABC/CGI-C Responder

The 2 primary efficacy parameters were further analyzed by subgroups, age, sex, Tanner stage scores, Intelligent quotient (IQ) scores, and the use of anti-convulsant medication. The effect of somnolence on the change from baseline to end point in the Irritability subscale of the ABC scores was also analyzed.

Safety: The safety of study medication was assessed by adverse event profiling including the Side Effect Review form, clinical laboratory tests, vital signs and physical examination, body weight, height electrocardiogram (ECG), Extrapyramidal Symptom (EPS) rating using the Simpson-Angus Rating Scale (SARS) and the Abnormal Involuntary Movement Scale (AIMS).

Pharmacokinetic/Pharmacodynamic Relationships: Not applicable

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

Efficacy: Change from baseline in ABC subscales, CGI-S, and Vineland Maladaptive Behavior Score at every time point and the 8-week end point: ANCOVA model including treatment group and site as factors and baseline value as a covariate. CGI-C response (percentage with much or very much improved) and combined ABC/CGI-C response (CGI-C responder with ≥25% improvement on ABC Irritability subscale) at every postbaseline time point and 8-week end point: CMH test.

Safety: Adverse events: Number and percentage of subjects with adverse events by group. Change from baseline in vital signs, body weight, ECG, SARS, and AIMS: Descriptive statistics and percentage of subjects exceeding pre-defined limits. Between–group comparisons by ANOVA model including treatment group and site as factors for vital signs, body weight, and ECG; for SARS and AIMS, Van Elteren's test controlling for site.

Laboratory safety: descriptive statistics and percentage of subjects exceeding pre-defined limits.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS: Not applicable

EFFICACY RESULTS: Treatment with risperidone was significantly (p<0.001) more effective than placebo as measured by the change from baseline in the Irritability subscale of ABC. At end point, a 14.9 ± 10.4 (mean ± SD) decrease from baseline was observed in the risperidone group compared to a 3.5 ± 8.1 decrease in the placebo group. Improvement was seen as early as Week 2 (p=≤0.001) and was maintained at Weeks 4, 6 and 8. The rate of improvement was significantly (p<0.001) greater in the risperidone group than the rate in the placebo group.

The responses based on CGI-C indicated that a significantly higher percentage of subjects in the risperidone group (75.5%) than in the placebo group (11.5%) had CGI-C scores that were "very much improved" or "much improved" at end point (p<0.001).

In addition, risperidone showed statistically significant differences compared to placebo on all other ABC subscales in improving Lethargy/Social Withdrawal, Stereotypic Behavior Hyperactivity/noncompliance, and Inappropriate Speech. A statistical significant difference was also noted on overall response ("responder analysis") as measured by ≥25% improvement on ABC Irritability subscale and much or very much improved CGI-C rating.

SAFETY RESULTS: Forty eight (98.0%) subjects in the risperidone group and 46 (88.5%) subjects in the placebo group experienced adverse events (AE). The most frequently reported adverse event was appetite increased, 34 (69.4%) and somnolence (63.3%) in the risperidone group. The adverse events that occurred more frequently in the placebo group than the risperidone group were insomnia (30.8% vs 22.4%), diarrhea (21.2% vs 16.3%), nausea (11.5% vs 10.2%), dyspepsia (15.4% vs 8.2%), and fever (19.2% vs 16.3%). Irritability, coded to nervousness, was experienced as an adverse event in the risperidone group, 6.1% and 3.8% in the placebo group. The rate of discontinuation due to adverse events (AE) was low, 1.9% in the placebo group and 2.0% in the risperidone group. The most common reason for discontinuation was insufficient response, 23.1% in the placebo group and 4.1% in the risperidone group.

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SAFETY RESULTS (Continued): There were no deaths reported during the study. No treatment-emergent serious adverse events (SAE) occurred in the risperidone group and 1 subject in the placebo group who had an SAE discontinued from the study due to surgery required for a shunt removal.

Aside from the investigator reporting EPS-related side effects, EPS-related side effects were identified by the changes in baseline scores using the SARS and AIMS scales. Sixteen (32.7%) subjects in the risperidone group and 6 (11.5%) subjects in the placebo group had EPS-related AE. However, evaluation of EPS using SARS and AIMS scales showed no difference between groups. Tremor and hypertonia were the most frequently occurring EPS-related AEs for both treatment groups. All EPS-related AEs were rated mild or moderate.

Overall, there were no clinically relevant differences between both treatment groups for clinical chemistry, hematology, and urinalysis measurements.

No subjects in the risperidone group had any clinically relevant abnormal ECG values.

There were no unexpected findings with regard to vital signs. Although, the risperidone group had more subjects with pulse rates that changed from baseline to end point of $\geq$ 120 bpm, between group comparisons of mean change at end point showed no statistical significant differences. The mean weight change from baseline to end point was 2.7 kg in the risperidone group and 0.7 kg in the placebo group. Even though the risperidone subjects had an increased appetite, overall, they were not obese, (1 subject, 2.1%) and only 4 (8.3%) were overweight. There were statistically significant differences between treatment group comparisons at end point for weight (p=0.004) and BMI (p=0.021).

Somnolence occurred more frequently in the risperidone group, 31 (63.3%) than the placebo group, 16 (30.8%). Additionally, risperidone subjects were somnolent for a longer time (median 18.0 days) compared to placebo subjects (median 5.5 days).

Potentially prolactin-related AEs were low, 3 (5.8%) in the placebo group and 1 (2.0%) in the risperidone group.

There were no glucose-related adverse events.

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CONCLUSION: The results of this study demonstrate that risperidone at an average oral daily dose of 2.0 mg significantly improves symptoms of Autistic Disorder and is well-tolerated in children and adolescents 5 to 17 years 2 months of age. Risperidone was statistically superior to placebo in reducing irritability in children and adolescents with Autistic Disorder as measured by the Irritability subscale of the ABC. Improvement was seen as early as Week 2 and was maintained at Weeks 4, 6, and 8. The rate of improvement was much greater than with placebo

In addition, the CGI-C also demonstrated that risperidone was statistically superior to placebo in improving the symptoms of Autistic Disorder, and the responder-analysis showed more subjects in the risperidone group who had a consistent response to treatment (a 25% change from baseline in the ABC-Irritability subscale at end point and a CGI-C score of "much improved" or "very much improved') compared with subjects in the placebo group.

Risperidone significantly improved symptoms of Autistic Disorder as measured by the Irritability, Lethargy/Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance, and Inappropriate Speech subscales of the ABC and the significant improvement on personal and social sufficiency as measured by the Vineland Adaptive Behavior Scale (VABS).

Although more subjects treated with risperidone had an AE of somnolence, the presence of this AE had no bearing on the effectiveness of risperidone treatment as subjects with and without somnolence improved similarly.

Risperidone was well tolerated, and its safety profile was comparable to previous studies with risperidone. Increased appetite was the most frequently reported adverse event in the risperidone group. Even though the risperidone subjects had an increase appetite, overall, they were not obese (only 2.1% of risperidone subjects) and only 8.3% were considered to be overweight. There were no unexpected adverse events or safety findings for risperidone that have not already been reported. Although there were more EPS-related AEs in the risperidone group, no one discontinued from the study due to EPS AEs. In addition, there were no significant differences between risperidone and placebo in EPS as evaluated by total AIMS or SARS scores at end point.

Date of the report: 26 November 2003

SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. 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-USA-150 Part 2/3

Title of Study: An open-label continuation study of risperidone in children and adolescents with Autistic Disorder followed by a double-blind, placebo-controlled discontinuation

Principal Investigator: ▮▮▮▮▮▮▮ Ph.D., M.S.N. – ▮▮▮▮▮▮▮▮▮▮▮▮▮▮ U.S.A.

Publication (Reference): None

Study Initiation/Completion Dates: 9 August 1999 / 14 August 2001	**Phase of development:** 3

Objectives: The primary objectives were to determine safety and longer-term efficacy of risperidone in treatment of children and adolescents with significant behavioral disturbances within the context of Autistic Disorder; and to assess the relapse rate of risperidone responders after randomization to either continued risperidone treatment or to placebo substitution. The secondary objective was to test whether subjects randomized to placebo will show fewer ratings of dyskinetic movements versus subjects continued on risperidone as measured by the Abnormal Involuntary Movement Scale (AIMS).

Methodology: RIS-USA-150 was a 3-part, multicenter study. Part 1 (an 8-week, double-blind, placebo-controlled study) is described in a separate study report. At the end of Part 1, risperidone responders could enter Part 2, a 4-month, open-label risperidone treatment period. Placebo nonresponders (PNR) from Part 1 could enter an 8-week, open-label risperidone treatment period, and responders from this period could then enter an additional 4-month, open-label, risperidone treatment period (Part 2). Risperidone responders who completed Part 2 were randomized to either continued risperidone treatment or to a placebo substitution arm for an additional 8-week, double-blind, randomized withdrawal period (Part 3). In the placebo substitution arm, risperidone was tapered down during the first 3 weeks. For both parts of this study risperidone was dosed once or twice daily and flexibly according to weight (up to 4 mg/day for subjects weighing <45 kg and up to 6 mg/day for subjects weighing ≥45 kg).

Number of Subjects (planned and analyzed): Planned enrollment: approximately 50 subjects for the Randomized Withdrawal phase; 70 subjects participated in Part 2 and 39 subjects were randomized to Part 3.

Diagnosis and Main Criteria for Inclusion: The target population included children and adolescents between the ages of 5 and 17 years 6 months with a DSM-IV diagnosis of Autistic Disorder; weight ≥ 15 kg; previous treatment with risperidone assessed as producing a Clinical Global Impression – Improvement (CGI-I) score of "much improved" or "very much improved" by the parent and clinician; no need for other psychotropic medications besides risperidone; and a mental age of at least 18 months as measured by the Wechsler Intelligence test (WISC-III-R) or the revised Leiter or Mullen. Anticonvulsants used for the treatment of a seizure disorder were permitted if the dosage had been stable for 4 weeks and the patient was seizure free for at least 6 months. Entry into Part 2 and 3 required that the subject have a decrease of ≥25% in the Aberrant Behavior Checklist (ABC) Irritability score from baseline in Part 1 and CGI-I ratings of "much improved" or "very much improved."

Test Product, Dose and Mode of Administration, Batch No.: Dosing throughout the study was once daily (preferably at bedtime) or twice daily (morning and bedtime).

Risperidone 0.5 mg tablets batch numbers: 97G02/F9, 99E18/F9; Risperidone 1 mg tablets batch number 97G01/F5.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo tablets batch number 95I11/F7.

Duration of Treatment: Treatment with open-label risperidone for 4 months followed by double-blind placebo or risperidone for 8 weeks, or treatment with open-label risperidone for 8 weeks, followed by another 4 months of open-label risperidone treatment, and subsequent 8-week double-blind placebo or risperidone.

SYNOPSIS (CONTINUED)

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Criteria for Evaluation:

Pharmacokinetics: Not applicable

Efficacy: The primary efficacy variable is the rate of relapse during the Randomized Withdrawal (RWD) phase. Relapse was defined by the occurrence of both of the following events during the Randomized Withdrawal phase.

1. Clinical Global Impression of Change (CGI-C) score of "much worse" or "very much worse" than baseline ratings (Week 16) for 2 consecutive weeks, and an increase of ≥25% from baseline ABC Irritability score (baseline defined as ABC score on entry into the Randomized Withdrawal phase).

The secondary efficacy measures were evaluated as follows:

1. CGI-C score of "much worse" or "very much worse" than baseline ratings (Week 16) for 2 consecutive weeks; and an increase of ≥25% from baseline ABC Irritability score (baseline defined as ABC score on entry into the Randomized Withdrawal phase); or any withdrawal related to lack of efficacy that does not meet either of the first 2 criteria;

2. The time to relapse compared across treatment groups.

Safety: The safety of study medication was assessed by adverse events profiling (i.e., Side Effect Review form), clinical laboratory tests, vital signs and physical examination, body height and weight, body mass index (BMI), electrocardiogram (ECG), extrapyramidal symptom (EPS) rating using the Simpson-Angus Rating Scale (SARS) and the Abnormal Involuntary Movement Scale (AIMS).

Pharmacokinetic/Pharmacodynamic Relationships: Not applicable

Statistical Methods: Interim analysis set was used for the primary efficacy analysis of the relapse rate at the Randomized Withdrawal phase. Intent-to treat (ITT) analysis sets was used for all remaining analysis.

Efficacy: Mantel-Haenszel Chi-square test was used for assessing the association of treatment with relapse rate. Kaplan-Meier estimates and log-rank test were used to compare the time to relapse at the Randomized Withdrawal phase. Descriptive statistics were generated for change from baseline in ABC subscales, CGI-C, Clinical Global Impression – Severity scale (CGI-S), and Vineland Maladaptive Behavior Score (VMBS) at every timepoint and end point.

Safety: Number and percentage of subjects with adverse events by group were summarized. Change from baseline in vital signs, body height and weight, BMI, ECG, SARS, and AIMS were summarized with descriptive statistics, and with percentage of subjects exceeding pre-defined limits for vital signs, ECG, body weight and BMI.

Laboratory safety: Descriptive statistics and percentage of subjects exceeding pre-defined limits.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS: Not applicable

SYNOPSIS (CONTINUED)

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EFFICACY RESULTS: Risperidone was effective in children and adolescents 5 to 17 years of age with a dose of approximately 2 mg/day for subjects in all phases. As measured by ABC, CGI-C and Vineland, the positive effect of risperidone in treating symptoms of Autistic Disorder was maintained – with continued treatment of risperidone - for at least 4 months in children and adolescents who had previously responded to 8 weeks of double-blind treatment during Part 1 of the study.

After 8 weeks of open-label risperidone treatment, subjects who were placebo nonresponders in Part 1 had ABC/CGI-C scores that stabilized to levels similar to those of subjects who had responded to risperidone at the end of Part 1.

There were 81% CGI-C responders (relative to double-blind baseline) at the end of the 4-month Open-Label phase.

Risperidone was effective in improving (reducing) all 5 ABC subscale scores during the initial 8-week double-blind treatment phase (Part 1 of the study), and in maintaining the effect during the 4-month Open-Label phase.

Data from the interim analysis (which was pre-planned to determine whether the study was to be stopped), showed that the percentage of subjects who relapsed was significantly (p=0.001) lower in the risperidone group (12.5%) than in the placebo group (68.8%).

Risperidone subjects were 15.4 times less likely to relapse than those who switched to placebo, having responded to treatment with risperidone for 6 months.

The relapse rates at interim analysis, based on the Kaplan-Meier method were 0.86 and 0.15 in the placebo and risperidone treatment groups, respectively. Continued treatment with risperidone for 8 weeks was associated with an 83% (i.e., [0.86-0.15]/0.86) reduction in relapse rate relative to gradual switching to placebo. The difference in time to relapse between the placebo and risperidone treatment groups was significant (p=0.001).

For subjects switching to placebo treatment after responding to risperidone during the 4-month Open-Label phase, there was a statistically significant difference in time to relapse during the Randomized Withdrawal phase compared to subjects with continued risperidone treatment.

During the Randomized Withdrawal phase, risperidone showed an advantage over placebo in maintaining treatment effect as measured by all 5 ABC subscales - Lethargy/social withdrawal, Stereotypic behavior, Hyperactivity/noncompliance, Inappropriate speech, and Irritability.

CGI-C scores at end point of the Randomized Withdrawal phase indicated that a higher percentage of subjects in the placebo group than in the risperidone group had worsened symptoms.

Risperidone treatment was beneficial compared to placebo as measured by the Vineland Maladaptive Behavior Domain scales.

Overall, results of analyses based on the interim analysis data set during the Randomized Withdrawal phase were consistent with data analyses based on the intent-to-treat analysis set.

SYNOPSIS (CONTINUED)

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SAFETY RESULTS: Risperidone was safe and well tolerated in children and adolescents with autism. The long-term safety profile was similar to that observed with 8 weeks of risperidone treatment. There were no deaths and no treatment-emergent serious adverse events during the study.

There were no glucose-related and very few prolactin-related adverse events (4 subjects in the 4-month Open-Label phase and 2 subjects in the placebo group of the Randomized Withdrawal phase). No subjects in the risperidone group received anti-EPS medication as a result of EPS-related adverse events. There were no events of tardive dyskinesia and no discontinuations due to EPS-related adverse events. Subjects randomized to placebo in the Randomized Withdrawal phase did not show different (fewer) ratings of dyskinetic movement as measured by AIMS. There were no significant differences between risperidone and placebo in EPS as evaluated by total AIMS or SARS scores at end point of the Randomized Withdrawal phase.

Body mass increases were observed during the first 8 weeks of risperidone treatment as observed in Part 1 of RIS-USA-150 and also in the Placebo Nonresponder group. An additional slight increase was measured during the first 4 weeks in the 4-month Open-Label phase. Thereafter the BMI during risperidone treatment was stable for the remainder (20 weeks) of Part 2/3 of study RIS-USA-150.

There were no clinically relevant differences between groups in the Randomized Withdrawal phase for vital signs, clinical chemistry, and hematology measurements. Although, the risperidone group had more subjects with pulse rates who changed from baseline to end point (RWD) of ≥ 120 bpm, the number of subjects was low, and increased pulse and tachycardia were not deemed to be clinically relevant. Only 1 subject had a QTc of ≥ 500 msec by QTcF and QTcLD (elevated at Week 3, no further elevations at any other timepoint). A cardiologist subsequently evaluated the ECG results for this subject and found them to be normal. There were no significant changes in QTc by any correction factor during the 4-month Open-Label phase and Randomized Withdrawal phase. There were 3 subjects in the 8-week open-label treatment period and 2 subjects in the 4-month Open-Label phase who experienced tachycardia reported by the investigator as an adverse event mild in severity, and considered as possibly, probably, or very likely related to study medication. None of the events of tachycardia were serious or required discontinuation from the study.

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CONCLUSION: The results of this study demonstrate that risperidone at a mean oral daily dose of 2 mg/day is safe and effective in treating children and adolescents with Autistic Disorder 5 – 17 years of age.

- Subjects who received risperidone for at least 4 months were significantly less likely to relapse compared to placebo subjects;

- Risperidone's effectiveness in treating the symptoms of Autistic Disorder in children and adolescents was maintained over at least a 6-month period (4-month Open-Label phase plus the 8-week Randomized Withdrawal phase) as measured by ABC, CGI-C and the Vineland Adaptive Behavior Scale;

- Risperidone was well tolerated, and its safety profile was comparable to previous studies with risperidone and across all 3 treatment periods of this study;

- The change in mean BMI values from baseline in Part 1 increased during the initial 12 weeks of risperidone treatment in study RIS-USA-150 (i.e., 8 weeks of treatment in Part 1 or the Placebo Nonresponder period and the first 4 weeks of the 4-month Open-Label phase) but stabilized thereafter, with little or no further increase during the remaining 12 weeks of the 4-month Open-Label phase. The change in mean BMI values from RWD baseline was stable during an additional 8 weeks of treatment in the risperidone group of the Randomized Withdrawal phase;

- No subject received anti-EPS medication as a result of an EPS-related adverse event, and no subject discontinued due to an EPS-related adverse event. In addition, there were no significant differences between risperidone and placebo in EPS as evaluated by total AIMS or SARS scores at end point of the Randomized Withdrawal phase.

Date of the report: 05 Dec 2003