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.: RIS-BIM-301 CR003631

Title of Study: Research on the Effectiveness of Risperidone in Bipolar Disorder in Adolescents and Children (REACH): A Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of Risperidone for the Treatment of Acute Mania in Bipolar I Disorder

Coordinating Investigator: M DelBello, MD, Psychiatric Professional Services Inc., 231 Albert Sabin Way, Cincinnati, OH 45267; USA.

Publication (Reference): Not applicable

Study Initiation/Completion Dates: 29 December 2003 to 22 December 2005 | **Phase of development:** 3

Objectives: The primary objective of this study was to determine the efficacy of 2 dose ranges of risperidone monotherapy (0.5-2.5 mg/day and 3-6 mg/day) versus placebo in children and adolescents with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of Bipolar I disorder who were experiencing a manic or mixed episode (Young Mania Rating Scale [YMRS] ≥20). Efficacy was primarily based on the improvement in severity of mania during the 3-week treatment period, measured by the change in total score (consensus final score) of the YMRS from baseline to endpoint.

Additional objectives were to: (1) determine the safety and tolerability of risperidone monotherapy; (2) assess the effects of risperidone monotherapy on secondary efficacy variables (including YMRS response, YMRS onset of maintained response, Clinical Global Impression Scale – Bipolar Disorder [CGI-BP] score and Brief Psychiatric Rating Scale for Children, revised [BPRS-C] depression score); (3) explore the pharmacokinetics and the relationship between pharmacokinetics and the efficacy and safety of risperidone; and (4) determine genes/genotypes that may be related to the response or metabolism of risperidone in children and adolescents with a DSM-IV diagnosis of Bipolar I disorder.

Methodology: This was a randomized, placebo-controlled, double-blind, 3-arm, multicenter study in children and adolescents with a DSM-IV diagnosis of Bipolar I disorder experiencing a manic or mixed episode. The study was composed of 2 phases: a screening phase (including a washout period, if required) and a 3-week double-blind treatment phase.

After successfully completing screening and baseline procedures, subject were randomized to receive 1 of 3 treatments: oral placebo tablets, oral risperidone tablets 0.5-2.5 mg (dosage group A), or oral risperidone tablets 3-6 mg (dosage group B). Study medication was titrated to the target dosage range by Day 7. The maximum tolerated dose within the target dose range was then maintained from Day 10 to Day 21.

Subjects were enrolled as outpatients or inpatients as clinically indicated. A subject was considered to have completed the study upon completion of all assessments at Week 3 of the double-blind phase.

Number of Subjects (planned and analyzed): 162 subjects were planned; 169 subjects were analyzed (intent-to-treat [ITT] population)

Diagnosis and Main Criteria for Inclusion: Subjects aged 10 to 17 years with a DSM-IV diagnosis of Bipolar I disorder and suffering from a current mixed or manic episode (total score ≥20 on the YMRS).

Test Product, Dose and Mode of Administration, Batch No.: Oral risperidone, 0.25 mg 03D18/F070, 04H24/F070; 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, 04J01/F007.

Duration of Treatment: 3 weeks

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Criteria for Evaluation:

Pharmacokinetics: Blood samples were collected at Days 7 (predose), 14 (pre- and postdose) and 21 (predose) for the determination of plasma concentrations of risperidone and 9-hydroxy-risperidone in subjects treated with risperidone. Plasma concentrations of the active moiety were calculated by summation of the risperidone and 9-hydroxy-risperidone plasma concentrations.

Efficacy: The primary efficacy variable was the change in total score (consensus final score) for the Young Mania Rating Scale (YMRS) from baseline to endpoint. Secondary efficacy variables included: (1) change from baseline in total YMRS at the secondary time points of Days 7 and 14; (2) change from baseline in the CGI-BP scores at all prescribed time points; (3) change from baseline in the Brief Psychiatric Rating Scale for Children (BPRS-C) depression score; other BPRS-C total and cluster scores at all time points; (4) number and percentage of subjects with clinical response to risperidone on the YMRS score (consensus final score), defined as at least a 50% reduction from the baseline score at Day 21 or at the last available postbaseline observation before Day 21; (5) onset of maintained YMRS response, defined as the first visit at which a 50% reduction on the consensus final score is achieved and subsequently maintained.

Safety: Safety was evaluated throughout the study using the monitoring of: adverse events, including extrapyramidal symptoms (EPS) using the Simpson Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS), and the Abnormal Involuntary Movement Scale (AIMS); clinical laboratory testing, including hematology, serum chemistry (including prolactin levels), and urinalysis; vital signs measurements; electrocardiograms (ECGs); urine drug screening; pregnancy testing; and physical examination and Tanner staging. If any laboratory results were abnormal, laboratory tests were repeated after fasting for at least 6 hours. A Data Safety Monitoring Board reviewed adverse event reports and laboratory findings throughout the study.

Pharmacokinetic/Pharmacodynamic Relationships: The relationship between the plasma concentrations of the active moiety and efficacy (YMRS) and safety parameters (QTcLD and SAS) was explored graphically via scatter plots.

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

The primary efficacy variable was the change in the total YMRS score (consensus score) from baseline to the Day 21 endpoint, i.e., the last post-baseline carried forward to the Day 21 endpoint. An analysis of covariance (ANCOVA) model was applied to the primary efficacy variable, with factors for treatment, center and diagnosis (manic/mixed) as factors and baseline YMRS total score as a covariate. The primary comparison was between each of the risperidone dosage groups and placebo. A step-down testing procedure was applied in comparing each of the risperidone dosage groups with placebo sequentially.

An ANCOVA model was also performed for secondary efficacy variables including change from baseline in YMRS at intermediate time points and CGI-BP (overall bipolar illness, mania and depression subscales) and BRS-C at every time point. Fischer's least significant difference test (LSD) was used to obtain p-values for pairwise comparisons of least square means between each active group and placebo. For YMRS response and distribution of onset of maintained response, Cochran-Mantel-Haenszel test (controlling for center and diagnosis) were used to analyze between-group differences.

No statistical tests were performed to evaluate between group for any of the safety, pharmacokinetic or pharmacokinetic/pharmacodynamic parameters.

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SUMMARY - CONCLUSIONS

PHARMACOKINETICS:

Predose plasma concentrations at steady-state were comparable between Days 14 and 21 for both risperidone treatment groups. Plasma concentrations increased with dose. Dosage-adjusted plasma concentrations were comparable between the 2 risperidone treatment groups. Average dose-normalized and dose-adjusted (to 0.04 mg/kg/day) pre- and postdose plasma concentrations of the active moiety were 14.2 ± 10.7 ng/mL (Days 14 and 21 combined) and 35.5 ± 25.2 ng/mL (Day 14), respectively (risperidone treatments combined).

EFFICACY RESULTS:

A summary of changes from baseline to the Day 21 endpoint for the primary (YMRS) and selected secondary efficacy parameters are shown below (ITT population):

		Mean (SD)			Between-group comparison	
Parameter Treatment	N	Baseline	Endpoint (LOCF)	Change	Diff in LS Mean Changes (95% CI)	p value[a]
YMRS						
Placebo	57	31.0 (7.46)	21.9 (9.51)	-9.1 (10.95)	—	—
RIS 0.5-2.5	49	31.1 (5.97)	12.6 (7.22)	-18.5 (9.70)	-9.2 (-12.69;-5.74)	<0.001
RIS 3-6	60	30.5 (5.92)	13.9 (9.70)	-16.5 (10.29	-8.0 (-11.33;-4.62)	<0.001
CGI-BP: Overall Bipolar						
Placebo	57	4.5 (0.71)	3.6 (1.20)	-1.0 (1.19)		
RIS 0.5-2.5	49	4.6 (0.67)	2.6 (1.01)	-2.0 (1.16)	-0.9 (-1.34;-0.46)	<0.001
RIS 3-6	59	4.5 (0.68)	2.7 (1.28)	-1.8 (1.30)	-0.8 (-1.27;-0.42)	<0.001
BPRS-C						
Placebo	57	33.4 (12.95)	21.7 (12.64)	-11.6 (12.22)		
RIS 0.5-2.5	49	31.1 (11.12)	13.2 (8.97)	-17.9 (10.10)	-7.0 (-10.83;-3.20)	<0.001
RIS 3-6	59	33.7 (10.72)	17.0 (13.17)	-16.6 (12.39)	-4.6 (-8.28;-0.91)	0.015

[a] p value: Comparison with placebo based on ANCOVA model with treatment, investigator, diagnosis as factors and baseline value as covariate (Fisher's LSD procedure).

Compared with placebo, both risperidone dose groups showed a significant reduction in YMRS score from baseline to the Day 21 endpoint (the primary efficacy variable). The observed differences in the change from baseline in YMRS between the risperidone dose groups and placebo groups were –9.2 and –8.0 for the 0.5-2.5 mg/day and 3-6 mg/day dose groups, respectively. Statistical differences between the placebo and risperidone groups were observed as early as Day 7 (the first clinical assessment of efficacy in this study) and were maintained for the duration of the study. Subgroup analyses showed treatment with both dose ranges of risperidone was consistently more effective than placebo regardless of age, sex, race (white versus non-white and black versus non-black), diagnostic subgroups, occurrence of somnolence during treatment, hospitalization status at screening. The improvement in all risperidone mode dose groups was statistically significant (nominal unadjusted p-values <0.001) compared with placebo. The between-group difference of the least-squares adjusted mean changes from baseline was between –9.9 and -7.4 in favor of the risperidone mode dose groups.

Subjects receiving risperidone also showed a significantly higher YMRS response rate. At the Day 21 endpoint, a ≥50% reduction in YMRS score was observed in 59% and 63% of subjects in the risperidone 0.5-2.5 mg and 3-6 mg groups, respectively, compared with 26% in placebo treated subjects ($p<0.002$, $p<0.001$ vs. placebo, respectively, Cochran-Mantel-Haenszel test). A clinical response was considered maintained if it was achieved for at least 2 consecutive measurements and for the remainder of the treatment. Overall, 45% and 42% of subjects in the risperidone 0.5-2.5 mg and 3-6 mg groups, respectively, and 16% of subjects in the placebo group achieved a maintained response.

Risperidone-treated subjects also showed a significant improvement on secondary endpoints of CGI-BP (overall bipolar illness and mania scales) and BPRS-C (total score) vs placebo at the Day 21 end point. No change in CGI-BP depression scale was observed.

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SAFETY RESULTS:

Risperidone was well tolerated in children (aged ≤12 years) and adolescents (aged >12 years) in this study. The frequency of treatment-emergent adverse events was similar (90% and 95%) for the 0.5-2.5 mg and 3-6 mg risperidone groups (76% for placebo). There were no deaths and the incidence of serious adverse events was low (5% to 8%) for all treatment groups in this study. The risperidone 3-6 mg dose range was associated with a higher incidence of discontinuations due to adverse events (16%) than placebo (7%) or risperidone 0.5-2.5 mg (6%).

The most common adverse events were somnolence, headache and fatigue. The incidence of headache was similar across all treatment groups. There was a dose-related increase in the incidence and severity of somnolence. The incidence of fatigue also increased with increasing doses of risperidone, though fatigue was generally mild in all treatment groups. Somnolence and fatigue tended to start earlier and last longer in risperidone-treated subjects, though there were no clear dose-related trends in time of onset or duration, and these adverse events typically resolved within a few days of the last dose of study medication.

Treatment-emergent (≤4 days postdose) suicidal ideation was reported in 6 subjects (5 risperidone-treated subjects and 1 subject in the placebo group). Additionally, 3 risperidone-treated subjects had suicidal ideations with onset >4 days after the last dose of study medication. One additional placebo subject had a suicide attempt. There were no completed suicides. Based on an additional, comprehensive, blinded review of all potentially suicide-related adverse events, no clinically meaningful differences were detected between risperidone and placebo subjects in this controlled study that constituted a safety signal in pediatric bipolar mania.

Overall, there was a low incidence of treatment-emergent EPS-related adverse events, consistent with the lack of clinically significant differences in EPS scores for symptoms of dyskinesia (AIMS), akathisia (BARS), and parkinsonism (SAS). The incidence of reported treatment-emergent EPS-related adverse events was higher in the risperidone 3-6 mg group (25%) than in the placebo (5%) and risperidone 0.5-2.5 mg (8%) groups.

There was some suggestion that risperidone treatment was associated with a dose-dependent increase in prolactin levels and in the number of subjects with elevations of prolactin from within pathological limits (0-100 ng/mL) at baseline to above those limits postbaseline (mean changes from baseline in serum prolactin were about 1 ng/mL, 40 ng/mL, and 60 ng/mL, and the proportion of subjects outside pathological limits for prolactin postbaseline were 0%, 11%, and 25% for the placebo, risperidone 0.5-2.5 mg, and risperidone 3-6 mg groups respectively). In spite of the increase in prolactin, the emergence of potentially prolactin-related adverse events was low (2%, 4%, and 5% in the placebo, risperidone 0.5-2.5 mg, and risperidone 3-6 mg groups respectively).

Mean increases in body weight from baseline to end point were 0.65 kg, 1.9 kg, and 1.44 kg for the placebo, risperidone 0.5-2.5 mg, and risperidone 3-6 mg groups, respectively. Corresponding mean increases in height were small (<0.5 cm) and comparable for all treatment groups. There was a treatment-related increase in the number of subjects with clinically significant (>7%) increases in body weight (5%, 14% and 10% for the placebo, risperidone 0.5-2.5 mg, and risperidone 3-6 mg groups, respectively). No subject in the risperidone-treated groups went from <85th BMI percentile at baseline to the >95th BMI percentile during the study.

There was a small increase in glucose (approximately 0.25 mmol/L) from baseline to end point in both risperidone groups that was not noted for placebo. There were no treatment-emergent glucose-related adverse events. One subject (risperidone 3-6 mg) had a fasting postbaseline glucose level (7.0 mmol/L) that was above the potentially clinically important upper limit of 6.4 mmol/L and met ADA criteria for diabetes. This subject did not have any related adverse events and, in follow-up with the investigator, was considered most likely not fasting at the time of the elevated glucose. This subject has continued on risperidone treatment without further elevations of glucose or other metabolic parameters.

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There was a small (<6 bpm) increase in mean pulse rate from baseline to Day 21 for both risperidone groups. There were no apparent changes in mean blood pressure, body temperature or respiration rate.

There were no clinically significant changes in ECG parameters from baseline to end point, including changes in QTcF and QTcLD.

The safety profile of the compound in children and adolescents in this study was qualitatively similar and in the range seen in other studies of the compound in pediatric populations for other indications and in adult patients with bipolar mania.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

Graphical exploration (i.e., scatter plots) of the pharmacokinetic/pharmacodynamic relationship showed no apparent trend or relationship between predose active moiety plasma concentrations at steady state and selected measures of efficacy (YMRS) and safety (QTcLD and SAS) or their respective shifts from baseline.

CONCLUSIONS:

Risperidone treatment, at daily doses of 0.5-2.5 mg and 3-6 mg, was unequivocally superior to placebo in children and adolescents with an acute manic or mixed episode of bipolar I disorder.

Overall, risperidone was well tolerated by children and adolescents in this study. The safety profile of the compound in children and adolescents was qualitatively similar to that seen in other studies of the compound in both the pediatric and adult populations.

Overall assessment of the data indicates that the benefit-risk of treatment with risperidone 0.5-2.5 mg in children and adolescents with Bipolar I disorder may be better than with the higher dose range of 3-6 mg.

This study is the first double-blind placebo-controlled study of risperidone in this population. The results of this study complement results from risperidone treatment studies in adults with acute manic or mixed episodes of Bipolar I disorder.

Date of the report: 1 December 2006

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