SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: Risperidone 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.: CR002020 **Title of Study:** Risperidone in the prevention of relapse: a randomized, double-blind, placebo-controlled trial in children and adolescents with conduct and other disruptive behavior disorders		
Coordinating Investigator: Paz Toren, M.D., Mental Health Community Center, 9, Hatzvi St. Tel Aviv 67197 Israel		
Publication (Reference): None		
Study Initiation/Completion Dates: 08 August 2001 - 11 September 2003		**Phase of development:** 3
Objectives: The primary objective was to assess the efficacy of risperidone as maintenance therapy in the prevention of relapse in children and adolescents with conduct and other disruptive behavior disorders, using the time to relapse as the principal efficacy measure. Secondary objectives were 1) to test for a difference in the relapse hazard for placebo- and risperidone-treated subjects; 2) to compare the efficacy of risperidone and placebo as rated on the Nisonger Child Behavior Rating Form (N-CBRF), Clinical Global Impression (CGI), Visual Analogue Scale for the most troublesome symptom (VAS-MS), and the Children's Global Assessment Scale (C-GAS); and 3) to document the safety profile of risperidone.		
Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study consisting of 3 phases: 1) acute treatment (6-week open-label risperidone), 2) continuation treatment (6-week single-blind risperidone), and 3) double-blind maintenance treatment (6-month double-blind treatment). Only those subjects categorized as responders at the end of acute phase 1 could continue into continuation phase 2. Subjects categorized as sustained responders at the end of phase 2 were randomized to risperidone or placebo treatment for the double-blind maintenance phase 3. Subjects who completed phase 3 or who prematurely discontinued double-blind treatment due to relapse could enroll in an open-label follow-on study (CR002149).		
Number of Subjects (planned and analyzed): The planned number of randomized subjects (Phase 3) was 225, requiring that an estimated 364 subjects enter phase 1 of the study. The all-subjects analysis set (all subjects who received at least 1 dose of study treatment) included 527 subjects who were included in the analysis of safety data. Five hundred and twenty-seven subjects entered the acute phase 1, 436 subjects entered the continuation phase 2 and 335 subjects were randomized to the double-blind maintenance phase 3 (163 subjects switched to placebo and 172 continued to receive risperidone). The intent-to-treat (ITT) analysis set (all randomized subjects who received at least 1 dose of double-blind study medication following randomization), which was used in the analysis of efficacy data during phase 3, consisted of 335 subjects.		
Diagnosis and Main Criteria for Inclusion: A DSM-IV diagnosis of conduct disorder (312.8), oppositional defiant disorder (313.81), or disruptive behavior disorder not otherwise specified (312.9). The presence of ADHD (314.xx; 314.9) was not exclusionary for entry.		
Inclusion Criteria: Subjects were eligible for this study if they met the following criteria: • Male or female children or adolescents aged 5 to 17 years (extremes included); • Met DSM-IV criteria for Conduct Disorder (312.8), Oppositional Defiant Disorder (313.81), or Disruptive Behavior Not Otherwise Specified (312.9); • Had a score of at least 24 on the Conduct Problem subscale of the N-CBRF at screening (Visit A1) and at Day 1 (Visit A2); • Had a conduct problem sufficiently serious that the investigator felt a trial of risperidone was warranted;		

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Inclusion Criteria (Continued):

- Provided informed assent, and signed an assent form, if capable of doing so. In addition, the subject's parents/legal guardians were to provide informed consent (permission) and sign an informed consent document;
- A responsible person (parent, legal representative, or professional caregiver—hereafter referred to as the caregiver) was available (1) to help the investigational site ensure follow-up of the subject, (2) to accompany the subject to the investigational site on each assessment day, (3) to provide reliable information for the rating scales, and (4) to accurately and reliably dispense the study medication as directed;
- Had no other serious (e.g., liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, psychiatric, or metabolic disturbances), acute, unstable, and/or significant and untreated medical illnesses (e.g., infection, unstable diabetes, or uncontrolled hypertension);
- Was physically healthy on the basis of a physical examination, medical history, anamnesis, ECG (no clinically significant ECG abnormalities), and the results of blood biochemistry tests, hematology tests, and urinalysis performed less than 7 days before the first intake of study treatment.

Test Product, Dose and Mode of Administration, Batch No.: Risperidone was supplied as a 1-mg/mL oral solution (Batch numbers: 00H17/648 and 01C30/276) and was administered using a graduated pipette. It was administered once daily in the morning, but could be given once daily in the evening or as twice-daily divided doses if indicated (e.g., due to sedation, breakthrough symptoms). In phase 1 of the study, the investigator adjusted the dose according to efficacy and tolerability: the dose was titrated upwards over the first 5 days, and a maintenance dose in the range 0.5–1.5 mL/day (subjects ≥50 kg) or 0.25–0.75 mL/day (subjects <50 kg) was to be administered from Day 5. At the start of phases 2 and 3, the dose was to be the same as that during the preceding phase, and was to be maintained throughout the phases if clinically feasible.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo oral solution *(*Batch numbers, 00H16/817 and 01D09/093*)*. The dose and titration regimen for placebo were identical to those for risperidone.

Duration of Treatment: Total 36 weeks (6 weeks risperidone in acute phase 1, 6 weeks risperidone in continuation phase 2, and 6 months placebo or risperidone in maintenance phase 3).

Criteria for Evaluation:

Pharmacokinetics: Not applicable, no pharmacokinetic samples were taken.

Efficacy: The primary parameter, time from randomization to relapse in maintenance phase 3, was measured by the N-CBRF and CGI assessments. Subjects had to meet at least 1 of the following 2 criteria on 2 consecutive visits to be considered relapsed. The same criteria must have been met at each of the 2 visits: CGI-S: a deterioration from the start of phase 3 (Visit 1) by 2 points or more compared to Visit B3 in Phase 2 **or** N-CBRF Conduct Problem subscale score: a deterioration from the start of phase 3 (Visit 1) of 7 points or more compared to Visit B3 phase 2. A 7-point deterioration corresponds with a 40% to 50% change, and reflects an important deterioration of symptoms.

The N-CBRF and the VAS-MS were rated by the subject's caregiver under the guidance of study staff; the CGI and C-GAS were rated by an experienced clinician. The N-CBRF, VAS-MS, and CGI assessments were performed at screening and at each visit during phases 1, 2, and 3 of the study (phase 1, Day 1, and Weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, and 36, or the subject's end point visit). The C-GAS assessments were performed at screening and at the last visit in phases 2 and 3 (Weeks 12 and 36, or the subject's end point visit).

Safety: Safety parameters included adverse events, clinical laboratory tests, vital signs, ECG, physical examinations, Tanner staging, height and body weight, and cognitive tests.

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Statistical Methods: Descriptive statistics summarized demographic and baseline data and extent of exposure information. The change from baseline was summarized with descriptive statistics for N-CBRF total score and subscales, VAS-MS, CGI-S; and CGI-C score. Summary statistics were generated for C-GAS.

Efficacy: The ITT analysis set was used in all efficacy analyses during maintenance phase 3 based on all subjects randomized and who received 1 dose of double-blind study medication. The all subjects analysis set was used in efficacy analyses during acute phase 1 and continuation phase 2 based on all subjects who received at least 1 dose of risperidone in these phases. A Kaplan Meier, Cox proportional hazard model, and a sensitivity analysis were used to calculate the time to relapse in phase 3. The Cochran-Mantel-Haenszel test for general association controlling for country was used for assessing the rates of relapse

Safety: Safety analyses were performed for all subjects who received at least 1 dose of study treatment during any phase. The number and percent of subjects with adverse events including serious adverse events, discontinuations due to adverse event, EPS-related, glucose-related, potentially prolactin-related, weight-related, and somnolence adverse events were summarized. Change from screening and baseline in vital signs, laboratory tests and ECG, and cognitive tests were summarized with descriptive statistics. Changes from screening and baseline in height and weight were summarized by descriptive statistics transformed to z-scores.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS: Not applicable

EFFICACY RESULTS: Risperidone, at a median dose of 0.75 mg for subjects <50 kg and 1.496 mg for subjects ≥ 50 kg, had a beneficial acute and maintenance effect on disruptive behavioral symptoms and additionally prevented relapse: subjects who continued treatment with risperidone experienced relapse later than subjects who switched to placebo ($p< 0.001$). The relapse rates were 42.3% in the placebo group compared to 27.3% in the risperidone group ($p<0.001$). The mean conduct disorder subscale scores were significantly improved during the acute phase of the study when all subjects received risperidone. The initial improvement was better maintained with continued treatment on risperidone than after switching to placebo. During the double-blind maintenance phase, the difference between risperidone and placebo was significant in favor of risperidone for the subscores of conduct disorder ($p<0.001$), hyperactive ($p=0.007$), compliant/calm ($p<0.001$) and adaptive social ($p=0.006$).

Profiles of CGI-severity scores were similar to those of the N-CBRF conduct disorder subscale: significant improvements were observed during the acute phase of the study when all subjects received risperidone. This effect was better maintained with continued treatment on risperidone versus switching to placebo ($p<0.001$). Scorings on CGI-change (compared to condition at baseline of double-blind) also confirmed that the initial treatment effect after acute treatment with risperidone was better maintained when continuing on risperidone than when switching to placebo treatment ($p<0.001$).

The profiles of the other N-CBRF subscales followed a similar pattern as that of the conduct disorder subscale: improvements during the acute phase of the study when all subjects received risperidone. The initial improvement was better maintained with continued treatment on risperidone than after switching to placebo.

For the majority of all treated subjects, the most troublesome symptom on the Visual Analogue Scale (VAS) fell into the categories aggression and oppositional defiant. Scorings on the most troublesome symptoms of aggression and oppositional defiant behavior and Children's Global Assessment Scale (C-GAS) also confirmed that the initial beneficial effect after acute treatment with risperidone was better maintained when continuing on risperidone than switching to placebo treatment (VAS $p=0.010$ and C-GAS $p<0.001$). There were significant improvements in functioning observed in all subjects with 9 months of continuous risperidone treatment. Exploration of possible prognostic factors (sex, age, hospitalization at study start, diagnosis, IQ, baseline score, phase 2 dose) did not reveal an effect of any factor on either time to relapse, relapse rate or change in conduct problem subscale.

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SAFETY RESULTS: Risperidone was safe and well-tolerated when dosed in the range of 0.25-0.75 mg/day for subjects weighing <50 kg and 0.5-1.5 mg/day for subjects weighing ≥50 kg. There were no new or unexpected adverse events reported during any phase of the study. Most treatment-emergent serious adverse events occurred during the acute treatment phase (14 subjects) with only 2 events reported during continuation treatment. During the maintenance phase, 5 placebo- and 6 risperidone-treated subjects reported a serious adverse event. During the acute treatment phase, 5 subjects reported a treatment-emergent serious adverse event of aggressive reaction and 3 subjects reported condition aggravated. Otherwise, serious adverse events during all phases of treatment were not reported in more than 2 subjects.

During 12 weeks of combined acute and continuation risperidone treatment, 18 (3.4%) treated subjects had treatment-emergent adverse events that led to discontinuation of treatment. During 6-months of maintenance treatment, 3 (1.7%) risperidone- and 1 (0.6%) placebo-treated subjects had onset of a treatment-emergent adverse event that led to discontinuation of study treatment. Additionally, 4 subjects (3 placebo and 1 risperidone) discontinued maintenance treatment as a result of adverse events with onset during the acute or continuation phases. No individual adverse event associated with discontinuation was reported in more than 2 subjects.

The incidence of treatment-emergent EPS-related adverse events was low. There were no reports of tardive dyskinesia. Incidence of somnolence was greatest during the initial 2 weeks of risperidone treatment and decreased in incidence with continued treatment with risperidone. Modest increases in weight and BMI were seen in risperidone-treated subjects compared to placebo-treated subjects. Weight changes, based upon z-scores over time, stabilized after the first 12 weeks of treatment through Week 36 and did not increase beyond normal. Weight gain disappeared when subjects were switched from risperidone to placebo at the end of Week 12. Development as assessed by Tanner staging and height measurements progressed at a normal rate.

There were no glucose-related adverse events reported and no subject met criteria for diabetes in this study.

Risperidone treatment was associated with increases in mean prolactin levels. Increases were transient and peaked after 12 weeks of risperidone treatment; values then decreased in all groups regardless of age and sex. There were no discontinuations because of high prolactin levels. Clinical symptoms potentially related to high prolactin levels were uncommon. There were no consistent changes in testosterone levels and no correlation between prolactin and testosterone levels observed. Mean changes in other clinical laboratory values, ECG data and vital signs during risperidone treatment were generally unremarkable.

CONCLUSION: The results of study CR002020 demonstrated that treatment with risperidone had a beneficial acute and maintenance effect on disruptive behavioral symptoms and prevented symptom relapse in children and adolescents of average intelligence with conduct and other disruptive behavior disorders.

A review of adverse events, laboratory results, vitals signs, ECG data, and cognitive test results showed that up to 9 months of treatment with risperidone was safe and well tolerated in this population of children and adolescents with conduct disorders.

Date of the report: 5 November 2004

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