

SYNOPSIS

<u>NAME OF SPONSOR/COMPANY:</u> Johnson & Johnson Pharmaceutical Research & Development, L.L.C. <u>NAME OF FINISHED PRODUCT:</u> Risperidone <u>NAME OF ACTIVE INGREDIENT(S):</u> Risperidone (R064766)	<u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u> Volume: Page:	<u>(FOR NATIONAL AUTHORITY USE ONLY)</u>
Protocol No.: CR002149		
Title of Study: Risperidone in the treatment of children and adolescents with conduct and other disruptive behavior disorders – an open label follow-up trial of CR002020.		
Coordinating Investigator: Paz Toren, M.D., Mental Health Community Center, 9 Hatzvi St., Tel Aviv 67197 Israel		
Publication (Reference): None		
Study Initiation/Completion Dates: 10 January 2002 to 17 July 2004	Phase of development: 3	
Objectives: The primary objective was to accumulate long-term safety data of risperidone as maintenance therapy in children and adolescents with conduct and other disruptive behavior disorders, in an open study designed to follow, for a period of 1 year, subjects who completed or discontinued the double-blind treatment phase of CR002020 after meeting the relapse criteria. The secondary objective was to collect and evaluate long-term efficacy data for risperidone 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).		
Methodology: This was an open label, international, multicenter study in children and adolescents aged 5 to 17 years with conduct or other disruptive behavior disorders who completed the double-blind phase of study CR002020, or who had dropped out during the double-blind phase, after meeting the relapse criteria. The total study duration was one year.		
Number of Subjects (planned and analyzed): Two hundred and thirty-three subjects entered this study; 232 were treated. Children and adolescents aged 5 to 17 years at the time of entry to CR002020, including average IQ with conduct and other disruptive behavior disorders were treated with flexible dose risperidone for up to 1 year.		
Diagnosis and Main Criteria for Inclusion: At entry to CR002020, subjects met DSM-IV criteria for a diagnosis of conduct disorder (312.8), oppositional defiant disorder (313.81), or disruptive behavior disorder not otherwise specified (312.9). The presence of ADHD was not exclusionary for entry.		

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Inclusion Criteria Subjects who met all of the following criteria were eligible for this study: <ul style="list-style-type: none"> Completed CR002020 (including the final evaluation), or discontinued CR002020 during phase 3 (double-blind) after meeting the relapse criteria and completed a final evaluation; No more than 7 days elapsed between last medication intake in CR002020 and the start of the CR002149; Provided informed assent and signed an assent form if capable. In addition, the subject's parents/legal guardians were to provide informed consent and signed an informed consent document; A responsible person (primary caregiver) must have been 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, metabolic disturbances), acute, unstable and/or significant and untreated medical illnesses (e.g. infection, unstable diabetes, uncontrolled hypertension); Was otherwise physically healthy on the basis of a physical examination, medical history, anamnesis, electrocardiogram (i.e. no clinically significant ECG abnormalities) and the results of blood biochemistry tests, hematology tests, and a urinalysis carried out 7 days or less before study entry. 		
Test Product, Dose and Mode of Administration, Batch No.: Risperidone was supplied as a 1-mg/mL oral solution. (Batch numbers 00H16/027, 00H17/648, 01C30/276, and 02BB/143) and was administered using a graduated pipette. It was administered once daily in the morning, but could be administered once daily in the evening or as twice-daily divided doses if indicated (e.g., due to sedation, breakthrough symptoms). Since the blind was unbroken from CR002020, the initial doses for all subjects were titrated. 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 mg/day (subjects ≥50 kg) or 0.25–0.75 mg/day (subjects <50 kg) was administered from Day 5. In exceptional cases (e.g. subject weighing 49 kg), subjects may have needed more than 0.75 mg/day. Under no conditions could the daily dose exceed 1.5 mg/day.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable		
Duration of Treatment: One year		
Criteria for Evaluation: The end point evaluation for CR002020 served as the baseline for CR002149. <u>Pharmacokinetics:</u> Not applicable, no pharmacokinetic samples were taken. <u>Efficacy:</u> 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 Weeks 2, 4, 8, and 12, and Months 6, 9, and 12, or the subject's end point visit. C-GAS assessments were performed at Month 12 or the subject's end point visit. <u>Safety:</u> Safety parameters included adverse events, clinical laboratory tests, vital signs, ECG, physical examinations, Tanner staging, height and body weight. <u>Pharmacokinetic/Pharmacodynamic Relationships:</u> Not applicable.		

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<p>Statistical Methods: Descriptive statistics summarize demographic and double-blind and open-label baseline data and extent of exposure information. The changes from both baselines were summarized with descriptive statistics for most efficacy and safety parameters. The emphasis in this report is on the changes from the open-label baseline.</p> <p>Efficacy: The intent-to-treat (ITT) analysis set was used in all efficacy analyses, based on all subjects who received at least 1 dose of study medication. The changes from both baselines were summarized with descriptive statistics for N-CBRF total score and subscales, VAS-MS, CGI-S, and C-GAS scores. The results are provided for the observed case data and using the last-observation-carried-forward (LOCF) approach.</p> <p>Safety: Safety analyses were performed for all subjects who received at least 1 dose of study treatment. 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 both baselines in vital signs, laboratory tests and ECG were summarized with descriptive statistics. Changes from both baselines in weight, height, and body mass index were summarized with descriptive statistics transformed to z-scores.</p> <p>SUMMARY - CONCLUSIONS</p> <p>PHARMACOKINETICS: Not applicable.</p> <p>EFFICACY RESULTS: The results from the conduct disorder subscale score on the N-CBRF and the CGI-severity scale demonstrate that continued improvements of disruptive behavioral symptoms with risperidone were achieved and maintained for up to 12 additional months.</p> <p>Scorings on the most troublesome symptoms (VAS) of aggression and oppositional defiant behavior and C-GAS also indicate that the beneficial effect after treatment with risperidone was further improved and maintained. Functioning, as assessed by the C-GAS, approached normal levels after 12 months of treatment.</p> <p>Relapsed status at the conclusion of CR002020 correlated to worse mean baseline severity scores across all measures and subsequently greater overall improvement versus non-relapsers.</p> <p>In general, the mean scores approximately 2 weeks post-open-label baseline were similar regardless of whether subjects had been randomized to placebo or risperidone, or had been relapsers on nonrelapsers, in the double-blind phase of CR002020. This suggests that subjects were not refractory to treatment with risperidone and could benefit from re-challenge.</p>		

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<p><u>SAFETY RESULTS:</u> 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 the study and there were no deaths. The most common reason for study discontinuation was withdrawal of consent in 19 (8%) subjects followed by insufficient response (15 subjects, 6%) and non-compliance (11 subjects, 5%). Eight (3%) subjects discontinued due to an adverse event. Treatment-emergent serious adverse events occurred in 20 (8.6%) subjects during open-label risperidone treatment. The incidence of serious adverse events was similar between the PLA/RIS and RIS/RIS groups. Ten subjects (5 PLA/RIS and 5 RIS/RIS) reported a treatment-emergent serious adverse event of condition aggravated. Otherwise, serious adverse events were not reported in more than 2 subjects in either group. Treatment-emergent adverse events led to discontinuation of treatment for 8 (3.4%) subjects (5 PLA/RIS and 3 RIS/RIS). No individual adverse event associated with discontinuation was reported in more than 2 subjects.</p> <p>Suicide attempt was reported as an adverse event for 2 (1.7%) PLA/RIS and 1 (0.9%) RIS/RIS subject. For 2 of these 3 subjects with events coded to 'suicide attempt', the investigator verbatim was 'suicidal ideations' and 'suicide thoughts', not actual suicide attempts.</p> <p>The incidence of treatment-emergent EPS-related adverse events was low (10 subjects, 4.3%) although higher in the PLA/RIS group (6 subjects, 5.1%) than the RIS/RIS group (4 subjects, 3.5%). There were no adverse events of tardive dyskinesia.</p> <p>When z-score corrections were applied, weight changed for all subjects by a mean of 0.04, height by a mean of 0.07 and BMI by a mean of -0.02 from open-label baseline to end point. Therefore, subjects continued to grow at a normal rate throughout the study when these data were compared to population norms for children and adolescents. Subjects treated with double-blind placebo had a mean increase in weight z-scores of 0.11 (SD 0.4) while subjects from the RIS/RIS group had a weight decrease of -0.04 (SD 0.3) from open-label baseline. A transient increase in weight by z-scores was seen in placebo-treated subjects when open-label risperidone was initiated. The initial weight increase occurred through Month 3 and thereafter remained stable.</p> <p>Most subjects were at Tanner stage 1 at open-label baseline but as expected in this age group, there was a trend toward increased sexual maturity throughout the study. Development as assessed by Tanner staging and height measurements progressed at a normal rate.</p> <p>There were no glucose-related adverse events reported and no subject met criteria for type 2 diabetes mellitus based on current ADA guidelines. The combined data on glucose, insulin, and lipids indicate no evidence of an increased risk of metabolic syndrome in this population with 1-year of risperidone treatment.</p> <p>Risperidone treatment was associated with increases in mean prolactin levels. Increases were transient and peaked by Month 6 of open-label risperidone treatment; values then decreased in all groups regardless of sex. Overall, 37% of subjects (46% PLA/RIS and 25% RIS/RIS) had prolactin values that were normal at open-label baseline and outside of pathological ranges at some point during the study. During the 1-year open-label risperidone treatment, 3 (1.3%) of 232 treated subjects (2, 1.7% PLA/RIS and 1, 0.9% RIS/RIS) reported a treatment-emergent potentially prolactin-related adverse event; no subject had elevated prolactin levels at onset of the adverse event. There were no discontinuations because of elevated prolactin levels. There were no consistent changes in testosterone levels. Mean changes in other clinical laboratory values, ECG data and vital signs during risperidone treatment were generally unremarkable.</p> <p><u>PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:</u> Not applicable.</p>		

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<p><u>CONCLUSION:</u> In study CR002149, a review of adverse events, laboratory results including endocrine tests, vitals signs, and ECG data showed that up to 1 year of treatment with risperidone was safe and well tolerated in this population of children and adolescents with conduct disorders and other disruptive behavior disorders. There were no new or unexpected safety findings.</p> <p>In addition, treatment with risperidone continued to show beneficial effects on a wide variety of disruptive behavioral symptoms in children and adolescents of average intelligence with conduct and other disruptive behavior disorders for a period of 1 year.</p> <p>Date of the report: 23 MAY 2005</p>		

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