

SYNOPSIS

<u>NAME OF SPONSOR/COMPANY:</u> Janssen-Ortho Inc.	<u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u> Volume: Page:	<u>(FOR NATIONAL AUTHORITY USE ONLY)</u>
<u>NAME OF FINISHED PRODUCT:</u> Risperdal®		
<u>NAME OF ACTIVE INGREDIENT(S):</u> Risperidone (R 064766)		
Protocol No.: RIS-CAN-23		
Title of Study: Efficacy and Safety of Risperidone in the Treatment of Children with Autistic Disorder and Other Pervasive Developmental Disorders: A Canadian, Multicenter, Double-Blind, Placebo-Controlled Study		
Coordinating/Principal Investigator: [REDACTED] M.D. – [REDACTED] Canada		
Publication (Reference): N/A		
Study Initiation/Completion Dates: 10 Aug 1999 to 04 Dec 2001		Phase of development: 3
Objectives: The primary objective of the study was to assess the superiority of risperidone oral solution 0.02 to 0.06 mg/kg/day over placebo in the treatment of behavioral symptoms in children with Autistic Disorder and other pervasive developmental disorders (PDD) aged 5 to 12 years inclusive.		
Methodology: This was a randomized, double-blind, parallel-group, multicenter study to assess the safety and efficacy of risperidone versus placebo in the treatment of symptoms of Autistic Disorder and other PDDs in children aged 5 to 12 years inclusive.		
Number of Subjects (planned and analyzed): A total of 106 subjects were planned to be enrolled with a minimum of 8 subjects per center to provide 74 evaluable subjects assuming 30% discontinuation rate. Eighty subjects (41 and 39 subjects in the risperidone and placebo groups, respectively) were randomized in the study. Seventy-nine subjects received at least one dose of study medication and were analyzed: 40 subjects and 39 subjects in the risperidone and placebo groups, respectively. Fifty-five (69.6%) of the subjects in this study were diagnosed with Autistic Disorder (28 and 27 subjects in the placebo and risperidone groups, respectively).		
Diagnosis and Main Criteria for Inclusion: <ol style="list-style-type: none"> Subjects aged between 5 and 12 years. DSM-IV Axis I diagnosis of Pervasive Developmental Disorders with a total score of ≥ 30 on the Childhood Autism Rating Scale with or without mental retardation. Verbal assent from the child and, if capable, signed the informed consent. Child's parent, guardian or legal representative signed the informed consent form. A responsible parent or caregiver was available to accompany the subject on each assessment day, could provide reliable information for the rating scales, and could reliably and accurately dispense the study medications as directed. 		
Test Product, Dose and Mode of Administration, Batch No.: Risperidone 1 mg/mL oral formulation. Starting dose was 0.01 mg/kg/day orally, Reference # 329714 (included Lot No. 97F24/918 [1 mg/mL] with expiry date January 2000) and # 333656 (included Lot No. 99A18/672 [1 mg/mL] with expiry date December 2001).		
Reference Therapy, Dose and Mode of Administration, Batch No.: Identical placebo 0 mg/mL oral formulation. Reference # 329714 (included Lot No. 97A29/F71 [0 mg/mL] with expiry date January 2000) and # 333656 (included Lot No. 98L16/F71 [0 mg/mL] with expiry date December 2001).		
Duration of Treatment: 8 weeks		
Criteria for Evaluation: <u>Pharmacokinetics:</u> Not applicable		

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<p><u>Efficacy:</u> The primary efficacy parameter was the change from baseline to end point in the Irritability subscale of the Aberrant Behavior Checklist (ABC).</p> <p>The secondary efficacy parameters were the changes from baseline to end point as measured on the following scales:</p> <ol style="list-style-type: none"> 1. ABC subscales – Hyperactivity/Non-compliance, Lethargy/Social Withdrawal, Stereotypic Behavior, and Inappropriate Speech. 2. CGI-C – change in clinical global impression of severity. 3. N-CBRF (Parent Version) subscales – Conduct Problem, Insecure/Anxious, Hyperactivity, Self-injury/Stereotypic, Self-isolated/Ritualistic, Overly Sensitive, Adaptive social, and Compliant/Calm 4. VAS – most troublesome symptom. 5. Global behavioral response based on $\geq 50\%$ decrease in behavioral symptoms in at least 2 of the 5 ABC subscales with no worsening ($\geq 10\%$ increase) in the other subscales. <p><u>Safety:</u> The safety of the study drug was assessed by adverse events profiling, clinical laboratory tests, vital signs and physical examination, body weight, electrocardiogram and the Extrapyramidal Symptom Rating Scale (ESRS).</p> <p><u>Pharmacokinetic/Pharmacodynamic Relationships:</u> Not applicable (no blood samples for drug plasma levels were taken).</p>		
<p>Statistical Methods: Intent-to-treat (ITT) population was used for all analysis.</p> <p>Efficacy: Change from baseline in ABC subscales, N-CBRF subscales, and VAS of most troublesome symptom 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 at every post-baseline time point and 8-week end point: CMH mean scores test using modified ridit scores (Van Elteren’s test). Overall behavioral response (based on all 5 ABC subscales) at every post-baseline time point and the 8-week end point: CMH test for general association controlling for site.</p> <p>Safety: Adverse events: Number and percentage of patients with adverse event by group. Change from baseline in vital signs, body weight, and ESRS: Descriptive statistics and percentage of patients exceeding pre-defined limits. Between-group comparisons by ANOVA model including treatment group and site as factors; for ESRS, Van Elteren’s test controlling for site. Laboratory safety: descriptive statistics and percentage of patients exceeding pre-defined limits.</p> <p>SUMMARY - CONCLUSIONS</p> <p><u>PHARMACOKINETICS:</u> Not applicable</p> <p><u>EFFICACY RESULTS:</u> Significant differences in the Irritability subscale of ABC between the 2 treatment groups were detected. At end point, a 12.1 ± 5.81 (SD) decrease from baseline was observed in the risperidone group, compared to a 6.5 ± 8.41 (SD) decrease in the placebo group ($p < 0.001$).</p> <p>In addition, risperidone showed statistically significant differences compared to placebo on all other ABC subscales in improving Hyperactivity/noncompliance, Inappropriate speech, Lethargy/social withdrawal, and Stereotypic behavior as well as on overall response (“responder analysis”) as measured by the ABC. Statistically significant differences in favor of risperidone were also observed at end point in the Conduct problem subscale of the N-CBRF ($p = 0.001$), VAS rating of the most troublesome symptom ($p = 0.036$) and in the CGI-C ($p < 0.001$). Somnolence did not affect efficacy since there was a similar effect size on the ABC Irritability subscale irrespective of the presence/absence of somnolence.</p> <p><u>SAFETY RESULTS:</u> All 40 subjects (100%) in the risperidone group and 31 (79.5%) in the placebo group reported at least one adverse event during the study. The most frequently reported adverse event was somnolence in the risperidone group (72.5%) and aggressive reaction in the placebo group (20.5%). In 18 of the 29 risperidone</p>		

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<p><u>SAFETY RESULTS:</u> (continued)</p> <p>subjects with somnolence, somnolence was resolved either by dividing the daily dose into bidaily intakes (N = 6), or by shifting study drug administration from morning to evening (N = 12).</p> <p>There were no deaths reported during the study. Three serious adverse events were reported: 2 in the risperidone group (appendicitis; extrapyramidal symptoms due to study drug overdose) and 1 in the placebo group (study drug overdose).</p> <p>Hematology, blood chemistry and urinalysis parameters were similar between treatment groups. Vital signs and physical examination findings showed significant increases from baseline at end point in the risperidone group compared to placebo in mean pulse rate (baseline 90.2 bpm + 8.9 bpm vs. baseline 95.0 bpm – 0.6 bpm, respectively; p = 0.003) and systolic blood pressure (+ 4.0 mmHg vs. – 0.7 mmHg, respectively; p = 0.009). A significant (p = 0.001) increase in mean weight was observed at end point in the risperidone group (+2.7 kg) compared to the placebo group (+1.0 kg). There were no clinically meaningful differences between treatment groups with regard to ECG parameters.</p> <p>Eleven subjects (27.5%) in the risperidone group and 5 subjects (12.8%) in the placebo group had EPS-related adverse events or EPS-related symptoms. No statistically significant change from baseline in the total score of ESRS was observed between the two groups.</p> <p><u>PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:</u> Not applicable</p> <p><u>CONCLUSION:</u></p> <p>The results of this study demonstrate that risperidone administered orally at an average daily dose of 0.04 mg/kg/day significantly improves symptoms of Autistic Disorder or other PDDs and is well-tolerated in children 5 - 12 years of age.</p> <ul style="list-style-type: none"> – Risperidone was statistically superior to placebo in reducing irritability in children with Autistic Disorder or other PDDs as measured by the Irritability subscale of the ABC. – Risperidone significantly improved symptoms of Autistic Disorder or other PDDs as measured by the Hyperactivity/noncompliance, Inappropriate speech, Lethargy/social withdrawal, and Stereotypic behavior subscales of the ABC, and the Behavioral disturbances of conduct subscale of the N-CBRF. – The majority of subjects in this study were diagnosed with Autistic Disorder, and the results of treatment with risperidone are relevant for this major subtype of the total PDD population. The differences between risperidone and placebo in the Irritability, Lethargy, and Hyperactivity subscales in the Autistic Disorder subgroup were significant (p<0.05); between-treatment differences for Stereotypic Behavior and Inappropriate Speech were marginally significant (p<0.06) due to the smaller sample sizes in the Autistic Disorder subgroup. – Risperidone was well tolerated, and its safety profile was comparable to previous studies with risperidone. Somnolence was the most frequently reported adverse event in the risperidone group. In the majority of the cases, somnolence resolved spontaneously or by adjusting the dosing schedule/dose. Although there were more EPS-related adverse events or EPS-related symptoms in the risperidone group, the change in the total ESRS scores was comparable between the 2 groups. – A significant increase in systolic blood pressure and pulse rate was observed at end point in the risperidone group compared to placebo group. A significant increase in body weight was also reported in the risperidone group at end point. The clinical relevance of these increases was considered to be minor. <p>Date of the report: 31 January 2006</p>		