SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development*
Name of Finished Product	RISPERDAL®
Name of Active Ingredient	R064766 (risperidone)

Protocol No.: RIS-AUT-4002 CR014740

Title of Study: Risperidone in the Treatment of Children and Adolescents With Autistic Disorder: A Double-Blind, Placebo-Controlled Study of Efficacy and Safety, Followed by an Open-Label Extension Study of Safety.

NCT No.: NCT00576732

Clinical Registry No.: CR014740

Principal Investigator: Michael Aman, PhD

Publication (Reference): None

Study Period: 3 December 2007 to 9 March 2010

Phase of Development: 4

Objectives: The primary efficacy objective of the 6-week double-blind phase of the study was to assess the efficacy of 2 dose levels of risperidone in the treatment of irritability and related behaviors associated with Autistic Disorder in children and adolescents as measured by the Aberrant Behavior Checklist–Irritability (ABC-I) Subscale.

Major secondary efficacy objectives of the double-blind phase were to evaluate the efficacy of risperidone compared with placebo as measured by: (1) ABC-I response rate (≥25% improvement from double-blind baseline); (2) Change from double-blind baseline in Clinical Global Impression of severity (CGI-S); and (3) Percent of subjects with much or very much improvement based on the Clinical Global Impression of Change (CGI-C) at the double-blind endpoint. The continued efficacy of risperidone was assessed during the 6-month open-label phase.

The safety objectives for both phases of the study were: Overall safety of risperidone in children and adolescents with autism; Effects of risperidone on glucose homeostasis, including fasting glucose, fasting insulin, and insulin resistance, as measured by the homeostatic model assessment (HOMA); Effects of risperidone on other metabolic laboratory parameters including fasting triglycerides, fasting cholesterol, and full lipid profile; Effects of risperidone on laboratory parameters associated with the growth hormone axis (insulin-like growth factor-1 [IGF-1] and insulin-like growth factor binding protein-3 [IGF-BP-3]); Effects of risperidone on nighttime sleep quality and daytime drowsiness as measured by visual analog scales (VAS); Effects on growth, weight, and sexual maturation. In the double-blind phase of the study, an additional safety objective was to evaluate the overall safety of risperidone versus placebo in children and adolescents with autism.

Plasma concentrations of risperidone and 9-hydroxy-risperidone were determined at Week 6 as a measure of exposure.

Methods: This was a Phase 4, randomized, double-blind, placebo-controlled fixed-dose, multi-site study, followed by a 6-month (26-week), flexible-dose, open-label extension, to evaluate the efficacy and safety of risperidone in subjects 5 to 17 years of age with a diagnosis of Autistic Disorder. Randomization was stratified by site and baseline weight (20 to <45 kg or ≥45 kg). The study examined 3 parallel treatment groups: placebo, risperidone low dose (0.125 mg/day for subjects 20 to <45 kg; 0.175 mg/day for subjects ≥45 kg), and risperidone high dose (1.25 mg/day for subjects 20 to <45 kg; 1.75 mg/day for subjects ≥45 kg). Subjects who completed the 6-week double-blind phase, or

were withdrawn from the double-blind phase after ≥3 weeks for reasons other than tolerability, were eligible to enter a 6-month open-label risperidone treatment phase.

Number of Subjects (planned and analyzed): Approximately 120 subjects were planned to be enrolled in this study to ensure that 93 subjects were randomly assigned into the double-blind treatment phase (approximately 31 subjects per treatment group).

Analyzed**:** A total of 145 subjects were enrolled, all in the US, of which 96 subjects from 16 sites (consolidated to 9 pooled centers for analysis) who met the inclusion and exclusion criteria as per protocol were randomized in the double-blind phase (placebo group n=35, risperidone low dose group n=30, risperidone high dose group n=31). All randomized subjects received at least 1 dose of study drug. Seventy-nine of the 96 randomized subjects entered the open-label phase.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, between 5 and 17 years of age (inclusive), with a body weight of at least 20 kg, DSM-IV diagnosis of Autistic Disorder (299.00), corroborated by standard cut-off scores on the Autism Diagnostic Interview-Revised, ABC-I Subscale score of 18 or more, CGI-S of 4 or more (ie, at least moderate severity), mental age more than 18 months, in good physical health, no history of prior or current DSM-IV psychotic disorders, no history of pervasive developmental disorder not otherwise specified, no history of Asperger's or Retts, no neurologic disorders, and no history of existing moderate or severe extrapyramidal symptoms (EPS) or tardive dyskinesia, were enrolled in this study. Before entering the open-label extension phase of the study the subject had either completed the 6-week double-blind, placebo-controlled phase, or had discontinued from the double-blind phase after at least 3 weeks for reasons other than tolerability; and who needed risperidone treatment in the judgment of the investigator.

Test Product, Dose and Mode of Administration, Batch No.: Risperidone was administered as an oral solution once-daily in the morning (or evening, if sedation occurred in the morning), for 6 weeks (or until early withdrawal, if applicable), during the double-blind phase of the study. During the double-blind phase, subjects randomized to receive risperidone were administered with either 0.1 mg/mL or 1.0 mg/mL oral solution of risperidone depending on their baseline weight: risperidone low dose (0.125 mg/day for subjects 20 to <45 kg; 0.175 mg/day for subjects ≥45 kg), and risperidone high dose (1.25 mg/day for subjects 20 to <45 kg; 1.75 mg/day for subjects ≥45 kg).

During the open-label extension phase, risperidone was administered as oral tablets (supplied as 0.25, 0.5, and 1 mg white tablets) for 26 weeks (or until early withdrawal, if applicable). Two flexible dose regimens of risperidone were applied as determined by the subject's weight class and were titrated to acceptable tolerability and effectiveness. The allowable dose ranges in the open-label phase were 0.125 to 1.25 mg/day for subjects with a baseline weight of 20 to <45 kg, and 0.175 to 1.75 mg/day for subjects with a baseline weight of ≥45 kg.

Batch numbers: 0.25 mg oral tablet = 07B01/F070; 0.5 mg oral tablet = 07B07/F009; 1.0 mg oral tablet = 07C05/F005; 0.1 mg/mL oral solution = 07D05/F118.

Reference Therapy, Dose and Mode of Administration, Batch No.:

The placebo solution for oral administration was identical in appearance and smell compared with the risperidone solutions, and contained no active drug.

Batch number: Risperidone 0 mg/mL oral solution = 07F01/F071.

Duration of Treatment: The total duration of the study, including the 3 phases (up to 3 weeks of screening, 6 weeks double-blind treatment, and 26 weeks of open-label treatment), was approximately 35 weeks.

Criteria for Evaluation:

Efficacy evaluations: The primary efficacy parameter was the change from baseline to endpoint of the double-blind phase (last non-missing, post-baseline assessment of the double-blind phase) on the ABC-I Subscale (rated by the parent or primary caregiver under guidance of the investigator). Secondary efficacy parameters included the changes from baseline on the ABC-I Subscale at other

timepoints of the double-blind and open-label extension phases. ABC-I response rate (≥25% improvement from baseline) and the changes from baseline on the other ABC Subscales, CGI-C, CGI-S, and the compulsions subscale of the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) were assessed at each visit and at endpoint during the double-blind and the open-label extension phases.

Pharmacokinetic evaluations: Two venous blood samples (4 mL each) for determination of the plasma concentrations of risperidone and 9-hydroxy-risperidone were obtained at Week 6. Plasma concentrations of risperidone and 9-hydroxy-risperidone were determined using a validated bioanalytical method.

Safety evaluations: Safety was assessed on the basis of adverse events, serious adverse events, laboratory evaluations (including fasting glucose, insulin, triglycerides, cholesterol, IGF-1, IGF-BP-3, HOMA-IR, TSH, thyroxine, prolactin); electrocardiogram (ECG); vital signs; physical examination (including Tanner staging, body weight, and height); EPS as assessed using the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Rating Scale (BARS), and the Simpson-Angus Rating Scale (SARS); VAS for Nighttime Sleep Quality and Daytime Drowsiness.

Statistical Methods:

Sample Size Determination: Twenty-nine subjects per treatment group were required, to have 80% power to detect a between-group difference of 6 for the change from baseline to endpoint in ABC-I, assuming a standard deviation of 8, and a 2-sided significance level of 0.05. Assuming that 5% of randomized subjects would have no postbaseline ABC-I assessment, the total number of randomized subjects required was 31 per treatment group. Approximately 120 subjects were planned to be enrolled in this study to ensure that 93 subjects were randomly assigned into the double-blind treatment phase.

No formal sample size calculation was performed for the open-label phase of the study. Subjects who completed the double-blind phase or had discontinued for reasons other than tolerability and completed at least 3 weeks of the double-blind phase, were eligible to enter the open-label phase.

Efficacy Analysis: The efficacy data analyses were performed on all randomized subjects who received at least 1 dose of the double-blind study drug (intent-to-treat [ITT] analysis set). The primary efficacy variable was the change from double-blind baseline in the ABC-I score at double-blind last observation carried forward (LOCF) endpoint. The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with factors for center (after pooling small centers) and baseline weight stratification (<45 kg, ≥45 kg) and baseline ABC-I score as covariate. Two hierarchical null hypotheses (H1 and H2) were defined *a priori*. The hypotheses were tested in sequence. H2 was tested only if H1 was rejected. The null hypotheses were: H1 = No difference between the risperidone high dose group and placebo on the primary efficacy endpoint; H2 = No difference between the risperidone low dose group and placebo on the primary efficacy endpoint.

Pharmacokinetic Analysis: The concentrations of risperidone, 9-hydroxy-risperidone, and the active moiety from the predosing and postdosing plasma samples collected at Week 6 were listed and descriptive statistics were calculated.

Safety Analysis: Safety data were analyzed descriptively. Safety analyses for the double-blind and open-label extension phases were performed using the ITT analysis set. For the analysis of data from the open-label extension phase, change from the baseline of the double-blind phase was calculated in addition to the change from the baseline of the open-label extension phase. Subjects were grouped according to their previous treatment group assignment in the double-blind phase (placebo/RIS, risperidone low dose/RIS, and risperidone high dose/RIS). Results were presented by these subject groups and for the combined group of all subjects.

RESULTS:

DEMOGRAPHIC RESULTS: Seventy-seven (80%) subjects completed the double-blind phase. The most common reasons for withdrawal during the double-blind phase were insufficient response (7%) and subject choice (5%). A higher percentage of subjects in the placebo group discontinued due to insufficient response than in the risperidone groups (17% versus 3% in the risperidone low dose and

0% in the risperidone high dose groups) during the double-blind phase. For subjects who continued into the open-label phase, 56 (71%) subjects completed. The most common reasons for withdrawal during the open-label phase were insufficient response (9%), adverse event (6%), and lost to follow-up (5%). The proportion of subjects who discontinued due to insufficient response during the open-label phase, was similar across treatment groups.

Most of the subjects who entered the double-blind phase were male (88%) and less than 12 years of age (77%). More than 90% of the subjects were antipsychotic naïve before entering the study. The placebo group had a smaller percentage of white subjects (57%) than the risperidone low and high dose groups (70% and 81%, respectively). The risperidone low dose group had a greater percentage of subjects ≥12 years of age (33%) than the placebo and risperidone high dose groups (14% and 23%, respectively). Otherwise, treatment groups were balanced with respect to demographic characteristics. Demographic characteristics of the open-label population were similar to those of the double-blind population and the treatment groups were balanced with respect to demographic characteristics.

PRIOR AND CONCOMITANT THERAPIES: A total of 33 (34.4%) subjects received prior psychotropic medication for autism, with methylphenidate hydrochloride and obetrol being the most frequently used (8 [8.3%] subjects for each). The most common concurrent medications that were prescribed in the double-blind phase were antihistamines followed by anti-inflammatory drugs. Three subjects received methylphenidate during both phases of the study: 2 subjects in the risperidone groups were taking methylphenidate prior to the study and continued its use during the study; 1 subject in the placebo group started methylphenidate during the double-blind phase. During the open-label phase, 21 (70%) subjects in the placebo/RIS group, 14 (58.3%) subjects in the risperidone low dose/RIS group, and 16 (64%) subjects in the risperidone high dose/RIS group received concomitant medications. The most common medications that were prescribed were antibacterials, analgesics, and antihistamines. The 3 subjects receiving methylphenidate in the double-blind phase continued taking methylphenidate into the open-label phase (1 each in the placebo/RIS, risperidone low dose/RIS, and risperidone high dose/RIS treatment groups).

Other psychotropic medications, (classified as psycholeptics; alprazolam, melatonin), were used by 2 subjects in the placebo group during the study. Alprazolam was taken by 1 subject during the double-blind phase and melatonin was taken by 2 subjects over both phases (one of these subjects is the same subject who took alprazolam).

PHARMACOKINETIC RESULTS: Dose-normalized (to 1.25 mg/day) plasma concentrations of the active antipsychotic fraction, risperidone and 9-hydroxy-risperidone, were lower in subjects from the higher body weight class (≥45 kg) compared with subjects from the lower body weight class (20 kg to <45kg). Within each body weight class group, dose-normalized (to 1.25 mg/day) plasma concentrations of the active antipsychotic fraction, risperidone and 9-hydroxy-risperidone, were similar for the risperidone high and risperidone low dose groups.

After body weight correction (to 0.02 mg/kg/day), dose-normalized plasma concentrations of the active antipsychotic fraction, risperidone and 9-hydroxy-risperidone, were similar across all dosing groups.

The average trough and postdose dose-normalized and body weight adjusted plasma concentrations (to 0.02 mg/kg/day) of the active antipsychotic fraction were 4.99 ± 4.07 ng/mL and 19.6 ± 11.7 ng/mL, respectively. These observed plasma concentrations in children are in line with previous observations of the pharmacokinetic study RIS-USA-160.

Based on graphical exploration, no effects of age, creatinine clearance and the corrected glomerular filtration rate were observed on the dose normalized and body weight corrected active antipsychotic fraction trough and postdose concentrations.

EFFICACY RESULTS: There was a statistically significant improvement in the ABC-I subscale in the risperidone high dose group ($p<0.001$), compared with placebo. The difference in LS means between the risperidone high dose group and placebo was -7.9 (2.18) with 95% CI [-12.19;-3.52]. As this comparison was statistically significant, the step-down procedure continued to the risperidone low dose group versus placebo comparison. The difference in LS means between the risperidone low dose group and placebo was -3.0 (2.17) with 95% CI [-7.36;1.27]. The improvement in risperidone low dose

group compared with placebo was not statistically significant (p=0.164) at double-blind endpoint. These findings for the ABC-I subscale confirmed that the risperidone high dose group (1.25 mg/day in subjects weighing 20 to <45 kg; 1.75 mg/day in subjects weighing ≥45 kg) was efficacious and demonstrated assay sensitivity. Evidence that the low-dose level of risperidone (0.125 mg/day in subjects weighing 20 to <45 kg; 0.175 mg/day in subjects weighing ≥45 kg) is efficacious was not established.

The primary efficacy findings were corroborated by the secondary efficacy analyses. A significantly greater percentage of subjects in the risperidone high dose group (p=0.004), but not in the risperidone low dose group (p=0.817), had an improved ABC-I response rate (defined as ≥25% improvement on ABC-I), compared with the placebo group. In other ABC subscales: a significantly greater improvement in hyperactivity was observed at double-blind endpoint for the risperidone high dose group (p=0.019) but not in the risperidone low dose group (p=0.778), compared with placebo; and a significantly greater improvement in stereotyped behavior was observed at double-blind endpoint for the risperidone low dose group (p=0.008) but not in the risperidone high dose group (p=0.068), compared with placebo. Other secondary efficacy measures, including CGI-S, CGI-C, and CY-BOCS, were consistent with the primary efficacy findings, with efficacy seen in the high dose group relative to placebo. Secondary efficacy assessments generally improved among subjects who continued into the open-label phase. Primary and secondary efficacy assessments generally were maintained or continued to improve among subjects who continued into the open-label phase.

SAFETY RESULTS:

There were no deaths in the study. There were 2 SAEs, one each in the double-blind and open-label phases, which resolved and were considered not related to study drug. Overall, TEAEs were consistent with the known profile of risperidone. Treatment-emergent adverse events that led to study discontinuation were reported in 2 subjects in the double-blind phase and 5 subjects in the open-label phase.

With respect to adverse events of interest for antipsychotic drugs, the incidences of somnolence- and fatigue-related adverse events were highest in the risperidone high dose group (55%) in the double-blind phase and were highest in the placebo/RIS group (30%) in the open label phase. The incidence of EPS-related adverse events was highest in the risperidone high dose group during the double-blind phase, with the most commonly occurring adverse event being akathisia (13%). The incidence of EPS-related adverse events was consistent with the known safety profile of risperidone. Two subjects (both girls) experienced treatment emergent potentially prolactin-related adverse events during the study (i.e., oligomenorrhoea and menstruation irregular, respectively). The potentially prolactin-related adverse events were not SAEs and no action was taken with respect to study drug. The potentially prolactin-related adverse events were consistent with the background rates of such events in females of this age group. The incidence of glucose metabolism-related adverse events reported during the double-blind phase (increased appetite, weight increased, and thirst), was highest in the risperidone high dose group (35%, 13%, and 6%, respectively). For subjects who continued into the open-label phase, the incidence of these events was highest in patients who had previously been administered placebo in the double-blind phase. None of the glucose metabolism-related adverse events were considered as SAEs during the study and only 1 event led to treatment discontinuations (Weight increased in a subject in the placebo/RIS group).

There was no significant difference between the treatment groups in change from baseline for insulin resistance. There were no clinically meaningful increases in mean fasting glucose levels or cholesterol, LDL, or HDL levels from baseline to double-blind endpoint following treatment with risperidone. Very few subjects had treatment-emergent markedly abnormal glucose, insulin, or lipid values during the double-blind treatment phase, and there were no clinically meaningful differences between the treatment groups. In general, mean fasting glucose, insulin and HOMA-IR increased further during the open-label phase before plateauing. The only exception to this plateauing effect was observed in patients who had previously received placebo during the double-blind phase as their mean fasting glucose values continued to increase up to the open-label endpoint.

Analysis of IGF-1 and IGF-BP-3(a carrier protein for IGF-1) showed that mean IGF-1 increased over time in all treatment groups from the double-blind baseline to the open-label endpoint, consistent with the known effects of risperidone. Shifts to markedly abnormal values were few and did not show any consistent dose response or difference from placebo. Prolactin increases occurred in both dosage groups and were consistent with the known profile of risperidone. Increase in mean alkaline phosphatase levels from the double-blind baseline to double-blind endpoint was observed in the risperidone high dose group compared with the risperidone low dose group and placebo group. Alkaline phosphatase levels continued to increase in the risperidone high dose/RIS group compared with risperidone low dose/RIS, and placebo/RIS group in subjects who continued in the open-label phase. There was a mean increase in creatine kinase in the 2 risperidone dose groups; while the placebo group showed a mean decrease in creatine kinase during the double-blind phase.

Mean pulse rate and systolic blood pressure increased in the risperidone high dose (5.8 bpm and 2.5 mmHg, respectively) and low dose groups (3.4 bpm and 1.0 mmHg, respectively) at the double-blind endpoint but did not continue to increase over a longer treatment period for subjects who continued into the open-label phase (and had both double-blind baseline and open-label endpoint assessments). Shifts to markedly abnormal values did not show a consistent dose response at double-blind endpoint, and there was no apparent worsening in the incidence of markedly abnormal values at open label endpoint. There were no clinically relevant changes observed during ECG assessment. The data from vital signs and ECG assessments were consistent with the known safety profile of risperidone.

Increased mean body weight and BMI, and mean body weight and BMI z-scores were observed from baseline to endpoint. The increases followed a similar pattern as observed in previous studies with risperidone (ie, initial increases followed by a plateau during extended treatment). Height z-scores were within the expected range throughout the study. Sexual maturity, as assessed by Tanner stage, was within the expected range throughout the study, with the majority of subjects remaining in the same Tanner stage, and the remainder increasing by 1 Tanner stage from double-blind baseline to open-label endpoint. There were no noteworthy differences in change from baseline in Tanner staging between the 3 treatment groups. There was minimal to no effect on EPS as assessed by AIMS, BARS, and SARS. Improvements were seen in nighttime sleep quality following risperidone treatment. There was no clear difference observed between the risperidone groups and the placebo group on daytime somnolence.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSION:

In this fixed-dose study, the risperidone high dose group (1.25 mg/day or 1.75 mg/day, depending on weight class) was effective in the treatment of irritability and related behaviors associated with Autistic Disorder in children and adolescents, as measured by the primary efficacy endpoint and corroborated by the secondary efficacy analyses. Efficacy of risperidone high dose continued to improve among subjects who continued into the 6-month open-label extension phase. Efficacy was not demonstrated in the risperidone low dose group (0.125 mg/day or 0.175 mg/day, depending on weight class) relative to placebo. Subjects randomly assigned to the low dose group received doses of risperidone lower than the current recommended and labeled dose for this indication. In view of the findings for the lower doses studied, no change is warranted to the current posology of risperidone for children and adolescents with Autistic Disorder.

Safety data, including results on glucose homeostasis, metabolic parameters, and growth and sexual maturation, were consistent with the known profile of risperidone as described in the current safety information for risperidone and in previous studies with risperidone in subjects with Autistic Disorder and/or conduct and other disruptive behavior disorders. The adverse events observed in this study are listed or there are similar adverse event terms listed in the current safety information for risperidone.

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