U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 20272/S-065, 20588/S-053, 21444/S-041
Drug Name:	Risperdal®
Indication(s):	Autism in Children and Adolescents
Applicant:	Janssen Pharmaceuticals, Inc
Date(s):	Stamp Date: Oct 5, 2011
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Jinglin Zhong, Ph.D.
Concurring Reviewers:	Peiling, Yang, Ph.D.; H.M. James Hung, Ph.D.
Medical Division:	Division of Psychiatry Products
Clinical Team:	Cheri Lindberg, M.D.; Robert Levin, M.D.
Project Manager:	Ann Sohn, Pharm.D.

Keywords:

double blind, clinical studies, , mixed models, endpoint analysis/LOCF, stratification, intent-to-treat, multi-center

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1 EXECUTIVE SUMMARY

2 INTRODUCTION

2.1 Overview

In the supplement approval letter dated 06 October 2006, FDA listed several post-marketing commitments agreed by the Sponsor. One of the commitments is a Phase 4 study in autistic children and adolescents to determine the lowest effective dose of risperidone in this indication, and to evaluate the effect of risperidone treatment on fasting glucose, fasting insulin, and insulin resistance in this population. In the letter, FDA recommend that the initial treatment design include three arms [placebo, 0.125 mg risperidone, 1 mg risperidone] with a six-week duration of treatment. FDA also indicated that 25 patients per treatment arm would be considered adequate. In completion of this post-marketing commitment, Janssen Pharmaceutical conducted trial RIS-SUT-4002.

RIS-SUT-4002 is a prospective, randomized, 6-week, double-blind, placebo-controlled, fixed-dose, multicenter study, followed by a 6-month (26 week), flexible-dose, open-label extension phase, to evaluate the efficacy and safety of risperidone at 2 doses (0.125 mg/day and 1.25 mg/day for subjects with a baseline weight of 20 kg to less than 45 kg; and 0.175 mg/day and 1.75 mg/day for subjects with a baseline weight of 45 kg or more). A total of 96 subjects, all in US, were randomized 1:1:1 to placebo, low dose risperidone, high dose risperidone stratified by center and baseline weight (20 kg to <45 kg; or ≥45 kg). Seventy-seven (80%) subjects completed the double blind phase (27 subjects in placebo, 25 subjects in low dose risperidone, and 25 subjects in high dose risperidone). Study drug was administered once-daily in the morning (or evening, if sedation occurred).

2.2 Data Sources

Study Report:
\\Cdsesub1\evsprod\NDA020272\0057\m5\53-clin-stud-rep\535-rep-effic-safety-stud\irritability-associated-with-autistic-disorder\5351-stud-rep-contr\ris-aut-4002

Analysis datasets and define files of the data variables:
\\Cdsesub1\evsprod\NDA020272\0079\m5\datasets\ris-aut-4002\analysis\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis quality are acceptable.

3.2 Evaluation of Efficacy

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3.2.1 Study Design and Endpoints

This is a prospective, randomized, 6-week, double-blind, placebo-controlled, fixed-dose, multicenter study, followed by a 6-month (26-week), flexible-dose, open-label extension phase, conducted in 16 centers, all in US. A total of 96 subjects were randomized into placebo (n=35), risperidone low dose (n=30), and risperidone high dose (n=31). Seventy-seven (80%) subjects completed the double-blind phase (27 subjects in placebo, 25 subjects in low dose risperidone, and 25 subjects in high dose risperidone).

The study population includes male or female subjects from 5 to 17 years of age, with a Diagnostic and Statistical Manual of Mental Disorder, fourth edition (DSM-IV) diagnosis of Autistic Disorder and associated irritability and related behavioral symptoms. The diagnosis of Autistic Disorder was corroborated by standard cut-off scores on the Autism Diagnostic Interview - Revised (ADI-R), with an ABC-I Subscale score of $\geq$ 18 and a CGI-S score of $\geq$ 4 (ie, at least moderate severity). All enrolled subjects were in good physical health, with a body weight of at least 20 kg, a mental age > 18 months and met the inclusion and exclusion criteria.

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.

The primary efficacy parameter was the change from baseline to endpoint in the double-blind phase (last nonmissing, postbaseline assessment of the double-blind phase) on the ABC-I (rated by the parent or primary caregiver under guidance of the investigator). Two hierarchical null hypotheses (H1 and H2) were defined to address the primary objective of the trial. 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 the placebo group on the primary efficacy endpoint.
- H2: No difference between the risperidone low dose group and the placebo group on the primary efficacy endpoint

The sample size was calculated to have 80% power to detect the between-group differences of 6 and the standard deviation of 8 and a 2-sided significant level of 0.05. Twenty-nine subjects per group were required. Assuming 5% drop out rate, a total number of randomized subjects was 31 per arm (93 in total).

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

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. All randomized subjects received at

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least 1 dose of study drug. Seventy-seven (80%) subjects completed the double-blind phase. Table 1 provides information on numbers of subject withdrew and reasons for withdrawal.

Table 1: Study Completion/Withdrawal Information – Double-Blind Phase

Subject Status Reason for Withdrawal/Termination	Placebo (N=35) n (%)	Ris Low Dose (N=30) n (%)	Ris High Dose (N=31) n (%)	Total (N=96) n (%)
Total no. subjects with disposition	35 (100)	30 (100)	31 (100)	96 (100)
Completed	27 (77)	25 (83)	25 (81)	77 (80)
Withdrawn	8 (23)	5 (17)	6 (19)	19 (20)
Adverse event	0	0	1 (3)	1 (1)
Lost to follow up	0	1 (3)	1 (3)	2 (2)
Subject choice (subject withdrew consent)	1 (3)	1 (3)	3 (10)	5 (5)
Insufficient response	6 (17)	1 (3)	0	7 (7)
Study medication non-compliance	1 (3)	0	0	1 (1)
Other	0	2 (7)	1 (3)	3 (3)

Note: Percentages calculated with the number of subjects in each group as denominator.
Reference: Sponsor's Table 8 on Page 58 of the study report, ris-aut-4002-csr.pdf.

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).

Table 2: Demographic and Baseline Characteristics (ITT Analysis Set)

	Placebo (N=35)	Ris Low Dose (N=30)	Ris High Dose (N=31)	Total (N=96)
Age (years), n (%)				
0 - <12	30 (86)	20 (67)	24 (77)	74 (77)
12 – higher	5 (14)	10 (33)	7 (23)	22 (23)
Sex, n (%)				
Female	4 (11)	5 (17)	3 (10)	12 (13)
Male	31 (89)	25 (83)	28 (90)	84 (88)
Race, n (%)				
White	20 (57)	21 (70)	25 (81)	66 (69)
Non White	15 (43)	9 (30)	6 (19)	34 (31)
Weight (kg), n (%)				
<45 kg	28 (80)	20 (67)	22 (71)	70 (73)
≥ 45 kg	7 (20)	10 (33)	9 (29)	26 (27)
Height (cm)				
Mean (SD)	136.0 (15.94)	141.7 (21.48)	136.7 (16.84)	138.0 (18.10)

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Reference: Sponsor's Table 10 on Page 59 of the study report, ris-aut-4002-csr.pdf.

3.2.3 Statistical Methodologies

Sponsor's Analysis Methodology:

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).

An analysis of covariance (ANCOVA) model were applied in the analysis of the primary efficacy variable, with dose level (placebo, RIS low dose, RIS high dose), baseline weight group (20 to <45 kg or ≥45 kg) and pooled analysis center as factors and baseline ABC-I score as covariate. Between-group comparisons will be based on the least-squares means obtained from the ANCOVA model. The difference in least squares means between each treatment group and placebo (risperidone minus placebo) and the 95% confidence intervals for the differences were estimated.

The difference between the risperidone high dose group and placebo was tested first. Since this comparison was statistically significant, the step-down procedure continued to the resperidone low dose group versus placebo comparison

3.2.4 Sponsor's Results

Table 3 summarizes the primary analysis 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 the ABC-I subscale in the risperidone low dose group compared with placebo was not statistically significant ($p = 0.164$).

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.

Table 3: Aberrant Behavior Checklist – Irritability at Double-Blind Endpoint
(Intent-to-Treat Analysis Set)

	Placebo	Ris Low Dose	Ris High Dose
	(N=35)	(N=30)	(N=31)
Irritability Double-blind Endpoint (DB)			
Value at Baseline			
N	34	29	29
Mean (SD)	28.9 (6.10)	27.1 (6.26)	28.0 (7.81)
Change from Baseline			
N	34	29	29
Mean (SD)	-3.5 (10.67)	-7.4 (8.12)	-12.4 (6.52)
P-value(minus Placebo)[a,b]		0.164	<0.001
Diff. of LS Means (SE)		-3.0 (2.17)	-7.9 (2.18)
95% CI		(-7.36;1.27)	(-12.19;-3.52)

[a] Test for no difference between treatment from ANCOVA model with factor(s) treatment, pooled center, baseline weight strata, and baseline ABC-I score (type III SS).
[b] Pairwise comparison: P-values and CI associated with Fisher's LSD procedure.
Note: Results for Value at Baseline and Change from Baseline are based on subjects with both baseline and end point data.
Key: SD: standard deviation
Reference: Sponsor's Table 28 on Page 80 of the study report, ris-sut-4002-csr.pdf.

Least square mean change from baseline in ABC-I during the double-blind phase (based on LOCF analysis) is represented graphically in Figure 1. Differences between the risperidone low dose group and placebo were statistically significant at Day 4 and Day 8 ($p \leq 0.036$), but not at subsequent timepoints. Differences between the risperidone high dose group and placebo were statistically significant at Day 8, Day 15, Day 29, and Day 43 ($p < 0.001$), but not at Day 4 ($p=0.106$). Note that subjects had a 3-day titration period at the beginning of the double-blind period before starting their target dose.

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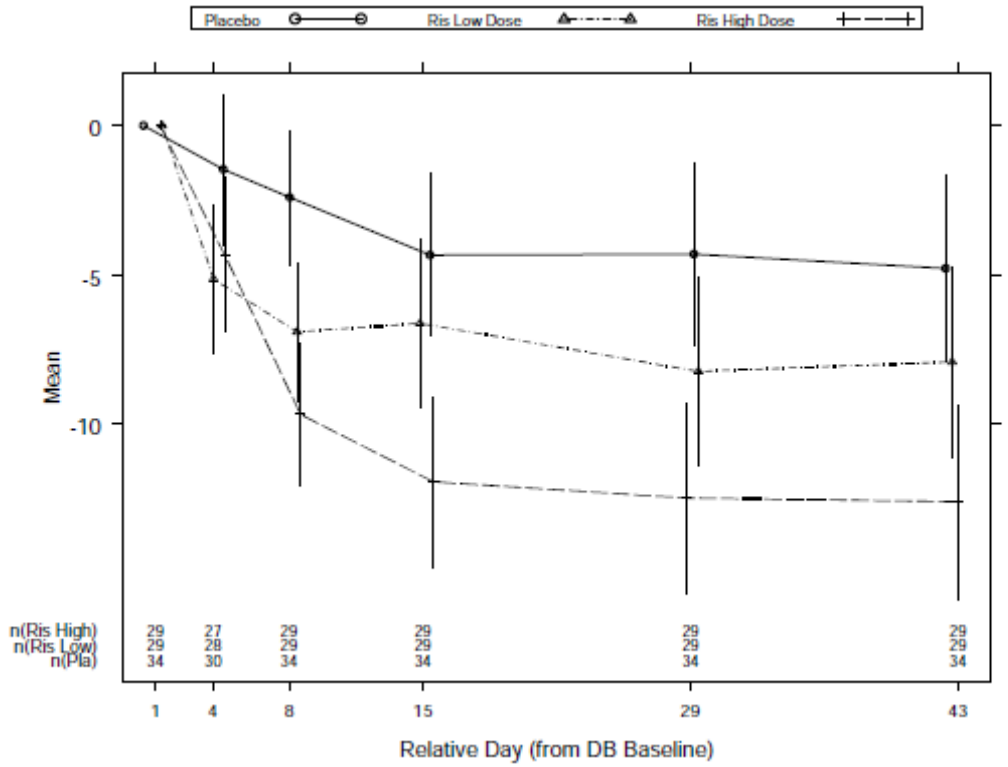
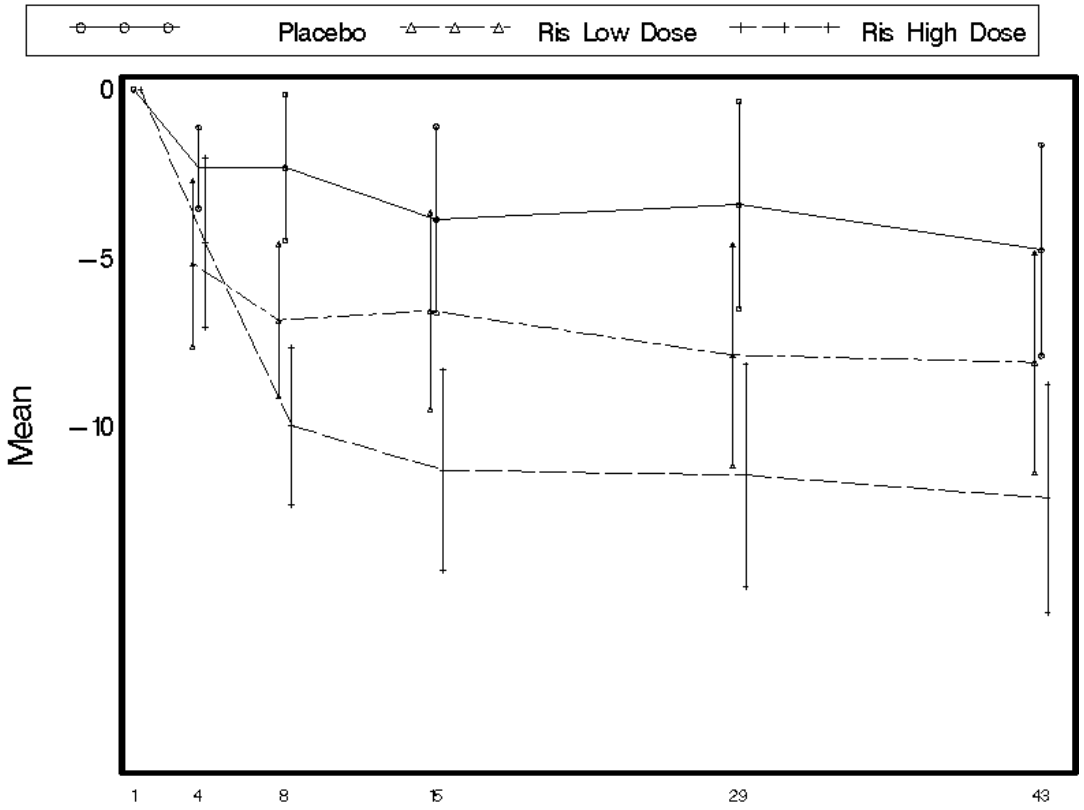
Figure 1: Least Squares Means and 95% Confidence Intervals of Change from Double-Blind Baseline Over Time in ABC Irritability Subscale (LOCF) – Double Blind Phase



Reference: Sponsor's Figure 2 on Page 81 of the study report, ris-aut-4002-csr.pdf.

A mixed model repeated measures (MMRM) analysis yielded results that were consistent with the LOCF end point analysis. Estimates of the between-group differences with placebo at Day 43 from the MMRM model were -7.4 (p=0.002) for the risperidone high dose group and -3.3 (p=0.141) for the risperidone low dose group. Figure 2 graphically represents the results from MMRM analysis.

Figure 2: Least Squares Means and 95% Confidence Intervals of Change from Double-Blind Baseline Over Time in ABC Irritability Subscale (MMRM) – Double Blind Phase



Reference: Reviewer's plot.

3.2.5 Reviewer's Results

In the supplement approval letter dated 06 October 2006, FDA stated that 25 patients per treatment arm would be considered adequate. The sample size, 29 patients per arm, was calculated to have 80% power to detect the between-group differences of 6 and the standard deviation of 8 and a 2-sided significant level of 0.05. However, the observed group difference between the low dose and placebo is 3.0, while the standard deviation is 10.67 for the placebo group, and 8.12 for the risperidone low dose group. The sample size of the study was not enough to detect the observed group difference 3.0. Nevertheless, the clinical team considers the group difference 3.0 not clinically relevant. Therefore, the sponsor's conclusion seems reasonable.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

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The study is conducted in US. Most of the subjects who entered the double-blind phase were male (88%) and less than 12 years of age (77%). Therefore, no subgroup analysis is needed for geographic region, gender, and age group.

4.2 Other Special/Subgroup Populations

The study was stratified by center and baseline weight (< 45 kg; or ≥ 45 kg). However, the < 45 kg group contains 73% of the total sample. Therefore, subgroup analysis by weight is skipped because it would not provide useful information in such a relatively small study.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The results from the primary endpoint confirm that the risperidone high dose group was efficacious and demonstrated assay sensitivity. There is not enough evidence to support the efficacy of the risperidone low dose group.

5.2 Conclusions and Recommendations

Based on the results from this trial, the sponsor concluded that the risperidone high dose group was effective in the treatment of irritability and related behaviors associated with Autistic Disorder in children and adolescents. Efficacy was not demonstrated in the risperidone low dose group relative to placebo. After investigating the primary analyses, the sponsor's conclusion seems reasonable.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Jinglin Zhong, Ph.D.
Date: June 18, 2012

Concurring Reviewer(s): Peiling Yang, Ph.D.; H.M. James Hung, Ph.D.

Statistical Team Leader: Peiling Yang, Ph.D.

Biometrics Division Director: HM James Hung, Ph.D.

cc:
Project Manager
Medical Officer
Medical Team Leader
Primary Statistical Reviewer
Statistical Team Leader
Biometrics Division Director
Lillian Patrician

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/s/

JINGLIN ZHONG
06/18/2012

PEILING YANG
06/18/2012

HSIEN MING J HUNG
06/18/2012