20272-S-65 Cross-Discipline Team Leader Review Memo

Date	July 22, 2012
From	Robert L. Levin, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	20-272/S-065; 20-588/S-053; 21-444/S-041
Sponsor	Janssen Pharmaceuticals, Inc.
Submission Date	October 3, 2011
Related IND	31,931
Proprietary / Established name	Risperidone Risperdal Tablets, Oral Solution, Orally Disintegrating Tablet
Therapeutic Class	Atypical antipsychotic
Dosage forms / strength	Oral Solution (0.1 mg/mL and 1 mg/mL)
Proposed Indication	Irritability associated with Autistic Disorder
Recommendation:	Approval

1. Introduction and Summary

The sponsor submitted this supplemental NDA to fulfill a Postmarketing Commitment. Risperidone was approved for the treatment of Irritability associated with Autistic Disorder on October 6, 2006. The approval was based on 2 short-term, placebo-controlled studies in pediatric patients with irritability and related behaviors associated with autism. The sponsor was required to conduct and additional study in children and adolescents with irritability associated with Autistic Disorder, in order to determine the lowest effective dose of risperidone. The previous studies used flexible doses of risperidone (0.25 to 3.5 mg); thus, it was not possible to formally assess dose-response relationships for efficacy and safety. The approved dose range for the indication is 0.5 mg to 3 mg per day. The current study used 2 weight-based fixed doses of risperidone (low-dose and high-dose). The low dose was 0.125 mg per day for patients for patients weighing 20 to < 45 kg, and it was 0.175 mg per day for patients weighing $\geq$ 45 kg. The high dose was 1.25 mg per day for patients weighing 20 to < 45 kg, and it was 1.75 mg per day for patients weighing $\geq$ 45 kg.

The study demonstrated the efficacy of high-dose risperidone, but it did not demonstrate efficacy for low-dose risperidone. The statistical reviewer, Jinglin Zhong, Ph.D. replicated the sponsor's findings, and she has concluded that the study demonstrated the efficacy of high-dose risperidone but not low-dose risperidone. I agree with Dr. Zhong's conclusions.

In the 6-week placebo-controlled study and the 6-month open-label extension phase, risperidone was reasonably safe and well tolerated in pediatric patients with irritability and related behaviors associated with autistic disorder. The safety profile of risperidone in this study population was highly similar to that in the previous two studies in pediatric

patients with irritability and autism. There were no new or unexpected findings. As in the previous studies, the most important and common findings were increased appetite, increased weight, and sedation.

As part of the postmarketing commitment, the sponsor assessed the effects of risperidone treatment on growth, glucose metabolism, and related endocrine parameters. The two consultants from the Division of Metabolic and Endocrine Products (Lisa Yanoff, M.D. and Ali Mohamadi, M.D.) have concluded that treatment with risperidone in this study was not associated with clinically significant changes in fasting glucose, fasting insulin, homeostatic model of insulin resistance (HOMA-IR), insulin growth factor-1 (IGF-1), and insulin growth factor-BP3 (IGF-BP3). I agree with Dr. Yanoff and Dr. Mohamadi.

In my opinion, the sponsor has fulfilled the postmarketing commitment to conduct an adequate and well controlled study to assess the efficacy of 2 fixed-doses of risperidone, in order to determine the minimum effective dose. The high dose in the approved range was efficacious, but the low dose below the approved range was not. I recommend approval of the supplement. I do not recommend any further postmarketing commitments or regulatory actions. We have included a description of the study and results in the Pediatric Use section and the Clinical Studies section, and the sponsor has accepted our labeling language for these sections. It is not necessary to revise the Dosage and Administration section. We're in the process of discussing with the sponsor revisions to other sections of labeling. The sponsor has proposed revisions to the adverse reactions and drug interactions sections.

2. Background and Regulatory History

On December 19, 2003, the sponsor submitted supplemental NDA 020272/S-036 to support the approval of risperidone for the treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years. The specific treatment targets included: aggression, deliberate self- injurious behavior, and temper tantrums. Risperidone was the first drug approved for treatment of irritability associated with autistic disorder. There are no approved to treat the core symptoms of autistic disorder.

The initial risperidone clinical program (NDA 020272/S-036) included two pharmacokinetic studies and two 8-week, randomized, double-blind, placebo-controlled studies, CAN-23 and USA-150/Part I (conducted in Canada and the U.S., respectively) from 1999 through 2001. A total of 180 patients were studied in these two efficacy studies. There were 83 patients with autistic disorder exposed to risperidone.

<u>Study USA-150/Part 1</u>

Study USA-150/Part 1 was an 8-week, multicenter, randomized, double-blind, placebo-controlled trial of flexible-dose risperidone (0.25 to 3.5 mg per day). The study was conducted by the Autism Network of the Research Units on Pediatric Psychopharmacology, between June 1999 and April 2001. The study included 101 pediatric patients (ages 5 to 17 years) with autistic disorder. There were 88 children (5-12

years of age) and 13 adolescents (13-17 years of age). The mean age was 8.8 years. There were 82 males and 19 females. Subjects were randomly assigned to risperidone (n=49) or placebo (n=52).

This was a flexible-dose study using weight-based dosing. Subjects in the weight range of 20-45 kg received doses of 0.25 mg to 2.5 mg per day. Subjects weighing more than 45 kg received doses in the range of 0.5 to 3.5 mg per day.

The two co-primary efficacy measures were the Aberrant Behavior Checklist-Irritability (ABC-I) subscale and the Clinical Global Impressions-Improvement (CGI-I). The primary endpoints were the mean change from baseline to the end of Week-8 in the ABC-I score and the mean CGI-I at Week 8. Table 1 summarizes the results for the mean change in (ABC-I) scores. There was a statistically significant reduction in the mean ABC-I score in the risperidone group compared to placebo at the end of Week 8.

Table 1. Aberrant Behavior Checklist-Irritability (ABC-I) Subscale Scores

Treatment group	Baseline ABC-I	Week 8 ABC-I	Change (LS Mean)	P-value
Risperidone (N=49)	26.1	11.3	-14.6	<0.001
Placebo (N=52)	25	21.6	-4.0	

The CGI-I results were also significant. For the CGI-I, 76% of the risperidone group and 12% of the placebo group were in the "very much improved" or "much improved" categories at Week 8 ($p<.001$).

Study RIS-CAN-23

Study RIS-CAN-23 was an 8-week, multicenter, randomized, double-blind, placebo-controlled, flexible-dose study to assess the safety and efficacy of risperidone in the treatment of children with behavioral symptoms associated with pervasive developmental disorder (PDD) or autistic disorder. The study included 79 children (ages 5-12 years). There were 24 subjects with a diagnosis of PDD and 55 subjects with a diagnosis of autistic disorder. The majority of subjects were males. The mean age was 7 years.

Dosing was based on weight. The dose range was 0.02-0.06 mg per kg per day. Subjects were treated with risperidone oral solution, administered once daily in the morning. If sedation occurred, the dose could be administered in the evening or in divided dose (twice daily). For all subjects, the initial risperidone dose was 0.01 mg/kg/day. The dose was increased to 0.02 mg/kg/day on Day 3. It could be increased by increments of 0.02 mg/kg/day, up to 0.04mg/kg/day on Day 8. After the initial titration, the dosage could be increased or decreased at weekly intervals, based on the investigator's judgment of the subject's response. Maximal daily increments were 0.02 mg/kg/day, and the maximum dose was 0.06 mg/kg/day. There were no limits for decreasing the dosage.

The primary endpoint was the change from baseline to Week 8 in the ABC-I score rated by a parent or caregiver. There was a statistically significant reduction in the mean ABC-I score, compared to placebo. Table 2 summarizes the primary efficacy results

Table 2. Aberrant Behavior Checklist-Irritability (ABC-I) Subscale Scores

Treatment group	Baseline ABC-I	Week 8 ABC-I	Change (LS Mean)	P-value
Risperidone (N=37)	18.9	6.9	-11	<0.001
Placebo (N=38)	21.2	14.7	-4.8	

The results were similar for the PDD and autistic disorder subgroups.

The mean CGI-I score was a secondary endpoint. At Week 8, 54% of risperidone patients and 18% of placebo patients were in the "very much improved" or "much improved" categories (p<.001).

Postmarketing Commitment upon Approval of NDA 020272/S-036

At the time of approval (October 2006) the Division requested that the sponsor conduct a fixed-dose, randomized, double-blind, placebo-controlled trial to determine the lowest effective dose of risperidone in the treatment of irritability associated with Autistic Disorder. In addition to evaluating the fixed-dose response, the postmarketing commitment study was intended to evaluate the effect of risperidone on various metabolic factors, including: fasting glucose, fasting insulin, insulin resistance, growth hormone (GH), and insulin-like growth factor (IGF-1).

October 6, 2006: NDA 020272/S-036 Approval Letter issued indicating agreed upon postmarketing commitments. The following 'Advice and Recommendations Regarding Studies to Meet Phase 4 Commitments' is extracted from the Approval Letter:

Advice and Recommendations Regarding Studies to Meet Phase 4 Commitments

1. Juvenile rat toxicity study: we recommend that you increase the number of animals to 15/sex/group for each subset in this study, and that you measure motor activity using the Figure 8 Activity Maze during the treatment phase of the study as well as during the recovery period. The proposed design is otherwise generally acceptable.

2. Juvenile dog toxicity study: we have not considered the proposed doses in the dog study in our evaluation of the proposed protocol design. However, the proposed design is otherwise generally acceptable.

3. Clinical / Clinical Safety / Clinical Pharmacology Study: With respect to the third Phase 4 commitment listed above, we recommend that the initial treatment design include

three arms [placebo, 0.125 mg risperidone, 1 mg risperidone] with a 6-week duration of treatment. Study RIS-CAN-25 included 25 patients per group; for this Phase 4 commitment study, 25 patients per treatment arm would be considered adequate. We also note that although the 0.125 mg dose could be administered using the commercially available 1 mg/mL solution, accurate measurement of this dose [1/8 mL] will be challenging for parents and practitioners; you are therefore advised to consider whether a less concentrated solution should be developed to support dosing at this level.

With regard to the hormone assessment section of this study, we consider that 6-week study duration may not be sufficient time to allow for capture of significant data on hormone levels and the effects of any changes in these levels. We therefore recommend that you add a three to six month open-label treatment phase to this study, during which additional data on glucose, fasting insulin, IGF-1, and GH levels, as well as insulin resistance, would be collected."

The following is a brief timeline of regulatory activities regarding the clinical program in irritability associated with autistic disorder:

- April 1, 2003: The division met with the applicant to discuss the proposed indication. (b) (4)
- July 31, 2003: Applicant-sponsored Clinical Advisory Board meeting concluded that the Aberrant Behavior Checklist was an acceptable instrument for measuring change in the study.
- December 19, 2003: NDA 020272/S-036 was submitted for the treatment of irritability associated with autistic disorder in children and adolescents.
- June 18, 2004: Approvable letter issued requesting a Phase 4 commitment to a fixed-dose study to provide dose response data.
- November 18, 2004: Applicant responded to Approvable letter.
- May 19, 2005: Not Approvable (NA) action taken, citing that a convincing argument was not made to support dosing recommendations.
- December 7, 2005: Division and ODE Directors met with the Applicant; the decision was made to amend the deficiencies identified in the first and second action letters.
- January 17, 2006: Complete Response to NA letter of May 19, 2005 was submitted.

- July 14, 2006: Approvable Letter issued requesting a Phase 4 Commitment in the form of a fixed-dose, placebo controlled trial to determine the lowest effective dose of risperidone in this indication. In addition, the Approvable Letter requested a Phase 4 commitment to study children and adolescents with autistic disorder to determine the effect of risperidone treatment on fasting glucose, fasting insulin, and insulin resistance.

- August 11, 2006: Complete Response to the July 14, 2006 action letter received.

- October 6, 2006: NDA 020272/S-036 Approval Letter issued indicating agreed upon postmarketing commitments. The following 'Advice and Recommendations Regarding Studies to Meet Phase 4 Commitments' is extracted from the Approval Letter:

3. Chemistry Manufacture and Controls (CMC) Issues

There are no unresolved CMC issues. No new CMC data were submitted.

4. Nonclinical Pharmacology/Toxicology

There are no unresolved nonclinical issues. No new nonclinical pharmacology or toxicology data were submitted. The pharmacology/toxicology team has recommended revisions to relevant sections of labeling. These sections include: Specific Populations-Pregnancy and Nursing Mothers, Clinical Pharmacology, and Nonclinical Toxicology.

On November 3, 2010 the Division issued a letter to the applicant indicating that the juvenile rat toxicity study and the juvenile dog toxicity study were reviewed and the postmarketing commitments for pharmacology and toxicology were fulfilled. Of note, the review of these studies resulted in labeling changes to the product label (Section 8.4 Pediatric Use).

5. Clinical Pharmacology/Biopharmaceutics

There are no unresolved clinical pharmacology or Biopharmaceutics issues. The OCP team has recommended revisions to relevant sections of labeling. These sections include: Dosage and Administration, Drug Interactions, and Clinical Pharmacology-Drug Interactions.

6. Clinical Review of Efficacy

The review of efficacy was based on the findings from a single controlled study **(**RIS-AUT-4002). The study is entitled:

"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"

6.1 Design of Study RIS-AUT-4002

Study RIS-AUT-4002 was a 6-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose study of risperidone in the treatment of 96 male and female children and adolescents (aged 5 to 17 years) with irritability and behavioral disturbances associated with autistic disorder. There were 2 fixed dose levels of risperidone (low-dose and high-dose). Within each of the low-dose and high-dose levels, there were 2 fixed doses which were determined based on body weight. For subjects weighing between 20 kg and less than 45 kg, the low dose was 0.125 mg per day, and the high dose was 1.25 mg per day. For subjects weighing 45 kg or more, the low dose was 0.175 mg per day, and the high dose was 1.75 mg per day.

The 6-week controlled study was followed by a 26-week, open-label, flexible-dose, extension phase. The study was conducted at 21 U.S. sites, from 3 December 2007 to 9 March 2010.

6.2 Objectives of the Study

The primary objective was to assess the efficacy and safety of two fixed-dose levels (high-dose and low-dose) 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 main objective was to determine the lowest effective dose of risperidone by directly comparing doses in the approved range for the indication with a dose range below the approved range. The approved dose range for autism is 0.5 mg to 3 mg per day.

There were no designated key secondary endpoints. The secondary objectives were to evaluate the efficacy of risperidone compared with placebo as measured by:

- Aberrant Behavior Checklist (ABC) subscales (lethargy or social withdrawal, stereotypic behavior, hyperactivity, and inappropriate speech)
- Clinical Global Impression of Change (CGI-C)
- Clinical Global Impression of Severity (CGI-S)
- Response rate (≥25% improvement in ABC-I from baseline)
- Compulsions subscale of the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

6.3 Study Population

Inclusion Criteria

Subjects were males or females 5 to 17 years of age with a diagnosis of Autistic Disorder per DSM-IV criteria. The diagnosis was corroborated by using the Autism Diagnostic Interview-Revised (ADI-R) scale. Key inclusion criteria included the following:

- Aberrant Behavior Checklist (ABC) Irritability subscale (ABC-I) score ≥18 and Clinical Global Impression Severity (CGI-S) score ≥4. Subjects were males or females 5 to 17 years of age.
- Body weight at least 20 kg at screening and baseline
- mental age >18 months at screening
- No evidence of endocrine, metabolic, cardiac, renal, hepatic or pulmonary disease
- Must have been seizure free for at least 6 months, with a stable anticonvulsant dose for 4 weeks
- No concomitant psychotropic medication

Key Exclusion Criteria

- history of psychotic disorder
- received risperidone within 3 months of screening
- history of poor clinical response to risperidone
- unstable neurologic disorder in the past 6 months
- pregnant or lactating females
- moderate to severe extrapyramidal symptoms (EPS) or tardive dyskinesia (TD)
- alcohol or substance abuse or dependence

6.4 Primary Efficacy Measure, Primary Endpoint, and Statistical Analysis

Primary Efficacy Measure

The primary efficacy measure was the Aberrant Behavior Checklist – Irritability Subscale (ABC-I). The Aberrant Behavior Checklist consists of 58 items. It is scored by the parent or caregiver, under the guidance of the investigator, at each scheduled visit in both the double-blind and open-label phases. The score for each item ranges from 0 to 3; higher scores indicate greater severity: 0= not at all a problem, 1= slight problem, 2= moderately serious, and 3= severe problem. The ABC-I subscale (range 0-45) is the total of the 15 items listed below:

- injures self on purpose
- aggressive to others (verbal or physical)
- screams inappropriately
- tempter tantrums
- irritable and whiny
- yells at inappropriate times
- depressed mood
- demands must be met immediately
- cries over minor annoyances and hurts
- mood changes quickly
- cries and screams inappropriately
- stamps feet or bangs objects or slams doors
- deliberately hurts self

- does physical violence to self
- tantrums when does not get own way

Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline in the ABC-I subscale at the at the end of the placebo-controlled phase of the study (Week 6)

Primary Statistical Analysis

The primary statistical analysis was an analysis of covariance (ANCOVA). Factors included the dose level (placebo, risperidone low dose, and risperidone high dose), baseline weight group (20 to <45 kg and >45 kg), and clinical study center. The covariate was the baseline ABC-I score. Between-group comparisons were based on least-squares means (LSM) obtained from the ANCOVA mode. The difference in LSM between each risperidone treatment group and placebo and the 95% confidence intervals for the differences were estimated.

Subgroup analyses were performed on the change from baseline in ABC-I score at Week 6 based on age, gender, race, and baseline severity. The treatment effect was estimated from an ANCOVA model applied to the individual subgroup.

All statistical tests and confidence intervals were to be 2-sided with a significance level of 0.05. A step-down closed testing procedure was to be employed for the analysis of the primary efficacy variable. After calculation of total scores or subscale scores as above, missing values were imputed by the last observation carried forward (LOCF) approach.

6.5 Study Phases

Screening Period

The screening period was up to 3 weeks. Screening procedures included: assent from the subject and consent from the parent or legal representative, historical data collection regarding autism history (age of onset, prior psychotropic medications, and abnormal movement history), ADI-R to confirm the clinical diagnosis and severity of symptoms, a wash-out period of prohibited medications. Subjects were required to be medication-free from psychotropics for at least one week (4 weeks for fluoxetine and 8 weeks for depot medications). Stable dose of anticonvulsants were permitted. Sedatives, anticholinergic drugs, and antihistamines were permitted for short durations.

Baseline Period

Baseline evaluations included the following:
- Inclusion and exclusion criteria
- ABC rating
- CGI-S

- CY-YBOCS
- Nighttime sleep quality and daytime drowsiness visual analog scale
- SAS
- AIMS
- BARS
- Clinical laboratory analyses
- Serum pregnancy test and urine drug screen
- Adverse events
- Concomitant medications

Placebo-Controlled Phase

Subjects who met all study entry criteria at screening and baseline were randomized to treatment with low-dose risperidone, high-dose risperidone, or placebo. There were 2 weight groups: lower (20 to < 45 kg) and higher (≥ 45 kg). For subjects in the lower weight group, the low dose was 0.125 mg per day, and the high dose was 1.25 mg per day. For subjects in the higher weight group, the low dose was 0.175 mg per day, and the high dose was 1.75 mg per day. Risperidone and matching placebo were provided as oral solutions. Because of the need for lower doses, two oral solutions were provided: 0.1 mg/mL and 1 mg/mL. The placebo solution was identical to the risperidone solution in appearance and smell. Study drug was administered once daily in the morning (or evening if sedation occurred). Titration for each of the risperidone fixed-dose groups was as follows:

- risperidone 0.125 mg/day: 0.005 mg for Days 1-3; and 0.125 mg beginning Day 4
- risperidone 1.25 mg/day: 0.5 mg on Days 1-3; and 0.5 mg beginning on Day 4
- risperidone 0.175 mg/day: 0.075 mg on Day 1-3; and 0.175 beginning on Day4
- risperidone 1.75 mg/day: 0.75 mg on Day 1-3 and titrated to 1.75 mg on Day 4

Subjects were evaluated at baseline, Day 4, Weeks 1, 2, 4, 6, and at early discontinuation. The evaluations included:

- ABC (total scores and subscale scores assessed)
- CGI-S and CGI-C
- CY-BOCS
- Adverse events (including extrapyramidal symptoms)
- Clinical laboratory tests (hematology, chemistry, and urinalysis)
- Vital signs (pulse and blood pressure)
- Physical examinations at screening and end of double-blind phase
- Electrocardiograms
- Body weight and height
- Nighttime Sleep Quality and Daytime Drowsiness
- Tanner staging at screening and end of double-blind phase

Open-Label Extension Phase

Subjects were eligible to continue in the open-label extension phase if they completed the 6-week controlled study or had discontinued for reasons other than tolerability and completed at least 3 weeks of the controlled phase. The open-label extension consisted of a baseline visit followed by an open-label treatment phase up to 26 weeks. Subjects were treated with flexible doses of risperidone, based on body weight. The dose ranges were: 0.125 to 1.25 mg/day for the lower weight class and 0.175 to 1.75 mg/day for the higher weight class. Efficacy and safety evaluations were conducted at baseline, Weeks 1, 2, 4, 13, 26, and upon early discontinuation.

6.6 Study Findings: Demographics and Disposition

Baseline Demographics Features

Generally, the 3 treatment groups (placebo, risperidone low dose, and risperidone high dose) were well balanced with respect to baseline demographic features (age, gender, race/ethnicity, body weight/BMI, Tanner Stage, age at diagnosis, and history of antipsychotic use). The majority (88%) of subjects were male, which reflects the fact that the diagnosis of Autistic Disorder is 4-5 times more common in males than females. The majority (80%) of the study population was younger than 12 years of age. The mean and median age was approximately 9. Approximately 70% of subjects were Caucasian, 20% were African American, and 10% were Other. Approximately 26% of subjects were Latino. The majority (73%) of subjects had a body weight less than 45 kg. The mean and median body weights were approximately 40 kg and 33 kg, respectively. The range was 20 to 117 kg. The mean and median body mass index was 19.7 and 18.5, respectively. Approximately 74% of subjects had a Tanner stage of 1 or 2, and 26% had a Tanner stage of 3, 4, or 5. The mean and median age at diagnosis of autism was 4.3 and 3 years, respectively. The majority (91%) of subjects were antipsychotic-naïve. Table 3 summarizes the baseline demographic features (reproduced from the sponsor's Table 10 from the Clinical Study Report for RIS-AUT-4001).

Table 3. Demographics and Baseline Characteristics

Table 10: Demographic and Baseline Characteristics
(Study RIS-AUT-4002: Intent-to-Treat Analysis Set)

	Placebo (N=35)	Ris Low Dose (N=30)	Ris High Dose (N=31)	Total (N=96)
Age (years)				
Category, n (%)				
0 - <12	30 (86)	20 (67)	24 (77)	74 (77)
12 – higher	5 (14)	10 (33)	7 (23)	22 (23)
Mean (SD)	8.6 (2.57)	10.2 (3.42)	9.3 (3.11)	9.3 (3.07)
Median	8.0	9.5	9.0	9.0
Range	(5;16)	(5;17)	(5;17)	(5;17)
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)
White/Asian	1 (3)	0	0	1 (1)
Black or African American	10 (29)	6 (20)	3 (10)	19 (20)
Asian	1 (3)	1 (3)	1 (3)	3 (3)
Asian Indian	2 (6)	1 (3)	0	3 (3)
American Indian or Alaskan native/Asian Indian	0	1 (3)	0	1 (1)
Other	1 (3)	0	2 (6)	3 (3)
Ethnicity, n (%)				
Hispanic or Latino	8 (23)	6 (20)	11 (35)	25 (26)
Not Hispanic/Latino	27 (77)	24 (80)	20 (65)	71 (74)
Weight (kg)				
Category, n (%)				
<45 kg	28 (80)	20 (67)	22 (71)	70 (72.9)
≥ 45 kg	7 (20)	10 (33)	9 (29)	26 (27.1)
Mean (SD)	37.8 (17.75)	44.5 (25.13)	37.1 (14.87)	39.7 (19.65)
Median	31.3	33.1	33.1	32.5
Range	(20;88)	(20;117)	(21;81)	(20;117)
Height (cm)				
Mean (SD)	136.0 (15.94)	141.7 (21.48)	136.7 (16.84)	138.0 (18.10)
Median	131.8	139.8	135.9	134.4
Range	(113;177)	(107;182)	(112;169)	(107;182)

Table 3. Demographics and Baseline Characteristics (Continued)

	Placebo (N=35)	Ris Low Dose (N=30)	Ris High Dose (N=31)	Total (N=96)
Body mass index (kg/m²)				
Category, n (%)				
Normal <25	31 (89)	25 (83)	30 (97)	86 (90)
Overweight 25-<30	3 (9)	2 (7)	0	5 (5)
Obese ≥ 30	1 (3)	3 (10)	1 (3)	5 (5)
Mean (SD)	19.5 (5.00)	20.5 (5.73)	19.2 (4.43)	19.7 (5.05)
Median	18.3	18.6	18.6	18.5
Range	(13;35)	(14;37)	(10;35)	(10;37)
Baseline tanner stage				
N	33	29	30	92
Category, n (%)				
1 – 2	27 (82)	17 (59)	24 (80)	68 (74)
3 – 5	6 (18)	12 (41)	6 (20)	24 (26)
Mean (SD)	1.5 (0.87)	2.2 (1.38)	1.6 (1.27)	1.8 (1.21)
Median	1.0	2.0	1.0	1.0
Range	(1;4)	(1;5)	(1;5)	(1;5)
Age at first diagnosis of autism				
N	33	29	31	93
Mean (SD)	4.5 (2.67)	4.5 (2.90)	3.8 (1.83)	4.3 (2.50)
Median	3.0	3.0	3.0	3.0
Range	(2;11)	(2;14)	(2;10)	(2;14)
Previous antipsychotic use, n (%)				
Yes	3 (9)	4 (13)	2 (6)	9 (9)
No	32 (91)	26 (87)	29 (94)	87 (91)
Family history of type 2 diabetes, n (%)				
N	34	30	31	95
Yes	1 (3)	2 (7)	1 (3)	4 (4)
No	33 (97)	28 (93)	30 (97)	91 (96)

Subject Disposition

There were 96 subjects in the placebo-controlled study who received at least one dose of study drug. The majority (80%) completed the controlled phase (77%, 83%, and 81% of the placebo, risperidone low dose, and risperidone high dose, respectively). Only one subject (in the high dose group) discontinued because of an adverse event. The most common reason for discontinuation was insufficient clinical response (17%, 3%, and 0% of the placebo, low dose, and high dose groups, respectively). The second most common reason for discontinuation was subject choice or withdrew consent (0, 3%, and 10% of the placebo, low dose, and high dose groups, respectively). The table below is reproduced from the sponsor's Table 8 in the Clinical Study Report.

Table 4. Subject Disposition

Table 8: Study Completion/Withdrawal Information - Double-Blind Phase
(Study RIS-AUT-4002: Intent-to-Treat Analysis Set)

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)

6.7 Efficacy Results

In the risperidone high-dose group, there was a statistically significant treatment effect (compared to placebo) as measured by the mean change in ABC-I score at the end of Week 6. There was not a significant treatment effect in the risperidone low-dose group (compared to placebo). The efficacy results are summarized in the table below.

Table 5. Primary Efficacy Results: Mean Change in ABC-I Score at Week 6 (LOCF)

	Placebo N = 35	**RIS Low-dose N = 30**	**RIS High-dose (N = 31)**
Baseline ABC-I Mean (SD)	28.9 (6.1)	27.1 (6.26)	28 (7.81)
End ABC-I Mean (SD)	25.4 (12.05)	19.2 (9.46)	15.5 (8.25)
Change in ABC-I Mean (SD)	-3.5 (10.67)	-7.4 (8.12)	-12.4 (6.52)
Difference of LS Means (SE) (95% CI)		-3 (2.17) (-7.36;1.27)	-7.9 (2.18) (-12.19;-3.52)
p-value		0.164	<0.001

The magnitude of the effect in the risperidone high dose group was relatively large. The difference in least square means between the risperidone high-dose and placebo groups (-7.9) was approximately 2.3 times the change in the placebo group. The difference in LS means between the risperidone low-dose and placebo groups was -3.0. The modest change was approximately 0.86 times the change in the placebo group. The treatment effect in the risperidone high-dose group was significant beginning at Day 8.

Subgroup Analyses

The total sample size in the study was relatively small (96 subjects); thus, the subgroups were quite small. Nevertheless, the consistency of the treatment effect was examined based on the following factors: age, gender, race/ethnicity, body weight, and baseline ABC-I score. The interpretation of the results by age, sex, and race was confounded by the small numbers of subjects in the following subgroups: less than 12 years of age, female, and non-Caucasian. Estimates of the treatment effect were similar based on baseline severity of illness (ABC-I scores). For ABC-I severity < 50^{th} percentile, the placebo-subtracted change was -6.8; for ABC-I severity > 50^{th} percentile, the placebo-subtracted difference was -7.4.

Exploratory Secondary Efficacy Analyses

- ABC-I responder analysis (> 25% decrease): 83% of the risperidone high-dose group, 52% of the risperidone low-dose group, and 41% of the placebo group were considered responders. The difference between the placebo and high-dose group was statistically significant (p= 0.004). The difference between the placebo and low-dose groups was not significant (p= 0.817)
- ABC-Hyperactivity Subscale Score: In the risperidone high-dose group, there was a significant decrease in the mean ABC Hyperactivity subscale score. The effect was not significant in the low-dose group.
- ABC-Stereotyped Behavior Subscale Score: The difference was not significant in the high-dose group, but it was significant in the low-dose group.
- ABC Inappropriate Speech or Lethargy/Social Withdrawal Subscale Scores: there were no significant effects in any of the treatment groups
- Clinical Global Impression-Severity: there was a significant improvement in mean CGI-S score in the risperidone high-dose group, but not in the low-dose group.
- Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS): In the risperidone high-dose group, there was a significant decrease in the mean CY-BOCS score. The change was not significant in the low-dose group.

7. Biostatistics Consult Review

Jinglin Zhong, Ph.D. performed the statistical review. Dr. Zhong confirmed the sponsor's efficacy findings. She has concluded that high-dose risperidone was efficacious in the treatment of irritability and related behaviors associated with autistic disorder. Low-dose risperidone was not efficacious.

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, and H2: No difference between the risperidone low dose group and the placebo group on the primary efficacy endpoint.

The efficacy data analyses were performed on all randomized subjects who received at least one dose of the double-blind study drug (intent to treat [ITT] analysis set). An analysis of covariance (ANCOVA) model was 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 were 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 risperidone low dose group versus placebo comparison.

Dr. Zhong replicated the sponsor's efficacy findings. There was a statistically significant reduction in the ABC-I subscale score 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]. Because this comparison was statistically significant, the stepdown 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 ($p = 0.164$). The findings for the ABC-I score 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.

Dr. Zhong notes that the least square mean 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 time points. 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 ($p=0.106$).

An MMRM analysis yielded results that were consistent with the LOCF 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.

8. Clinical Safety Review

8.1 Description and Adequacy of the Safety Database

The source of the safety data are the controlled phase and the open-label extension phase of Study RIS-AUT-4002. In the controlled study, 96 subjects received at least one dose of study drug and were included in the safety analyses. In the open-label, extension phase, there were X subjects. All of these subjects had been exposed to risperidone in the controlled phase of the study.

The studies included the standard types of safety assessments. In addition, the sponsor fulfilled the postmarketing commitment to assess safety parameters related to glucose metabolism and endocrine functions. The sponsor evaluated the effect of risperidone on the following parameters: fasting glucose, fasting insulin, insulin resistance, growth hormone (GH), and Insulin-like Growth Factor (IGF-1) in this population. The study was conducted as recommended by the Division. All evaluations reasonably applicable were conducted to assess the safety and tolerability of risperidone in pediatric patients with irritability associated with autistic disorder. The types and frequencies of safety evaluations used to assess adverse reactions, vital signs, clinical laboratory parameters, and other tests were adequate. The sponsor adequately assessed the metabolic and endocrine parameters as required.

8.2 Exposure Data

In the controlled study, 61 subjects were treated with risperidone for a total exposure of 6.7 subject-years. There were 30 subjects in the low-dose group and 31 in the high-dose group. In the low-dose group, the mean and median doses were 0.13 mg and 0.12 mg, respectively. In the high-dose group, the mean and median doses were 1.24 mg and 1.2 mg, respectively. The mean and median duration of risperidone treatment was approximately 40 days and 43 days, respectively.

In the open-label phase, 79 subjects were treated with risperidone for a total exposure of 32.7 subject-years. Of these, 30 had been treated with placebo, and 49 had been treated with risperidone in the controlled study. The median duration of treatment in the open-label phase was 178 days. There were 33 (42%) subjects treated with risperidone for up to 6 months. In the lower weight group, the median mode dose was 0.88 mg/day. In the higher weight group, the median mode dose was 1 mg/day.

For the controlled and open-label periods combined, 91 subjects were exposed to at least one dose of risperidone for a total exposure of 39.3 subject-years. The median duration of exposure was 182 days. There were 48 subjects exposed to risperidone for at least 6 months.

This was an adequate exposure database for assessing the safety and tolerability of risperidone in this population.

8.3 Deaths, Serious Adverse Events, and Adverse Associated with Discontinuation

There were no deaths during the study. Two subjects experienced serious adverse events. Subject 00103207 in the risperidone 1.25 mg group had 2 serious adverse events: thrombotic thrombocytopenic purpura (TTP) and hydrocele. It is possible that TTP was related to treatment with risperidone. Subject 00102203 in the placebo group had an increase in aggression. The SAE was unrelated to study drug treatment.

SAE Narrative for Subject 00103207

The subject was a 9 year-old Caucasian male with a diagnosis of autism at age 3. He apparently had no other significant medical history. At baseline, he had a normal physical examination, and the platelet count was 302,00/ mm^3. He was not treated with any concomitant medications during the study. He completed 6 weeks of treatment with risperidone 1.25 mg/day end then entered the open-label phase of the study and continued treatment with 1.25 mg/day. At the end of the controlled phase on Day 43, his platelet count was 210,000/ mm^3. On Day 140 the platelet count was 221,000. On Day 108 he was diagnosed with a hydrocele, and he had surgical repair on Day 132. On Day 171, he developed a rash on the back and legs, and on Day 179 he was diagnosed with thrombotic thrombocytopenic purpura. The platelet count was 14,000/ mm^3. The subject was treated with intravenous RH+ antibody on Day 182. On Day 187 the investigator decided that the subject should be terminated early from the study, but the subject's mother continued administering risperidone and requested that he continue in the study. On Day 187, the platelet count had increased to 145,000. The investigator decided that the subject could continue in the study while monitoring the platelet count. Between Days 200 and 214, the platelet counts were 90,000 and 130,000. On Days 214 and 230 (end of the study), the platelet counts were 155,000 and 197,000, respectively. On Day 230, the subject's physician reported that here was no purpura or petechiae. The subject had no other significant findings during the study.

It is possible that the development of TTP is related to the risperidone. TTP is included in risperidone labeling, based on at least one postmarketing case report.

Adverse Events Associated with Discontinuation from the Study

In the controlled study, only 2 subjects discontinued because of adverse events. One subject in the risperidone high-dose group discontinued because of sedation on Day 4. The sedation was related to treatment with risperidone. One subject in the placebo group discontinued because of aggressiveness on Day 6.

In the open-label extension phase, 5 subjects treated with risperidone discontinued because of adverse events. One subject previously treated with placebo in the controlled

study developed the following adverse events on Day 4 of treatment with high-dose risperidone: blepharospasm, confusion, crying, decreased appetite, irritability, self-injurious behavior, and somnolence. Somnolence and blepharospasm were probably related to treatment with risperidone. Three additional subjects who had been treated with placebo in the controlled study discontinued during treatment with risperidone. There was one case of each of the following: mild neutropenia (Day 90), weight increased (Day 70), and fatigue (Day 97). One patient treated with high-dose risperidone in the controlled phase discontinued because of vomiting on Day 15 of the open-label phase.

It is difficult to determine the relationship between these events and risperidone. The patient with neutropenia was an African American girl; it is possible that this was a case of benign ethnic neutropenia. Her baseline neutrophil count was 1,770 and the low neutrophil count was 880. Risperidone was permanently discontinued. Three days after discontinuing risperidone, her neutrophil count normalized to 1,980. Three weeks later, the count was 2,227. The subject had no clinical signs or symptoms associated with the mild neutropenia.

8.4 Common Adverse Events

The types and frequencies of adverse reactions in this study were essentially identical to those reported in the 2 previous studies in pediatric patients with autism and irritability. There were no new or unexpected adverse events. The most common adverse reactions in the controlled study were increased appetite (26% and 6% in the risperidone and placebo groups, respectively), sedation/somnolence (15/11% vs. 0/3%), weight increased (11% vs. 6%)

Table 8 represents adverse events that occurred at a rate greater than placebo during the double-blind phase; the information was extracted from the JMP data sets for this submission.

Table 6 Adverse Events in the Placebo-Controlled Study				
System Organ Class/Adverse Event	**PBO n=35 n (%)**	**Ris Low n=30 n (%)**	**Ris High n=31 n (%)**	**Ris Total n=61 n (%)**
Nervous System Disorders				
Somnolence	2 (6)	1 (3)	17 (55%)	18 (30)
Akathisia	3 (9)	1 (3)	4 (13)	5 (8)
Dyskinesia	1 (3)	0	1 (3)	1 (2)
Dystonia	1 (3)	0	1 (3)	1 (2)
Parkinsonism	0	0	1 (3)	1 (2)
Unsteadiness	0	0	1 (3)	1 (2)
Slurred speech	0	0	1 (3)	1 (2)
Dizziness	0	0	1 (3)	1 (2)
Psychiatric Disorders				
Depression	0	0	2 (6)	2 (3)
Night terror	0	0	1 (3)	1 (2)
Metabolism and Nutrition Disorders				
Increased Appetite	2 (6)	5 (2)	11 (35)	16 (26)
Gastrointestinal Disorders				
Vomiting	2 (6)	2 (7)	2 (6)	4 (7)
Constipation	1 (3)	0	4 (13)	4 (7)
Abdominal pain	0	1 (3)	3 (10)	4 (7)
Nausea	1 (3)	1 (3)	2 (6)	3 (5)
Drooling	0	0	1 (3)	1 (2)
Investigations				
Weight gain	2 (6)	3 (10)	4 (13)	7 (11)
Increased triglycerides	0	0	1 (3)	1 (2)
Increased white blood cell count	0	0	1 (3)	1 (2)
General Disorders				
Fever	0	0	2 (6)	2 (3)
Thirst increased/excessive	0	0	2 (6)	2 (3)
Fatigue	0	0	1 (3)	1 (2)
Respiratory				
Rhinorrhea	1 (3)	1 (3)	1 (3)	2 (3)
Asthma	0	1 (3)	0	1 (2)
Nasal Congestion	0	0	1 (3)	1 (2)
Epistaxis	0	0	2 (6)	2 (3)
Infections and Infestations				
Urinary tract infection	0	0	1 (3)	1 (2)
Viral syndrome	0	0	1 (3)	1 (2)
Upper respiratory infection	2 (6)	1 (3)	5 (16)	6 (10)
Ear infection	0	0	2 (6)	2 (3)
Pharyngitis	0	0	1 (3)	1 (2)
Renal and Urinary Disorders				
Enuresis/bedwetting	0	2 (7)	2 (6)	4 (7)
Respiratory				

Asthma	0	1 (3)	0	1 (2)
Nasal Congestion	0	0	1 (3)	1 (2)
Epistaxis	0	0	2 (6)	2 (3)
Skin				
Rash	0	2 (7)	0	2 (3)

The most common AEs for the open-label phase of the study were increased appetite (11%), increased weight (9%), vomiting (9%), sedation (8%), and fever (8%).

Table 7 Adverse Events in the Open-Label Phase

Adverse Event	**Total n=79 n (%)**
Somnolence	10 (13)
Increased Appetite	9 (11)
Weight increased	7 (9)
Fever	6 (8)
Vomiting	7 (9)
Dyskinesia	4 (5)
Dystonia	4 (5)
Fatigue	4 (5)
Diarrhea	4 (5)
Nasopharyngitis	5 (6)

8.5 Vital Signs, ECG, and Clinical Laboratory Tests

Pulse Rate and Blood Pressure

In the risperidone low-dose and high-dose groups in the controlled study, there was a small increase in pulse rate, systolic blood pressure, and diastolic pressure compared to the placebo group. The change in pulse rate was -2.4, +3.4, and + 5.5 in the placebo, low-dose, and high-dose groups, respectively. The change in SBP was -.6, +1, and +2.5 in the placebo, low-dose, and high-dose groups, respectively. The change in DSB was +1.4, +1.7, and +0.2 in the placebo, low-dose, and high-dose groups, respectively. These changes are probably not clinically significant. A small proportion of subjects in each treatment group had shifts in vital sign measurements that were potentially clinically significant.

In the open-label study, no subjects had significant changes in vital signs from the baseline of the open-label phases.

Changes in Body Weight

In the controlled study, there were dose-related mean increases in body weight and BMI. The changes in weight were +0.7 kg, +1.2 kg, and +2.4 kg in the placebo, low-dose, and high-dose groups, respectively. The changes in BMI were +0.1, +0.4, and +1.1 in the

placebo, low-dose, and high-dose groups, respectively. Two subjects in the low dose group, and 4 subjects in the high dose group had shifts in BMI to a higher BMI category. There were dose-related mean changes in z-scores for weight and BMI. For weight, the changes were 0.01, 0.11, and 0.23 in the placebo, low-dose, and high-dose groups, respectively. For BMI, the changes were 0.02, 0.06, and 0.5 in the placebo, low-dose, and high-dose groups, respectively.

In the open-label phase, the mean increase in body weight was 4.8 kg, and the mean increase in BMI was 1.5. For z-scores, the increase in weight was 0.32 and the increase in BMI was 0.4.

ECG Findings

In the controlled study, there were no significant mean changes in ECG parameters in any treatment group. No subjects had significant changes in ECG parameters. In the open-label phase, there were no significant mean changes. Three subjects had sinus tachycardia, and 2 subjects had sinus bradycardia. Two subjects had a prolonged QTc interval; however, the QTc was less than 450 msec and the change was < 60 msec in both subjects. There were no significant clinical findings in these 2 subjects.

9. Division of Metabolic and Endocrine Products (DMEP) Consult Reviews

There are 2 separate DMEP reviews. Lisa B. Yanoff, M.D. performed the review of the glucose metabolism data. Ali Mohamadi, M.D. performed the review of the endocrine data. Dr. Yanoff and Dr. Mohamadi have concluded that the glucose metabolism and endocrine findings are not clinically significant, and they recommended that we do not include labeling language related to the glucose metabolism or endocrine findings from the study.

As part of the postmarketing commitment, the Division requested that the sponsor collect long-term data on fasting glucose, fasting insulin, insulin growth factor-1 (IGF-1), growth hormone, and insulin resistance parameters. The sponsor conducted adequate assessments of these parameters in Study RIS-AUT-4002 during the 6-week controlled phase and the 6-month open-label phase. The Division consulted the Division of Metabolic and Endocrine Products for an assessment of the metabolic and endocrine data from the study. The Division posed the following questions to DMEP: 1) What is your assessment of the metabolic and endocrine findings from the controlled and long-term, open-label phases of the study; 2) Are any of the findings potentially clinically significant; and 3) Would it be useful to include any of the findings in labeling.

Glucose Metabolism Findings (Dr. Yanoff)

Dr. has stated that, for diabetes products, DMEP recommends a minimum of 12 weeks for assessing changes in glucose metabolism. Glucose-related adverse events were summarized using the standardized MedDRA query (SMQ) of hyperglycemia/new onset diabetes mellitus. Glucose and insulin samples were obtained with subjects in a fasted

state for at least 8 hours prior to collection. Insulin resistance was quantitatively assessed by the homeostatic model of insulin resistance (HOMA-IR), based on the fasting insulin and glucose values, and calculated using the formula (fasting insulin [uU/L] multiplied by fasting glucose [mmol/L] divided by 22.5). A value above 3 was considered abnormal.

Dr. Yanoff notes that during the short-term and long-term study periods, there were no serious adverse events or adverse events leading to discontinuation related to glucose metabolism. However, there were non-serious adverse events potentially related to glucose metabolism: appetite increased, weight increased, and thirst that appeared to occur in a dose-dependent manner. There were no reports of hyperglycemia, glucose increased, diabetes mellitus, ketoacidosis, hyperosmolar coma, or other adverse events specifically related to hyperglycemia. The table below is reproduced from Dr. Yanoff's review.

Table 8 – AE Potentially Related to Glucose Metabolism (Controlled Phase)

	Placebo N-34 n(%)	RIS Low Dose N=30 n(%)	RIS High Dose N=30 n(%)	RIS Total N=60 n(%)
Appetite increased	2(6)	5(17)	11(35)	16(26)
Weight increased	2(6)	3(10)	4(13)	7(11)
Thirst	0	0	2(6)	2(3)

Source: Attachment 4.20 Clinical Study Report RIS-AUT-4002

For the analysis of laboratory results, Dr. Yanoff focused on the short-term controlled period because the extension period was uncontrolled and voluntary. Dr. Yanoff concluded that there were no clinically relevant changes in mean fasting glucose, mean fasting insulin, or HOMA-IR within or between groups. Table 9 summarizes the results.

Table 9 – Glucose, Insulin, and HOMA-IR in the Controlled Study			
	Placebo n=35	Ris Low Dose n=30	Ris High Dose n=31
Glucose (mg/dl)			
n	22	23	23
Mean Baseline	88	87	92
Mean Value (SD)	88 (6.7)	87 (6.8)	92 (7.0)
Mean Change (SD)	-0.4	-0.1	-0.3
% Change from Baseline	<1%	<1%	<1%
Insulin (µU/mL)			
n	22	22	23
Mean Baseline	8.6	5.0	5.6
Mean Value (SD)	8.6 (9.7)	5.8 (3.1)	7.9 (4.2)
Mean Change (SD)	-0.04 (13.1)	0.74 (3.1)	2.36 (3.5)
% Change from Baseline	<1%	15%	42%
HOMA-IR			
n	21	22	22
Mean Baseline	2.0	1.1	1.3
Mean Value (SD)	2.0 (2.4)	1.3 (0.7)	1.8 (1.0)
Mean Change (SD)	-0.01 (3.0)	0.14 (0.8)	0.5 (0.9)
% Change from Baseline	<1%	13%	38%
Source: Table 49 Clinical Study Report RIS-AUT-4002			

In the glucose outlier analysis, no subjects in the risperidone groups had shifts from normal glucose to abnormal glucose (>125 mg/dL), and no subjects had a shift from normal insulin level to abnormal insulin level (>25 uU/mL) during the short-term, controlled period. In the HOMA-IR outlier analysis, 2 subjects in the placebo group, one in the risperidone low dose group, and 3 in the risperidone high dose group shifted from normal to abnormally high HOMA-IR during the controlled period.

Dr. concluded that the glucose, insulin, and HOMA-IR results were similar for the open-label phase.

In summary, Dr. Yanoff concluded that the study did not demonstrate a clinically meaningful negative effect on glucose homeostasis in children and adolescents over the 6-week period. However, she notes that the study's small sample size and short duration of assessment is a limitation, and no conclusions can be made on the long-term effects of risperidone on glucose metabolism. In addition, it is possible that the study was underpowered to assess glucose metabolism. Dr. Yanoff also concludes that the study results are similar to findings from the previous autism studies, and these results are

already included in labeling for metabolic effects. Furthermore, DMEP considers HOMA-IR and other estimations of insulin resistance that rely on calculated values to be surrogate markers of beta cell function, and they generally do no include this information in labeling for diabetes products. Thus, Dr. Yanoff recommends that we do not include a description of the glucose metabolism data in labeling.

Endocrine Findings (Dr. Mohamadi)

Dr. Mohamadi notes that for the controlled and uncontrolled phases of the study, there were no serious adverse events or adverse events leading to discontinuation associated with factors related to growth, development, or their associated biochemical evaluations (IGF-1 or IGF-BP3). There were no apparent clinically relevant changes in mean insulin growth factor-1 (IGF-1) or insulin growth factor-BP3 (IGF-BP3) in the controlled phase. (The results are summarized in Table 10). In addition, there were no significant changes in these values when analyzed according to age groups (< 12 years or ≥12 years).

Table 10 - Growth-Related Factors in the Controlled Phase (IGF-1 and IGF-BP3

	Placebo n=35	**Ris Low Dose n=30**	**Ris High Dose n=31**
IGF-1 (EIA) (ng/mL)			
n	31	26	27
Mean Baseline	162	168	144
Mean Value (SD)	187 (100)	180 (72)	177 (79)
Mean Change (SD)	25 (38)	12 (40)	33 (64)
% Change from Baseline	15%	7%	23%
IGF-BP-3 (EIA)			
n	30	26	27
Mean Baseline	2980	2702	2837
Mean Value (SD)	2810 (729)	2783 (770)	2917 (703)
Mean Change (SD)	-170 (728)	82 (491)	81 (913)
% Change from Baseline	-6%	3%	3%
Source: Table 55 CSR 4002 ITT analysis set			

Dr. Mohamadi concluded that there were no clinically relevant changes in mean IGF-1 or IGF-BP3 values from the end of the controlled period to the end of the open-label extension phase. In addition, the age subgroup analysis demonstrated that there were no clinically significant changes during the extension period.

In summary, Dr. Mohamadi concluded that treatment with risperidone in the short-term controlled study and long-term open-label period did not result in clinically significant effects on parameters of growth in children and adolescents in the study population. However, Dr. Mohamadi has concluded that there are major limitations regarding the

strength of evidence provided by the results of Study RIS-AUT-4002. The analyses should be considered exploratory or hypothesis generating, at best. The study was quite small, the controlled phase was short-term, and it was not powered for analyses of IGF-1, IGFBP-3, height, or patient subgroups. Because of these limitations, Dr. Mohamadi recommends that we do not include the endocrine data in labeling.

10. Pediatric use/PREA waivers/deferrals

This application did not trigger PREA.

11. DSI Inspections

The results of the DSI inspections are pending.

12. Labeling

We have conducted a detailed labeling review, and we've made numerous revisions to the risperidone PLR label. The specific revisions regarding this additional study are contained in Section 8.4 Specific Populations-Pediatric Use and Section 14. Clinical Studies. The sponsor proposed language to describe the new study in Section 8.4 but not in Section 14. Below is the Division's proposed language for these sections. For Section 8.4, the Division's revisions to the sponsor's proposed language is presented with tracked changes.

8.4 Pediatric Use – Autistic Disorder

(b) (4)

A third study was a 6-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose study to evaluate the efficacy and safety of a lower than recommended dose of risperidone in subjects 5 to 17 years of age with autistic disorder and associated irritability, and related behavioral symptoms. There were two weight-based, fixed doses of risperidone (high-dose and low-dose). The high dose was 1.25 mg per day for patients weighing 20 to < 45 kg, and it was 1.75 mg per day for patients weighing > 45 kg. The low dose was 0.125 mg per day for patients weighing 20 to < 45 kg, and it was 0.175 mg per day for patients weighing > 45 kg. The study demonstrated the efficacy of high-dose risperidone, but it did not demonstrate efficacy for low-dose risperidone.

14.4 Irritability Associated with Autistic Disorder

A third trial was a 6-week, multicenter, randomized, double-blind, placebo-controlled, fixed-dose study to evaluate the efficacy and safety of a lower than recommended dose of risperidone in subjects (N=96) 5 to 17 years of age with autistic disorder (defined by DSM-IV criteria) and associated irritability and related behavioral symptoms. Approximately 77% of patients were younger than 12 years of age (mean age = 9), and

88% were male. Most patients (73%) weighed less than 45 kg (mean weight = 40 kg). Approximately 90% of patients were antipsychotic-naïve before entering the study.

There were two weight-based, fixed doses of risperidone (high-dose and low-dose). The high dose was 1.25 mg per day for patients weighing 20 to < 45 kg, and it was 1.75 mg per day for patients weighing ≥ 45 kg. The low dose was 0.125 mg per day for patients weighing 20 to < 45 kg, and it was 0.175 mg per day for patients weighing ≥ 45 kg. The dose was administered once daily in the morning, or in the evening if sedation occurred.

The primary efficacy endpoint was the mean change in the Aberrant Behavior Checklist – Irritability subscale (ABC-I) score from baseline to the end of Week 6. The study demonstrated the efficacy of high-dose risperidone, as measured by the mean change in ABC-I score. It did not demonstrate efficacy for low-dose risperidone. The mean baseline ABC-I scores were 29 in the placebo group, 27 in the risperidone low-dose group, and X in 28 in the risperidone high-dose group. The mean changes in ABC-I scores were -3.5, -7.4, and -12.4 in the placebo, low-dose, and high-dose group respectively. The results in the high-dose group were statistically significant ($p< 0.001$) but not in the low-dose group ($p=0.164$).

The sponsor has accepted our proposed revisions to sections 8.4 and 14.4. For other sections of labeling, the sponsor has proposed revisions to our proposed version. Most of these pertain to adverse reactions and drug interactions. We're in the process of negotiating labeling with the sponsor.

13. Conclusions and Recommendations

13.1 Recommended Regulatory Action

I recommend approval of the supplemental NDA. I recommend that we release the sponsor from the postmarketing commitment. I do not recommend any additional postmarketing commitments or regulatory actions.

The study demonstrated the efficacy of high-dose risperidone, but it did not demonstrate efficacy for low-dose risperidone. The statistical reviewer, Jinglin Zhong, Ph.D. replicated the sponsor's findings, and she has concluded that the study demonstrated the efficacy of high-dose risperidone but not low-dose risperidone. I agree with Dr. Zhong's conclusions.

In the 6-week placebo-controlled study and the 6-month open-label extension phase, risperidone was reasonably safe and well tolerated in pediatric patients with irritability and related behaviors associated with autistic disorder. The safety profile of risperidone in this study population was highly similar to that in the previous two studies in pediatric patients with irritability and autism. There were no new or unexpected findings. As in the

previous studies, the most important and common findings were increased appetite, increased weight, and sedation.

As part of the postmarketing commitment, the sponsor assessed the effects of risperidone treatment on growth, glucose metabolism, and related endocrine parameters. The two consultants from the Division of Metabolic and Endocrine Products (Lisa Yanoff, M.D. and Ali Mohamadi, M.D.) have concluded that treatment with risperidone in this study was not associated with clinically significant changes in fasting glucose, fasting insulin, homeostatic model of insulin resistance (HOMA-IR), insulin growth factor-1 (IGF-1), and insulin growth factor-BP3 (IGF-BP3). I agree with Dr. Yanoff and Dr. Mohamadi.

In my opinion, the sponsor has fulfilled the postmarketing commitment to conduct an adequate and well controlled study to assess the efficacy of 2 fixed-doses of risperidone, in order to determine the minimum effective dose. The high dose in the approved range was efficacious, but the low dose below the approved range was not. I recommend approval of the supplement. I do not recommend any further postmarketing commitments or regulatory actions. We have included a description of the study and results in the Pediatric Use section and the Clinical Studies section, and the sponsor has accepted our labeling language for these sections. It is not necessary to revise the Dosage and Administration section. We're in the process of discussing with the sponsor revisions to other sections of labeling. The sponsor has proposed revisions to the adverse reactions and drug interactions sections.

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/s/

ROBERT L LEVIN
07/22/2012
I recommend approval of this sNDA.