DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	16 JAN 2006
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
609-730-6212	609-730-3091
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
1125 Trenton-Harbourton Road Titusville, NJ 08560-0200	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 20-272/S-036

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
risperidone	RISPERDAL® Tablets

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*
3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

CODE NAME *(if any)*
R064766

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	0.25, 0.5, 1, 2, 3, 4 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
RISPERDAL® is indicated for the treatment of irritability associated with autism in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☒ Prior Approval (PA)

REASON FOR SUBMISSION
Complete Response to 19 May 2005 FDA Action Letter - AUTISM

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
NDA 20-588/S-024, NDA 21-444/S-008

PLAINTIFF'S EXHIBIT 55

Exhibit
Adusumalli-22
12.20.13

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* **Complete Response to 19 May 2005 FDA Action Letter - AUTISM**

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 505A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Harindra R. Abeysinghe	Harindra R. Abeysinghe, Ph.D. Associate Director, Regulatory Affairs	16 JAN 2006

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560-0200	(609) 730-6212

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Risperidone for the Treatment of Irritability of Autism in Children & Adolescents

Complete Response to the Food and Drug Administration Not Approvable Letter of 19 May 2005

Re: Supplemental New Drug Application (sNDA) 20-272/S-036
(Cross-Referenced to NDA 20-588/S-024 and NDA 21-444/S-008)

January 2006

R064766 (risperidone)

Issue/Report Date: 12 January 2006
Department: Drug Development
Document No.: EDMS-PSDB-5044329: 3.0

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1. SUMMARY AND BACKGROUND TO THE sNDA APPLICATION

This NDA amendment (NDA 20-272) is a Complete Response to the 19 May 2005 Not Approvable Letter, with requirements amended as agreed at the 7 December 2005 End of Review Conference. This amendment is to support an indication for the use of oral RISPERDAL® in the treatment of irritability associated with autism in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums and quickly changing moods.

In a meeting between the Division of Neuropharmacologic Drug Products and Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD, hereafter referred to as the Company) on 1 April 2003, the Division recognized the major unmet medical need in the treatment of autism and informed the Company that an sNDA for RISPERDAL (risperidone) treatment in children and adolescents with autism would undergo a priority review.

On 19 December 2003, the Company submitted a supplemental application (NDA 20-272/S-036). On 18 June 2004, J&JPRD received an Approvable Letter from the Agency acknowledging that the Company had demonstrated the effectiveness of risperidone in the treatment of irritability associated with autism in children and adolescents, as evidenced in the two pivotal trials, and requesting additional information. The Company submitted a Complete Response on 18 November 2004 addressing the issues raised in the 18 June 2004 Approvable Letter.

On 19 May 2005, J&JPRD received a Not Approvable Letter from the Agency. The major reasons cited for this action were lack of identification of a minimally effective dose, unacceptably high risk of adverse events at the lowest dose tested, and continuing concerns over long-term safety. The Company disagreed with the conclusions of the Not Approvable Letter and submitted a Briefing Document on 16 August 2005, to outline the Company's position on the issues raised and request a meeting with the Agency to further discuss the file.

At the meeting held on 7 December 2005, the FDA indicated that they were persuaded by the arguments made in the 16 August 2005 Briefing Document, particularly regarding the safety findings. It was recommended that the Company conduct additional analyses to improve understanding of

the dose response and explore the need for an increase in dose beyond Week 3. The FDA indicated that they could potentially approve the file without the conduct of any additional clinical studies following their review of a Complete Response containing the additional information as discussed at the meeting. Both the Company and FDA minutes of the meeting are provided in Appendix 1.

This submission constitutes a Complete Response to the 19 May 2005 Not Approvable Letter and provides all of the required elements of the Complete Response, as amended by the FDA at the 7 December 2005 meeting, as follows:

a) Indication for risperidone in children and adolescents with autism

b) Dose analyses, including mean dose by week and Sheiner analyses, and dosing recommendations

c) Responses to safety concerns cited in the Not Approvable Letter, including clarification of evaluable EKG data and a reanalysis of dyskinesia events

d) New safety information, including glucose-related data, prolactin and leptin data from studies RIS-USA-150 and RIS-INT-84

e) A safety update, including a pharmacovigilance report and serious adverse events from ongoing pediatric studies

f) Juvenile rat toxicity study report

g) Worldwide literature search and appropriate references

h) Company and FDA minutes from the 7 December 2005 FDA meeting

i) Regulatory status update, with worldwide registration status and foreign labeling with English translations

2. OVERVIEW OF COMPLETE RESPONSE

2.1. Background

Autism is a serious and debilitating neurodevelopmental disorder, with core deficits in communication, socialization and brain processing of stimuli. The disorder is commonly accompanied by a range of behavioral symptoms, stereotypies, posturing, unusual movements, fidgetiness, anxiety, abnormal reactions to even ordinary environmental and social stimuli, and can result in profound dysfunction. There is a clear and significant unmet medical need for this condition, which has no approved medication, often requires life-long supportive care, and may even result in significant periods of institutionalization. Psychosocial and educational treatments remain at the core of management of children and adolescents with autism. However, many children and adolescents who manifest irritability, aggression, temper tantrums, self-injuriousness, and mood instability are unable to remain calm enough to be receptive to, or benefit from, psychosocial and educational treatments. In an autistic child or adolescent with moderate to severe behavior difficulties, psychosocial treatments are ineffective, even in the context of an optimal living and family environment. Medication treatments such as risperidone have the potential to reduce these behavior problems to a significant degree.

In current clinical practice, substantially higher doses (>3 mg/day of risperidone) than those recommended by J&JPRD for autism are often being used off-label (according to prescription information collected from prescription claims database PHARMetrics). Therefore, provision of well-defined dosing guidance that is based on data from controlled studies to treat children and adolescents with autism is critical for the treating physician. Although physicians are familiar with recognizing the adverse events associated with risperidone, there is a pressing need for the label to communicate and educate on the use of safe and effective doses in children and adolescents.

The short-term efficacy was established in two pivotal trials, RIS-USA-150 and RIS-CAN-23, which showed large effect sizes (0.9 and 1.3) for the cluster of symptoms on the primary endpoint, the ABC-I (Attachment 1.1). In fact, the effect sizes in short-term trials were among the largest seen for any psychopharmacological compound. The longer-term relapse prevention trial also demonstrates unequivocal efficacy, with the potential to prevent 55 relapses for every 100 patients who receive maintenance treatment. In

addition, based on a full review of the safety data, J&JPRD concludes that the adverse events in children and adolescents with autism were largely mild to moderate and/or transient, with very few patients being discontinued from the autism trials due to adverse events. Overall, there were no adverse events with risperidone use in autistic children and adolescents that were qualitatively different from those seen with other indications for this treatment.

2.2. Summary of Complete Response

During the meeting with the FDA on 7 December 2005, the Agency acknowledged that the Company's arguments regarding the short- and long-term safety issues, as identified in the 19 May 2005 Not Approvable Letter and addressed in the 16 August 2005 Briefing Document, were reasonable and acceptable. The Agency, however, sought further analyses on dosing and additional data on glucose and prolactin changes, and asked the Company to submit a Complete Response to address these issues. If such approaches (including dose by week for ABC-I and Sheiner analysis) proved useful, they might reasonably substitute for an additional dose response trial.

Following the recommendations of the FDA at the 7 December 2005 meeting and an internal review of data from the pivotal trials, the following analyses of doses of risperidone were conducted: dose over time; maximum dose by response; dose response analysis based on Sheiner et al. (Clin. Pharmacol. Ther. 1989; 46: 63-77); and an analysis by mode dose group. These analyses support a response to risperidone in children and adolescents with autism at doses ≤1 mg per day; some patients respond to higher doses; a plateau of efficacy is reached at the dose given approximately 3 weeks after treatment initiation in the pivotal studies, the maximum daily doses of risperidone in one of the pivotal studies (RIS-CAN-23) at Week 3, when the therapeutic effect reached a plateau, was 1.0 mg in patients <20 kg, 2.5 mg in patients ≥20 kg and 3.0 mg in patients ≥45 kg; and in both studies combined, 90% of patients who respond do so at doses between 0.5 and 2.5 mg/day.

Based on the multiple analyses of data from the pivotal trials, and the desire to promote prudent clinical practice, the Company has provided cautious dosing recommendations. These are further elaborated and clarified in this document and the proposed labeling. They allow physicians to find a low, effective and tolerable dose on an individual patient-by-patient basis. The

dosing recommendations support the target of the recommended doses (0.5 mg/day for patients <20 kg; 1 mg/day for patients ≥20 kg), that any dose increase should be based only on demonstrated lack of efficacy and acceptable tolerability, and that there should be an adequate treatment trial at each dose. Further, after maintenance of efficacy for a reasonable period, every attempt should be made to reduce the dose of risperidone.

Although J&JPRD has indicated its willingness to conduct a fixed-dose Phase 4 trial, it is the Company's position that the currently proposed dosing recommendations will allow the identification of a low individualized effective and safe dose on a patient-by-patient basis. The dosing recommendations give clear guidance about a recommended low dose, an adequate duration of trial at each dose, and provide information about a dose range within which therapeutic benefit most likely lies.

Risperidone is an established, atypical antipsychotic with one of the most comprehensive safety databases in the pediatric and adult populations for a medication of its class. The Company has performed in-depth analyses relating to the FDA's concerns about the safety of risperidone in children and adolescents with autism. Most of these analyses were included in the Complete Response of 18 November 2004, and others have been completed subsequent to the Not Approvable Letter of 19 May 2005 and were described in the 16 August 2005 Briefing Document. Based on these analyses, it is evident that the adverse events in children and adolescents with autism were largely mild to moderate and/or transient, and very few (1.3%) patients discontinued from the trials due to adverse events. Overall, there were no adverse events seen with risperidone use in autistic children and adolescents that were qualitatively different from the adverse events seen in the other indications in children or adults with this treatment. Further, a review of long-term safety, with particular reference to tardive dyskinesia, prolactin, growth and maturation, and glucose, did not elicit any significant findings to cause concern. The FDA acknowledged that the safety analyses and interpretations thereof, as presented in the 16 August 2005 Briefing Document, were persuasive and acceptable. This information is repeated in this Complete Response. In addition, EKG data has been clarified and new data on prolactin, leptin and glucose are included. These data continue to be reassuring over the safety of risperidone in children and adolescents.

Data from the J&JPRD Benefit Risk Management worldwide safety (SCEPTRE) database and a review of serious adverse events from the ongoing pediatric exclusivity trials in schizophrenia and bipolar disorder, show that the adverse events and safety profile of risperidone is qualitatively similar to that in the pivotal trials in autism.

The FDA requested that the Company submit the completed juvenile rat toxicology study and stated that they would follow up with the FDA toxicology reviewer to determine if the juvenile dog toxicology study would be required as a Phase 4 study, following their review and evaluation of the data in the juvenile rat study report. The results of this nonclinical study are presented in Section 5.5 and the completed study report is presented in Module 4. The juvenile toxicity study with risperidone in rats showed that after weaning, body weight gains were generally comparable with controls in all treated groups. Pup pre-weaning development and long bone growth were unaffected, and behavioral tests showed no effect of risperidone. As expected, due to the dopamine D2-antagonistic action of risperidone, serum prolactin levels were increased at the higher doses tested (0.16 and 0.63 mg/kg/day) in male pups, while in female pups the increase was more pronounced, dose-related and present in all treated groups. This prolactin increase was associated with prolactin-mediated changes in the female reproductive system; however, reproductive performance was not affected.

An updated review of literature of the use of risperidone in children and adolescents with autism and other psychiatric disorders further supports the growing evidence for efficacy and safety of this compound. This literature update is consistent with the efficacy and safety findings from previous literature searches and provides no indication of any new safety concerns.

In summary, it is the Company's position there is considerable evidence of a positive benefit-risk to support the approval of risperidone for the treatment of irritability associated with autism in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums and quickly changing moods. Approval by the FDA will not only bring evidence-based practice to children and adolescents suffering from autism, but will also provide appropriate safety and dosing guidance to physicians on the use of risperidone in this population.

3. INDICATION

At the meeting with FDA on 7 December 2005, it was agreed that the indication to be considered was to be confined to the primary endpoint scale, the Aberrant Behavior Checklist Irritability Subscale (ABC-I). This was based on the fact that risperidone demonstrated unequivocal efficacy with large effect sizes for the symptoms of irritability associated with autism in children and adolescents, as measured by the ABC-I subscale, the primary endpoint in the trials. The Agency also indicated that it would be willing to reconsider the language for the indication, providing that it reflects the symptoms assessed in the ABC Irritability subscale.

In the proposed labeling included with this submission (see Label), the indication is described as follows:

"RISPERDAL® is indicated for the treatment of irritability associated with autism in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods."

The specific symptoms in this indication statement are all part of the ABC-I subscale, the primary endpoint in the pivotal trials, and there was statistically significant improvement in each of these symptoms with risperidone treatment. It is the opinion of the Company that elaborating these symptoms, as in the proposed indication above, would allow physicians to more precisely identify target symptoms for treatment.

4. DOSE ANALYSES AND DOSING RECOMMENDATIONS

In the 7 December 2005 meeting, the FDA recommended that further analyses ('dose over time' and 'dose response' analyses) should be applied to the data from the pivotal trials (RIS-USA-150 and RIS-CAN-23), if feasible, to explore the dose response (see Appendix 1). The Agency recommended a method, that of Sheiner et al (Clin. Pharmacol. Ther. 1989; 46: 63-77), to analyze existing data and stated that these analyses could substitute for a fixed-dose study.

The Company had also analyzed dosing data from the pivotal trials in order to identify the lowest doses at which a clinical response is seen and the dose range across patients who responded.

Study of the results from the analyses suggested by FDA at the 7 December 2005 meeting and the analyses conducted by the Company for the 18 November 2004 Complete Response support the dosing recommendations in the proposed label.

4.1. Dose Over Time Analysis

Table 1 summarizes daily dose by week in studies RIS-USA-150 and RIS-CAN-23 (autistic disorder subset); the daily doses summarized in this table are those from the day before a subject's visit for the given week (RIS-CAN-23 did not have Week 4 or 6 visits). To compare dosing trends between the placebo and risperidone groups, the 'risperidone-equivalent' dose is summarized for placebo subjects based on the number of tablets (RIS-USA-150) or volume of solution (RIS-CAN-23) that was administered. Mean dose by week is also plotted in Figure 1 overlayed on mean ABC Irritability subscale scores (ABC-I; ABC assessments were not made at every visit in RIS-USA-150.

In RIS-USA-150, dose in the risperidone group increased through Week 3 (Week 3 mean: 1.76 mg, median: 2 mg) and was stable from Week 4 to Week 8 (means: 1.96 mg to 1.84 mg, medians: 2 mg). Mean ABC-I scores improved throughout the 8-week treatment period, but the rate of improvement was greater from Baseline to Week 4 than from Week 4 to Week 8. Risperidone-equivalent doses in the placebo group suggest continued increasing of the dose through Week 4, when a plateau of approximately 2.5 mg was reached. This seemed to have been in response to the lack of effect evidenced by the relatively flat mean ABC-I curve.

In RIS-CAN-23, dosing patterns in the two treatment groups were similar. In the risperidone group, mean dose increased throughout the study, although at a greater rate from Baseline to Week 3 than from Week 3 to Week 8. This correlates well with the pattern of improvement demonstrated by mean ABC-I scores over time.

Table 1: Dose by Week – RIS-USA-150 and RIS-CAN-23 (Autistic Disorder Subjects)

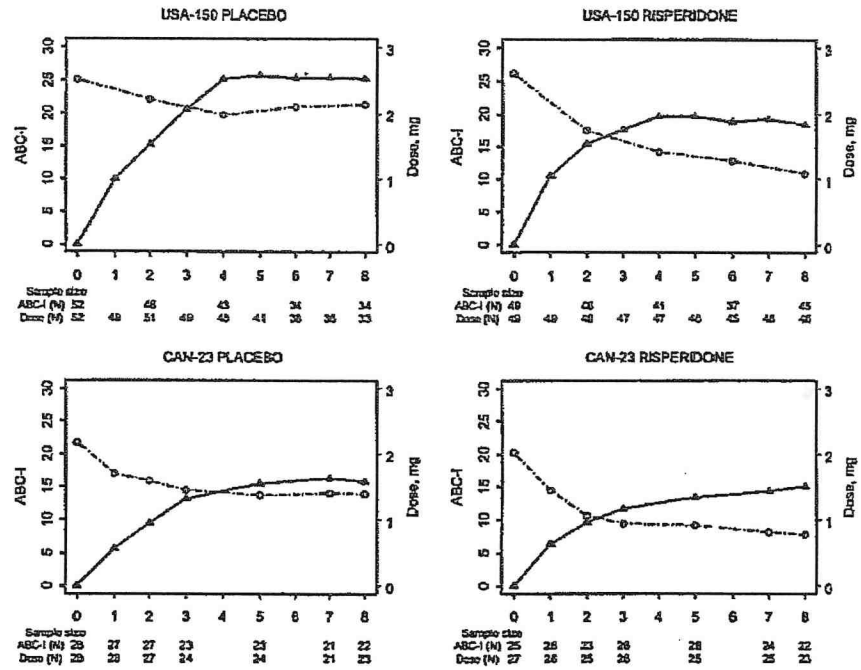
Study	Placebo[a]			Risperidone		
Time point	N	Mean (SD)	Med (Min, Max)	N	Mean (SD)	Med (Min, Max)
RIS-USA-150						
Week 1	49	0.99 (0.22)	1 (0.5, 1.5)	49	1.05 (0.19)	1 (0.5, 1.5)
Week 2	51	1.51 (0.34)	1.5 (0.5, 2.5)	46	1.53 (0.32)	1.5 (1, 2.5)
Week 3	49	2.06 (0.44)	2 (1, 3)	47	1.76 (0.54)	2 (0.5, 3)
Week 4	48	2.52 (0.50)	2.5 (1, 3.5)	47	1.96 (0.63)	2 (0.5, 3.5)
Week 5	41	2.57 (0.44)	2.5 (1.5, 3.5)	48	1.96 (0.62)	2 (0.5, 3.5)
Week 6	38	2.54 (0.54)	2.5 (1, 3.5)	45	1.88 (0.75)	2 (0, 3.5)
Week 7	36	2.54 (0.54)	2.5 (1, 3.5)	46	1.92 (0.65)	2 (0.5, 3.5)
Week 8	33	2.53 (0.53)	2.5 (1, 3.5)	46	1.84 (0.71)	2 (0, 3.5)
RIS-CAN-23						
Week 1	28	0.56 (0.19)	0.5 (0.4, 1.1)	26	0.63 (0.25)	0.6 (0.3, 1.4)
Week 2	27	0.94 (0.32)	0.8 (0.5, 1.7)	25	0.96 (0.36)	0.9 (0.4, 2.1)
Week 3	24	1.31 (0.41)	1.2 (0.8, 2.4)	26	1.17 (0.54)	1 (0.4, 2.8)
Week 5	24	1.54 (0.49)	1.4 (0.8, 2.9)	25	1.34 (0.72)	1.2 (0.5, 4.2)
Week 7	21	1.62 (0.60)	1.4 (0, 3.4)	25	1.43 (0.71)	1.2 (0.5, 4.2)
Week 8	23	1.57 (0.69)	1.4 (0, 3.4)	23	1.51 (0.70)	1.3 (0.7, 4.2)

Source: Attachment A1

[a] Risperidone-equivalent dose is summarized for placebo subjects.

SD: Standard deviation, Med: Median, Min: Minimum, Max: Maximum.

Figure 1: Mean Dose (Triangles) and Mean ABC-I Score (Circles) by Week - RIS-USA-150 and RIS-CAN-23 (Autistic Disorder Subjects)



Individual subject plots are presented in Attachment 1.2; these are of a similar format to Figure 1 and show a horizontal reference line indicating 25% improvement from that subject's baseline ABC-I score.

Dose by week is summarized by subgroup based on baseline body weight (<20 kg; ≥20 kg to <45 kg; ≥45 kg) in Attachment 1.3. The pattern of dose change over time seen in Table 1 was also seen across the weight subgroups: mean dose tended to increase through Weeks 3 or 4, after which mean dose was stable.

Week 3 results (from Attachment 1.3) are shown in Table 2. Mean and maximum doses reached at Week 3 (the time point when improvement on ABC-I reached a plateau) were positively correlated with weight. In RIS-CAN-23, the maximum doses at Week 3 were 1 mg in subjects <20 kg (n=5), 2.4 mg in subjects ≥20 kg and <45 kg (n=19), and 2.8 mg in subjects ≥45 kg (n=2).

Table 2: Dose at Week 3 by Baseline Body Weight – RIS-USA-150 and RIS-CAN-23 (Autistic Disorder Subjects)

Study	Placebo[a]			Risperidone		
Time point	N	Mean (SD)	Med (Min, Max)	N	Mean (SD)	Med (Min, Max)
RIS-USA-150						
Week 3						
<20 kg	6	1.92 (0.20)	2.0 (1.5, 2.0)	4	1.38 (0.75)	1.5 (0.5, 2.0)
≥20 kg, <45 kg	34	1.93 (0.31)	2.0 (1.0, 2.5)	34	1.69 (0.41)	2.0 (1.0, 2.5)
≥45 kg	8	2.63 (0.52)	3.0 (2.0, 3.0)	5	2.50 (0.71)	3.0 (1.5, 3.0)
RIS-CAN-23						
Week 3						
<20 kg	4	1.13 (0.10)	1.2 (1.0, 1.2)	5	0.84 (0.26)	1.0 (0.4, 1.0)
≥20 kg, <45 kg	19	1.30 (0.38)	1.2 (0.8, 2.4)	19	1.17 (0.47)	1.0 (0.5, 2.4)
≥45 kg	1	2.30 (--)	2.3 (2.3, 2.3)	2	1.95 (1.20)	1.95 (1.1, 2.8)

Source: Attachment 1.3

[a] Risperidone-equivalent dose is summarized for placebo subjects.

SD: Standard deviation, Med: Median, Min: Minimum, Max: Maximum.

4.2. Maximum Dose by Response

The distribution of maximum daily dose of risperidone subjects by response status at end point is summarized in Table 3. Overall, 89.6% of responders were treated with a maximum daily dose ≤2.5 mg.

Table 3: Distribution of Maximum Daily Dose by Response Status at End Point - RIS-USA-150 and RIS-CAN-23 (Risperidone Subjects With Autism)

	Nonresponder			Responder			Total		
	n	%	Cum.%	n	%	Cum.%	n	%	Cum.%
Max. daily dose, mg									
>0.5, <=1.0	2	7.4	7.4	2	4.2	4.2	4	5.3	5.3
>1.0, <=1.5	7	25.9	33.3	13	27.1	31.3	20	26.7	32.0
>1.5, <=2.0	8	29.6	63.0	12	25.0	56.3	20	26.7	58.7
>2.0, <=2.5	10	37.0	100.0	16	33.3	89.6	26	34.7	93.3
>2.5, <=3.0	0	0.0	100.0	2	4.2	93.8	2	2.7	96.0
>3.0, <=3.5	0	0.0	100.0	2	4.2	97.9	2	2.7	98.7
>3.5	0	0.0	100.0	1	2.1	100.0	1	1.3	100.0
Total	27			48			75		

Response: >=25% improvement on ABC Irritability subscale and CGI-C rating of much or very much improved at end point

Source: Attachment A2

4.3. Dose-Response Analysis

In their paper, 'Study designs for dose ranging' (*Clin. Pharmacol. Ther.* 1989; 46:63-77), Sheiner, et al discuss a number of study designs to assess dose response and the statistical models to appropriately analyze each study design. One study design discussed was a dose escalation design. In a dose escalation study, all subjects are exposed to the lowest dose for a fixed period of time. At the end of this period, subjects who meet the response criteria are maintained on this dose and subjects who do not meet the same

criteria are increased to the next highest dose. This process is repeated for subsequent periods of equal duration until the total study duration period is completed. At the end of the study, subjects will have been exposed to, and assessed at, varying numbers of doses. Some subjects may have only received the lowest dose, whereas others may have received each dose in the dose range studied. Every subject will have an assessment linked to each dose the subject took. For each subject, therefore, a dose-response curve can be drawn. Individual subject dose-response curves can then be combined using nonlinear mixed effects modeling to arrive at a population dose-response curve.

The designs of the autism studies, RIS-USA-150 and RIS-CAN-23, differ from the dose escalation study design in several respects:

- Subjects were not exposed to each dose for a fixed period of time.
- Dose increases were not determined as rigorously as in a dose escalation study. As shown in Attachment 1.2, subjects had increases in dose at times when ABC assessments were not made and increases in dose occurred for some subjects even after having met predefined response criteria for ABC-I (≥25% improvement from baseline).
- The autism studies had a concurrent placebo control, unlike the dose escalation study design described by Sheiner, et al.

Although these differences in study design may limit the feasibility of applying the statistical model suggested by Sheiner, et. al. to the data from the autism pivotal trials, the pattern of dosing in the studies resembles a dose escalation, as seen in Figure 1 and Attachment 1.2. Dose increased over approximately 3 weeks and was maintained for the rest of the subject's participation in the study. The dose at around Week 3 was presumably based on the subject's response. Therefore, the autism studies do provide ABC-I assessments made at different doses for individual subjects and the nonlinear mixed effect model approach suggested by Sheiner, et. al., can theoretically be applied.

One design difference between the autism studies and the dose escalation study is helpful to the analysis. Having a concurrent placebo control allows for an estimate of a time effect at 0 dose, which in turn allows for an estimate of the effect of dose over and above the effect of time. To demonstrate that there is a time effect in the autism studies, the following nonlinear mixed effects model was applied to the placebo subjects for each study:

Model 1: $y_{it} = (\beta_0 + b_{0i}) - [(\beta_1 + b_{1i})^*(1 - e^{-kt})] + \varepsilon_{it}$ where,

y_{it} = ABC-I score for subject i at Day t,
β_0, β_1 = Fixed effects for baseline (β_0) and change (β_1),
b_{0i}, b_{1i} = Subject-specific random effects for baseline (b_{0i}) and change (b_{1i}),
k = Fixed effect for slope associated with time, and
ε_{it} = Residual error.

Estimates of the fixed effects from this model are summarized in Table 4 (all nonlinear mixed effects modeling in this section were performed using the 'nlme' function in S-Plus version 6.0.).

Table 4: Fixed Effect Estimates From Model 1: Placebo Subjects

Study (N)	Fixed Effect	Estimate (SE)	p-value
RIS-USA-150	β_0	25.1 (0.97)	<0.001
(N=52)	β_1	4.5 (1.00)	<0.001
	k	0.16 (0.09)	0.101
RIS-CAN-23	β_0	21.3 (1.84)	<0.001
(N=28)	β_1	7.7 (1.31)	<0.001
	k	0.11 (0.03)	0.002

Source: Attachment A3
SE: Standard error

The estimates in the above table are consistent with the mean ABC-I plots for the placebo groups in Figure 1. Estimates for β_0 are similar to the observed means for ABC-I at baseline. Improvement in the RIS-CAN-23 placebo group was greater than in the RIS-USA-150 placebo group (β_1 for RIS-CAN-23 is greater than β_1 for RIS-USA-150).

Estimates for the slope parameter, k, are similar for the two studies, but more precisely estimated (smaller standard error) for RIS-CAN-23 than for RIS-USA-150. Individual subject fits from Model 1 are shown in Attachment 2.1 and Attachment 2.2 for RIS-USA-150 and RIS-CAN-23, respectively. Individual subject fits are good for both studies (estimated values from Model 1 fit the observed values well); thus, time is an important explanatory variable, which should be accounted for in a dose response analysis.

Sheiner, et al employed an E_{max} model in their analysis of the dose escalation study design. Model 1, above, can be adapted to an E_{max} model (Model 2, below) including all subjects (with dose for placebo subjects set to 0 mg).

Model 2: $y_{itd} = (\beta_0 + b_{0i}) - \{[(\beta_1 + b_{1i}) + ((E_{max}*d)/(ED50 + d))]*(1 - e^{-kt})\} + \varepsilon_{itd}$, where:

y_{itd} = ABC-I score for subject i at Day t and dose d,
β_0, β_1, b_{0i}, b_{1i} , k are as in Model 1,
E_{max} = Maximal effect,
ED50 = Dose at which half of maximal effect is observed, and
ε_{itd} = Residual error

Model 2 without the $(1 - e^{-kt})$ time effect reduces this model to the model described by Sheiner, et al.

Estimates of the fixed effects from Model 2 are summarized in Table 5. The estimates of ED50 are quite poor for both studies (the standard errors are large relative to the estimates). The estimate is negative for RIS-USA-150 and is just above 0 mg (0.08), i.e., less than the minimum risperidone dose taken, in RIS-CAN-23. Since 0 mg was placebo, the model suggests that any risperidone dose is more effective than placebo but the model cannot detect much of a dose response relationship among risperidone doses.

Table 5: Fixed Effect Estimates From Model 2: Autistic Disorder Subjects

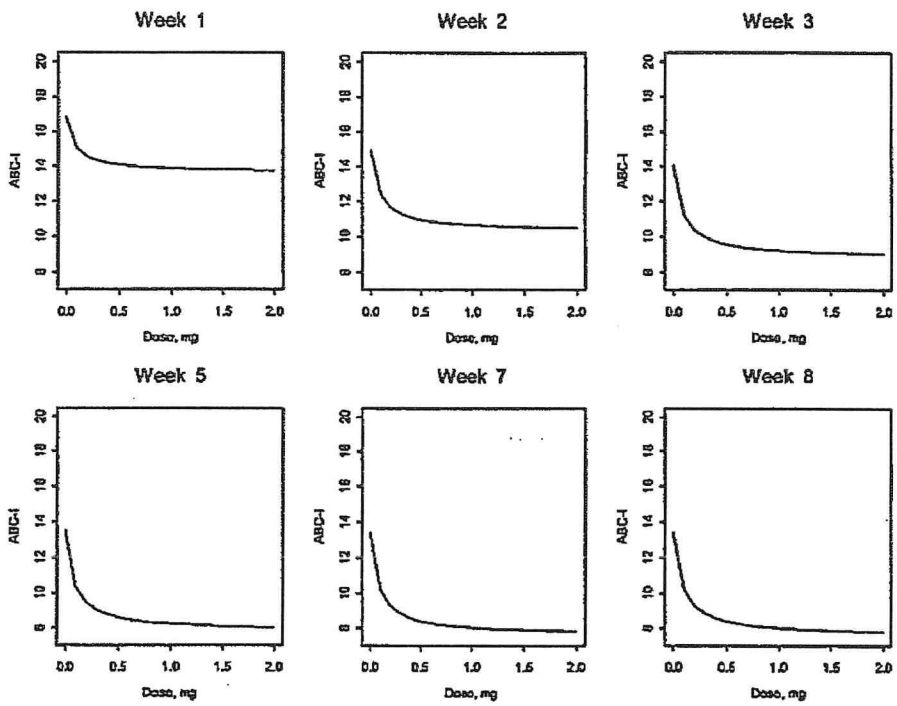
Study	Fixed Effect	Estimate (SE)	p-value
RIS-USA-150	β_0	25.7 (0.78)	<0.001
Placebo, N=52	β_1	6.4 (1.16)	<0.001
Risperidone, N=49	k	0.08 (0.01)	<0.001
	Emax	6.6 (1.83)	<0.001
	ED50	-0.06 (0.26)	0.825
RIS-CAN-23	β_0	20.9 (1.24)	<0.001
Placebo, N=28	β_1	7.6 (1.09)	<0.001
Risperidone, N=27	k	0.11 (0.02)	<0.001
	Emax	5.8 (2.17)	0.008
	ED50	0.08 (0.38)	0.827

Source: Attachment A4
SE: Standard error

Nevertheless, for RIS-CAN-23, estimated dose response curves can be made (estimated dose response curves cannot be made for RIS-USA-150, because of the negative value for ED50). Estimated dose response curves at each week are shown in Figure 2 for RIS-CAN-23. At each week, there is a sharp drop in ABC-I score between 0 mg and 0.5 mg, but very little change between 0.5 mg and 2 mg. This depicts the previous observation that

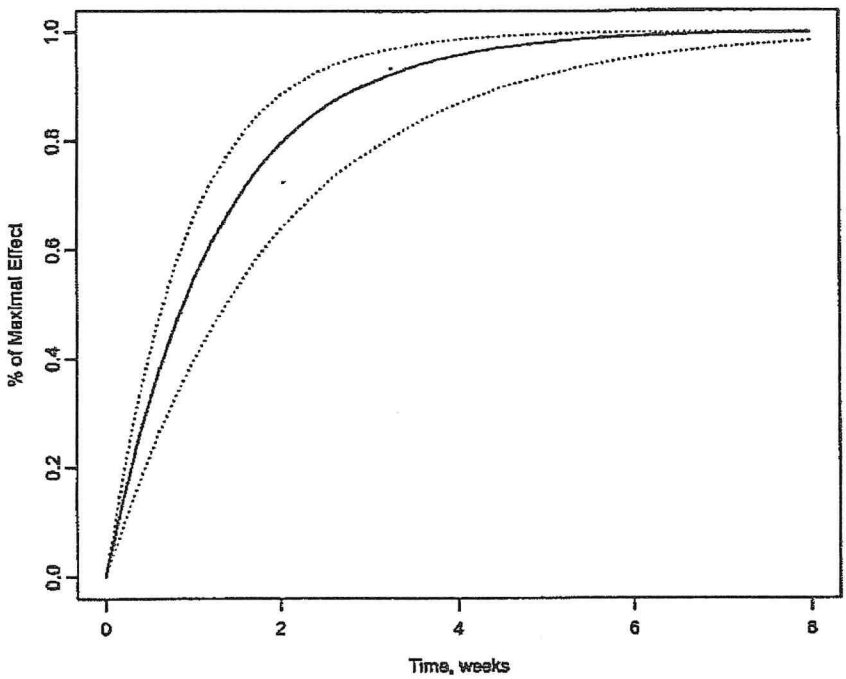
Model 2 is detecting a difference between placebo (0 mg) and risperidone (≥0.5 mg), but not detecting a dose response among risperidone doses (0.5 mg to 2 mg). Figure 2 also shows increasing benefit from Week 1 to Week 3, which is maintained through Week 8. Model 2, therefore, was successful in detecting the ABC-I trend over time shown in Figure 1 for study RIS-CAN-23.

Figure 2: Estimated Dose Response by Week (Model 2) - RIS-CAN-23 (Autistic Disorder Subjects)



The Model 2 formulation allows for an estimate of the percent of maximal effect at a given time. The estimated percent of maximal effect over time for RIS-CAN-23 is shown in Figure 3. Approximately 90% of maximal effect is achieved by Week 3 according to Model 2.

Figure 3: Estimated Percent of Maximal Effect by Week (Model 2) - RIS-CAN-23 (Autistic Disorder Subjects)



The feasibility of the E_{max} model approach was inhibited by the design of the autism studies. In RIS-USA-150, the protocol allowed for subjects to be exposed to up to 3 different (increasing) doses prior to the first post-baseline assessment of the parent-rated ABC at Week 2. Individual subject figures in Attachment 1.2 show that this occurred for most risperidone subjects. For some subjects (e.g., O7009 and Y9003), more than 3 different doses were taken during this time. In the primary analysis, there was already a statistically significant separation between placebo and risperidone for change from baseline in ABC-I at Week 2. Lower doses prior to Week 2 did not have ABC-I assessments associated with them, thereby limiting the feasibility of a dose response analysis for RIS-USA-150. The RIS-CAN-23 protocol also allowed for up to 3 different (increasing) doses during the first 2 weeks, but doses were generally lower than in RIS-USA-150 and RIS-CAN-23 had a Week 1 parent-rated ABC assessment. This allowed for a slightly better estimate of ED50 than in RIS-USA-150. However, this

estimate could only lead to the conclusion that risperidone was more effective than placebo in the dose range studied.

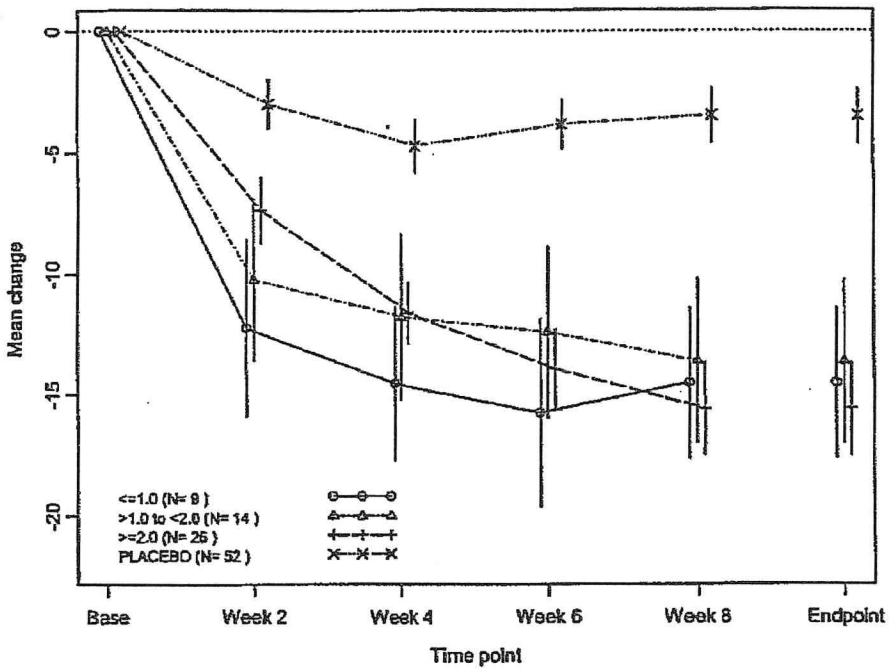
A definite conclusion regarding dose response is not possible given the designs of the autism studies.

4.4. Analyses by Mode Dose Group

In the 18 November 2004 Complete Response, an analysis of change from baseline in ABC-I by mode risperidone dose groups was presented. Results at Week 2 and endpoint are summarized for each study in Attachment 3.1. Mean change over time is plotted for each study in Attachment 3.2; the plot for RIS-USA-150 is also shown below (Figure 4).

These analyses showed that risperidone-treated subjects reached their optimal effective response at end point, but with different time courses and at different mode-dose levels. At Week 2, those subjects in the ≤1 mg/day mode dose group reached the most pronounced response, and this response was maintained with limited further mean improvement at subsequent evaluations in both studies. Therefore, a treatment duration at the recommended dose of 1 mg or lower (0.5 mg in children <20 kg body weight) should be maintained for a minimum of 14 days.

Figure 4: Change From Baseline (Mean ± SE) in ABC Irritability Subscale (LOCF) - RIS-USA-150



There was evidence to suggest that, although many patients do show early improvement at low doses, some patients benefit from higher doses. Specifically, a subset of patients with mode doses between >1 and <2 mg/day, and with mode doses ≥2 mg/day, clearly demonstrated improvement at endpoint despite less than optimal improvement at Week 2 (Attachment 3.1, Attachment 3.2). The Company acknowledges, however, that some of those patients might eventually have responded on their initial low dose as well.

4.5. Conclusions From the Dose Analyses

- Clinical response can be seen in some patients at doses ≤1 mg/day of risperidone. Subjects responding at this dose level reached the most pronounced response within 14 days.
- There is a subset of patients who did not respond maximally at a low dose but did so at a higher dose.
- Among risperidone treated subjects, mean ABC-I score improved as mean dose increased during the first 3 to 4 weeks of each study; mean dose and mean ABC-I scores were stable through Week 8, indicating a plateau in clinical efficacy from approximately Week 3.

- 90% of patients who showed a clinical response (>25% improvement on the ABC-I) did so with a daily dose of between 0.5 mg and 2.5 mg risperidone.
- In one of the pivotal trials (RIS-CAN-23) at Week 3, when the therapeutic effect reached a plateau, the maximum daily dose was 1.0 mg in patients <20 kg, 2.5 mg in patients >20 kg and 3.0 mg in patients >45 kg.
- Despite the limitations posed by a flexible dosing design in the pivotal trials, these additional analyses offer useful information and, thus, are the basis of the dosing recommendations below (see Label).

4.6. Dosing Recommendations

In current clinical practice, substantially higher doses than those recommended by J&JPRD in the proposed labeling for autism are often being used off-label; therefore, providing well-defined dosing guidance that is based on data from controlled studies to treat children and adolescents with autism is important. Although physicians are familiar with recognizing the adverse events associated with risperidone, there is a pressing need for communication and education about the use of safe and effective doses in children and adolescents.

The dosing recommendations below and presented in the proposed label (see Label) are based both on analyses of data from the pivotal trials and a prudent and cautious clinical approach to treatment, taking into account efficacy, and tolerability and safety. These recommendations are different from the proposals in the Complete Response of 18 November 2004 and the 16 August 2005 Briefing Document and is reflective of the aforementioned additional analyses, as discussed with the FDA at the 7 December 2005 meeting.

The key components of the dosing recommendations, as mentioned in the label, are outlined below:

a) The underlying clinical principle is to 'start low, and go slow'.
b) After initiating risperidone treatment at 0.25 mg/day and 0.5 mg/day for patients <20 kg and >20 kg, respectively, it is proposed that dose increments to the recommended dose of 0.5 mg/day and 1 mg/day for <20 kg and >20 kg patients may be done from Day 4 onwards.
c) The recommended dose should be tried for at least 14 days, if tolerable.
d) Further dose increments of 0.25 mg/day and 0.5 mg/day for <20 kg and >20 kg patients should be based on efficacy and tolerability assessments and should also be given a trial of not less than 14 days at each dose.

e) Analyses demonstrated that 90% of patients who showed a response (>25% response on the primary endpoint, ABC-I subscale) received doses of risperidone between 0.5 mg and 2.5 mg per day.

f) In one of the pivotal trials (RIS-CAN-23), at Week 3, when the therapeutic effect reached a plateau, the maximum daily dose of risperidone was 1.0 mg in patients <20 kg, 2.5 mg in patients >20 kg, and 3.0 mg in patients >45 kg.

g) Gradual lowering of doses should be attempted after efficacy has been achieved and maintained, to ensure adequate balance of efficacy and safety.

h) Patients experiencing persistent somnolence may benefit from risperidone being administered once daily at bedtime or half the daily-dose twice daily (RIS-CAN-23; see "Somnolence" in Section 5.1.1.4. of this document).

Although the Company has indicated its willingness to conduct a fixed-dose Phase 4 trial, it is the position of J&JPRD that the currently proposed dosing recommendations (see Label) will allow the identification of a low individualized effective and safe dose on a patient-by-patient basis. The dosing recommendations give clear guidance about a recommended low dose, an adequate duration of trial at each dose, and provide information about a dose range within which therapeutic benefit most likely lies.

5. OVERVIEW OF SAFETY

In response to the Agency's concerns over the safety of risperidone in children with autism, a thorough review of the safety of risperidone in children was undertaken. Much of this information was provided in the 18 November 2004 Complete Response, supplemented by information in the 16 August 2005 Briefing Document. In the 7 December 2005 meeting, the FDA acknowledged that the Company's arguments regarding the short- and long-term safety issues, as addressed in the 16 August 2005 Briefing Document, were reasonable and acceptable. The Agency, however, sought additional data on glucose and prolactin changes, and J&JPRD also agreed to present new safety data available from RIS-USA-150 and RIS-INT-84.

The key conclusions from the safety review are as follows:

- The adverse events in children and adolescents with autism were largely mild to moderate and/or transient, and rarely associated with treatment discontinuation. None of these adverse events were qualitatively different than those seen in other indications in either children or adults. Most adverse events were seen across a range of doses. Coding of particular adverse events (akathisia and tardive dyskinesia) was reviewed and confirmed to be accurate.
- A review of long-term safety, with particular reference to tardive dyskinesia, prolactin elevation, and growth and maturation, did not elicit any specific or significant findings of concern.
- Although the data are limited, there is no evidence that risperidone treatment has an adverse effect on cognitive functioning.
- New safety information, subsequent to the 18 November 2004 Complete Response and the 16 August 2005 Briefing Document, is limited to additional data on prolactin and leptin (from Study RIS-USA-150), and data from a 1-year open-label extension study in children with Disruptive Behavioral Disturbances (DBD) (RIS-INT-84), including glucose data:
  - With respect to prolactin, the findings in autism were consistent with those observed previously over a similar time course in children and adolescents with DBD: increases in prolactin peaked during short-term treatment and subsequently tended to decrease with longer-term exposure.
  - For leptin, increases in the autism population were similar to those observed in DBD, but the clinical relevance of these changes is uncertain.

- There were no negative effects on glucose regulation in the RIS-INT-84 study, and the combined data on glucose, insulin, and lipids indicated no increased risk of metabolic syndrome.
- Analyses of weight have also confirmed that initial increases occur through Month 3, and thereafter generally remain stable.

- On the basis of a cumulative review of postmarketing experience in children and adolescents, no new pattern of adverse drug reactions was identified for pediatric over adult populations treated with risperidone. Although an increased frequency of weight gain in children and adolescents was seen, which may indicate that children are more susceptible to this labeled adverse drug reaction than other age groups, this cannot be determined from the current dataset. No disproportionality for children or adolescents was observed with respect to events involving suicide or suicidal ideation, disorders of glucose, lipid or other metabolism, hyperprolactinemia, extrapyramidal syndromes, or sedation.
- Four clinical studies of risperidone in adolescent subjects with schizophrenia or children and adolescents with bipolar disorder were ongoing as of 30 November 2005. Eighty-five serious adverse events have been reported for 65 cases for the period from 1 July 2004 to 30 November 2005. In these ongoing studies in children and adolescents, the most frequently reported serious adverse events were schizophrenia (22 subjects), suicidal ideation (10 subjects), bipolar disorder (6 subjects), and psychotic disorder (6 subjects). One subject completed suicide and 4 subjects attempted suicide. These data are qualitatively and quantitatively similar to those reported in the previous safety update (of 18 November 2004) and offer no new safety information of clinical relevance.
- Results of a nonclinical study, in which rat pups were given oral risperidone (0, 0.04, 0.16 and 0.63 mg/kg/day) from Day 12 to Day 50 of age, indicate the occurrence of ptosis at 0.16 and 0.63 mg/kg due to the exaggerated pharmacological activity of the test compound. Body weight gain between Days 12 and 21 was lower at all dose levels, but improved after Day 21 of age and normalized by Day 50. Long bone growth was unaffected. Behavioral tests showed no effect of risperidone. Serum prolactin levels were increased at 0.16 and 0.63 mg/kg/day in male pups, while in female pups the increase was more pronounced, dose-related and present in all treated groups; this increase was associated with prolactin-mediated changes in the female reproductive system, but reproductive performance was unaffected.
- Based on an updated review of worldwide literature, safety of risperidone in children and adolescents with autism was consistent with previously published literature; weight gain, sedation, and extrapyramidal symptoms were reported most frequently. Safety information reported in studies of nonautistic patients was consistent

with safety findings in studies of children and adolescents with autism. This literature update is consistent with the previous literature summaries provided in the initial submission and the 18 November 2004 Complete Response.

- Based on an overall review of the safety information from the pivotal trials and a recent pharmacovigilance review, the Company has proposed precautionary text with regards to somnolence, weight gain, and hyperprolactinemia in the labeling (see Labcl).

5.1. Responses to Safety Concerns Cited in the Not Approvable Letter

In the Not Approvable Letter of 19 May 2005, the Agency stated:

"The fact that a lowest effective dose has not been identified, although never ideal, may be acceptable if the lowest dose studied is not associated with an unacceptable risk. We continue to believe that the lowest doses used (in your analyses, <1 mg/day as a modal dose) are associated with an unacceptably high incidence of important adverse events (e.g., somnolence, 'parkinsonism', confusion, fatigue), and may be associated with an unacceptable risk of long-term consequences (e.g., tardive dyskinesia, sequelae of prolonged increased prolactin)."

In Request 4 of the 19 May 2005 Not Approvable Letter, the Agency commented that many cases the Company had coded as nervousness, anxiety, or agitation, might have been *"more appropriately coded as 'akathisia'"* and that many of the events coded as 'dyskinesia' seemed to be *"more appropriately coded as 'tardive dyskinesia'"*. The Agency also recommended that the Company should *"...analyze the akathisia items in the various relevant rating scales performed in your controlled trials."*

The Company provided information to address each of the issues in the 16 August 2005 Briefing Document; the following sections repeat the specific analyses and arguments presented therein. Further information to address other requests in the Not Approvable Letter and further requests from the 7 December 2005 meeting is presented in Section 5.2.

5.1.1. Adverse Events

5.1.1.1. Overview of Adverse Events

The incidence of adverse events in children and adolescents with autism who received risperidone in the pivotal trials should be viewed in the following context:

- In one of the pivotal studies, RIS-USA-150, many adverse events were elicited through a questionnaire, rather than via spontaneous reporting as is commonly performed in clinical trials. This may have led to an increased reporting of some adverse events, e.g., fatigue.
- Children with autism commonly have fidgetiness, movements and posturing that are inherent to this medical condition. These symptoms can often be incorrectly reported as adverse reactions to medication or can even mimic extrapyramidal symptoms (EPS). There was no systematic screening for movement disorder inherent to autism through parental interviews at baseline. ESRS, AIMS and physical examination at baseline are cross-sectional clinical assessments. These cannot substitute for a history from a parent or other caregiver, as some movement problems are not continuously present, may come and go intermittently within days, and may not be present at the time of an ESRS or other rating assessment. Follow-up data from investigators on all of the dyskinesia cases that were reported as "not recovered' have confirmed that there were either a variety of involuntary movements at baseline, and/or that the involuntary movements reported as "dyskinesia' were intermittent manifestations of the underlying autistic disorder, or early onset transient movement disorders with resolution of symptoms (see patient narratives [Attachment 7] for follow-up information).
- The vast majority of children and adolescents with autism who experienced somnolence or other adverse events were treatment-naïve. This is in contrast with patients, especially adults, being treated for other psychiatric disorders, who have often experienced and adapted to adverse events of psychotropic medications before participating in a formal study. Antipsychotic treatment naïve patients are known to be more sensitive to the adverse events of these drugs.

In patients with autism, adverse events occurred in 82.5% (66 of 80) of placebo-treated patients and in 98.7% (75 of 76) of risperidone-treated patients (Attachment 4.1).

Adverse events in the pivotal trials of risperidone in children and adolescents with autism were largely mild to moderate and transient. Somnolence was the most frequently reported adverse event in the risperidone group (51/76, 67.1%; Attachment 4.1), the majority of events being reported as mild (61%) or moderate (35%) (Attachment 4.2).

The number of discontinuations due to adverse events in the autism trials was very low, with 1 (1.3%) of 80 placebo-treated patients and 1 (1.3%) of 76 risperidone-treated patients discontinuing because of an adverse event during the DBPC autism trials (Attachment 4.3). These data support the conclusion that risperidone was well tolerated in the vast majority of subjects with autism.

Overall, the findings described above for children and adolescents with autism are similar to the safety data from trials in risperidone-treated children and adolescents with DBD or other PDD.

5.1.1.2. Review and Analysis of Adverse Events

In order to ascertain the clinical meaningfulness and accuracy of coding of adverse events, the following review and analyses of adverse events were performed by:

- Incidence of adverse events by mode dose group
- Severity, onset and duration of adverse events of interest
- Review of the adverse event of akathisia
- Review of all cases of dystonia, and more recent follow-up information on cases of dyskinesia, in order to determine if they were accurately coded and that they did not have tardive dystonia or tardive dyskinesia

5.1.1.3. Adverse Events and Dose

A major challenge in the course of these analyses was that there were very few patients who had moderate or severe adverse events, and very few patients had remained on a mode dose of 1 mg or lower at the end of the trials. The flexible dosing design of the pivotal trials did not allow for analysis of a dose response relationship with adverse events.

In our Complete Response of 18 November 2004, we summarized adverse events by mode dose group (≤1 mg, >1 to <2 mg, and ≥2 mg, Attachment 4.4). For many adverse events, most notably somnolence, confusion, and Parkinsonism, there was a higher incidence of adverse events in the lower mode dose groups. Conversely, for other adverse events such as fatigue, there was a suggestion of increasing incidence with higher mode dose group. The finding of adverse events at lower doses may reflect a combination of the majority of patients being medication-naïve and the trial using a flexible dose titration design, where investigators likely adjusted dose on the basis of efficacy as well as tolerability findings.

5.1.1.4. Adverse Events of Clinical Interest

The findings below should be interpreted together with data submitted in the Complete Response of 18 November 2004. A summary of the analyses for adverse events of clinical interest in children and adolescents with autism is provided below. It is important to note that in one of the pivotal trials, RIS-USA-150, some adverse events were elicited via a specific side-effect questionnaire, which would be expected to yield a higher incidence for those adverse events.

Extra-Pyramidal Symptoms (EPS):

Extensive training of investigators was provided on evaluation of adverse events and standard scales for EPS. In the autism trials, there was a higher frequency of EPS in the risperidone group (27.6%) than in the placebo group (10.0%) (Attachment 5.1); however, there was no consistent pattern across mode dose groups in the occurrence or severity of these events.

Parkinsonism was highest in the ≤1 mg/day mode dose group (4/17 [24%] vs. 1/30 [3%] in the >1 to <2 mg/day mode dose group and 1/29 [3%] in the ≥2 mg/day mode dose group [Attachment 4.4]). Overall, the incidence of parkinsonism was 8% (6/76) in the risperidone group and 0% in the placebo group (Attachment 5.1). Of the 6 events of parkinsonism in the risperidone group, the dose at onset was ~0.5 mg for 2 subjects, 1 mg for 1 subject, and ~2 mg for 3 subjects (Attachment 5.2), clearly demonstrating that this event occurred over a broad range of doses.

Because these were few parkinsonism-like events, the incidence of "any EPS-related AE" has also been summarized (Attachment 5.3). Again, no evidence of a relationship of this group of AEs to mode dose group (29% for ≤1 mg/day, 30% for >1 to <2 mg/day, and 21% for ≥2 mg/day) was observed. A total of 41 EPS events were reported for the 20 patients on risperidone who had at least one EPS adverse event. The majority of these events were mild, with variable onset and duration. Of the 41 EPS adverse events in the risperidone group, 31 (76%) occurred at a dose above 1 mg.

Of note, the majority of patients enrolled in the studies were treatment-naïve. In clinical practice, it is understood that these patients may have a variety of movements and abnormalities of muscle tone that are inherent to this medical condition, including odd behavior and posturing.

No conclusions can be drawn regarding the relationship of dose with EPS as the trial design, using flexible dosing, did not study this particular relationship.

Akathisia:

Following the 19 May 2005 FDA Not Approvable Letter, further analyses were performed on the data from the autism trials to rule out the possibility of miscoding of 'akathisia'. The results showed that if all events of treatment-emergent agitation, nervousness and anxiety are assumed to represent possible akathisia and were thereby re-coded as EPS, the incidence of "EPS" increases significantly in the placebo group, but only minimally in the risperidone group. The analyses show that 21 (26.3%) of 80 patients in the placebo group and 31 (40.8%) of 76 patients in the risperidone group had "EPS" with the inclusion of these terms (Attachment 5.1). This is a narrower difference than that based on the original selection of EPS-related adverse events (10.0% versus 27.6%), since the majority of the terms coded as agitation or nervousness occurred in the placebo group. In other words, no increase in the relative incidence of EPS with risperidone vs. placebo is demonstrated, suggesting that these cases are much more likely to represent symptoms of the underlying psychiatric disorder, rather than undiagnosed akathisia. Consistent with the above, most of the additional patients with agitation, nervousness, and anxiety were in the placebo group rather than the risperidone group (13 vs. 10).

In Attachment 6, baseline and end point scores on the akathisia items of the ESRS ('akathisia' and 'restless, nervous, unable to keep still') are summarized for the combined DBPC trials of risperidone in adolescents and children in which ESRS was assessed (DBD trials RIS-NED-9, RIS-CAN-19, and RIS-USA-93, and autism trial RIS-CAN-23) and also separately for the patients with autism in RIS-CAN-23. ESRS was not assessed in RIS-USA-150. Median scores for both items were 0 (absent) for both groups at baseline and at end point. Mean changes (reductions) at end point were numerically larger in the risperidone group than in the placebo group, suggesting that these items may have been measuring symptoms of the underlying psychiatric disorder.

Tardive Dyskinesia:

Although no cases were coded as tardive dyskinesia among risperidone-treated patients with autism, the narratives of all events coded as

"dyskinesia" were closely reviewed, as per the Division's request, and are provided in Attachment 7. We have also obtained further clinical follow-up information from the investigators, for those cases where the symptoms were reported as unresolved during the trials. All 5 patients with events coded as "dyskinesia" in double-blind placebo-controlled studies were risperidone-treated patients with autism. All of the dyskinesia events for these 5 patients had an early onset, between Day 2 and Day 45 after treatment initiation. According to the generally accepted definition, treatment-emergent tardive dyskinesia occurs after at least 3 months of exposure to antipsychotic medications (American Psychiatric Association 2000). Two of the 5 patients had a reported outcome of recovery during the clinical study, suggesting that these were not tardive dyskinesia. In all 3 remaining patients, new follow-up information confirmed that the movements were either present at baseline, before administration of risperidone, or were intermittently present during treatment and eventually resolved, and the investigators thus concluded that these events were very unlikely to be tardive dyskinesia. Based on clinical course, time of onset of dyskinesia symptoms relative to initiating risperidone treatment, and eventual resolution of symptoms, these events cannot be categorized as tardive dyskinesia. As mentioned previously, patients with autism have a variety of mild to severe movement, posturing and stereotypies that can be incorrectly assessed by a rater as dyskinesia associated with medication treatment.

To further ensure that there were no undiagnosed cases of tardive dyskinesia or tardive dystonia, all cases of "dystonia" in the double-blind placebo-controlled autism trials were reviewed in detail. These consisted primarily of adverse events with the preferred-terms "hypertonia" or "muscle contractions involuntary" mapped to the EPS grouped-term "dystonia." There were 14 patients with dystonia (5 placebo, 9 risperidone). Particular attention was paid to past medical history, neurological examination, verbatim description of the adverse events, severity, duration and outcome of the adverse event (recovered or not recovered), associated adverse events, and AIMS score. With the exception of one moderate adverse event, all of the events were classified as mild in severity. Outcome was reported as 'recovered' in all except 2 placebo patients, and duration ranged from 2 to 16 days for the recovered events. Therefore, it does not appear that there were any events of tardive dyskinesia/dystonia among risperidone-treated patients with the adverse event of dystonia.

Somnolence:

Somnolence was the most frequently reported adverse event in the autism trials (risperidone: 51/76, 67.1%; placebo: 18/80, 22.5%; Attachment 4.1). According to the severity of somnolence, in the risperidone group, 61% of the events were mild, 35% were moderate and 4% were reported as severe (Attachment 4.2); the corresponding numbers for the placebo group were: 89% (mild) and 11% (moderate). There were no reports of somnolence of severe intensity in the placebo group. Somnolence was more frequent in patients in the ≤1 mg and >1 mg to <2 mg mode dose groups than in the ≥2 mg mode dose group (77-82% vs. 48%; Attachment 8). Although frequent, somnolence was most often mild and transient in duration. Somnolence was most frequently a time-related phenomenon, with the peak incidence occurring at Weeks 1 to 2, then decreasing over subsequent weeks. The median duration of this event was 16 days for risperidone and 8.5 days for placebo. A total of 89 events of somnolence were reported for the 51 risperidone subjects with autism who had at least one event. The number of events with onset after Day 15 increases with increasing mode dose group (Attachment 8), from 29% (7/24) in the ≤1 mg mode dose group, to 37% (15/41) in the >1 to <2 mg mode dose group, and 50% (12/24) in the ≥2 mg mode dose group. These data suggest that while some patients experience somnolence early and may remain on low doses, for others treated with higher doses of risperidone, there may be a later onset of somnolence. Nevertheless, for these patients as well, the event is generally mild, transient, and not treatment limiting. Somnolence has been reported in all adult and pediatric trials performed to date with risperidone. The incidence of somnolence may be higher in children, including this autistic population, because they were largely treatment- naïve or more prone to this adverse event, albeit for a limited period of time.

In the event of somnolence, the protocol for RIS-CAN-23 allowed the investigator to use twice daily dosing or a once daily dose at bedtime, rather than a single morning dosing schedule. The majority of risperidone-treated subjects with changes in dosing schedule (20 [70.0%] of 29 subjects) concomitantly reported somnolence. Somnolence was resolved in 18 of the 20 subjects after change of dosing schedule, either by dividing the daily dose into twice daily (6 of 15 subjects), or by changing once daily drug administration from morning to evening (12 of 14 subjects).

Fatigue:

Fatigue was more frequent in the ≥2 mg mode dose group (16/29 [55%]) than in the lower dose groups (5/17 [29%] for the ≤1 mg/day mode dose group and 11/30 [37%] for the >1 to <2 mg/day mode dose group) (Attachment 4.4). Similar to somnolence, onset of the first event of fatigue was most frequently during Weeks 1 to 2. Events of fatigue tended to have longer duration than somnolence (Attachment 9); median duration of this event was 32 days for risperidone and 5 days for placebo. In the majority of cases this adverse event was rated as mild in severity, with a few cases rated as moderate, and none resulted in discontinuation.

Prolactin:

It is well known that prolactin levels differ with age and sex throughout puberty; however, there are no well-established normative reference data for prolactin in children and adolescents.

As reported in the Safety Update (18 November 2004), a detailed review of prolactin in children with DBD treated for up to 12 months showed that, while mean prolactin levels increased in the first few weeks of treatment, mean levels peaked at approximately Weeks 4 to 6 and returned to within normal limits by Month 12. An analysis of the safety data showed no correlation between prolactin levels and adverse events that are potentially attributable to prolactin.

Further, in a separate analysis in children and adolescents with DBD who were treated with risperidone for up to 12 months (Dunbar et. al., Amer. Jour. Psychiat, 2003), there was no delay in growth and maturation in children and adolescents treated with risperidone. Despite transient increases in prolactin, the children grew according to published population reference standards and continued to mature as expected when compared with published norms. Thus, the data showed that there was no interference with either growth or pubertal progression in children and adolescents treated with risperidone.

See Section 5.2.2.1 for additional information on prolactin effects.

Confusion:

Confusion was only reported as an adverse event in the ≤1 mg and ≥2 mg mode dose groups (2/17 [12%] and 2/29 [7%]), respectively (Attachment 4.4). The total number of reported cases was 5 (1 subject had

2 reports), 3 of which were classified as mild and 2 as moderate in severity, with duration varying from 1 to 16 days (median duration 8.5 days) (Attachment 10). Based on the infrequency, and limited severity and duration, this does not appear to be a clinically meaningful adverse event. There was no incidence of confusion reported in the >1 to <2 mg mode dose group or the placebo group; thus, there was no consistent pattern across the mode dose groups in the occurrence of this adverse event.

5.1.2. Clarification of Additional Queries

The following sections provide responses to the Agency's queries regarding clarification of EKG data (Request 2) and interpretation of cognitive testing (Request 6) indicated in the Not Approvable Letter.

Clarification of EKG Data in RIS-CAN-23:

In Request 2 of the 19 May 2005 Not Approvable Letter, the Agency questioned a discrepancy between the apparent number of patients with EKG data available (66, as indicated by the Agency) and the number of patients included in the data summary tables (77) provided by J&JPRD. The Company can provide the following clarification.

In the RIS-CAN-23 study report, qualitative results of post-baseline ECGs were available for 78 of 79 subjects. In response to the FDA's request for quantitative ECG data, the Company obtained the ECG tracings from the investigative sites as follows:

- No EKG information were available for one subject
- 65 original tracings were available
- 12 copies of tracings were provided (all from one investigator site)
- One tracing was not obtained due to lack of patient consent

Measurements were made for all 77 tracings, or copies thereof, that were obtained and it was these results that were summarized in the 18 November 2004 Complete Response, in the response to Question 6 of the Approvable Letter of 18 June 2004.

Cognitive Testing:

In Request 6 of the 19 May 2005 Not Approvable Letter, the Agency questioned the interpretation of cognitive testing, considering the small number of patients for which cognitive tests were actually performed.

The Company acknowledges that the pivotal trials, which were not primarily designed to examine cognition, yielded limited but useful data in this domain. Since many subjects were limited by their intellectual capacity or behavioral problems, cognitive testing could not be performed on all subjects. A battery of cognitive tests was selected by the RUPP network to assess broad domains of cognitive function in study RIS-USA-150. In general, no significant differences in these assessments of cognitive function were found between the risperidone and placebo groups at end point. In fact, the only significant difference seen between groups at end point favored risperidone and was in the recognition memory task of the Verbal Learning Test. These results suggest that risperidone treatment did not negatively impact, and perhaps improved, the ability of patients to complete a wide range of tests measuring cognitive domains, including eye-hand coordination, attention, verbal learning, memory, reasoning and problem solving.

In Request 6 of the 19 May 2005 Not Approvable Letter, the Agency also queried the apparent calculation of differences from baseline in the absence of baseline measurements for some tests in this request.

In the 18 November 2004 Complete Response, a table (Table 20, Page 50-51, reproduced in part below) presented descriptive statistics summarizing the change from baseline to end point of Part 1 for each cognitive test. This table included only subjects who had post-baseline observations (i.e., an end point). Some subjects with post-baseline data did not have baseline observations, which is why the N at baseline is often less than the N at end point: subjects with post-baseline data but no baseline data were included in the end point N but not in the baseline N. Change from baseline, however, was calculated only for subjects who had both baseline and end point data. The table presented includes a column showing N for change at end point. In every case, N for change at end point is the same as the N at baseline. That is, only subjects with both baseline and end point values had differences calculated.

Reproduction of Table 20 From November 2004 Complete Response:

Table 20: Descriptive Statistics of Parameters From 5 Measures of Cognitive Function in RIS-USA-150

(Analysis Set: Intent-to-Treat; Subjects With End Point Observations Only)

Test	Placebo						Risperidone					
Parameter				Change						Change		
Timepoint	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Perdue Pegboard Task												
Dominant Hand												
Baseline	21	18.9	11.8				24	27.9	17.6			
End point	29	23.5	12.3	21	5.6	9.5	33	25.7	16.0	24	1.3	8.9
Drops Dominant Hand												
Baseline	21	2.0	2.2				24	2.2	2.1			
End point	29	4.1	7.2	21	0.8	3.5	33	3.4	3.9	24	1.4	4.8
Non-Dominant Hand												
Baseline	21	17.0	12.4				24	23.0	17.2			
End point	29	18.4	10.4	21	1.9	9.3	32	22.5	14.6	24	2.0	8.4
Drops Non-Dominant Hand												
Baseline	21	1.9	2.4				24	3.5	4.9			
End point	29	4.2	6.7	21	1.2	3.9	32	3.4	3.3	24	0.2	6.0
Dot Test												
Average No-Delay Distance (cm)												
Baseline	6	3.7	1.4				10	3.5	2.3			
End point	8	5.1	3.4	6	0.6	2.1	17	4.9	2.8	10	0.2	1.1
Average 10-Second Delay Distance (cm)												
Baseline	5	5.5	2.3				9	5.9	2.2			
End point	7	6.1	2.3	5	0.1	1.4	16	5.2	2.0	9	-1.0	2.3
Working Memory Deficit												
Baseline	5	1.9	1.8				9	2.2	3.0			
End point	7	1.1	3.1	5	-0.2	3.2	16	0.7	2.2	9	-1.1	2.3

5.2. Additional Safety Information

The following section provides new safety information, which was not available at the time of the 18 November 2004 Complete Response.

The additional safety information is derived from data from:

- RIS-USA-150: one of the pivotal trials in children and adolescents with autism.
- RIS-INT-84: a long-term (1-year) safety study of risperidone in children and adolescents with conduct and other disruptive behavior disorders. This was a follow-on study to RIS-INT-79, a double-blind placebo-controlled relapse prevention study - 232 subjects entered the study from RIS-INT-79 and 169 subjects completed RIS-INT-84. Subjects were aged 5 to 17 years (inclusive) at entry to RIS-INT-79 and had either completed 6 months of double blind treatment or had discontinued (after meeting relapse criteria) double blind treatment in RIS-INT-79. Subjects in RIS-INT-84 were grouped according to their randomization group in RIS-INT-79 (i.e., placebo or risperidone); subjects previously randomized to placebo were termed "PLA/RIS", while subjects previously randomized to risperidone were termed "RIS/RIS". The clinical study report for RIS-INT-84 was submitted to NDA-20-272 (6 January 2006).

5.2.1. Glucose-Related Data

In Request 3 of the 19 May 2005 Not Approvable Letter, the Agency asked the Company to analyze the data for adverse events possibly related to loss of glucose control, as well as examine the proportion of patients who met clinically relevant outlier criteria for serum glucose.

Adverse events that were potentially related to impaired glucose tolerance or diabetes were analyzed as part of the Safety Update (Section 2.1.5.2) included in the 18 November 2004 Complete Response.

No serum glucose results were available from any autism or DBD study until RIS-INT-79, a DBD trial in children and adolescents. Fasting serum glucose results (taken at baseline, Month 3, Month 6, and Month 9 [end point]) from RIS-INT-79 were discussed in the 18 November 2004 Complete Response (response to Question 8) and in the RIS-INT-79 study report, which was also submitted as part of the 18 November 2004 response. There were no findings of negative effects on glucose regulation. In RIS-INT-84, a long-term (1-year) open-label follow-up study to RIS-INT-79, laboratory samples, including serum glucose, were taken at Month 6 and Month 12. No glucose-related adverse events were reported and no subject met criteria for

diabetes, with changes in insulin levels during the study being in accordance with age-appropriate norms - specifically, increasing levels up to Tanner Stage 3 with a subsequent decline. There was no correlation between insulin levels and glucose values. The combined data on glucose, insulin, and lipids indicate no evidence of an increased risk of metabolic syndrome in these subjects.

5.2.2. Prolactin and Leptin Data

As agreed at the 7 December 2005 meeting, additional information on prolactin and leptin data from Study RIS-USA-150 are provided in the following sections, together with prolactin and leptin data from a long-term open-label safety study (RIS-INT-84).

Subjects in RIS-INT-84 had laboratory samples, including prolactin and leptin, taken starting from baseline of the preceding study (RIS-INT-79); at Months 3, 6, and 9 (end point) of RIS-INT-79; and at Months 6 and 12 of RIS-INT-84.

Subjects in RIS-USA-150 had laboratory samples, taken at baseline of Part 1 and at the end points of Part 1 and each succeeding period, namely, end point of the 8-week open-label risperidone treatment period for placebo nonresponders; end point of the 4-month open-label risperidone treatment period (Part 2); and end point of the 8-week double-blind randomized withdrawal period (Part 3). Leptin was assessed at each of these time points. Prolactin was not assessed at end point of Part 3.

5.2.2.1. Prolactin

RIS-USA-150 (Part 1):

Prolactin data were obtained from the RUPP investigators. Laboratory reference ranges were not provided.

Table 6 summarizes mean prolactin values at baseline and end point of RIS-USA-150 Part 1.

Table 6: Prolactin (ng/mL) - RIS-USA-150 Part 1: All Subjects Analysis Set

	N	Mean (SD)	Mean Change from Baseline (SD)
PLACEBO			
Treatment			
Baseline	48	10.88 (9.943)	
End point	38	10.12 (8.664)	0.79 (6.016)
RISPERIDONE			
Treatment			
Baseline	46	9.39 (7.707)	
End point	45	39.36 (18.718)	29.70 (19.236)

SD = Standard deviation.
Source: Attachment A5

Prolactin values had increased at end point of RIS-USA-150 Part 1, relative to baseline, for most subjects in the risperidone group (Figure 5); the maximum prolactin value observed during the study was 83.8 ng/ml (Subject L6017, at endpoint of risperidone treatment).

Figure 5: Prolactin Values for Individual Subjects at Baseline and End Point of RIS-USA-150 Part 1

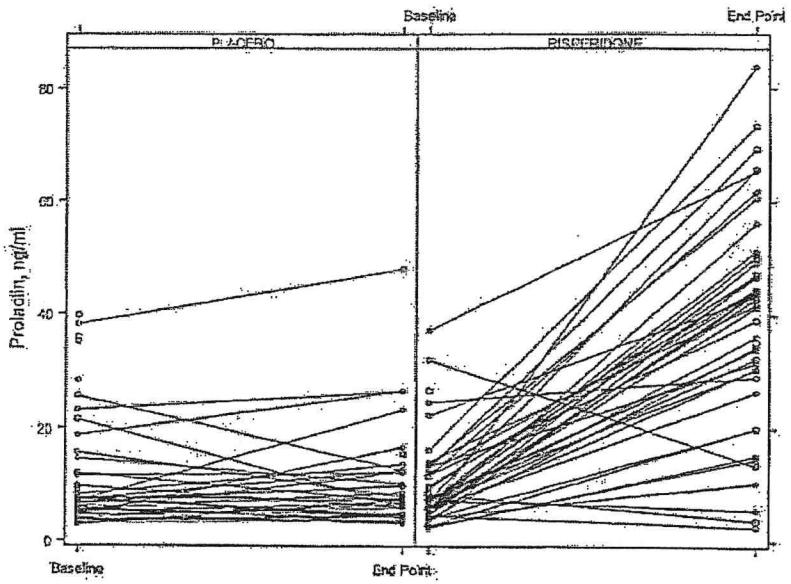


Table 7 summarizes mean prolactin values and changes from baseline of Part 1 at the end points of each part of the study through Part 2, namely: end point of Part 1 ["End point DB"]; end point of the 8-week open-label risperidone treatment period for placebo nonresponders ["End point (PNR)"]; and end point of the 4-month open-label risperidone treatment

period ["End point (OL)"]. This summary includes subjects who continued beyond Part 1 only.

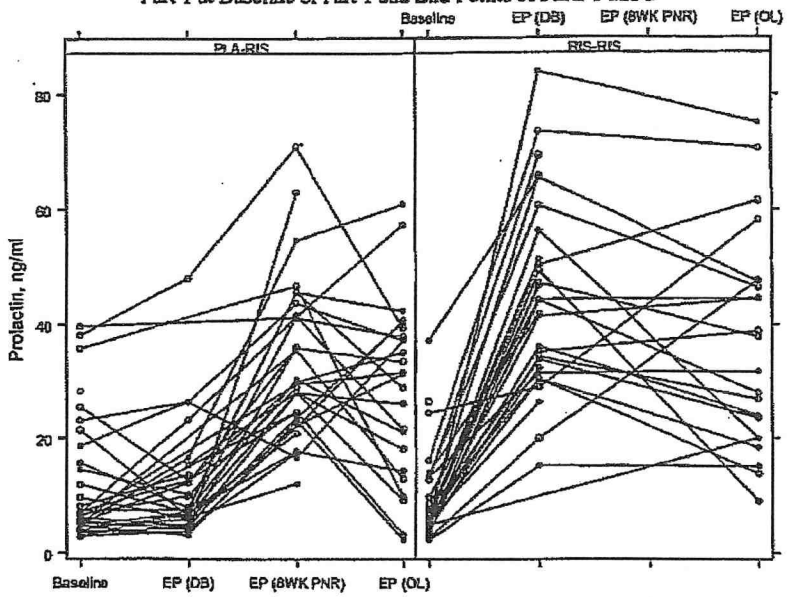
Table 7: Prolactin (ng/mL) - RIS-USA-150, Parts 1 and 2: All Subjects Analysis Set

	N	Mean (SD)	Mean Change from Baseline (SD)
PLA DB-RIS OL			
Treatment			
Baseline	34	11.64 (10.738)	
End point (DB)	30	10.91 (9.511)	1.07 (6.708)
8 week PNR			
End point(PNR)	30	33.55 (13.778)	22.87 (14.060)
Open-label			
End point(OL)	25	29.15 (15.222)	16.27 (19.771)
RIS DB-RIS OL			
Treatment			
Baseline	31	9.21 (7.769)	
End point (DB)	29	44.66 (16.424)	35.84 (16.315)
Open-label			
End point(OL)	22	36.50 (18.679)	27.46 (17.647)
All Subjects			
Open-label			
End point(OL)	47	32.59 (17.144)	21.61 (19.411)

SD = Standard deviation: PLA = Placebo; RIS = Risperidone
DB = Double-Blind; PNR = Placebo nonresponders; OL = Open-Label
Source: Attachment A6

For most subjects, prolactin decreases were noted after the first 8 weeks of risperidone treatment (Figure 6).

Figure 6: Prolactin Values for Individual Subjects who Continued Beyond RIS-USA-150 Part 1 at Baseline of Part 1 and End Points of Parts 1 and 2



The trends for prolactin observed in risperidone-treated subjects with autism are similar to the trends observed in the November 2004 Safety Update for risperidone-treated subjects with DBD. Increases in prolactin peaked during short-term treatment and tended to decrease during longer-term treatment.

No subject in RIS-USA-150 had a prolactin value above 100 ng/mL, which was considered to be a 'potentially clinical important' upper limit in the absence of a universal lab reference range for prolactin.

RIS-INT-84:

Consistent with observations from other studies in adults and pediatric patients, prolactin levels increased during the first 3 months of treatment in RIS-INT-79 and its 1-year open-label extension, RIS-INT-84. There was a gradual decline through Month 12 of RIS-INT-84 in subjects who received risperidone continuously; the mean value at Month 12 of RIS-INT-84 (~15 ng/mL) was above that at baseline of RIS-INT-79 (~8 ng/mL). In subjects withdrawn from risperidone at Month 3 of RIS-INT-79, mean prolactin values returned to near baseline levels at Months 6 and 9 of RIS-INT-79, but increased again with the resumption of risperidone treatment in RIS-INT-84. The mean prolactin level at Month 12 of RIS-INT-84 in these

subjects was similar to that for subjects treated continuously with risperidone throughout both RIS-INT-79 and RIS-INT-84 (21 months).

Clinical symptoms that were potentially related to elevated prolactin levels were uncommon during long-term risperidone treatment in RIS-INT-84, with 3 (1.3%) of 232 treated subjects reporting a treatment-emergent adverse event that was potentially prolactin-related (Table 8). Two (1.7%, both males) of those 3 subjects reported treatment-emergent gynecomastia but had normal prolactin values throughout open-label risperidone treatment; both subjects received double-blind placebo in RIS-INT-79 ("PLA/RIS"). One (0.9%, female) subject reported dysmenorrhea twice and had an increase in prolactin values at end point; this subject received double-blind risperidone in RIS-INT-79 ("RIS/RIS").

Table 8: Potentially Prolactin-Related Treatment-Emergent Adverse Events by Sex and Age - RIS-INT-84: All Subjects Analysis Set

	Prolactin value	Age: Tanner Stage	Sex
Endocrine disorders			
Gynecomastia			
A30209	61 mU/L Screen	12: 2- INT-79 Screen	M
PLA/RIS	903 mU/L (AA) DB BL		
	112 mU/L OL BL	13: 2 - INT-84 BL	
	47 mU/L M 6	- : 2 - INT-84 EP	
	135 mU/L M 12		
A50389	108 mU/L Screen	12: 1 - INT-79 Screen	M
PLA/RIS	252 mU/L DB BL		
	108 mU/L OL BL	12: 1 - INT-84 BL	
	N/A M 6	- 3 - INT-84 EP	
	N/A M 12		
Reproductive disorders, female			
Dysmenorrhea			
A50392	118 mU/L Screen	13: 3 - INT-79 Screen	F
RIS/RIS	689 mU/L(AA) DB BL		
	545 mU/L OL BL	13: 3 - INT-84 BL	
	554 mU/L M 6	- : 4 - INT-84 EP	
	1144 mU/L (AA) M12		

M=month, OL BL=open-label baseline, Screen=screening RIS-INT-79, DB BL=double-blind baseline RIS-INT-79, EP=open-label end point, N/A=not available
Initial Tanner stage and age were from screening of RIS-INT-79 and thereafter at the time of the measurement.
B= value below reference limit for age group; AA=value above pathological limits
Laboratory normal ranges for prolactin are: 44-374 mU/L for boys and girls ages 5 and 10 years, 42-423 mU/L for boys ages 11 or older, 42-613 mU/L for girls ages 11 or older.

No subject discontinued treatment as a result of a potentially prolactin-related adverse event. No treatment-emergent prolactin-related adverse event was rated as serious or severe.

The overall pattern of prolactin levels was generally similar between sex and Tanner groups. When open-label risperidone was initiated, PLA/RIS subjects had a transient increase in prolactin that decreased with time, while RIS/RIS subjects demonstrated stable or declining prolactin values. Female subjects had an overall higher mean peak prolactin level than males but prolactin approached normal levels by Month 12.

No subject had elevated prolactin levels at onset of a potentially prolactin-related adverse event, moreover one subject (A30212) with a very elevated prolactin level (exceeding 2114 mU/L [100 ng/mL]) at open-label baseline reported no potentially prolactin-related adverse events.

5.2.2.2. *Leptin*

RIS-USA-150 (Part 1):

There is limited consensus in the literature about the clinical meaningfulness of changes in leptin. Pediatric endocrinology research demonstrates that leptin is a reflection of body fat mass, but the regulation of leptin levels during childhood is poorly understood. Leptin has been implicated as an independent stimulator of the reproductive axis and may have a facilitatory role in human pubertal development. There are no sex-related differences in leptin levels independent of adiposity. Leptin has been shown to correlate with fasting insulin, but not with insulin sensitivity in healthy children.

The RUPP investigators performed the initial analysis of the leptin data for publication (reference Martin, et al. Weight and leptin changes among risperidone-treated youths with autism: 6-month prospective data. Am J Psychiatry 2004; 161: 1125-1127).

As for prolactin, leptin data were obtained from the RUPP investigators without reference ranges, since there is insufficient information available in the literature to establish reference ranges for leptin.

Table 9 summarizes mean leptin values during RIS-USA-150 Part 1.

Table 9: Leptin (ng/mL) - RIS-USA-150: All Subjects Analysis Set

	N	Mean (SD)	Mean Change from Baseline (SD)
PLACEBO			
Treatment			
Baseline	47	5.76 (6.203)	
Week 8	30	7.49 (8.324)	1.75 (2.947)
End point	39	7.22 (8.320)	1.36 (2.718)
RISPERIDONE			
Treatment			
Baseline	44	4.51 (3.910)	
Week 8	40	6.16 (4.043)	2.18 (3.177)
End point	43	6.37 (4.158)	2.42 (3.264)

SD = Standard deviation.
Source: Attachment A7

The data from RIS-USA-150 Part 1 show increases in leptin in both the placebo and risperidone-treated groups. Although the increases are slightly higher in risperidone-treated subjects than in the placebo group, the clinical meaningfulness of this difference is unclear.

Figure 7 displays leptin values for individual subjects at baseline and end point of RIS-USA-150 Part 1.

Figure 7: Leptin Values for Individual Subjects at Baseline and End Point of Study RIS-USA-150 Part 1

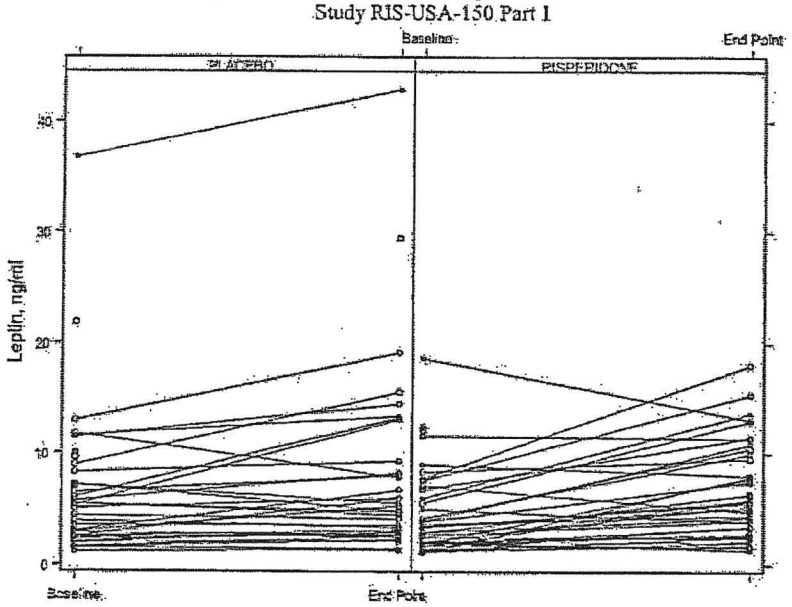


Table 10 summarizes mean leptin values and changes from Part 1 baseline during Parts 1 and 2 for subjects who continued beyond Part 1. Figure 8

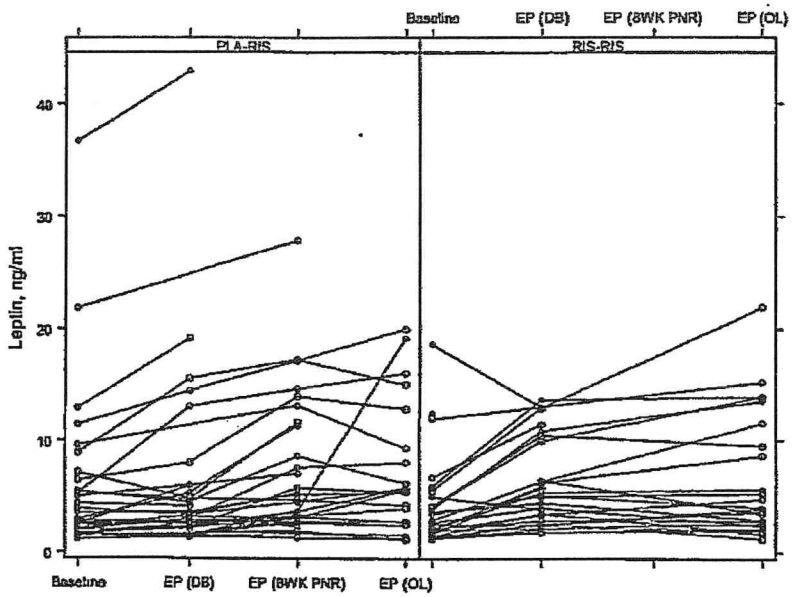
displays leptin values for these subjects at baseline of Part 1 and at succeeding end points in Parts 1 and 2.

Table 10: Leptin (ng/mL) - RIS-USA-150, Parts 1 and 2: All Subjects Analysis Set

	N	Mean (SD)	Mean Change from Baseline (SD)
PLA DB-RIS OL			
Treatment			
Baseline	34	5.43 (6.983)	
Week 8	22	7.22 (9.524)	1.82 (2.783)
End point (DB)	30	6.21 (8.307)	1.31 (2.529)
8 week PNR			
Week 8	26	6.66 (5.073)	3.04 (3.053)
End point(PNR)	30	7.07 (6.194)	2.81 (3.106)
Open-label			
Week 24	20	6.69 (5.330)	2.63 (3.580)
End point(OL)	22	7.07 (5.802)	3.29 (4.728)
RIS DB-RIS OL			
Treatment			
Baseline	28	4.43 (4.288)	
Week 8	27	6.00 (3.770)	2.47 (3.090)
End point (DB)	27	6.00 (3.770)	2.47 (3.090)
Open-label			
Week 24	23	6.44 (4.798)	3.21 (3.585)
End point(OL)	25	6.85 (5.662)	3.71 (4.581)
ALL TREATMENTS			
Open-label			
Week 24	43	6.55 (4.993)	2.91 (3.545)
End point(OL)	47	6.95 (5.666)	3.50 (4.603)

SD = Standard deviationPLA = Placebo; RIS = Risperidone
DB = Double-Blind; PNR = Placebo nonresponders; OL = Open-Label
Source: Attachment A8

Figure 8: Leptin Values for Individual Subjects who Continued Beyond RIS-USA-150 Part 1 at Baseline of Part 1 and End Points of Parts 1 and 2



Seven subjects randomized to placebo and 10 subjects randomized to risperidone during the withdrawal period of the study (Part 3) had leptin values after the baseline of this part of the study. These values are summarized in Table 11. No placebo subject during this part of study had a leptin value at Week 8.

Table 11: Leptin (ng/mL) - RIS-USA-150, Part 3: All Subjects Analysis Set

	N	Mean (SD)	Mean Change from Baseline (SD)
PLACEBO			
Treatment3			
Baseline(RWD)	16	7.70 (5.441)	
End point(RWD)	7	7.14 (5.428)	-1.09 (3.129)
RISPERIDONE			
Treatment3			
Baseline(RWD)	14	4.71 (2.998)	
Week 8	5	7.14 (5.437)	1.85 (3.349)
End point(RWD)	10	9.16 (7.513)	1.58 (2.566)

SD = Standard deviationRWD = Randomized withdrawal
Source: Attachment A9

Any interpretation of leptin values or differences between groups during Part 3 is likely to be invalid due to the small numbers of subjects with available data.

The mean change in leptin levels from baseline after 6 months of risperidone treatment for subjects with autism (2.91 [3.54 SD]) was similar to the change observed in RIS-INT-79 at 6 months (3.75 [10.591 SD], n=107).

RIS-INT-84:

Changes in serum leptin levels during RIS-INT-79/RIS-INT-84 followed a similar pattern of increase during the first 3 months of risperidone therapy followed by recovery in subjects switched to placebo during the randomized withdrawal phase and stabilization with continued risperidone treatment.

Leptin was measured at open-label baseline, Month 6 (Visit 6), and Month 12 end point or at the subject's end point in the 1-year open-label safety study. Mean leptin values increased from open-label baseline to end point for all subject groups (Table 12).

Table 12: Leptin (ng/ml) – RIS-INT-84 (From Open-Label Baseline)

Group	Treated	Evaluation	N	Mean (SD)	Median	Range
All	All RIS	OL baseline	223	9.126 (13.298)	3.400	1-91
		End point	214	10.91 (15.906)	5.300	1-139
		Change from BL to EP	208	1.079 (9.3117)	0.700	-55-57
	PLA/RIS	OL baseline	112	8.637 (14.880)	2.800	1-91
		End point	107	11.73 (19.297)	5.000	1-139
		Change from BL to EP	104	1.890 (10.965)	0.800	-55-57
	RIS/RIS	OL baseline	111	9.620 (11.533)	4.200	1-49
		End point	107	10.10 (11.606)	5.400	1-65
		Change from BL to EP	104	0.267 (7.2594)	0.400	-27-31

Reference ranges for leptin are not well established in childen.
EP=end point, OL=open-label, BL=baseline

Six treatment-emergent adverse events of a high leptin value were reported (Table 13), 3 of which occurred in subjects who received placebo during the double-blind treatment in RIS-INT-79. The investigator assessed all these adverse events as mild except for the moderate event reported by Subject A30063. Subject A30063 (PLA/RIS) discontinued open-label risperidone treatment as a result of this adverse event.

subjects treated with double-blind risperidone in RIS-INT-79 had a weight z-scores decrease of -0.04 (SD 0.3) from open-label baseline. A transient increase in weight by z-scores was seen in placebo-treated subjects when open-label risperidone treatment was initiated. The initial weight increase occurred through Month 3 and thereafter remained stable. This would indicate that weight increase was an initial effect, which generally did not continue with prolonged treatment and confirmed similar observations in previous long-term safety studies in children and adolescents, including subjects with autism.

5.2.3.2. *Treatment-Emergent Adverse Events*

In the long-term (1-year) follow-up study in children and adolescents, risperidone was safe and well-tolerated at doses of 0.25 to 0.75 mg/day for subjects weighing <50 kg and 0.5 to 1.5 mg/day for subjects weighing ≥50 kg. There were no deaths and no new or unexpected adverse events were reported.

Treatment-emergent serious adverse events occurred in 20 (8.6%) subjects during open-label risperidone treatment in RIS-INT-84. The incidence of serious adverse events was similar between those subjects treated with double-blind placebo (PLA/RIS; 11 subjects, 9.4%) and those treated with double-blind risperidone (RIS/RIS; 9 subjects, 7.8%) in RIS-INT-79. Five PLA/RIS and 5 RIS/RIS subjects reported a treatment-emergent serious adverse event of condition aggravated. Other types of serious adverse events were reported in no more than 2 subjects.

Treatment-emergent adverse events led to discontinuation of treatment for 8 (3.4%) subjects. Five PLA/RIS subjects and 3 RIS/RIS subjects discontinued as a result of a treatment-emergent adverse event. No individual adverse event associated with discontinuation was reported in more than 2 subjects in any treatment group.

The incidence of EPS-related treatment-emergent adverse events was low, with only 10 (4.3%) of 232 subjects experiencing such events. There were no reports of tardive dyskinesia.

5.3. Conclusions From Safety Analyses

Based on full review of the safety data, including the data submitted in the 18 November 2004 Complete Response and the information summarized above, the Company concludes that the adverse events in children and adolescents with autism were largely mild to moderate and/or transient, with very few (1.3%) patients being discontinued from the autism trials due to adverse events. Overall, there were no adverse events with risperidone use in autistic children and adolescents that were qualitatively different from the adverse events seen in the other indications with this treatment. Furthermore, review of the long-term safety of risperidone in children and adolescents, with particular reference to tardive dyskinesia, prolactin, weight, glucose and growth and maturation, did not give cause for significant concern with the available data.

Since the incidence of autism is low (<250,000 in the United States), the number of potential participants for clinical studies of putative treatments is small. To adequately assess the safety profile of oral risperidone in this population, the data from autistic subjects were combined with data from children and adolescents with other psychiatric disorders, primarily DBD. Therefore, for determination of safety, the safety dataset from the double-blind, placebo-controlled (DBPC) trials not only included 156 patients from the above trials in children and adolescents with autism, but also included 303 children and adolescents with DBD or other pervasive developmental disorders (PDDs) studied in placebo-controlled trials. Overall, 1348 children and adolescents (those in the autism DBPC trials plus patients with DBD or other PDDs in DBPC and open-label, uncontrolled trials) were treated with risperidone, of which 332 patients were treated for more than 12 months (248 for 13 to 15 months, and 84 for >15 months), with some patients treated for over 2 years (n=62). The safety database in this population should be viewed in the context of extensive data and clinical experience of the safety and tolerability of risperidone in both children and adults. Risperidone has been on the market since 1993 for the treatment of adults with substantial off-label use in children and adolescents in the USA, and is approved since 2001 for the treatment of children and adolescents in more than 25 countries; therefore, physicians are familiar with recognizing and managing the adverse events associated with risperidone.

New safety information, subsequent to the 18 November 2004 Complete Response and the 16 August 2005 Briefing Document, as described above,

consists primarily of additional data on prolactin and leptin (from RIS-USA-150), and data from a 1-year open-label extension study in children with DBD (RIS-INT-84), including additional prolactin, leptin, glucose and adverse event data.

- With respect to prolactin, the findings from RIS-USA-150 in autism were consistent with those observed previously over a similar time course in children and adolescents with DBD: increases in prolactin peaked during short-term treatment and subsequently tended to decrease with longer-term exposure. For most subjects, prolactin decreased after the first 8 weeks of risperidone treatment. Additionally, in a 1-year open-label extension trial of DBD (RIS-INT-84), there was a gradual decline in prolactin through month 21 in subjects who received risperidone continuously.
- For leptin, the data from RIS-USA-150 demonstrated increases in both the placebo and risperidone-treated groups. Although somewhat higher in the risperidone subjects than in the placebo group, the increases in the autism population were similar to those observed in DBD. The clinical relevance of these changes is uncertain.
- Concerning fasting glucose, the only available data were from the two DBD trials, RIS-INT-79 and its open-label extension RIS-INT-84. There were no negative effects on glucose regulation in either study, and the combined data on glucose, insulin, and lipids indicated no increased risk of metabolic syndrome.
- Additional longer-term data for changes in body weight have also come from the open-label safety study in children and adolescents with DBD (RIS-INT-84). These results have confirmed previous observations that initial increases in weight do not generally continue with prolonged treatment. Increases occurred through Month 3 and thereafter generally remained stable, with subjects continuing to grow at normal age-expected rates.
- No new safety signals were elicited from analyses of treatment-emergent adverse events (including those leading to treatment discontinuation) or serious adverse events in the long-term (1-year) follow-up study in children and adolescents with DBD (RIS-INT-84).

5.4. Pharmacovigilance Report (Through April 2005)

Postmarketing safety in children receiving risperidone was examined in the J&JPRD Benefit Risk Management worldwide safety (SCEPTRE) database, based on spontaneous reports received cumulatively through 30 April 2005. The full PV report is presented in Appendix 2. A summary of the methods used and results of the database search is presented below.

Proportional reporting rates of spontaneous adverse event reports regarding children aged 5 to 17 who were taking risperidone were compared with reports for risperidone from all other age groups. This was done for all System Organ Classes (SOCs) and for predefined areas of clinical interest (including suicidality, self-injurious behavior or ideation, overdose, glucose metabolism disorders, lipid metabolism disorders, weight gain, metabolic disorders, potentially prolactin-related events, EPS-related events, and sedation).

Searches were conducted of the J&JPRD Benefit Risk Management worldwide safety (SCEPTRE) database to identify all spontaneous reports regarding individuals aged 5 to 17 years ("child" or "adolescent") and the number of reports for all other age groups that were received through 30 April 2005. The proportions of all adverse events reported for risperidone in children and adolescents involving each Medical Dictionary for Regulatory Activities (MedDRA) SOC and selected Preferred Terms (PTs) of interest were calculated and compared with the respective proportions in all other age groups. When disproportionality of events within a particular SOC or predefined area of interest was observed, further analysis included clinical review of the cases of interest and an assessment of the population under treatment, in the context of both the worldwide pediatric exposure (approximately 732,214 person-years) and the known safety profile for risperidone.

Through 30 April 2005, there were 3,571 spontaneous case reports for risperidone involving children and adolescents. Less than 20% of these reports involved serious adverse events. In contrast, there were 24,912 case reports for all other age groups, more than one-third of which involved serious adverse events. Disproportionality of serious events was noted for children and adolescents in 1 SOC (Immune System Disorders); and disproportionality of nonserious events was noted in 1 SOC (Congenital, Familial and Genetic Disorders). All of these events were very rare, and the

observed Proportional Reporting Rates (PRRs) are likely reflective of the underlying pediatric population. Three of the predefined areas of special interest revealed disproportionate reporting rates in children and adolescents compared with all other age groups. Detailed review of two of these areas of interest, self-injurious behavior or ideation and gynecomastia, suggested a pattern of events consistent with the underlying disease being treated and normal developmental changes in pubertal males, respectively. The third area of interest demonstrating disproportionality involved the labeled event weight gain, which was reported rarely in children and adolescents. The majority of cases were not documented sufficiently to determine to what extent they represent normal growth patterns in this population. However, a number of cases reported weight gain clearly in excess of expected growth rates. No disproportionality for children or adolescents was observed with respect to events involving suicide or suicidal ideation, disorders of glucose, lipid or other metabolism, hyperprolactinemia, extrapyramidal syndromes, or sedation. In addition, cumulative reviews of overdose or reports with fatal outcome in children and adolescents did not suggest a new safety concern for risperidone.

Overall, this cumulative review of postmarketing experience in children and adolescents identified no new pattern of adverse drug reactions for pediatric populations treated with risperidone, compared with adult populations. Whether the increased frequency of weight gain in children and adolescents compared with all other age groups indicates that children may be more susceptible to this rare labeled adverse drug reaction cannot be determined from the current dataset. Overall, the benefit risk assessment for risperidone remains unchanged, and is adequately reflected in the proposed USPI.

5.5. Serious Adverse Events in Ongoing Pediatric Studies (July 2004 to November 2005)

Four clinical studies in adolescent subjects with schizophrenia and children and adolescents with bipolar disorder (RIS-BIM-301, RIS-USA-231, RIS-SCH-302, REDACTED) were ongoing as of 30 November 2005. Details of all serious adverse events reported in these studies, including subject narratives, are presented in Attachment 11; a summary is presented below.

In the ongoing clinical studies, 921 children and adolescents had been enrolled, of which 775 subjects had completed or discontinued as of

30 November 2005 (Attachment 11.1); the remaining 146 subjects were ongoing participants in the trials as of this cut-off date.

Serious adverse events were obtained from the J&JPRD Benefit Risk Management worldwide safety (SCEPTRE) database, including cases that occurred either during treatment or within 30 days of discontinuing treatment. Since the previous safety update (included in 18 November 2004 Complete Response, which included SAEs up to 30 June 2004), 85 serious adverse events have been reported for 65 cases for the period from 1 July 2004 to 30 November 2005. These events are provided in the CIOMS listings obtained from the worldwide safety database.

In the ongoing studies in children and adolescents, the most frequently reported serious adverse events (Attachment 11.2) were schizophrenia (24 subjects), suicidal ideation (10 subjects), bipolar disorder (7 subjects), and psychotic disorder (6 subjects). One subject completed suicide and 4 subjects attempted suicide. These data are qualitatively and quantitatively similar to those reported in the previous safety update and offer no new safety information of clinical relevance.

5.6. Juvenile Rat Toxicity Safety Study

In Request 1 of the 19 May 2005 Not Approvable Letter and at the 7 December 2005 meeting, FDA requested that the Company submit the completed juvenile rat toxicology study report and stated that they would follow up with the FDA toxicology reviewer to determine if the juvenile dog toxicology study would be required as a Phase 4 commitment, following their review and evaluation of the data in the juvenile rat study report.

The nonclinical study report for the juvenile rat toxicity study is presented in Module 4 of this NDA. A summary of the results of this study is presented below.

A juvenile toxicity study with risperidone was conducted in rats. Rat pups were dosed orally from Day 12 to Day 50 of age at dose levels of 0, 0.04, 0.16 and 0.63 mg/kg/day. Ptosis occurred at 0.16 and 0.63 mg/kg due to the exaggerated pharmacological activity of the test compound. Body weight gain between Day 12 and Day 21 of age was slightly lower at 0.16 and 0.63 mg/kg/day. After weaning, body weight gains were generally comparable with controls in all treated groups. Pup pre-weaning development and long bone growth were unaffected. Behavioral tests,

whether carried out during the treatment period or conducted a minimum of 14 days after the end of treatment, showed no effect of risperidone either. As expected due to the dopamine D_2-antagonistic action of risperidone, serum prolactin levels were increased at 0.16 and 0.63 mg/kg/day in male pups, while in female pups the increase was more pronounced, dose-related and present in all treated groups. This prolactin increase was associated with prolactin-mediated changes in the female reproductive system. However, reproductive performance (assessed when the animals were approximately 10 weeks of age) was not affected.

5.7. Worldwide Literature Search (July 2004 to November 2005)

From 1 July 2004 through 30 November 2005, 92 articles were published on risperidone use in the pediatric population. Of these, 5 were conducted in children with autism containing original clinical data. Of the remaining articles, 38 were in non-autistic pediatric populations containing original clinical data in which safety was reviewed. The full literature review is presented in Appendix 3. A summary is presented below.

There was wide variability in reported data on both safety and efficacy. The majority of trials were case reports (76%), while the remaining trials were mainly prospective (6 months or less) open-label studies.

Data from studies of children with autism suggest that treatment with risperidone provided clinical benefit (effectiveness and safety) on a range of symptoms over the short and longer term. Of particular interest was a replication of the RIS-USA-150 trial conducted by Troost et al (2005). This was a 3-phase, 32-week study of risperidone in children (aged 5 to 17 years) with autism, Asperger's, or PDD-NOS with severe behavioral disturbance. Responders to 8 weeks of open risperidone treatment (responder criteria identical to RIS-USA-150) continued open treatment with risperidone for an additional 18 weeks then received either placebo discontinuation or risperidone treatment for 8 weeks. Of the 36 patients initially enrolled, 24 (67%) completed the 24 weeks of open treatment (mean dose at 24-week endpoint = 1.81 mg/day). During double-blind discontinuation, 67% of placebo-treated patients relapsed versus 25% on risperidone ($p=0.049$). The most common adverse effects were increased appetite, anxiety, fatigue, and increased thirst (average weight gain = 5.7 ± 2.8 kg in 24 weeks; $p<0.0001$), though all reported adverse events were mild to moderate in severity.

Objective and subjective measures found a low incidence of movement disorders, consistent with RIS-USA-150. The authors concluded that risperidone was effective and safe in reducing tantrums, aggression, and self-injurious behavior in autistic children over several months, but weight gain may limit its use.

This literature update is consistent with the efficacy and safety findings from the previous literature searches provided with the 19 December 2003 file and the 18 November 2004 Complete Response (available on request), as well as J&J-PRD sponsored research, and provides no indication of any new safety concerns.

6. REGULATORY STATUS UPDATE

6.1. Worldwide Registration Status

6.1.1. Countries That Have Approved

The following countries have approved the autism indication (specific indications are provided in Section 6.2):

Finland, Poland, Ireland, France, Portugal, Australia, Latvia, New Zealand, Argentina, Singapore, Thailand, and Philippines.

The country-specific labels, together with English translations where appropriate, are presented in Appendix 4.

6.1.2. Countries With Approval Pending

Approval of the autism indication is pending in the following countries:

UK, Netherlands, Sweden, Switzerland, Belgium, Austria, Spain, Hong Kong, Korea, Indonesia, Venezuela.

6.1.3. Countries That Have Rejected

The application for the autism indication was rejected in Italy. The Agency letter to reject the filing is presented in Appendix 5.

6.1.4. Countries in Which File Withdrawn

The Company withdrew the application for the autism indication in Canada. The Company letter to withdraw the filing is presented in Appendix 5.

6.2. Foreign Labeling

Specific indications for autism in countries outside the US where RISPERDAL® is approved are presented below (see also Appendix 4):

Finland - Treatment of autistic disorder related irritability, social withdrawal and hyperactivity in children (5 years of age and over) and adolescents. Risperdal is recommended for the treatment of autistic disorder only with prescription by Child Neurologists, Child and Adolescent Psychiatrists or physicians conversant with treatment of autistic disorders in children and adolescents.

Poland - Short-term treatment of autism in children and adolescents.

Ireland - Treatment of severe disruptive behavioral symptoms in children and adolescents with autism and pervasive developmental disorders.

France - Children aged 5 to 11 years: Treatment of behavioural disorders (such as hetero-aggression, self-mutilation, major impulsiveness and severe stereotypy) observed in autistic syndromes, in monotherapy.

Portugal - RISPERDAL® is indicated for the treatment of autism in children and adolescents.

Australia - RISPERDAL is indicated for the treatment of behavioral disorders associated with autism in children and adolescents.

Latvia – RISPERDAL® is indicated for the treatment of autism in children and adolescents.

New Zealand - RISPERDAL is indicated for the treatment of autism in children and adolescents.

Argentina - RISPERDAL® is indicated for the treatment of patients having autism as from 5 years old.

Singapore - Risperdal® is indicated for the treatment of behavioural disorders associated with autism (eg irritability, social withdrawal, stereotypic behaviour, hyperactivity and inappropriate speech) in children and adolescents.

Thailand - RISPERDAL® is indicated for the treatment of autism in children and adolescents.

Philippines - RISPERDAL (risperidone) is used for the treatment of autism in children and adolescents.

SUPPORTING DATA

Attachment 1.1: Summary of Effect Sizes for ABC

ABC Subscale	RIS-USA-150[a]	RIS-CAN-23[a] All Subjects	RIS-CAN-23[a] Autistic Subjects Only
Irritability	1.3	1.0	0.9
Lethargy/Social Withdrawal	0.5	0.6	0.7
Stereotypic Behavior	0.7	0.5	0.6
Hyperactivity	1.2	1.0	1.0
Inappropriate Speech	0.8	0.6	0.5

[a] Effect size is defined as the absolute risperidone-placebo difference in change from baseline to end point (using the least squares means from an ANCOVA model including factors for treatment and center and baseline score as a covariate) divided by the pooled standard deviation (also from the ANCOVA model).