CLINICAL REVIEW

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Established Name	Risperidone
Trade Name	Risperidal®
Therapeutic Class	Antipsychotics
Applicant	Janssen
Priority Designation	P
Formulation	[redacted] oral solution, Orally disintegrating tablets
Dosing Regimen	0.5–2.5mg [redacted]
Indication	Bipolar Disorder
Intended Population	Age 10-17 year-old

b(4)

BIPOLAR DISORDER

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend the Division taking an Approvable action on the application of using risperidone (dosage limited to 0.5mg to 2.5mg per day only) for the treatment of bipolar I disorder (mania and mixed episode) in children and adolescents age 10-17 year-old.

From clinical point of view, the following should be addressed prior to taking a final approval action on this application: Analysis of treatment-emergent common adverse events needs to be corrected. The labeling also needs to be revised accordingly along with other revisions in the labeling. In addition, marked outlier analysis of laboratory test needs to be submitted.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Postmarketing risk management should include collecting data on tardive dyskinesia, risk of suicide, and the drug effects on metabolism, including growth hormone and glucose metabolism.

1.2.2 Required Phase 4 Commitments

This sNDA submission, together with the other sNDA for using risperidone to treat schizophrenia in children and adolescents, are in response to the Agency Written Request. The Division has granted the partial waiver for studying children age 9 years-old or younger with bipolar disorder.

1.2.3 Other Phase 4 Requests

No new Phase 4 commitment study is required at present.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Risperidone is an atypical antipsychotic agent. Its formulation includes [redacted] orally disintegrating tablets, oral suspensions, and long acting injections. b(4)

In response to the Agency's Written Request, this submission includes one pivotal efficacy trial (Study RIS-BIM-301) on treatment of bipolar I disorder (mania and mixed episode) in children

and adolescents age 10 –17 year-old. A total of 169 patients were enrolled in this study. A separate longer term open-label study on treatment of schizophrenia (RIS-US-234) in children and adolescents was also included for safety review. Also included in the submission is Study US-160, a pharmacokinetic study in children and adolescents with various behavior and psychotic disorders. (For more details, please see Section 4, Data Source, Review Strategies, and Data Integrity.)

1.3.2 Efficacy

The efficacy study (Study RIS-BIM-301) is a double-blind, placebo-controlled study with two dosage groups (risperidone 0.5–2.5 mg/day and 3–6 mg/day). The primary efficacy variable is change from baseline to endpoint of the consensus score of Young Mania Rating Scale. CGI-C was one of the secondary variables with no key secondary variable defined. Both dosages show adequate efficacy with comparable effect size.

1.3.3 Safety

The primary safety database for this review is comprised of the three above mentioned studies: 1) US-160 PK study, 2) the three-week, double-blind, placebo-controlled study with two risperidone dosage groups, and 3) the six-month, open-label study in schizophrenia in children and adolescents.

Generally speaking, incidences of adverse events are higher in risperidone higher dose (3–6 mg/day) group than those in lower dose (0.5–2.5 mg/day) group. List of treatment-emergent common adverse events should not be concluded after comparing with the events in adults as the sponsor did in the submission.

1.4 Dosing Regimen and Administration

Although the sponsor wants to claim [redacted] dosage for treatment of bipolar disorder (mania and mixed episode) in children and adolescents for the following reasons: b(4)

[redacted] b(4)

1.5 Drug-Drug Interactions

There was no new study submitted for drug-drug interaction.

1.6 Special Populations

This treatment has not been studied in children younger than 10 years old.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Risperidone (Risperidal®) is an atypical (also called second generation) antipsychotic agent. It has been approved for the treatment of schizophrenia and as a short-term monotherapy for bipolar mania (acute manic and mixed episodes) in adults. It is also indicated for the treatment of irritability associated with autistic disorder in children and adolescents.

Currently, there are four risperidone formulations: (b) (4) (NDA#20272), oral suspensions (NDA#20588), orally disintegrating tablets (NDA#21444), and long-acting injection (trade name Consta®).

As the response to the Agency's Written Request, the sponsor submits two sNDA's to support the proposal of using all above mentioned formulations of risperidone for the treatment of schizophrenia and bipolar disorder I in children and adolescents; [redacted] b(4)

2.2 Currently Available Treatment for Indications

No medication has been approved by the Agency for the treatment of either indication in the Agency WR.

2.3 Availability of Proposed Active Ingredient in the United States

Risperidone has been widely available and used in the U.S. A new application was added for irritability associated with autism late last year. Major safety concerns in pediatric population include somnolence, weight gain, and elevated growth hormone and prolactin levels in pediatric patients.

2.4 Important Issues with Pharmacologically Related Products

Atypical agents are listed in the table below along with the important safety concerns associated with each.

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Table 1. Major Safety Concerns with Atypical Antipsychotics

Atypical Antipsychotics	Major Safety Concerns
Clozapine	Agranulocytosis Seizures Myocarditis Orthostatic hypotension Hyperglycemia Weight gain
Risperidone	Prolactin elevation Orthostatic hypotension Weight gain
Olanzapine	Orthostatic hypotension Weight gain Hyperglycemia
Quetiapine	Orthostatic hypotension Weight gain ? Cataracts
Ziprasidone	Q-T interval prolongation
Aripiprazole	No known major toxicities
Paliperidone	Q-T interval prolongation
Sertindole (not marketed)	QT interval prolongation Sudden death

2.5 Presubmission Regulatory Activity

The Written Request (WR) for studying both indications (schizophrenia and bipolar disorder I in children and adolescents) was issued on November 25, 2002.

Detailed issues specified in the WR can be found in the Pediatric Exclusivity Determination Template. Below is a summary of the main issues in the WR:

- Indications to be studied: Schizophrenia and bipolar I disorder in pediatric population
- Types of the studies and study design:
  1) Pediatric PK study that can be either traditional or population kinetic approaches applied to the controlled efficacy or safety trials;
  2) Efficacy studies: A randomized, double-blind, parallel-group, placebo-controlled acute trial, with a recommended duration of at least 6 to 8 weeks for schizophrenia study and a similar one of at least 3 weeks for bipolar study. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled... At least 50% of patients assigned to active drug must complete to the nominal endpoint of this trial in order for it to be considered a completed trial; Fixed-dose study is strongly recommended.

3) Pediatric Safety studies: In addition to collect safety data in the controlled efficacy trials, safety data from long term of 6-months exposure to the drug can be collected from open-label studies. Such study for a single indication would be sufficient.

- Number of patients and power of study: Sufficient numbers and power of the study were emphasized and at least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety.
- Entry criteria:
- Age group and population of the studies: Adolescents (ages 13 to 17 years) must be included in schizophrenia study, and subjects of age 10 to 17 for bipolar study -- there must be a reasonable gender and age distribution within these samples for both studies.

Meetings on May 14, 2003 and Aug. 13, 2003 were held to clarify the WR and discuss changes in Written Request for Pediatric Studies, mainly involving study design, proposed dose ranges, and the low dose proposed being considered as placebo. Consequently, the WR was amended on December 19, 2003 (Amendment 1). The meeting held on May 7, 2004 resulted in Amendment 2.

The two amendments for the WR mainly addressed BPCA §18 regarding the minority children and categorization of ethnicity (Amendment 1).

The sponsor conducted these studies according to the WR and the Amendments under IND #31,931.

On September 19, 2006, the sponsor had a Type B Meeting with the Division to discuss plans for supplemental new drug applications for responding to the WR for indications in pediatric patients with schizophrenia and bipolar I disorder.

The Agency Pediatric Exclusivity Board met and granted the Exclusivity on Feb. 28, 2007.

2.6 Other Relevant Background Information

The sponsor didn't include foreign regulatory history in the original application of this NDA supplement. In response to our request in the fling letter, the sponsor indicates that "no marketing applications have been submitted for these new indications (adolescent schizophrenia and pediatric bipolar disorder) in any country outside the United States at this time."

To my knowledge, however, the sponsor has had approval for using risperidone for the treatment of autistic symptoms in children and adolescents in a number of countries, including in the U.S. (Details can be found in the reviews of N20272-S036 submitted Dec. 19, 2003, the application for using risperidone to treat irritability associated with autism.)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

There is no new chemistry information. However, the Agency Chemistry Reviewer identifies the new description of "capsule-shaped [redacted] " in the proposed labeling of this submission. A consultation has been sent to DDMAC with regard to the suitability of the description and the need of clarification. b(4)

3.2 Animal Pharmacology/Toxicology

There is no new information on Pharmacology-Toxicology for this submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The main source of clinical efficacy data for bipolar I disorder comes from Study RIS-US-301. The main safety data are from both Study RIS-US-301 and the long term open-label study for schizophrenia in adolescents. For clinical PK data, the sponsor submitted RIS-US-160, a traditional PK study in children and adolescents with various psychiatric diagnoses, as well as data from two population PK studies, Studies RIS-USA-301 and RIS-USA-231 (another efficacy study that the sponsor conducted in adolescents with schizophrenia). (See table below.) There were meetings regarding the Agency's WR for these studies (see section 2.5 for Presubmission Regulatory Issues).

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4.2 Tables of Clinical Studies

Table 2: Clinical Studies to Fulfill the Pediatric Written Request for Mania in Bipolar I Disorder

Study	Design and Dosage	Number of Patients
Pharmacokinetic Study		
RIS-USA-160	Multiple dose pharmacokinetic study of risperidone 0.01 to 0.08 mg/kg in children and adolescents (planned 5-17 years) with behavioral and psychotic disorders	24 children and adolescents (6-16 years) in equal numbers
Completed Study in Children and Adolescents With Bipolar I Disorder		
Double-Blind, Placebo-Controlled Phase III Study		
RIS-BIM-301[a,b]	Randomized, double-blind, placebo-controlled multicenter 3-week study in children and adolescents (ages 10-17 years) with acute mania in Bipolar I disorder Risperidone 0.5-2.5 mg/day Risperidone 3-6 mg/day Placebo	Treated: 169 patients with Bipolar I disorder (67 ≤12 years old; 102 >12 years old) PLA n=58 RIS 0.5-2.5 mg n=50 RIS 3-6 mg n=61
Safety Study		
Long Term Open-Label Study		
RIS-USA-234	Open-label, 6-month, multicenter study in adolescents with schizophrenia. Subjects entered from RIS-USA-231 or RIS-SCH-302 or entered directly. Risperidone 2–6 mg/day	Analyzed: 297[c] RIS n=297 (including 11 ≤12 years old and 4 with schizophreniform disorder) 119 with mode dose ≥3 mg/day and duration ≥180 days

[a]Included in the Pediatric sNDA for Bipolar I disorder
[b]Fulfills the Written Request requirement that at least 50% of patients assigned to active drug must complete to the nominal end point of the trial to be considered a completed trial
[c]Evaluated data set included subjects who completed or discontinued on or up to 31 March 2006; no directly enrolled subjects met this criterion

n = size of a subsample; PLA = placebo; RIS = risperidone; sNDA = supplemental New Drug Application

Note: children = ≤12 years of age; adolescents = 13-17 years of age

4.3 Review Strategy

Since there is only one efficacy study for the study indication, this will be reviewed and in the main body of the review instead of placing it in the Appendix. Safety review will rely on both the clinical trials mentioned above and the review of literature.

PK data and statistical issues will be reviewed by the Agency Biopharmaceutical Science Reviewer, Andre Jackson, Ph.D. and the Agency Statistician, John Lawrence, Ph.D., respectively.

4.4 Data Quality and Integrity

Inspection sites were selected based on the overview of statistic data and the numbers of subjects enrolled for the efficacy study. DSI inspection report is in process.

The sponsor conducted appropriate coding of verbatim terms to preferred terms.

4.5 Compliance with Good Clinical Practices

The sponsor reports that all subjects complied with treatment except one who was withdrawn from the study because he didn't take study drug (placebo) on Day 2due to adverse event and Day 7 due to unclear reason.

Up to 33% subjects had protocol deviations (see table below). They are fairly evenly distributed in each treatment group. The reasons for these deviations are listed in the following table. Treatment (dose) deviation is the most common one in both risperidone treatment groups (24% and 15%). Rates of concurrent forbidden therapy are fairly similar in each treatment group (10%, 8% and 7%). Placebo group had most randomization deviations (9%). See subsection 6.1.4 for more details.

For site specific issues, please DSI report. Otherwise, the study seems to be conducted in accordance with acceptable ethical standards.

4.6 Financial Disclosures

The sponsor adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure for Clinical Investigators. Financial disclosure couldn't be obtained from only one of the clinical sub-investigators' [redacted]) in Study RIS-US-301. Otherwise, there were none for disclosure for all other clinical investigators in this study.

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5 CLINICAL PHARMACOLOGY

The Agency Biopharmaceutical Science Reviewer, Andre Jackson, Ph.D. reviews the PK studies submitted by the sponsor.

5.1 Pharmacokinetics

According to Dr. Jackson, there is no dose adjustment required for pediatrics, exposure was similar to adults. Please see Dr. Jackson's review for details.

Information from previous review of risperidone regarding Drug Interactions is summarized below:

- Psychostimulants such as methylphenidate or atomoxetine didn't appear to affect the pharmacokinetics of risperidone.

- Hepatic enzyme inducers, such as carbamezapine, phenytoin and others can decrease the plasma level by 50%.

- Risperidone increases Cmax of valproate by 20% based on sponsor's previous study (information from Dr. Duan). Compared with historical data, there was no increase of risperidone level when combined with valproate. There is no data on combination of risperidone and other antiseizure medications, such as lamotrigine, vigabatrin, gabapentin and tiagabine.

- Paroxetine or fluoxetine co-administration increased the Cmax and AUC values of active moiety up to 45%. Therefore, caution should be used if risperidone is co-administered with medications that inhibit the CYP2D6 system. If such medications co-administration is stopped, re-evaluation of the risperidone dosage is needed.

5.2 Pharmacodynamics

Risperidone is a dopamine receptor-2 (D_2) antagonist. It also antagonizes serotonin-2 receptors ($5\text{-}HT_2$) and D_1, $5\text{-}HT_{1A}$, $5\text{-}HT_{1C}$, and $5\text{-}HT_{1D}$ weakly to moderately.

Moreover, risperidone also has effects on other receptors, including α_1 and α_2 adrenergic and histaminergic-1 receptors, but with low potency. Its alpha blocker effect will potentiate other hypotensive drugs.

It has no affinity for cholinergic muscarinic or alpha-1 or alpha-2 adrenergic receptors.

Please see the review conducted by the Agency Biopharmaceuticals Science Reviewer, Andre Jackson, PhD.

5.3 Exposure-Response Relationships

The sponsor reports that the correlation between the predose active moiety plasma concentrations at steady-state and selected measures of efficacy (YMRS) and safety (QTcLD and SAS) was explored graphically, via scatter plots. Scatterplots of active moiety plasma concentrations versus SAS (actual and change from baseline). No apparent trends or relationships are observed between the predose active moiety plasma concentrations at steady-state and the selected measures of efficacy or safety.

In Study US-BIM-301, most subjects were treated for 11 days or longer. The patient-year was 2.7 and 3.1 in risperidone lower dose and higher dose groups, respectively.

Table 3: Summary of Treatment Duration (RIS-BIM-301; Intent-to-Treat Analysis Set)

Total duration, days	Placebo	RIS 0.5–2.5 mg	RIS 3–6 mg
N	58	50	61
Category, n (%)			
≤10	5 (9)	2 (4)	6 (10)
≥11	53 (91)	48 (96)	55 (90)
Mean (SD)	19.14 (4.714)	19.68 (4.043)	18.44 (5.182)
Median	21.00	21.00	21.00
Range	(2.0; 24.0)	(2.0; 24.0)	(1.0; 24.0)
Total exposure (subject years)	3.0	2.7	3.1

Once the dose was fixed, the mode dose was 2.5 mg in the risperidone lower dose group (57% subjects) and 6mg in the risperidone higher dose group (41%).

6 INTEGRATED REVIEW OF EFFICACY

[redacted]

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The diagnostic criteria are based on DSM-IV with no lower age limit. Like bipolar I disorder in adulthood, bipolar I disorder in pediatric population includes a phase of mania with or without a phase of major depression. However, child patients have different presentations for these mood changes and that the criteria established for adults may not fit those of pediatric patients. When manic, children and adolescents are more likely to be irritable and prone to destructive outbursts than to be elated or euphoric. When depressed, the symptoms may be expressed physically with complaints such as headaches, muscle aches, stomachaches or tiredness, frequent absences from school or poor performance in school, talk of or efforts to run away from home, irritability, unexplained crying, and extreme sensitivity to rejection or failure. Alcohol or substance abuse and difficulty with relationships can also be part of the manifestations. There has been suggestion that bipolar disorder beginning in childhood or early adolescence may be a different, possibly more severe form of the illness than older adolescent- and adult-onset bipolar disorder.

The prevalence of this disorder in children and adolescents is unclear – Different consensus about the diagnosis in the clinical community and the lack of epidemiological studies probably contributes to this status.

Major differential diagnoses in pediatrics include conduct disorder, oppositional defiant disorder, ADHD, anxiety disorders, eating disorders, substance-related disorders, and among others.

The sponsor studied bipolar I disorder in subjects aged 10 to 17 years old in the pivotal efficacy study (Study RIS-US-301).

6.1.1 Methods

The Agency WR requires the sponsor to conduct a randomized, double-blind, parallel group, placebo-controlled acute trial with a recommended duration of at least 3 weeks. Thus, the sponsor provides clinical data from Study RIS-US-301 as the only source for supporting the proposed efficacy claim. (See Study Design in the subsection below.)

6.1.2 General Discussion of Endpoints

The Agency WR indicates that a scale specific to mania and sensitive to effects of drug treatment of main in the target population should be used... it may also be useful to add a global measure, e.g., the Clinical Global Impression (CGI).

The sponsor states that they used changes of Young Mania Rating Scale (YMRS) adolescent version from baseline to endpoint as primary efficacy outcome for the study.

YMRS is a commonly used instrument for evaluation of severity of mania in adults and is useful for monitoring changes in manic symptoms with treatment or over time. The scale was essentially designed to be given by the clinicians. Like its adult version, the parent/child version provided by the sponsor, which was also referred to as "adolescent version" in the submission, also comprises an 11-item checklist, seven of them scoring from 0 – 4 and four items (irritability, speech, content, and disruptive-aggressive behavior) scoring 0 - 8. Total score of the scale is 0 – 60, with a higher score indicating a more severe condition. It appears that this scale has been applied to many such trials published. Below illustrates the items and scores of this scale:

Table 4. Items and Scores of the YMRS Adolescent Version Used in RIS-BIM-301

Item number	Item Description	Score range
1	Elevated mood	0-4
2	Increased motor activity	0-4
3	Sexual interest	0-4
4	Sleep	0-4
5	Irritability	0-8
6	Speech (rate and amount)	0-8
7	Language-thought disorder	0-4
8	Content	0-8
9	Disruptive-aggressive behaviour	0-8
10	Appearance	0-4
11	Insight	0-4
Total	TOTAL YMRS	0-60

The scale was administered at Screening, Baseline, Day 7, Day 14, Day 21 or early termination.

According to the protocol, if possible, the same clinician administered this scale at all visits. The score was based on the subject's and parent's reports of the subject's condition over the previous 7 days and the clinician's behavioral observations during the interview (consensus final score), with emphasis on the latter. Thus, the final/composite score is not a summed total but an interpreted score based on the investigator's own interview and his/her interpretation of the parent and child interview scores. This practice is uncommon. Though the sponsor wrote to us that the scale was developed and validated by Kowatch, et al, a Medline search using the combination of the scale name (YMRS adolescent version) and the acclaimed author's name (Kowatch) resulted zero.

The sponsor used CGI-BP as secondary efficacy endpoint to assess the severity of illness (1=normal, not ill; 2=minimally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=very severely ill).

No key secondary endpoint was specified. The following table shows the scales measured during the study:

Table 5. Schedule for Efficacy Assessments Performed in the RIS-BIM-301 Study in Children or Adolescents With Bipolar I Disorder

	Screening	Baseline	Double-Blind Treatment Phase			
Visit:	1	2	3	4	5	6 (or Early Termination)
Day:		0	7	10	14	21
Young Mania Rating Scale (YMRS)[a]	X	X	X		X	X
Clinical Global Impression-Bipolar (CGI-BP)		X	X		X	X
Brief Psychiatric Rating Scale for Children (BPRS-C)		X	X		X	X

[a] All subjects were required to have a YMRS score ≥20 at screening and baseline.

6.1.3 Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, 3-arm study in children and adolescents with a DSM-IV diagnosis of Bipolar I disorder. The length of study is three weeks. Randomization was stratified by center, and the two levels of diagnosis (mixed versus manic) - Two separate randomization lists were generated for this purpose.

Dosage

The three dose groups are placebo, risperidone 0.5-2.5mg (referred as "dosage group A"), and 3-6mg (referred as "dosage group B"). Each dosage group is assigned with four dose-cards: For placebo group, Cards A, B, C, and D are all 0 mg; Dose-cards A, B, C, and D are given doses 0.5mg, 1mg, 1.5mg, and 2mg, respectively in dosage group A (lower dosage group) and 3mg, 4mg, 5mg, and 6mg, respectively in dosage group B (higher dosage group).

After Screening, the subjects were randomized to the above three groups and started on 0.25mg/day in the both of the risperidone dosage groups. The dosages were titrated up to the targeted dosage range by Day 7. The table below illustrates the titration schedule.

In the initial titration is regarded as "segment 1" (typically Days 1-6), followed by a flexible dose period within the target range ("segment 2") (Days 7-10), and then the fixed dose stage ("segment 3") (Days 11-21). The dose established at the end of segment 2 (flexible dose stage, Day 10) determined the dosing card (A, B, C, or D) used for segment 3 (fixed dose stage). The risperidone dose was always within the defined range for the subjects' randomization group (0.5-2.5 mg or 3-6 mg)

Table 6. Dosage Titration Schedule (RIS-BIM-301)

Day	Risperidone Dosage Group A* (0.5-2.5 mg/day)	Risperidone Dosage Group B* (3-6 mg/day)	Notes
1	0.25 mg/day	0.25 mg/day	
2-3	0.25 mg/day	0.5 mg/day	Titration could be accelerated or decelerated to targeted dosage range, if needed
4-5	0.5 mg/day	1 mg/day	
6	0.5 mg/day	2 mg/day	
7	0.5 mg/day	3 mg/day	Target range achieved.
8-10	0.5-2.5 mg/day	3-6 mg/day	Subjects were titrated to the maximum tolerated dosage within the target dosage range.
11-21	0.5-2.5 mg/day	3-6 mg/day	Maximum tolerated dosage maintained for study duration.

* A subject should achieve a minimum dosage of 0.5 mg/day in dosage group A or 3 mg/day in dosage group B by Day 7. After Day 10, adjustments to the dosage reached by Day 10 were not to take place unless discussed and agreed upon with the Sponsor. If the subject could not be maintained within the target dosage range from Days 10 to 21, they were to be withdrawn from the study and could enter the aftercare program.

A washout period was five elimination half-lives of the disallowed substance (to a maximum of five days) unless the subject's psychiatric symptoms were much worse at Screening. Medications for agitation and insomnia were allowed during washout, up to 2 doses as necessary.

Prohibited Treatments

- Mood stabilizers, including lithium;
- Antidepressant drugs;
- Herbal and over-the-counter psychotropic agents;
- Antimanic drugs;
- Antipsychotics (including commercial RISPERDAL®)/neuroleptics, other than study medication;
- Psychostimulants and direct dopamine agonists;

- Sedatives/hypnotics/anxiolytics, other than as indicated below;
- Beta-adrenergic blockers, other than
- Antiparkinsonian/antidyskinetic drugs, other than as indicated below;
- Cholinesterase inhibitors.

For outpatients, formal group or individual supportive therapy and insight-oriented therapy were also prohibited. Supportive and educational approaches as well as group therapy were limited to ≤ 15minutes.

For inpatients, cognitive behavioral and insight oriented therapies were also prohibited. However, patients could receive supportive and special educational programs but limited to 5 hours/week.

Subject Selection

Male or female 10 to 17 years of age, inclusive, at the time of randomization with obtainable consent forms. The Kiddie-Schedule for Affective Disorder and Schizophrenia – Present and Lifetime (K-SADS-PL) was used by an adequately trained clinician based on a semi-structured interview to ensure the criteria of DSM-IV and the diagnosis of bipolar disorder is then confirmed by a child psychiatrist.

The sponsor presents major *inclusion* criteria as follows:

1. Met DSM-IV criteria for Bipolar I disorder, Most Recent Episode Manic or Most Recent Episode Mixed. This diagnosis must be confirmed on K-SADS-PL interview.
2. The following comorbid Axis I disorders are allowed: Attention Deficit Hyperactivity Disorder, Conduct Disorder, Oppositional Defiant Disorder, and Disruptive Behavior Disorder. No other comorbid Axis I or II disorders were acceptable, except substance dependence for nicotine and caffeine.
3. Received a total score of =20 on the YMRS at screening and at baseline.
4. If female:
   – Was premenarchal; or
   – Was incapable of pregnancy because of a hysterectomy, tubal ligation, or partner sterility; or
   – If sexually active and capable of pregnancy, was using an acceptable method of contraception (hormonal contraceptives, intrauterine device, spermicide and barrier) for at least a month prior to study entry and agreed to continue to use one of these for the duration of the study; or
   – If sexually abstinent and capable of pregnancy, agreed to continue abstinence or to use an acceptable method of birth control (either intrauterine device or spermicide and barrier) should sexual activity commence; and
   – Had a negative β-human gonadotropin hormone pregnancy test at screening and baseline.
5. Had a responsible person available to accompany the subject to the investigational site on each assessment day to provide reliable information and to accurately and reliably dispense the study medication as directed, if in the opinion of the investigator the subject could not otherwise be compliant with study procedures and medication.

The sponsor lists the following as *exclusion* criteria:

1. Known or suspected history of substance dependence (including alcohol, but excluding nicotine and caffeine) according to DSM-IV criteria within the 3 months prior to screening
2. Believed by the investigator to be at significant risk for suicidal or violent behavior during the course of the study
3. Was taking prohibited concomitant psychotropic medications that, in the opinion of the investigator, should not be discontinued/washed out
4. Continued to use, despite washout, any prohibited concomitant medication, substance of abuse, or alcohol within 5 half-lives (up to a maximum of 5 days) prior to baseline, as evidenced by history or as suggested by a positive urine drug screen at baseline
5. Received a depot antipsychotic within 2 treatment cycles before baseline
6. Received electroconvulsive therapy within 4 weeks of baseline
7. Was unable to swallow medication taken in the form of tablets. Tablets could be divided if needed, but not crushed. If a tablet was divided, the entire tablet must have been taken at 1 time.
8. Had clinically significant abnormalities identified during screening or baseline based upon medical history, physical examination, electrocardiogram and/or the results of the blood biochemistry, thyroid screening, hematology tests, and urinalysis
9. Known or suspected history of seizure disorder, tardive dyskinesia, or diabetes
10. History of neuroleptic malignant syndrome or similar encephalopathic syndrome
11. Known or suspected history of other serious, unstable illnesses
12. Hypothyroidism or hyperthyroidism, unless stabilized on appropriate medication for at least 3 months before screening (a normal thyroid-stimulating hormone level was required before randomization)
13. Female subject who was pregnant or nursing
14. Known or suspected history of hypersensitivity or intolerance to risperidone
15. Known or suspected history of severe drug allergy or hypersensitivity (i.e., Stevens-Johnson's Syndrome)
16. History of a poor antimanic response to risperidone when used in adequate dosages for an adequate period as the sole antimanic agent
17. Previously participated in this study or who participated in any investigational drug study within 30 days before screening
18. Known or suspected intelligence quotient (IQ) less than 70
19. Children of employees of the investigator or study center, when the employee had direct involvement in the proposed study or other studies under the direction of that investigator or study center.

Protocol Specific Analysis

On page 1758 of the study protocol, the sponsor defines the intent-to-treat analysis set is the primary analysis set for all efficacy and safety data analyses, which includes all randomized subjects who receive at least one dose of study medication. However, in a response to our inquiry regarding the efficacy ITT, the sponsor adds that patients with no baseline or pose

baseline assessments on the primary endpoint were not be included in the analyses of change from baseline.

The primary efficacy variable is the change in the total YMRS score (changed to "consensus final score" - see below protocol amendment of August 31, 2005) from baseline to the 3-week endpoint, i.e., the last post baseline observation carried forward to the 3-week endpoint. The LOCF endpoint was defined as the last non-missing, post-baseline measurement. Clinical response was defined as a ≥50% reduction from the baseline score. The Cochran-Mantel-Haenszel (CMH) test was used to analyze the clinical response rate for general association controlling for center and diagnosis. A response was considered maintained if at least two consecutive measurements were maintained for YMRS response (based on consensus final score of YMRS). Though the sponsor does not admit this is addition to the initial definition, this part was not under the ITT definition subsection in the submission.

The analysis of the primary efficacy variable is based on ANCOVA model, with treatment, diagnosis (manic versus mixed) and center as factors and baseline total YMRS score as covariate. Descriptive statistics for N, arithmetic mean, and standard deviation of the mean for the change from baseline total YMRS score are calculated.

The primary comparison between each treatment group is based on testing the between-group difference in least-squares means changes obtained from the ANCOVA model. The 95% confidence interval for the differences is estimated as the difference in least-squares means between each treatment group and placebo (risperidone minus placebo). In addition, a step-down testing procedure is applied in comparing each of the risperidone dosage groups with placebo sequentially.

Protocol Amendments and Post Hoc Changes

After the original protocol issued on October 17, 2003, there have been two amendments, INT-1 on Feb. 0, 2004 and INT-2 on August 31, 2005. The sponsor lists all the changes in the two tables, from page 1695 – 1715. Virtually all sections of the protocol had some revisions. Below is a summary of these changes.

In the first amendment, major changes include: Clarified the magnitude of response of YMRS as the effect and primary efficacy variable, frequency of laboratory tests during period of Screening to study Starting point (Baseline) and washout procedure; Slowed the rate of drug titration for safety and adjusted the titration procedures; Including inpatients and patients with mixed episode into the study and adding height in the physical examination and Tanner staging as well as prolactin level as part of the monitoring; Added diphenhydramine as allowed concurrent medication and a withdrawal criterion for patients who can't be maintained within the target dosage range from Days 10 to 21. Statistically, investigative site is added as analytic factor. In addition, genetic study for liver isoenzymes was added.

Diagnostically, in addition to clarifying that DSM-IV as diagnostic criteria, the sponsor also added that the diagnosis to be confirmed by a child psychiatrist and allowed comorbidity of ADHD and dependence for nicotine and caffeine.

In the second amendment, the sponsor added the wording "consensus final score" in the parenthesis after the total score of the YMRS in the text and defined it. Additionally, the sample size was increased from 144 to 162 with 54 subjects in each of the three treatment groups instead of 48. The Sagie linear method for QT interval correction was eliminated. Definition for clinically important limits for child and adolescent subjects were added, including QTc of 500. Further safety analysis also included weight, height, and BMI and they were to be transformed to z-scores. Finally, scores on BARS was corrected as categorical data.

The sponsor reports the following changes were performed statistically: After unblinding, primary efficacy results on YMRS total score by mode dose group and by age group, CGI-BP results by age group and by sex, BPRS-C results by age group and by sex. The mode dose group is based on a subject's mode dose during the fixed-dose phase.

6.1.4 Efficacy Findings

Subject Demographics

A total of 237 subjects were screened and the table below summarizes subjects' demographic information. More subjects were over 12 years old than those younger (60% vs. 40%). There were slightly more female patients (51%) than males (49%). Ethnically, the majority was Caucasian (77%) and about one fifth were black.

Weight, Height, BMI and Tanner are taken from Visit 1 (start of the study). Overall, the weight of the study population was relatively high for the subjects' age (median 53.5 kg), 43.8 kg for subjects ≤12 years of age and 63.8 kg for those >12 years of age, with most subjects weighing 50 kg. Median (range) values for weight, height, and BMI were similar across treatment groups, irrespective of age. All treatment groups had fairly similarly distributed Tanner Stages of 1 to 5 overall. Most subjects ≤12 years of age were Tanner Stage 2 and most subjects >12 years of age were Tanner Stage 4.

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Table 7. Subject Demographic (ITT set) of Study RIS-BIM-301

	PLACEBO (N=58)	RIS 0.5-2.5 mg (N=50)	RIS 3-6 mg (N=61)	Total (N=169)
Age, years				
N	58	50	61	169
Mean (SD)	13.1 (2.20)	13.4 (2.03)	13.1 (2.12)	13.2 (2.11)
Median	13.0	13.0	13.0	13.0
Range	(10;17)	(10;17)	(10;17)	(10;17)
Age in classes, n (%)				
N	58	50	61	169
≤12 years	24 (41)	18 (36)	25 (41)	67 (40)
>12 years	34 (59)	32 (64)	36 (59)	102 (60)
Sex, n (%)				
N	58	50	61	169
Female	30 (52)	22 (44)	35 (57)	87 (51)
Male	28 (48)	28 (56)	26 (43)	82 (49)
Race, n (%)				
N	58	50	61	169
American Indian/Alaskan Native	1 (2)	2 (4)	0	3 (2)
Asian	0	1 (2)	0	1 (1)
Black or African American	10 (17)	10 (20)	9 (15)	29 (17)
Mixed	2 (3)	2 (4)	2 (3)	6 (4)
White	45 (78)	35 (70)	50 (82)	130 (77)
Ethnicity (Hispanic/Latino?), n (%)				
N	58	50	61	169
No	54 (93)	48 (96)	59 (97)	161 (95)
Yes	4 (7)	2 (4)	2 (3)	8 (5)
Weight, kg				
N	58	50	61	169
Mean (SD)	57.1 (19.35)	56.7 (16.74)	58.5 (19.57)	57.5 (18.60)
Median	53.3	53.5	54.9	53.5
Range	(25;120)	(30;114)	(30;132)	(25;132)
Weight in classes, n (%)				
N	58	50	61	169
<50 kg	21 (36)	19 (38)	20 (33)	60 (36)
≥50 kg	37 (64)	31 (62)	41 (67)	109 (64)
Height, cm				
N	58	50	61	169
Mean (SD)	155.7 (11.70)	158.5 (13.30)	157.1 (13.17)	157.0 (12.69)
Median	157.5	158.1	158.8	157.7
Range	(124;179)	(124;191)	(125;188)	(124;191)
Body mass index (kg/m²)				
N	58	50	61	169
Mean (SD)	23.1 (5.81)	22.3 (4.54)	23.3 (5.59)	22.9 (5.37)
Median	21.0	21.4	21.9	21.6
Range	(15;43)	(15;36)	(14;42)	(14;43)

Tanner stage: maximum, n (%)				
N	58	50	61	169
1	8 (14)	3 (6)	7 (11)	18 (11)
2	7 (12)	9 (18)	12 (20)	28 (17)
3	12 (21)	14 (28)	10 (16)	36 (21)
4	19 (33)	13 (26)	17 (28)	49 (29)
5	12 (21)	11 (22)	15 (25)	38 (22)

At baseline, 38 (46%) male subjects had manic episode, and 44 (54%) had a diagnosis of mixed episodes at baseline. The proportion of female subjects with manic episodes at baseline was much lower (22 [25%]) than those with mixed episodes (65 [75%]). Thus, the manic diagnosis subgroup included a greater proportion of males (63%) than females (37%), whereas the mixed episodes subgroup had more females (60%) than males (40%).

Baseline Characteristics

Baseline disease characters are summarized in the following table.

Table 8. Baseline Disease Characters (ITT set) of Study RIS-BIM-301

	Placebo (N=58)	RIS 0.5-2.5 mg (N=50)	RIS 3-6 mg (N=61)	Total (N=169)
Diagnosis by DSM-IV criteria, Category, n (%)				
Bipolar I disorder, manic episode	19 (33)	20 (40)	21 (34)	60 (36)
Bipolar I disorder, mixed episode	39 (67)	30 (60)	40 (66)	109 (64)
Comorbid CD/DBD/ODD, Category, n (%)				
Yes	34 (59)	27 (54)	40 (66)	101 (60)
No	24 (41)	23 (46)	21 (34)	68 (40)
ADHD, Category, n (%)				
Yes	27 (47)	25 (50)	33 (54)	85 (50)
No	31 (53)	25 (50)	28 (46)	84 (50)
Age at onset of bipolar disorder				
Mean (SD)	10.9 (3.29)	10.8 (3.56)	10.9 (3.10)	10.9 (3.29)
Median	11.5	11.0	11.0	11.0
Range	(2;17)	(1;16)	(3;16)	(1;17)
Yrs since onset of bipolar disorder				
Mean (SD)	2.2 (2.58)	2.6 (2.89)	2.3 (2.30)	2.3 (2.58)
Median	2.0	1.0	2.0	2.0
Range	(0;15)	(0;11)	(0;9)	(0;15)
Hospitalized at Screening?				
Yes	26 (45)	19 (38)	26 (43)	71 (42)
No	32 (55)	31 (62)	35 (57)	98 (58)

ADHD=Attention Deficit Hyperactivity Disorder; CD=Conduct Disorder; DBD=Disruptive Behavioral Disorder; ODD=Oppositional Defiant Disorder; SD = standard deviation; yrs = years.

In each group and overall, there were more subjects diagnosed with mixed episodes than mania, irrespective of age. Mean age of onset was about 11 years old. Almost half (44%) of the subjects had an active comorbid psychiatric disorder. 60% of all subjects had some form of comorbid

behavioral disorder (Conduct Disorder [CD], Disruptive Behavior Disorder [DBD] or Oppositional Defiant Disorder [ODD]), and 50% were ADHD.

The sponsor reports that the majority subjects had no active concurrent medical illness and no significant medical history at screening, most common one being allergic/immunologic, and 17% had a comorbid neurological condition, mostly headaches.

Treatment and Dosages:

Table 9. Summary of Mode Dose/Card Distribution during the *Fixed-Dose Phase* (RIS-BIM-301: Intent-to-Treat Analysis Set)

Randomization Group Mode Dose/Card Distribution	All subjects n (%)	≤12 years n (%)	>12 years N (%)
PLACEBO	53	23	30
Card A (0 mg)	4 (8)	1 (4)	3 (10)
Card B (0 mg)	2 (4)	2 (9)	-
Card C (0 mg)	1 (2)	1 (4)	-
Card D (0 mg)	46 (87)	19 (83)	27 (90)
RIS 0.5-2.5 mg	47	17	30
Card A (0.5 mg)	7 (15)	3 (18)	4 (13)
Card B (1 mg)	6 (13)	3 (18)	3 (10)
Card C (1.5 mg)	7 (15)	1 (6)	6 (20)
Card D (2.5 mg)	27 (57)	10 (59)	17 (57)
RIS 3-6 mg	54	20	34
Card A (3 mg)	14 (26)	4 (20)	10 (29)
Card B (4 mg)	10 (19)	6 (30)	4 (12)
Card C (5 mg)	8 (15)	3 (15)	5 (15)
Card D (6 mg)	22 (41)	7 (35)	15 (44)

Note: Percentages calculated with the number of subjects entering the fixed-dose phase as denominator.
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Mean dose of risperidone lower dose group is 1.8mg and mean dose of risperidone higher dose group is 4.6mg. (See table below.)

Table 10. Summary of Treatment Dose (mg) in Fixed Target Phase (RIS-BIM-301: Intent-to-Treat Analysis Set)

Study Phase: Fixed target	PLACEBO	RIS 0.5-2.5 mg	RIS 3-6 mg
Mode dose (including days off drug)			
N	53	47	54
Mean (SD)	0.000 (0.0000)	1.862 (0.7988)	4.667 (1.3175)
Median	0.000	2.500	5.000
Range	(0.00;0.00)	(0.50;2.50)	(2.00;6.00)
Mean dose (including days off drug)			
N	53	47	55
Mean (SD)	0.000 (0.0000)	1.817 (0.7873)	4.639 (1.3010)
Median	0.000	2.273	5.000
Range	(0.00;0.00)	(0.43;2.50)	(2.20;6.00)

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The median treatment duration was 21 days during the 3-week study and 11 days during the *fixed-dose phase* for all treatment groups and age groups.

In each dosage group, more subjects received Card D than other cards, that is, more subjects received highest dosage in each group, regardless risperidone dosage groups or placebo group. (See above table.) The majority subjects had mean treatment duration of ≥ 11 days for all treatment groups.

Subject Disposition

The next table displays the subject disposition over the treatment course.

Table 11. Subject Disposition over Time in Study RIS-BIM-301 (Efficacy ITT set)

Time Interval	RIS 0.5-2.5mg	RIS 3-6mg	Placebo	Total N
*Randomized**	50*	61	58	169
Baseline N	49	60	57	166
Day 7	47	59	57	163
Day 14	47	53	49	149
Day 21	45	46	47	138

* Excluded one who didn't meet the inclusion criteria on YMRS

Protocol Deviation

The following table summarizes the protocol deviations in this study.

Table 12. Protocol Deviations in Study RIS-BIM-301

Deviation	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) N (%)	RIS 3-6 mg (N=61) n (%)	Total (N=169) N (%)
Total no. subjects with deviation	**19 (33)**	**19 (38)**	**18 (30)**	**56 (33)**
Intercurrent event[a]	0	0	1 (2)	1 (1)
Investigator mistake	0	0	1 (2)	1 (1)
Intercurrent therapy	6 (10)	4 (8)	4 (7)	14 (8)
Intercurrent forbidden therapy	6 (10)	4 (8)	4 (7)	14 (8)
Treatment deviation	2 (3)	12 (24)	9 (15)	23 (14)
Wrong dose	2 (3)	12 (24)	9 (15)	23 (14)
Randomization deviation[b]	5 (9)	1 (2)	3 (5)	9 (5)
Randomization deviation	5 (9)	1 (2)	3 (5)	9 (5)
Selection criteria not met	6 (10)	5 (10)	4 (7)	15 (9)
Baseline disease cond. out of limits[c]	1 (2)	1 (2)	0	2 (1)
Selection criteria not met[d]	5 (9)	4 (8)	4 (7)	13 (8)

Note: Percentages calculated with the number of subjects in each group as denominator.
[a] Subject was given incorrect study drug (used wrong box for the first 2 days).
[b] Subjects were dispensed wrong block of medication, or randomized with replacement medication.
[c] Baseline YMRS score was not between 20 and 60.
[d] Baseline YMRS decreased by 25% or increased by 50% from screening. Also 1 subject was listed as EXCLUSION #4 AND #8 MET. WAIVER GRANTED?
sub22.rtf generated by dvnm.sas.

Overall, up to 8% of subjects didn't meet selection criteria and most of them had baseline YMRS decreased 25% or more from screening.

The prohibited treatment given include psychodynamic psychotherapy, CBT, medications such as Abilify, four days post Lexapro (instead of five days), lorazepam, diphenydramine.

The problem occurred in randomization process are mostly due to wrong assignment of treatment group or wrong block of mediations.

Several patients also received "wrong dose at segment 3." The sponsor didn't define "segment" in the submission. Upon request for clarification, the sponsor replied that "segment 3" is basically the fixed dose stage, typically from Days 11- 21.

Overall, these deviations do not seem to affect the whole study process.

Concomitant Therapy

A total of 77% (85/169) subjects had concomitant medications during the study. They are fairly even distributed: Placebo 81%, risperidone low dose group 74% and high dose group 79%.

In addition to above mentioned prohibited treatment as protocol deviation, numerous other medications were given. The following table summarizes the concomitant use of psychotropic medications.

Table 13. Medications with Significant Effects on CNS Used Concomitantly in Study RIS-BIM-301 (ITT Set)

Concomitant Medications	Placebo	RIS 0.5- 2.5 mg	RIS 3-6 mg
Randomized	N=58	N=50	N=61
lorazepam	13 (22%)	5 (10)	8 (13)
Risperidone	5 (9)	2 (4)	4 (7)
Hydroxyzine embonate	1 (2)	0	1 (2)
Ziprasidone hydrochloride	0	0	1 (2)
Aripiprazole	1 (2)	0	0
Benzatropine mesilate	1 (2)	3 (5)	9 (15)
Trihexyphenidyl hydrochloride	1 (2)	0	0
Valproate semisodium	0	0	1 (2)
Gamma-aminobutyric acid	0	1 (2)	0
Topiramate	1 (2)	0	0
Methylphenidate hydrochloride	0	0	1

Other medications used that have clinical significance on mood states include levothyroxine sodium (1, placebo group), epinephrine (1, risperidone low dose group), and corticosteroids or hydrocortisons (3, RIS 3-6mg; 7, RIS 0.5-2.5mg) –among them, 3 were on systemic use

Efficacy Results

In the submission, the sponsor indicates the above data are restricted to subjects with Visit Day 21 Endpoint Data Only. Upon clarification, the sponsor explains that the data include those who dropped earlier than Day 21, which means they are LOCF data.

The next table displays the change from baseline to the Day 21 Endpoint in total YMRS consensus final score provided by the sponsor.

Improvement in both risperidone dose groups was statistically significant compared with placebo. Change in lower dose group (risperidone 0.5-2.5 mg) is even slightly more than that in the higher dose group (risperidone 3-6 mg).

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Table 14: Young Mania Rating Scale Adolescent Version (YMRS) Consensus Total Scores - Change From Baseline to Day 21 Endpoint (RIS-BIM-301: Efficacy ITT)

Parameter: Total YMRS consensus final	PLACEBO	RIS 0.5-2.5 mg	RIS 3-6 mg
Baseline			
N	57	49	60
Mean (SD)	31.0 (7.46)	31.1 (5.97)	30.5 (5.92)
Median (Range)	31.0 (19;45)	31.0 (16;44)	31.0 (20;44)
Day 21 endpoint			
N	57	49	60
Mean (SD)	21.9 (9.51)	12.6 (7.22)	13.9 (9.70)
Median (Range)	22.0 (3;44)	12.0 (0;30)	11.5 (0;40)
Change from Baseline			
N	57	49	60
Mean (SD)	-9.1 (10.95)	-18.5 (9.70)	-16.5 (10.29)
Median (Range)	-8.0 (-36;22)	-17.0 (-39;-3)	-18.0 (-35;6)
P-value(minus PLACEBO)(a,b)		<0.001	<0.001
Diff. of LS Means (SE)		-9.2 (1.76)	-8.0 (1.70)
95% CI		(-12.69;-5.74)	(-11.33;-4.62)

[a] Test for no difference between TREATMENT from ANCOVA model with factor(s) TREATMENT,base,invest,diagn (type III SS).
[b] Pairwise comparison: P-values and CI associated with Fisher's LSD procedure.
N is the number of subjects with both baseline and endpoint values for the parameter.
ymrs01a.rtf generated by ymrun.sas.

The following figure depicts the differences in the least-squares means ±95% confidence limits (that is least squares mean change in each risperidone group minus the least squares mean change in the placebo group) for each center. The improvement of both risperidone groups is greater than placebo for nearly every center. There seem no significant differences in score reduction between two dose groups, except two to three study centers where the lower dose groups seem to be better than the higher dose group.

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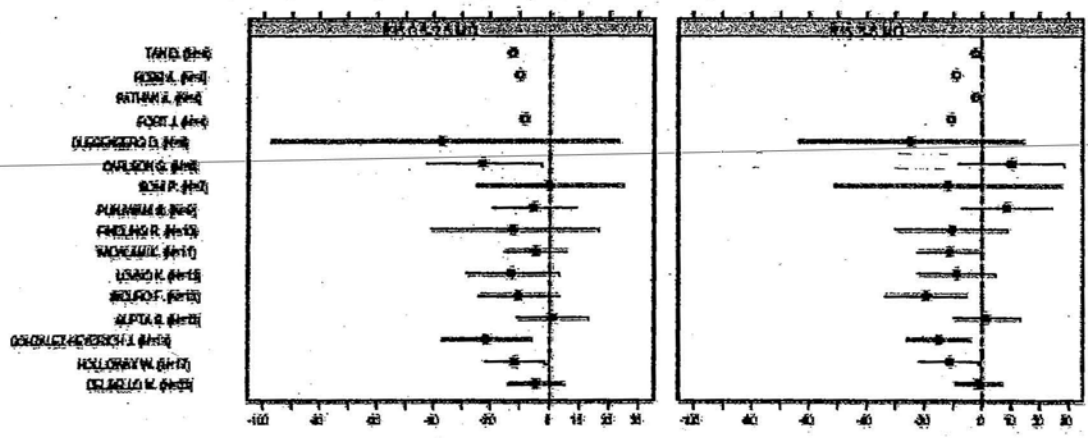
Figure 1. Total YMRS Consensus Final Score – Between Treatment Group Differences in Mean (+95% Confidence Limits) Change From Baseline at Day 21 Endpoint by Analysis Center (RIS-BIM-301)



Demographic effects on primary variable are shown in the following table provided by the sponsor.

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Table 15. Subgroup Analysis of Change from Baseline at Day 21 Endpoint in Total YMRS Consensus Score by Demographic Variables (RIS-BIM-301: ITT Analysis Set)

	Change From Baseline at Day 21 Endpoint in Total YMRS Score					
	PLACEBO		RIS 0.5-2.5 mg		RIS 3-6 mg	
	N	Mean (SD)	N	Mean (SD) Diff. of LS Means (95% CI)	N	Mean (SD) Diff. of LS Means (95% CI)
Sex						
Female	29	-10.7 (10.47)	22	-15.1 (7.06) -4.5 (-9.53;0.46)	35	-17.1 (9.98) -5.7 (-10.17;-1.22)*
Male	28	-7.5 (11.37)	27	-21.3 (10.77) -14.7 (-20.43;-8.95)***	25	-15.7 (10.85) -10.9 (-16.98;-4.78)***
Race						
Non-White	13	-7.8 (6.44)	14	-17.6 (9.92) -8.5 (-16.84;-0.11)*	10	-13.7 (12.52) -8.9 (-18.68;0.81)
White	44	-9.5 (11.99)	35	-18.9 (9.73) -9.0 (-13.25;-4.83)***	50	-17.1 (9.83) -8.5 (-12.40;-4.58)***
Race (Non-Black versus Black)						
Black	10	-6.8 (5.47)	9	-20.9 (9.60) -11.5 (-22.94;-0.12)*	9	-12.0 (11.99) -4.3 (-16.98;8.46)
Non-Black	47	-9.6 (11.77)	40	-18.0 (9.77) -8.6 (-12.58;-4.63)***	51	-17.3 (9.88) -8.6 (-12.35;-4.84)***
Age						
≤12 years	24	-6.1 (11.07)	18	-18.6 (10.00) -14.0 (-21.50;-6.54)***	24	-18.0 (9.51) -13.1 (-19.71;-6.40)***
>12 years	33	-11.3 (10.49)	31	-18.5 (9.69) -6.5 (-10.88;-2.03)*	36	-15.6 (10.80) -5.1 (-9.22;-1.03)*

* p value<0.05, *** p value<0.001; Comparisons between risperidone and placebo groups based on ANCOVA with treatment, investigator, diagnosis as factors, and baseline total YMRS score as covariate.
N is the number of subjects with both baseline and endpoint values for the parameter.

Within either risperidone dose group, change of total YMRS consensus score from baseline to Day 21 Endpoint in female patients is less significant than that in male patients; similarly, the change is less significant in adolescents who are > 12 years old than that in those who are ≤ 12 years of age. In either case, dose doesn't seem to affect the magnitude of change in total YMRS consensus scores. However, in the analysis of race groups, blacks in risperidone high dose group seem to have the least effect size.

In the subsection of Subgroup Analysis, the sponsor presents the analyses of YMRS changes from baseline to endpoint by diagnosis, presence of comorbidities (ADHD and ODD/DBD/CD). The following table displays the analysis by diagnosis variables:

Table 16. Subgroup Analysis of Change From Baseline at Day 21 Endpoint in Total YMRS Consensus Score by Diagnosis Variables (RIS-BIM-301: ITT Analysis Set)

	PLACEBO		RIS 0.5-2.5 mg		RIS 3-6 mg	
	N	Mean (SD)	N	Mean (SD) Diff. of LS Means (95% CI)	N	Mean (SD) Diff. of LS Means (95% CI)
Baseline total YMRS score						
Baseline Diagnosis						
Manic	19	32.0 (8.37)	19	31.7 (5.58)	21	32.1 (6.97)
Mixed	38	30.5 (7.02)	30	30.7 (6.27)	39	29.5 (5.14)
Presence of ADHD						
No	31	29.6 (7.27)	24	29.5 (6.02)	28	27.9 (4.95)
Yes	26	32.6 (7.49)	25	32.6 (5.62)	32	32.7 (5.86)
Presence of Comorbid CD/DBD/ODD						
No	24	29.9 (7.94)	22	31.7 (5.83)	21	28.5 (5.10)
Yes	33	31.8 (7.12)	27	30.6 (6.16)	39	31.5 (6.14)
Change from baseline at Day 21 endpoint in total YMRS score						
Baseline Diagnosis						
Manic	19	-6.8 (11.27)	19	-19.3 (10.17) -14.7 (-20.59;-8.75)***	21	-19.0 (9.21) -13.1 (-18.93;-7.29)***
Mixed	38	-10.3 (10.74)	30	-18.0 (9.53) -6.8 (-11.20;-2.46)*	39	-15.2 (10.69) -5.6 (-9.72;-1.48)*
Presence of ADHD						
No	31	-8.0 (10.97)	24	-18.3 (9.88) -9.0 (-13.81;-4.14)***	28	-15.0 (9.26) -8.6 (-13.33;-3.95)***
Yes	26	-10.4 (10.99)	25	-18.8 (9.73) -7.9 (-13.42;-2.46)*	32	-17.8 (11.09) -8.0 (-13.11;-2.88)*
Presence of Comorbid CD/DBD/ODD						
No	24	-11.7 (9.13)	22	-18.8 (10.66) -6.6 (-12.40;-0.89)*	21	-15.8 (9.76) -5.0 (-10.60;0.55)
Yes	33	-7.2 (11.87)	27	-18.3 (9.05) -12.3 (-16.80;-7.86)***	39	-16.9 (10.66) -10.0 (-14.13;-5.95)***

* p value<0.05, *** p value<0.001; Comparisons between risperidone and placebo groups based on ANCOVA with treatment, investigator, diagnosis as factors, and baseline total YMRS score as covariate (diagnosis not included in the model for the subgroup Diagnosis).
ADHD = Attention-Deficit Hyperactivity Disorder; CD/DBD/ODD = Conduct Disorder/Disruptive Behavior Disorder/Oppositional Defiant Disorder
N is the number of subjects with both baseline and endpoint values for the parameter.
ymrs08a.rtf generated by ymrun.sas; ymrs09a.rtf generated by ymrun.sas; ymrs10a.rtf generated by ymrun.sas

The effect is larger in subgroup of mania compared to subgroup of mixed episodes. The magnitude of effect was also larger in the subgroups with comorbid conditions of CD/DBD/ODD compared to those without these combidities. Presence of ADHD did not make any difference in terms of effect size.

There is no key secondary efficacy variable defined.

6.1.5 Efficacy Conclusions

Both risperidone groups were effective in adolescents with bipolar disorder I; change of primary variable from baseline is even slightly more in the lower dose group than that of the higher dose group. Although some subgroups have limited number of subjects (for instance, only nine black subjects in each of the risperidone group), the study result supports the proposed claim. The rapid recycling subtype is not mentioned or analyzed in this submission.

For correlation of effect size and plasma concentration of active moiety, please refer to the Agency Biopharmaceutical Science Reviewer, Dr. Andre Jackson's review.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Deaths, SAEs, and dropouts are reviewed based on the summary of the following three studies supporting the safety claim for this sNDA:

1) RIS-USA-160: A pharmacokinetic study during which the subjects (5- 17 year-old) took risperidone in a twice-daily dosing regimen at a daily dose of 0.01 - 0.08 mg/kg (the maximum daily dose during the last 7 days prior to the PK-monitoring day was 4 mg).
2) RIS-BIM-301: A double-blind, placebo controlled study in children and adolescents with bipolar I disorder
3) RIS-234: A long term, open-label study in adolescents with schizophrenia

The incidence of common adverse events, changes in laboratory tests, ECG, weight, height, and BMI will be reviewed only based on the double-blind, placebo-controlled trial, Study RIS-BIM-301.

7.1.1 Deaths

There was no death in Studies RIS-BIM-301 and RIS-USA-160.

In the six-month open-label trial on children and adolescents with schizophrenia, Study RIS-USA-234, one subject (#A36124) died from suicide after [redacted] of open-label treatment. The following is the case summary provided by the sponsor: b(6)

"This 17-year-old white female, with a diagnosis of paranoid schizophrenia (PANSS total score at baseline = 96) and no other relevant medical history, began treatment with risperidone (0.5 mg/day) on 28 Jan 2005. The risperidone dose was adjusted until the dose reached 4 mg/day on 30 Jan 2005; the subject continued on this dose until 8 Feb 2005. The dose was increased to 5 mg/day on 9 Feb 2005 and to 6 mg/day 2 days later; the subject continued on this dose until 24 Feb 2005. *The dose was decreased to 5 mg/day on 25 Feb 2005 and to 4 mg/day 2 days later; the*

subject continued on this dose until [redacted] Concomitant medications included zopiclon. On [redacted] the subject had suicidal thoughts (verbatim term, suicidal tendencies); the risperidone dose was increased and the subject recovered from this event on [redacted]. The subject was reported to be doing much better and returned home on [redacted] On [redacted] the subject committed suicide." b(6)

Though the investigator considered this event unrelated to the study medication, it is hard to rule out the possibility of drug-relatedness totally in my opinion.

7.1.2 Other Serious Adverse Events (SAEs)

The sponsor reports no SAEs in Study RIS-USA-160.

For Study US-BIM-301, the sponsor reports the treatment-emergent SAEs during the treatment period and within the 30 days of last medication; three subjects (5%) in the placebo group and eight in the risperidone groups had SAEs. List of these SAEs of this study is provided by the sponsor in the following table.

Table 17. Incidence of Treatment-Emergent Serious Adverse Events (RIS-BIM-301: ITT)
(RIS-BIM-301: Intent-to-Treat Analysis Set)

Study Phase: During treatment or within 30 days of last medication

AE System Organ Class Adverse Event Preferred Term	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)	ALL RIS (N=111) n (%)
Total no. subjects with serious AEs	3 (5)	3 (6)	5 (8)	8 (7)
Psychiatric disorders	3 (5)	2 (4)	4 (7)	6 (5)
Psychosis manic-depressive	2 (3)	1 (2)	4 (7)	5 (5)
Suicide attempt	1 (2)	2 (4)	2 (3)	4 (4)
Manic reaction	1 (2)	0	0	0
Body as a whole - general disorders	0	0	1 (2)	1 (1)
Allergic reaction	0	0	1 (2)	1 (1)
Respiratory system disorders	0	1 (2)	0	1 (1)
Asthma	0	1 (2)	0	1 (1)
Bronchospasm	0	1 (2)	0	1 (1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
AE = adverse event; N = total sample size; n = number with adverse event; no. = number; RIS = risperidone
ae06.rtf generated by aerun.sas.

There were more cases of "psychosis manic-depressive" as SAEs in risperidone higher dose group compared to the lower dose group and placebo – this reflects the same trend in both age groups: Age ≤12 years and > 12 years old. (Psychosis manic-depressive represents exacerbation or worsening of bipolar illness.) The table below is presented by the sponsor according to the age groups of incidence of treatment-emergent SAEs.

Table 18. Incidence of Treatment-Emergent Serious Adverse Events by Age Group (RIS-BIM-301: Intent-to-Treat Analysis Set)

Study Phase: During Treatment or Within 30 days of Last Medication

Age in Classes: ≤12 years				
AE System Organ Class Adverse Event Preferred Term	PLACEBO (N=24) n (%)	RIS 0.5-2.5 mg (N=18) n (%)	RIS 3-6 mg (N=25) n (%)	ALL RIS (N=43) n (%)
Total no. subjects with serious AEs	1 (4)	0	2 (8)	2 (5)
Body as a whole - general disorders	0	0	1 (4)	1 (2)
Allergic reaction	0	0	1 (4)	1 (2)
Psychiatric disorders	1 (4)	0	1 (4)	1 (2)
Psychosis manic-depressive	0	0	1 (4)	1 (2)
Manic reaction	1 (4)	0	0	0
Age in Classes: >12 years				
AE System Organ Class Adverse Event Preferred Term	PLACEBO (N=34) n (%)	RIS 0.5-2.5 mg (N=32) n (%)	RIS 3-6 mg (N=36) n (%)	ALL RIS (N=68) n (%)
Total no. subjects with serious AEs	2 (6)	3 (9)	3 (8)	6 (9)
Psychiatric disorders	2 (6)	2 (6)	3 (8)	5 (7)
Psychosis manic-depressive	2 (6)	1 (3)	3 (8)	4 (6)
Suicide attempt	1 (3)	2 (6)	2 (6)	4 (6)
Respiratory system disorders	0	1 (3)	0	1 (1)
Asthma	0	1 (3)	0	1 (1)
Bronchospasm	0	1 (3)	0	1 (1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
AE = adverse event; N = total sample size; n = number with adverse event; no. = number; RIS = risperidone
ae06age.rtf generated by aerun.sas.

The rates of suicide attempt are the same (6%) in both risperidone dose groups and are twice of that in placebo group (3%). More details will be reviewed in the subsection of Special Search for "Suicidal Analysis."

As displayed in above tables, majority SAEs are psychiatric. The only unexpected SAEs in Study-BIM-301 seems to be "severe asthma and severe bronchospasm" and is summarized below: Subject A30317 [Manufacturer's Control No.:US-JNJFOC-20050704042] is a 14-year old boy with a 5-year history of Bipolar I Disorder. He was enrolled in study with a mixed episode and randomized to receive risperidone (0.5-2.5 mg daily) for 3 weeks. He had a history of shortness of breath and sinusitis and was receiving over-the-counter allergy sinus medication and co-tylenol throughout the study. On Day 16 (while on risperidone dose of 1.5 mg) he experienced mild dyspnoea and was started on salbutamol treatment (6-8 puffs a day, as required). On Day 19 (on same dose of risperidone), his symptoms worsened and his mother took him to the emergency room. He was treated with a nebulizer and discharged. The events

were considered resolved on Day 20 and were assessed by the investigator as doubtfully related to study drug. The subject completed the study; the last dose was administered on Day 21. He continued to receive salbutamol as needed. *–The drug effect can't be totally ruled out in this case though his prior history is confounding.*

List of SAEs in Study RIS-US-234 are summarized in the table below provided by the sponsor.

Table 19. Incidence of SAE in Study RIS-US-234 (ITT set)

Trial Phase: During open-label or within 30 days of last medication

AE System Organ Class Adverse Event Preferred Term	PLA/RIS (N=41) n (%)	RIS/RIS (N=256) n (%)	ALL RIS OL (N=297) n (%)
Total no. subjects with serious AEs	3 (7)	43 (17)	46 (15)
Psychiatric disorders	2 (5)	39 (15)	41 (14)
Psychosis	1 (2)	24 (9)	25 (8)
Suicide attempt	1 (2)	13 (5)	14 (5)
Aggressive reaction	0	5 (2)	5 (2)
Depression	0	4 (2)	4 (1)
Anxiety	0	1 (<1)	1 (<1)
Emotional lability	0	1 (<1)	1 (<1)
Schizophrenic reaction	0	1 (<1)	1 (<1)
Body as a whole - general disorders	0	4 (2)	4 (1)
Injury	0	3 (1)	3 (1)
Lab values abnormal	0	1 (<1)	1 (<1)
Centr & periph nervous system disorders	0	1 (<1)	1 (<1)
Convulsions	0	1 (<1)	1 (<1)
Gastro-intestinal system disorders	1 (2)	0	1 (<1)
Vomiting	1 (2)	0	1 (<1)
Respiratory system disorders	0	1 (<1)	1 (<1)
Pharyngitis	0	1 (<1)	1 (<1)
Secondary terms	0	1 (<1)	1 (<1)
Inflicted injury	0	1 (<1)	1 (<1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
ae09.rtf generated by raerun.sas.

From this list, there seem no unexpected SAEs, except the case with lab values abnormal in risperidone group.

This subject (#A35111) is a 17-year-old Caucasian male (as female in narratives) with no relevant medical history. Concomitant medications include omeprazole 20mg/day, colestipol hydrochloride 2 tablets/day. He participated in the study from (b) (6) to (b) (6)

His fasting baseline triglyceride level was 4.19 mmol/L (normal range: 0.42 to 1.67 mmol/L) that was above the pathological limits (0.11 to 2.5 mmol/L). His triglycerides levels were above the pathological limits repeatedly, at Day 28 (4 mmol/L), Month 3 (3.4 mmol/L), and Month 9 (3.96 mmol/L). At Month 9, she was discontinued from the study because of multiple laboratory abnormalities, including increases in triglyceride, uric acid, LDH, alkaline phosphate, ALT, and AST levels. In addition, the sponsor also wrote, "Nine days after the last dose of study medication, the subject was admitted to the hospital because of 'mild lab values abnormal,' which lasted for 1 day." Neither narrative summary nor CRF provided exact lab values. A search of dataset reveals the subject was on risperidone 1.5 mg and then 2mg daily. His ECG showed premature atrial contractions on Nov.17, 2003 . His ALT was mildly elevated (65U/L, lab reference: 6-43 U/L) from the starting date and increased to 115 U/L at Month 9, June 2, 2004; his AST was normal at first but increased to 101 U/L (lab reference: 11-36 U/L) by Month 9. Total bilirubin remained normal (6–12 umol/l, lab reference: 3–21 umol/l) during the study course. Albumin was fluctuating from 46 – 53 g/l (lab reference 33–49g/l). Nevertheless, platelet count decreased from 299 (lab reference 140-400 giga/L) at the beginning to 226 (giga/L) by Month 9. Other lab values showed elevation on June 2, 2004 include LDH 493U/l (lab reference: 53–234 U/l), uric acid 547 umol/l (lab reference: 125 –488 umol/l), ALK 188 U/l (lab reference: 31–129 U/l), Cholesterol 5.55 mmol/l (lab reference: 2.95–5.12 mmol/l). This event was considered probably related to study medication.—*I agree with the relatedness to the study drug but the reason for hospitalization is still unclear to me. Together with the patient's gender issue, the sponsor needs to provide further clarification of this case.*

Again, cases with suicidal attempts will be further reviewed in "Suicidal Analysis" in the Subsection of Special Search.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In Study RIS-BIM-301, overall, 92% (137/169) of subjects completed the study. The table below summarized overall drop-out reasons and subject numbers; however, please note that "other reasons" lumped "insufficient response, withdrew consent, noncompliance, became ineligible" as described above, including so-called "other" reasons.

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Table 20. Subject Disposition and Discontinuation Reasons (Study RIS-BIM-301)

Study	Placebo	RIS 0.5-2.5 mg	RIS 3-6 mg	Total
RIS-BIM-301, n (%)				
Randomized	58	51*	61	170
ITT	58	50	61	169
Completed	46 (79)	45 (90)	46 (75)	137 (81)
Drop outs due to LOE	2 (3)	0	2 (3)	4 (2)
Drop outs due to AEs	4 (7)	3 (6)	10 (16)	17 (10)
Drop outs due to other reasons	6 (10)	2 (4)	3 (5)	11 (7)

* 1 subject was randomized but did not meet the inclusion criteria regarding YMRS score (attained a score of 19) and so did not receive study medication.
AE=adverse event; ITT=intent to treat analysis set; LOE=lack of efficacy.

There are more dropouts due to AEs in risperidone higher dose group than in lower dose group (16% vs. 6%); the dropout rate in lower dose group is comparable with that of placebo group's (6% vs 7%). Overall, subjects in higher dose group had more dropouts than those in lower dose group (25% versus 10%), regardless the reasons, although there were considerable subjects in placebo group dropped out (21%) for various reasons as well.

Dropouts due to AEs mainly started from the second week. Below is a brief summary of dropouts during the study course of Study RIS-BIM-301:

During the first week, two subjects were lost to follow-up: One in high dose group and one in placebo group; Two other subjects in placebo group dropped out also - one due to adverse event and one withdrew the consent.

By Day 10, three more subjects discontinued: One subject in low dose group dropped out due to adverse event, another subject in placebo group did so because of insufficient response, and a subject in high dose group withdrew consent.

During the second week, seven more subjects dropped out due to adverse events: Five in high dose group, one in low dose group and one in placebo group. Additionally, in high dose group, two subjects dropped due to insufficient response. One subject in low dose group became ineligible and two more subjects withdrew their consents (one from placebo group and one in low dose group).

During the last week, eight more subjects dropped out due to adverse events: Five in high dose group, one in low dose group and two in placebo group. Insufficient response was the reason for one subject in placebo group only, so was non-compliance. In high dose group, one subject lost to follow-up.

In Study RIS-US-234, the sponsor reports that treatment-emergent adverse events leading to dropouts were reported more often in subjects previously treated with risperidone than those previously treated with placebo (10% vs. 5%). Furthermore, more subjects who were previously

treated with risperidone discontinued from the study due to psychiatric disorders (primarily psychosis) compared with those who were on placebo in the previous treatment phase.

7.1.3.2 Adverse events associated with dropouts

There were no adverse events led to discontinuation during Study RIS-USA-160.

For Study RIS-BIM-301, AEs that led to drop-out can be seen in the following table provided by the sponsor displaying the incidence of dropouts due to AEs.

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Table 21. Incidence of Treatment-Emergent Adverse Events With Action Taken of Permanent Stop (RIS-BIM-301: Intent-to-Treat Analysis Set)

Study Phase: Treatment AE System Organ Class Adverse Event Preferred Term	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)	ALL RIS (N=111) n (%)
Total no. subjects with perm stop med	4 (7)	3 (6)	10 (16)	13 (12)
Psychiatric disorders	3 (5)	1 (2)	7 (11)	8 (7)
Somnolence	0	1 (2)	4 (7)	5 (5)
Psychosis manic-depressive	3 (5)	0	3 (5)	3 (3)
Aggressive reaction	0	0	1 (2)	1 (1)
Nervousness	0	0	1 (2)	1 (1)
Suicide attempt	2 (3)	0	1 (2)	1 (1)
Centr & periph nervous system disorders	0	1 (2)	3 (5)	4 (4)
Bradykinesia	0	0	1 (2)	1 (1)
Hyperkinesia	0	0	1 (2)	1 (1)
Hypertonia	0	0	1 (2)	1 (1)
Speech disorder	0	0	1 (2)	1 (1)
Vertigo	0	1 (2)	0	1 (1)
Gastro-intestinal system disorders	0	2 (4)	3 (5)	5 (5)
Abdominal pain	0	1 (2)	1 (2)	2 (2)
Nausea	0	2 (4)	1 (2)	3 (3)
Saliva increased	0	0	1 (2)	1 (1)
Vomiting	0	1 (2)	1 (2)	2 (2)
Body as a whole - general disorders	1 (2)	0	1 (2)	1 (1)
Allergic reaction	0	0	1 (2)	1 (1)
Syncope	1 (2)	0	0	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
AE = adverse event; med = medication; N = total sample size; n = number with adverse event; no. = number; perm = permanent; RIS = risperidone
ae04.rtf generated by aernn.sas.

The incidence of treatment-emergent adverse events leading to permanent discontinuation of study medication was similar in the placebo and risperidone 0.5-2.5 mg treatment groups, and approximately doubled in the risperidone 3-6 mg treatment group.

The following table provided by the sponsor lists the AEs that led to permanent discontinuation of study in Study RIS-234.

Table 22. Incidence of Treatment-Emergent Adverse Events With Action Taken of Permanent Stop (JNJPRD--TRIAL RIS-USA-234: Intent-to-Treat Analysis Set)

Trial Phase: Open-label

AE System Organ Class Adverse Event Preferred Term	PLA/RIS (N=41) n (%)	RIS/RIS (N=256) n (%)	ALL RIS OL (N=297) n (%)
Total no. subjects with perm stop med	2 (5)	26 (10)	28 (9)
Psychiatric disorders	0	19 (7)	19 (6)
Psychosis	0	11 (4)	11 (4)
Suicide attempt	0	6 (2)	6 (2)
Aggressive reaction	0	3 (1)	3 (1)
Agitation	0	1 (<1)	1 (<1)
Hallucination	0	1 (<1)	1 (<1)
Centr & periph nervous system disorders	0	3 (1)	3 (1)
Extrapyramidal disorder	0	2 (1)	2 (1)
Dystonia	0	1 (<1)	1 (<1)
Liver and biliary system disorders	0	2 (1)	2 (1)
SGPT increased	0	2 (1)	2 (1)
SGOT increased	0	1 (<1)	1 (<1)
Metabolic and nutritional disorders	1 (2)	1 (<1)	2 (1)
Hypertriglyceridemia	0	1 (<1)	1 (<1)
Hyperuricemia	0	1 (<1)	1 (<1)
LDH increased	0	1 (<1)	1 (<1)
Phosphatase alkaline increased	0	1 (<1)	1 (<1)
Weight increase	1 (2)	0	1 (<1)
Body as a whole - general disorders	0	1 (<1)	1 (<1)
Injury	0	1 (<1)	1 (<1)
Cardiovascular disorders, general	1 (2)	0	1 (<1)
ECG abnormal	1 (2)	0	1 (<1)
Endocrine disorders	0	1 (<1)	1 (<1)
Hyperprolactinemia	0	1 (<1)	1 (<1)
Reproductive disorders, female	0	1 (<1)	1 (<1)
Lactation nauperperal	0	1 (<1)	1 (<1)

Subject A36284 is a 17-year-old Asian female, with a diagnosis of undifferentiated schizophrenia and no other relevant medical history. She was started on risperidone (0.5 mg/day) on Jan 27, 2005. The dose reached 4.0 mg/day on Feb 1, 2005 and remained on Feb 2, 2005, on which day, she developed dyspnoea (verbatim term, breathlessness) and had an abnormal ECG (verbatim term, prolongation of QTc). Her ECG interval values and overall evaluation are summarized in the table below, provided by the sponsor. Consider her QTcB interval values met the CPMP criteria for borderline QTcB interval values (451 ms to 470 ms for female subjects),

she was discontinued from the study after receiving 7 days of open-label risperidone treatment. The two adverse events (abnormal ECG and dyspnea) resolved on Feb 10, 2005 and Feb 4, 2005, respectively. No concomitant medications were reported.

Table 23. ECG Results of Subject A36284

Parameter	Day 1 27 Jan 2005[a]	Day 7 2 Feb 2005[b]	Day 7 2 Feb 2005[b]	Day 7 3 Feb 2005[b]	Day 8 10 Feb 2005[b]
ECG intervals:					
QT (msec)	408	349	368	362	400
QTcB (msec)	432	454[c]	456[c]	457[c]	440
QTcF (msec)	424	416	424	423	426
QTcLD (msec)	425	416	–	423	427
ECG Evaluation	–	WNL, repolarization disturbance prolongation sinus rhythm tachycardia	WNL, repolarization disturbance prolongation	WNL, repolarization disturbance prolongation	WNL, repolarizatio n disturbance atypical
Heart rate (bpm)	67	102	92	96	72

– = data not available; WNL = within normal limits
a Open-label baseline; measurement obtained by MDS Pharma Services
b Measurement obtained by the investigator
c Met the CPMP criteria for borderline QTcB interval value for female subjects (451 to 470 ms)

Two subjects had elevated SGPT: One of them was Subject A36205 who discontinued the study primarily due to weight increase (from baseline 35.8 kg/m2 to 41.4 kg/m2 at Month 6 endpoint). The sponsor reports the subject's ALT was 63 U/L (lab reference 6-43 U/L) and AST 41 U/L (lab reference 10-40 U/L) at Month 4. No value for Month 6 endpoint or total bilirubin value is provided.

Another subject, Subject A36365, is a 17-year-old Asian male, with a diagnosis of undifferentiated schizophrenia and currently active insomnia but no other relevant medical history. He began treatment with risperidone (0.5 mg/day) on Jul 14, 2005. The dose was increased up to 5.0 mg/day on Jul 19, 2005 and it remained until 26 Jul 2005. But, on Jul 14, 2005, his ALT was elevated (see chart below, provided by the sponsor) (verbatim term, abnormal lab values =2 times SGPT values). He was discontinued from the study because of ALT increased after receiving 13 days of open-label risperidone treatment. A summary of the subject's ALT (SGPT), AST (SGOT), GGT, and LDH levels is provided in the table below. *No total bilirubin value is provided.* He was considered recovered from the event on Jul 27, 2005.

Table 24. Liver Function Test Results of Subject A36365

Parameter	Normal Range	Day 1 14 Jul 2005[a]	Day 14 27 Jul 2005
ALT (SGPT) (U/L)	6 to 43	90 H	48
AST (SGOT) (U/L)	10 to 40	58 H	26
GGT (U/L)	0 to 51	40	28
LDH (U/L)	105 to 235	286 H	216

H = above the upper limit of the normal range
a Open-label baseline

Subject A35362 is a 16 year-old Caucasian female who was hospitalized for psychosis during the initial period of treatment and then developed "lactation nonpuerperal" after being treated with risperidone (up to 4mg) for 148 days. The subject was not recovered at the time of reporting.

Subject A35113 is a 17-year-old Caucasian female who was discontinued from the study after receiving 269 days of risperidone (up to 3mg/day) due to hyperprolactinemia shown as the following:

Table 25. Results of Serum Prolactin Level of Subject A35113

Parameter	Normal Range	Day -4 2Sep2003[a]	Day 28 6Oct2003	Month 3 8Dec2003	Month 9 2Jun2004
Prolactin (µg/L)	4.2 to 39	42.22 H	105.7 H	109.2 H	85.61 H

H = above the upper limit of the normal range
a Open-label baseline

She was not recovered at the time of reporting.

7.1.3.3 Other significant adverse events

In Study USA-160, seven subjects (two children and five adolescents) reported a total of 10 adverse events. None seems to call for special concern. Four of these subjects are reported to be recovered after one day.

In Study RIS-BIM-301, one subject in placebo group had syncope. Both somnolence and fatigue are the most common adverse events (see next section on Common Adverse Events). The table below displays the incidences of these two AEs in each treatment group.

Table 26. Incidence of Treatment-Emergent Somnolence or Fatigue (RIS-BIM-301: Intent-to-Treat Analysis Set)

Study Phase: Treatment Adverse Event Preferred Term	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)	ALL RIS (N=111) n (%)
Total no. subjects with somnolence or fatigue	12 (21)	26 (52)	45 (74)	71 (64)
Somnolence	11 (19)	21 (42)	34 (56)	55 (50)
Fatigue	2 (3)	9 (18)	18 (30)	27 (24)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
N = total sample size; n = number with adverse event; no. = number; RIS = risperidone
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There were no differences in overall incidences between age groups, though fatigue was more commonly (8/32=25% of subjects) reported by subjects >12 years of age than by subjects <12 years of age (1/18=6% of subjects) in risperidone lower dose group. In risperidone higher dose group, incidences of fatigue were similar in subjects ≤12 years of age (7/25 = 28% subjects) and >12 years of age (11/36 = 31% subjects).
The severity of these symptoms increases with the increase of risperidone dosages. More subjects in risperidone higher dose group dropped out due to somnolence than the lower dose group (4:1). However, no subject dropped out due to fatigue and most of the cases were mild in severity.

The occurrences of these two AEs are also earlier than those in the placebo group. The following figures depictures the time to first occurrence of somnolence and fatigue, respectively. Note that the time is measured in days.

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Figure 2. Kaplan-Meier Curve of Time to First Occurrence of Somnolence (RIS-BIM-301)

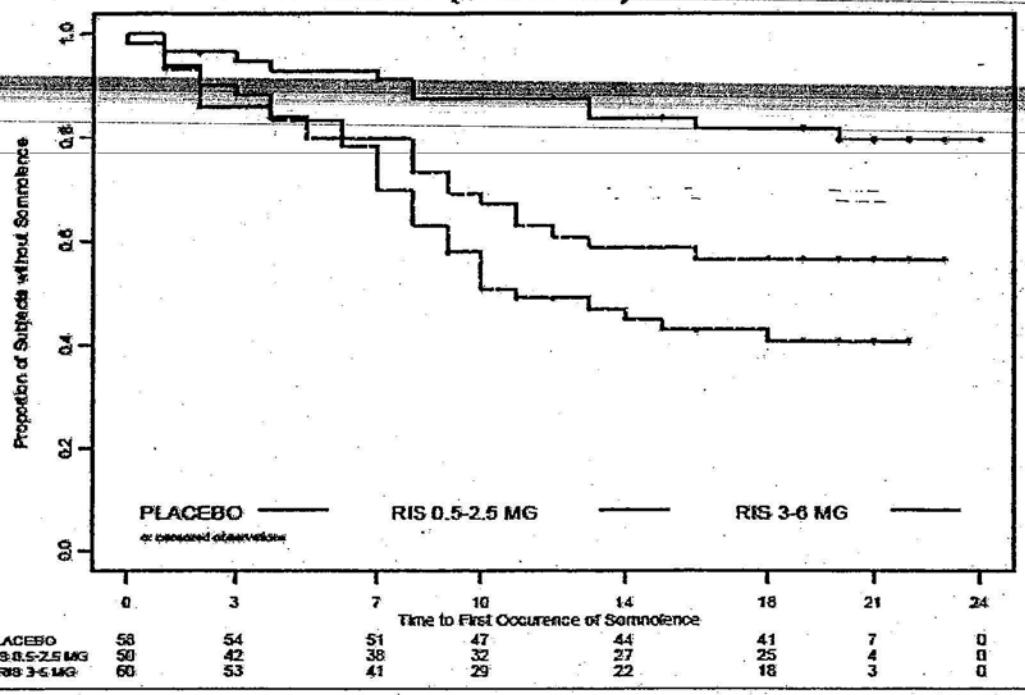
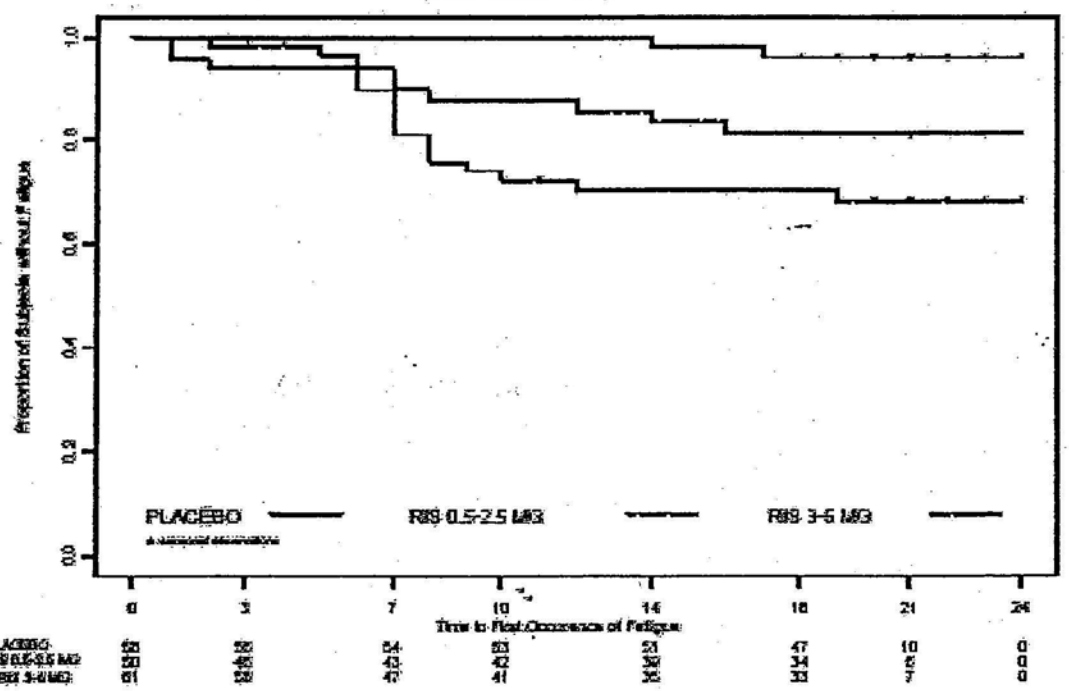


Figure 3. Kaplan-Meier Curve of Time to First Occurrence of Fatigue (RIS-BIM-301)



The durations of somnolence or fatigue are longer in risperidone treated groups than those in placebo group. The following table displays the duration of somnolence and fatigue.

Table 27. Number of Days and Percentage of Total Duration with Somnolence and Fatigue (RIS-BIM-301: ITT Analysis Set)

	PLACEBO (N=58)	RIS 0.5-2.5 mg (N=50)	RIS 3-6 mg (N=61)	ALL RIS (N=111)
Total days with somnolence				
N	11	21	34	55
Mean (SD)	5.3 (4.54)	9.0 (7.06)	8.2 (6.15)	8.5 (6.46)
Median	5.0	7.0	7.5	7.0
Range	(1;15)	(1;23)	(1;21)	(1;23)
% of total duration with somnolence				
N	11	21	34	55
Mean (SD)	28.9 (21.83)	43.8 (32.31)	41.3 (29.18)	42.3 (30.14)
Median	31.8	33.3	38.6	35.0
Range	(5;71)	(4;100)	(4;100)	(4;100)
Total days with fatigue				
N	2	9	18	27
Mean (SD)	1.0 (0.00)	8.2 (7.14)	7.3 (5.73)	7.6 (6.11)
Median	1.0	8.0	6.0	7.0
Range	(1;1)	(1;20)	(1;16)	(1;20)
% of total duration with fatigue				
N	2	9	18	27
Mean (SD)	6.2 (2.07)	40.3 (35.55)	37.7 (27.68)	38.5 (29.86)
Median	6.2	38.1	34.8	36.4
Range	(5;8)	(5;100)	(5;80)	(5;100)

N = total sample size; RIS = risperidone; SD = standard deviation
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Among 83 subjects who reported treatment-emergent somnolence or fatigue, 12 subjects reported both events. However, the sponsor reports that there was no overlap in the course of these events, that is, no subjects experienced fatigue with concurrent somnolence.

According to the sponsor, most of these episodes of fatigue or somnolence resolved while the subjects were on treatment except for four subjects who recovered from the event more than 4 days after the last treatment.

7.1.4 Other Search Strategies

7.1.4.1 Suicide analysis

For WHO-preferred term, the sponsor reports that the search includes the following text strings: "suicid", "overdos", "injury" or "aggress".

For verbatim term, the sponsor includes the following text strings: "'cut', 'contus', 'wound', 'aggres', 'agres', 'fall' (except 'falling asleep'), 'broke', 'abras', 'accid', 'alcoh', 'intox', 'injur', 'sprain', 'trauma', 'bit', 'black eye', 'bruis', 'bump', 'burn', 'fractu', 'fr.', 'commotio', 'disjointed', 'drinking', 'beverage intake', 'overdos', 'harm self', 'lacerat', 'fell' (except 'fell asleep'), 'hair pull', 'grazed', 'haematom', 'hematom', 'head butt', 'head hit', 'beat on', 'hit by car', 'self', 'suic', 'hurt ', 'hurt(', 'inflict', 'torsion', 'knowingly destroyed', 'damage', 'lesion', 'impact', 'scratch', 'chipped', ' car ', 'sexual abuse', 'sexual assault', 'dislocation', 'skin tear', 'smashed', 'throwing objects', 'tongue chew', 'twisted', 'violen', 'attempt', 'gas', 'hang', 'hung', 'jump', 'mutilat', 'shoot', 'slash', 'poison', 'asphyxiation', 'suffocation', 'firearm'."

The table below provided by the sponsor displays the events coded to suicide attempt and were classified as treatment emergent with the definition of occurring during the double-blind phase of the study or within four days of the last dose of the study medication.

Table 28. Overview of Suicide Attempts (RIS-BIM-301: ITT)

	PLACEBO (N=58)	RIS 0.5-2.5 mg (N=50)	RIS 3-6 mg (N=61)	ALL RIS (N=111)
	n	n	n	n
Events reported as SAE with onset ≤4 days of end of treatment	1	0	2	2
Events not reported as SAE with onset ≤4 days of end of treatment	1	1	2	3
Events reported as SAE with onset >4 and ≤30 days of end of treatment	0	2	0	2

The sponsor evaluated suicide cases using the following two ratings:

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Table 29. Comparison of Columbia Suicide Analysis and J&JPRD Scale

J&JPRD scale		Columbia scale	
1:	Completed suicide	1:	Complete suicide
2:	Suicide attempt (any behavior with apparent intent to die, including overdoses)	2:	Suicide attempt
3:	Suicidal ideation (thoughts, wishes, etc.)	3:	Preparatory actions towards imminent suicidal behavior
4:	Self-injurious behaviors (without apparent intent to die), self-aggression, and overdoses (unless clearly intended as a suicide attempt)	4:	Self-injurious behavior, intent unknown
5:	Motor vehicle accidents	5:	Suicidal ideation
6:	Other: alcohol/drug/abuse, injuries (abrasions, fractures, hematomas, etc.), other accidents, aggression, violence, intoxications (other than overdoses	6:	Not enough information
		7:	Self-injurious behavior, no suicide attempt
		8:	Other: accident
		9:	Other: psychiatric
		10:	Other: medical

The sponsor compares the rates using both the J&JPRD scale and the Columbia Suicide Analysis and concludes that the review of "potentially suicide-related events, there appears to be no indication of any clinically meaningful imbalances between placebo and active treatment with risperidone." The table below provided by the sponsor shows the result of Columbia Suicide Analysis.

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Table 30. Incidence of Treatment-Emergent Suicide-Related Adverse Events According to Columbia Suicide Analysis (STUDY RIS-BIM-301: ITT Analysis Set)

Study Phase: TREATMENT

Columbia Score Adverse Event Preferred Term	PLACEBO (N=58) n (%)	RIS 0.5-2.5 MG (N=50) N (%)	RIS 3-6 MG (N=61) n (%)	ALL RIS (N=111) n (%)
Total no. subjects with suicide-related AE	5 (9)	5 (10)	7 (11)	12 (11)
02 SUICIDE ATTEMPT	1 (2)	0	0	0
SUICIDE ATTEMPT	1 (2)	0	0	0
04 SELF-INJURIOUS BEHAVIOR, INTENT UNKNOWN	1 (2)	0	1 (2)	1 (1)
SUICIDE ATTEMPT	1 (2)	0	1 (2)	1 (1)
05 SUICIDAL IDEATION	0	1 (2)	3 (5)	4 (4)
SUICIDE ATTEMPT	0	1 (2)	3 (5)	4 (4)
08 OTHER: ACCIDENT	2 (3)	3 (6)	1 (2)	4 (4)
FALL	0	1 (2)	0	1 (1)
INJURY	2 (3)	2 (4)	1 (2)	3 (3)
09 OTHER: PSYCHIATRIC	3 (5)	0	3 (5)	3 (3)
AGGRESSIVE REACTION	3 (5)	0	3 (5)	3 (3)
10 OTHER: MEDICAL	0	1 (2)	0	1 (1)
INJURY	0	1 (2)	0	1 (1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
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The sponsor lumps not only the incidences of suicide attempts, suicide ideation, and self injurious behaviors but also accidents such as fall and injuries as well as aggressive reaction as "potentially suicide-related events." -- This over inclusion is unnecessary and inappropriate in my opinion. The sponsor needs to separate the events of completed suicide, suicide attempts, and suicide ideation from other categories in the analysis, although one can't totally exclude true suicide from those who had self-injurious behavior with unknown intent, esp. in children and adolescents.

Clearly, there were more subjects with suicidal ideation in risperidone groups (4% vs. 0 in placebo group), esp. the higher dose group (5% versus 2% in lower dose group) although based on this table actual suicide attempt only happened in one subject in placebo group and none in risperidone groups. Added together, the incidence of these two categories (suicide ideation and attempts) in each treatment group is: 5% (3/61) in risperidone higher dose group, 2% (1/50) in risperidone lower dose group, and 2% (1/58) in placebo group. Again, the incidence of suicide in risperidone treatment group, esp. the higher dose group, is higher than that of placebo group. However, the study has low power to detect this: Due to the small number of subjects, these differences (*p*-values) are not statistically significant enough.

The table below provided by the sponsor displays the analysis of so-called treatment-emergent "serious" suicide-related events. Again, subjects in risperidone groups have higher rate of suicidal ideation as well as behaviors of unclear intent.

Table 31. Incidence of Treatment-Emergent *Serious* Suicide-Related Adverse Events According to Columbia Suicide Analysis (STUDY RIS-BIM-301: ITT Analysis Set)

Study Phase: DURING TREATMENT OR WITHIN 30 DAYS OF LAST MEDICATION

Columbia Score Adverse Event Preferred Term	PLACEBO (N=38) n (%)	RIS 0.5-2.5 MG (N=30) N (%)	RIS 3-6 MG (N=61) n (%)	ALL RIS (N=111) n (%)
Total no. subjects with serious AEs	1 (2)	2 (4)	2 (3)	4 (4)
01 SUICIDE ATTEMPT	1 (2)	0	0	0
SUICIDE ATTEMPT	1 (2)	0	0	0
04 SELF-INJURIOUS BEHAVIOR, INTENT UNKNOWN	0	1 (2)	1 (2)	2 (2)
SUICIDE ATTEMPT	0	1 (2)	1 (2)	2 (2)
05 SUICIDAL IDEATION	0	1 (2)	1 (2)	2 (2)
SUICIDE ATTEMPT	0	1 (2)	1 (2)	2 (2)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
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In the placebo group, the attempt made by Subject A30112 was not regarded as serious after the start of treatment but the treatment-emergent suicidal ideation of another subject's (#A30289) was regarded as serious. Both were withdrawn from the study. Since subject A30015 had suicidal ideations before the start of treatment, it was not counted.

Similarly, though Subject A30347 in the risperidone 0.5-2.5 mg group had suicidal ideation, it was not regarded as serious while receiving 0.25 mg risperidone during the dose-titration phase. This adverse event resolved the same day and the subject completed treatment, receiving risperidone 1.5 mg in the fixed-dose phase. –This case is probably not treatment unrelated.

All 4 treatment-emergent adverse events coded to suicide attempt in the risperidone 3-6 mg group were actually suicidal ideations. Two of them were regarded as serious adverse events: Subject A30250 had suicidal ideations while receiving 6 mg risperidone, which resolved within 12 days after the subject was withdrawn from the study; and Subject A30345 had suicidal ideations while receiving 3 mg risperidone, but completed the study as planned and the adverse event resolved within 5 days. The other 2 subjects (Subjects A30014 and A30249) experienced suicidal ideations and resolved on the same day; both these subjects subsequently completed the study as planned—they are likely unrelated to the treatment.

Three additional subjects had serious adverse events that were coded to suicide attempt but onset >4 days after the last dose of study medication and so were not classed as treatment emergent. Subjects A30013 and A30185 in the risperidone 0.5-2.5 mg group were hospitalized, with

suicidal ideations resolving within 4 days. Subject A30074 in the risperidone 3-6 mg group reported suicidal ideation more than 30 days after the end of treatment, which resolved the same day.

For suicide-related adverse events, although based on the analysis of their external adult psychiatrist consultant, the sponsor concludes that "there is no detectable clinically meaningful relationship with these events attributable to risperidone treatment." Though I disagree with the sponsor's calculation because based on current provided data, some categories in the analysis carry more importance, such as suicide attempt and suicide ideation, than accidents or injury and it is important to look at them separately and compare them with placebo group category by category. However, as stated before, despite risperidone groups, esp. the higher dose group, show higher rate of suicide ideation and suicide attempts than placebo group, the differences (p-values) are not statistically significant. This study is not powered enough to detect this.

7.1.4.2 EPS-Related Events

The following table is provided by the sponsor displaying the incidences of EPS-related events.

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Table 32. Incidence of Treatment-Emergent EPS-Related Adverse Events by Grouped Term (RIS-BIM-301: ITT Analysis Set)

Study Phase: Treatment Grouped Term Adverse Event Preferred Term	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)	ALL RIS (N=111) n (%)
Total no. subjects with at least one EPS-related adverse event	3 (5)	4 (8)	15 (25)	19 (17)
Dystonia	1 (2)	4 (8)	8 (13)	12 (11)
Hypertonia	1 (2)	2 (4)	5 (8)	7 (6)
Dystonia	0	3 (6)	2 (3)	5 (5)
Tetany	0	0	2 (3)	2 (2)
Laryngismus	0	0	1 (2)	1 (1)
Muscle contractions involuntary	0	0	1 (2)	1 (1)
Akathisia	1 (2)	0	4 (7)	4 (4)
Hyperkinesia	1 (2)	0	4 (7)	4 (4)
Parkinsonism	1 (2)	1 (2)	4 (7)	5 (5)
Extrapyramidal disorder	1 (2)	1 (2)	3 (5)	4 (4)
Bradykinesia	0	0	1 (2)	1 (1)
Tremor	0	0	2 (3)	2 (2)
Tremor	0	0	2 (3)	2 (2)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
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Parkinsonism includes extrapyramidal disorder and bradykinesia. Both risperidone dose groups have higher incidence of dystonia. Incidences of all other symptoms of all category listed are significantly higher in risperidone higher dose group than those of lower dose group as well as placebo group. – They appear to be dose-related. There was no report of dyskinesia and the sponsor reports that there was no case of tardive dyskinesia. Overall, the incidence of EPS-related AEs were 25% in risperidone higher dose group, 8% in risperidone lower dose group, versus 5% in placebo group.

When separately analyzed by two different age groups, both risperidone dose groups showed significantly higher incidences of EPS-related AEs compared to placebo group in age group of ≤12 year-old, while in age group of > 12 year-old, higher overall incidence is only seen in the risperidone higher dose group. Individual category of symptoms, such as dystonia and parkinsonism, the incidences are higher in risperidone treated groups compared to placebo group, regardless the age groups. The table below is also provided by the sponsor showing incidences of EPS-related AEs by age group.

Table 33. Incidence of Treatment-Emergent EPS-Related Adverse Events by Grouped Term by Age Group (RIS-BIM-301: ITT Analysis Set)

Study Phase: Treatment

Grouped Term Adverse Event Preferred Term	PLACEBO (N=29) n (%)	RIS 0.5-2.5 mg (N=18) n (%)	RIS 3-6 mg (N=25) n (%)	ALL RIS (N=43) n (%)
Age in Classes: ≤12 years				
Total no. subjects with at least 1 EPS-related adverse event	0	2 (11)	4 (16)	6 (14)
Dystonia	0	2 (11)	2 (8)	4 (9)
Dystonia	0	1 (6)	1 (4)	2 (5)
Hypertonia	0	1 (6)	1 (4)	2 (5)
Parkinsonism	0	1 (6)	2 (8)	3 (7)
Bradykinesia	0	0	1 (4)	1 (2)
Extrapyramidal disorder	0	1 (6)	1 (4)	2 (5)
Akathisia	0	0	1 (4)	1 (2)
Hyperkinesia	0	0	1 (4)	1 (2)
Tremor	0	0	1 (4)	1 (2)
Tremor	0	0	1 (4)	1 (2)

Grouped Term Adverse Event Preferred Term	PLACEBO (N=34) n (%)	RIS 0.5-2.5 mg (N=32) n (%)	RIS 3-6 mg (N=36) n (%)	ALL RIS (N=68) n (%)
Age in Classes: >12 years				
Total no. subjects with at least 1 EPS-related adverse event	3 (9)	2 (6)	11 (31)	13 (19)
Dystonia	1 (3)	2 (6)	6 (17)	8 (12)
Hypertonia	1 (3)	1 (3)	4 (11)	5 (7)
Tetany	0	0	2 (6)	2 (3)
Dystonia	0	2 (6)	1 (3)	3 (4)
Laryngismus	0	0	1 (3)	1 (1)
Muscle contractions involuntary	0	0	1 (3)	1 (1)
Akathisia	1 (3)	0	3 (8)	3 (4)
Hyperkinesia	1 (3)	0	3 (8)	3 (4)
Parkinsonism	1 (3)	0	2 (6)	2 (3)
Extrapyramidal disorder	1 (3)	0	2 (6)	2 (3)
Tremor	0	0	1 (3)	1 (1)
Tremor	0	0	1 (3)	1 (1)

Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.
EPS = extrapyramidal symptoms; N = total sample size; n = number with adverse event; no. = number; RIS = risperidone
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The next table is provided by the sponsor presenting the analysis according to two weight groups: Those ≥ 50kg and those <50kg at start of Study.

Table 34. Incidence of Treatment-Emergent EPS-Related Adverse Events by Grouped Term by Weight at Start of Study (RIS-BIM-301: ITT Analysis Set)

Study Phase: Treatment

	PLACEBO			RIS 0.5-2.5 mg			RIS 3-6 mg			ALL RIS		
	Total	Weight in Classes, n (%)		Total	Weight in Classes, n (%)		Total	Weight in Classes, n (%)		Total	Weight in Classes, n (%)	
Grouped Term	(N=58)	<50 kg	≥50 kg	(N=50)	<50 kg	≥50 kg	(N=61)	<50 kg	≥50 kg	(N=111)	<50 kg	≥50 kg
Adverse Event Preferred Term	n (%)	(N=21)	(N=37)	n (%)	(N=19)	(N=31)	n (%)	(N=20)	(N=41)	n (%)	(N=39)	(N=72)
Total no. subjects with at least 1 EPS-related adverse event	3 (5)	0	3 (8)	4 (8)	3 (16)	1 (3)	15 (25)	4 (20)	11 (27)	19 (17)	7 (18)	12 (17)
Dystonia	1 (2)	0	1 (3)	4 (8)	3 (16)	1 (3)	8 (13)	2 (10)	6 (15)	12 (11)	5 (13)	7 (10)
Hypertonia	1 (2)	0	1 (3)	2 (4)	2 (11)	0	5 (8)	1 (5)	4 (10)	7 (6)	3 (8)	4 (6)
Dystonia	0	0	0	3 (6)	2 (11)	1 (3)	2 (3)	1 (5)	1 (2)	5 (5)	3 (8)	2 (3)
Tetany	0	0	0	0	0	0	2 (3)	0	2 (5)	2 (2)	0	2 (3)
Laryngismus	0	0	0	0	0	0	1 (2)	0	1 (2)	1 (1)	0	1 (1)
Muscle contractions involuntary	0	0	0	0	0	0	1 (2)	0	1 (2)	1 (1)	0	1 (1)
Akathisia	1 (2)	0	1 (3)	0	0	0	4 (7)	0	4 (10)	4 (4)	0	4 (6)
Hyperkinesia	1 (2)	0	1 (3)	0	0	0	4 (7)	0	4 (10)	4 (4)	0	4 (6)
Parkinsonism	1 (2)	0	1 (3)	1 (2)	1 (5)	0	4 (7)	3 (15)	1 (2)	5 (5)	4 (10)	1 (1)
Extrapyramidal disorder	1 (2)	0	1 (3)	1 (2)	1 (5)	0	3 (5)	2 (10)	1 (2)	4 (4)	3 (8)	1 (1)
Bradykinesia	0	0	0	0	0	0	1 (2)	1 (5)	0	1 (1)	1 (3)	0
Tremor	0	0	0	0	0	0	2 (3)	1 (5)	1 (2)	2 (2)	1 (3)	1 (1)
Tremor	0	0	0	0	0	0	2 (3)	1 (5)	1 (2)	2 (2)	1 (3)	1 (1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
EPS = extrapyramidal symptoms; N = total sample size; n = number with adverse event; no. = number; RIS = risperidone

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In risperidone lower dose group, those who weighed <50kg had higher incidences of EPS related events. In risperidone higher dose group, the incidences various among individual category of symptoms, however, incidences of parkinsonism and tremor are higher in those who weighed < 50 kg than those weighed ≥ 50 kg; incidences of dystonia and akathisia as well as overall incidence of all EPS-related AEs are higher in those who weighed ≥50 kg.

Rating scales for EPS, including AIMS[1], SAS[2], and BARS[3], were applied at Screening, Baseline, Day 7, 14, and 21 or Endpoint. Changes of overall scores of these scales from baseline to endpoint are provided by the sponsor in the next three tables.

[1]Abnormal Involuntary Movement Scale
[2]Simpson-Angus Scale
[3]Barnes Akathisia Rating Scale

Table 35. Summary of AIMS Total Score - Change from Baseline to Endpoint (RIS-BIM-301: Intent-to-Treat Analysis Set)

Higher Score Indicates Worse Condition	PLACEBO	RIS 0.5-2.5 mg	RIS 3-6 mg
Total severity score			
Treatment			
N	57	49	60
Mean baseline (SD)	0.21 (0.590)	0.12 (0.439)	-0.18 (0.596)
Mean change (SD)	0.11 (1.385)	-0.02 (0.433)	-0.08 (0.591)

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Table 36. BARS Global Clinical Rating at Baseline and Endpoint (RIS-BIM-301, ITT Analysis Set)

Higher Score Indicates Worse Condition Parameter Analysis Phase Time Interval Value Description	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)
Global clinical rating of akathisia			
Treatment			
Baseline	58	50	60
0	40 (69)	40 (80)	48 (80)
1	13 (22)	9 (18)	8 (13)
2	5 (9)	1 (2)	4 (7)
3	0	0	0
4	0	0	0
5	0	0	0
Endpoint	57	49	60
0	51 (89)	40 (82)	41 (68)
1	6 (11)	7 (14)	14 (23)
2	0	1 (2)	5 (8)
3	0	1 (2)	0
4	0	0	0
5	0	0	0

Table 37. Summary of SAS Total Score - Change from Baseline to Endpoint (RIS-BIM-301: Intent-to-Treat Analysis Set)

Higher Score Indicates Worse Condition	PLACEBO	RIS 0.5-2.5 mg	RIS 3-6 mg
Total			
Treatment			
N	57	49	59
Mean baseline (SD)	0.06 (0.162)	0.02 (0.071)	0.06 (0.123)
Mean change (SD)	-0.04 (0.164)	0.03 (0.107)	0.10 (0.317)

There is slight increase of SAS score from baseline to endpoint in risperidone higher dose group. There's minimal change of number of subjects rated higher on BARS from baseline to endpoint. Given the short term trial, it's not surprising that there are no meaningful changes in AIMS score from baseline to endpoint or comparing treatment groups and placebo.

7.1.4.3 Potentially Prolactin-Related AEs

A total of six subjects in Study RIS-BIM-301 developed treatment-emergent potentially prolactin-related AEs: Five are females (three in risperidone higher dose group, one in lower dose group, and one in placebo group); one is a male subject in risperidone lower dose group. The incidence of each treatment group is summarized in the table below.

Table 38. Incidence of Treatment-Emergent Prolactin-Related Adverse Events (RIS-BIM-301: ITT Analysis Set) by the Sponsor

Study Phase: Treatment AE System Organ Class Adverse Event Preferred Term	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)	ALL RIS (N=111) n (%)
Total no. subjects with prolactin-related AEs	1 (2)	2 (4)	3 (5)	5 (5)
Reproductive disorders, female	1 (2)	1 (2)	3 (5)	4 (4)
Lactation nonpuerperal	0	1 (2)	3 (5)	4 (4)
Breast enlargement	1 (2)	0	0	0
Breast pain female	1 (2)	0	0	0
Reproductive disorders, male	0	1 (2)	0	1 (1)
Ejaculation disorder	0	1 (2)	0	1 (1)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
AE = adverse event; N = total sample size; n = number with adverse event; no. = number; RIS = risperidone
ae11.rtf generated by aerun.sas.

Days to onset of these events range from 4–22 days of treatment; onset doses of risperidone range from 2–4 mg. All risperidone-treated subjects who experienced these events are ≥ 12 year-old.

Serum prolactin was measured at Screening, Baseline (Visit 2, if the baseline visit was >7 days after screening), and at Visit 6 (Endpoint). Prolactin level at endpoint almost doubled that of baseline in the two subjects of risperidone lower dose group and increased by 5–13 folds in subjects of risperidone higher dose group. (See Clinical Chemistry subsection in the Section of Laboratory Tests for details.)

According to the sponsor, no subject discontinued the trials due to prolactin-related AEs. However, the events of the subjects' in risperidone higher dose group had not been resolved by the end of the study; retrograde ejaculation observed in a 14 year-old male subject (#A30315) in risperidone lower dose group didn't resolve, either.

7.1.4.4 Glucose Metabolism Related AEs

The sponsor reports there were no glucose-related adverse events in Study RIS-BIM-301. Details on serum glucose levels can be found in clinical chemistry subjection of the Section of Laboratory Tests.

It is only a 3-week study. It is unlikely to show risperidone effect on glucose metabolism with resultant adverse event in glucose metabolism. Nevertheless, previous studies on children and adolescents with autism did show significant increase in weight and BMI, and even height. Considering the difficulties of conducting placebo controlled long term trials, future epidemiological study in this population will be needed.

7.1.4.5 Weight and BMI

(See subsection 7.1.15 Assessment of Effect on Growth)

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Common AEs are summarized based on the only acute, placebo-controlled trial, Study RIS-BIM-301. According to the protocol, all AEs that occurred between the first study-related (excluding signing the consent form) and the last study-related procedures were reported. Any safety information that was spontaneously reported by an investigator beyond the time frame specified was also to be evaluated by the sponsor. Though not specifically stated, it appears the AEs were reported spontaneously.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor used WHO-preferred terms to categorize adverse-events that started during the double-blind phase of the study or with onset of within 4 days f the last dose of study medication.

Upon examining the AE dataset, the coding from verbatim to preferred term was appropriate. otherwise, except the following:

Extrapyramidal disorder includes all the following: Stiffness at different joints, cogwheeling rigidity, festination gait, and "hype(?)." However, verbatim "EPS-Neck stiffness only" was coded as hypertonia; similarly, arm and leg stiffness, and some other cases of mild stiffness at elbows, neck, or shoulder were all coded as hypotonia instead of EPS. Thus, it is hard to differentiate the differences between these two terms. Moreover, verbatim "stiff jaw" was coded as "tetany" and thus not included in EPS category. Likewise, tremor or shakiness were coded as tremor and not counted as part of EPS symptoms.

7.1.5.3 Incidence of common adverse events

For common AEs, the sponsor provides the adverse events that occurred in at least 5% of the subjects in any group during the treatment phase of the trial.

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7.1.5.4 Common adverse event tables

Table 39. Incidence of Treatment-Emergent Adverse Events - Event with ≥ 5% Incidence in Either Group (RIS-BIM-301: Intent-to-Treat Analysis Set)

Study Phase: Treatment Adverse Event System Organ Class Adverse Event Preferred Term	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)	ALL RIS (N=111) n (%)
Total no. subjects with adverse events	44 (76)	45 (90)	58 (95)	103 (93)
Psychiatric disorders	20 (34)	24 (48)	45 (74)	69 (62)
Somnolence	11 (19)	21 (42)	34 (56)	55 (50)
Agitation	6 (10)	2 (4)	7 (11)	9 (8)
Anxiety	2 (3)	0	5 (8)	5 (5)
Appetite increased	1 (2)	2 (4)	4 (7)	6 (5)
Psychosis manic-depressive	3 (5)	0	4 (7)	4 (4)
Suicide attempt	2 (3)	1 (2)	4 (7)	5 (5)
Aggressive reaction	3 (5)	0	3 (5)	3 (3)
Insomnia	4 (7)	4 (8)	3 (5)	7 (6)
Nervousness	3 (5)	1 (2)	3 (5)	4 (4)
Centr & periph nervous system disorders	22 (38)	27 (54)	34 (56)	61 (55)
Headache	19 (33)	20 (40)	23 (38)	43 (39)
Dizziness	3 (5)	8 (16)	8 (13)	16 (14)
Hypertonia	1 (2)	2 (4)	5 (8)	7 (6)
Hyperkinesia	1 (2)	0	4 (7)	4 (4)
Extrapyramidal disorder	1 (2)	1 (2)	3 (5)	4 (4)
Dystonia	0	3 (6)	2 (3)	5 (5)
Gastro-intestinal system disorders	14 (24)	25 (50)	26 (43)	51 (46)
Abdominal pain	3 (5)	9 (18)	9 (15)	18 (16)
Nausea	4 (7)	8 (16)	8 (13)	16 (14)
Vomiting	4 (7)	6 (12)	6 (10)	12 (11)
Diarrhoea	1 (2)	4 (8)	4 (7)	8 (7)
Dyspepsia	2 (3)	8 (16)	3 (5)	11 (10)
Body as a whole - general disorders	13 (22)	18 (36)	23 (38)	41 (37)
Fatigue	2 (3)	9 (18)	18 (30)	27 (24)
Fever	3 (5)	2 (4)	2 (3)	4 (4)
Injury	2 (3)	3 (6)	1 (2)	4 (4)
Lab values abnormal	3 (5)	0	1 (2)	1 (1)

Respiratory system disorders	12 (21)	12 (24)	17 (28)	29 (26)
Rhinitis	6 (10)	7 (14)	8 (13)	15 (14)
Dyspnoea	0	1 (2)	3 (5)	4 (4)
Pharyngitis	3 (5)	5 (10)	2 (3)	7 (6)
Sinusitis	2 (3)	3 (6)	1 (2)	4 (4)
Skin and appendages disorders	3 (5)	5 (10)	7 (11)	12 (11)
Rash	1 (2)	0	4 (7)	4 (4)
Heart rate and rhythm disorders	1 (2)	0	6 (10)	6 (5)
Tachycardia	1 (2)	0	3 (5)	3 (3)
Reproductive disorders, female	4 (7)	1 (2)	4 (7)	5 (5)
Lactation nonpuerperal	0	1 (2)	3 (5)	4 (4)
Dysmenorrhoea	3 (5)	0	0	0
Urinary system disorders	0	0	4 (7)	4 (4)
Urinary incontinence	0	0	3 (5)	3 (3)
Vision disorders	2 (3)	3 (6)	4 (7)	7 (6)
Vision abnormal	0	2 (4)	4 (7)	6 (5)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
N = total sample size; n = number with adverse event; no. = number; RIS = risperidone

7.1.5.5 Identifying common and drug-related adverse events

In this submission, the sponsor defined common and drug-related adverse drug reactions are defined as those reported in 5% or more of risperidone-treated pediatric patients with bipolar disorder, showing only those adverse drug reactions that were either not reported in the studies in adult patients with bipolar disorder or that were reported at ≥ 2 times greater frequency than in the adult bipolar disorder studies. (See table below.)

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Table 40. Adverse Reactions in ≥ 5% of Risperidone-Treated Pediatric Patients with Bipolar I Disorder in a Double-Blind Study and With Greater Frequency than in Adult Bipolar Disorder Studies

Body System Adverse Reaction	Percentage of Patients Reporting Event		
	Risperidone 0.5-2.5 mg (N=50)	Risperidone 3-6 mg (N=61)	Placebo (N=58)
Body as a whole - general disorders			
Fatigue	18	30	3
Central and peripheral nervous system disorders			
Dizziness	16	13	5
Gastrointestinal system disorders			
Abdominal pain	18	15	5
Dyspepsia	16	5	3
Nausea	16	13	7
Vomiting	12	10	7
Diarrhea	8	7	2
Heart rate and rhythm disorders			
Tachycardia	0	5	2
Psychiatric disorders			
Somnolence	42	56	19
Appetite increased	4	7	2
Anxiety	0	8	3
Reproductive disorders, female			
Lactation nonpuerperal	2	5	0
Respiratory system disorders			
Rhinitis	14	13	10
Dyspnea	2	5	0
Skin and appendages disorders			
Rash	0	7	2
Urinary system disorders			
Urinary incontinence	0	5	0
Vision disorders			
Vision abnormal	4	7	0

From the table of incidence of treatment-emergent adverse events – events with ≥5% incidence in either group submitted by the sponsor, I summarize the common treatment-emergent events that are with ≥5% incidence and at least twice of those in placebo group in the following table.

Table 41. Adverse Events of ≥ 5% in Either Treatment Group AND Twice of Those in Placebo Group (RIS-BIM-301)

AE System Organ Class Adverse Event Preferred Term	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)
Total no. subjects with AEs	44 (76)	45 (90)	58 (95)
Psychiatric disorders	20 (34)	24 (48)	45 (74)
Somnolence	11 (19)	**21 (42)**	**34 (56)**
Anxiety	2 (3)	0	**5 (8)**
Appetite increased	1 (2)	**2 (4)**	**4 (7)**
Suicide attempt	2 (3)	1 (2)	**4 (7)**
Centr & periph nervous system disorders	22 (38)	27 (54)	34 (56)
Dizziness	3 (5)	**8 (16)**	**8 (13)**
Hypertonia	1 (2)	**2 (4)**	**5 (8)**
Hyperkinesia	1 (2)	0	**4 (7)**
Extrapyramidal disorder	1 (2)	1 (2)	**3 (5)**
Dystonia	0	**3 (6)**	**2 (3)**
Gastro-intestinal system disorders	14 (24)	**25 (50)**	26 (43)
Abdominal pain	3 (5)	**9 (18)**	**9 (15)**
Nausea	4 (7)	**8 (16)**	8 (13)
Diarrhea	1 (2)	**4 (8)**	**4 (7)**
Dyspepsia	2 (3)	**8 (16)**	3 (5)
Body as a whole - general disorders	13 (22)	18 (36)	23 (38)
Fatigue	2 (3)	**9 (18)**	**18 (30)**
Injury	2 (3)	**3 (6)**	1 (2)
Respiratory system disorders	12 (21)	12 (24)	17 (28)
Dyspnea	0	**1 (2)**	**3 (5)**
Pharyngitis	3 (5)	**5 (10)**	2 (3)
Sinusitis	2 (3)	**3 (6)**	1 (2)
Skin and appendages disorders	3 (5)	**5 (10)**	**7 (11)**
Rash	1 (2)	0	**4 (7)**
Heart rate and rhythm disorders	1 (2)	0	**6 (10)**
Tachycardia	1 (2)	0	**3 (5)**
Reproductive disorders, female	4 (7)	1 (2)	**4 (7)**
Lactation nonpuerperal	0	1 (2)	**3 (5)**
Urinary system disorders	0	0	**4 (7)**
Urinary incontinence	0	0	**3 (5)**
Vision disorders	2 (3)	**3 (6)**	**4 (7)**
Vision abnormal	0	**2 (4)**	**4 (7)**

*Bold typed ones indicate at least twice of the incidence than those of placebo group.

Thus, applying the Division criteria for TEAEs (incidence ≥ 5% and twice of those in placebo group) and comparing with what the sponsor submitted, reveal the following additional TEAEs: Suicide attempts, injury, hypertonia, hyperkinesia, dystonia, extrapyramidal disorder,

pharyngitis. (The term injury basically involves from abrasion of knee or skin tear, to scratched left cornea or broken arm.)

Additionally, as recommended to the sponsor for other applications related to this study drug before, the individual symptoms of extrapyramidal disorder should be lumped under one term as extrapyramidal disorder. Thus, the incidence rate should be recalculated as 23% (14/61) for risperidone higher dose group and 12% (6/50) in the lower dose group versus 5.1% (3/58) in placebo group.

7.1.5.6 Additional analyses and explorations

Dose dependency

Overall, subjects in risperidone high dose group (3-6 mg/day) developed more treatment-emergent adverse events, esp. suicide attempts, tachycardia, lactation nonpuerperal, urinary incontinence, dyspnea, and rash compared with those in risperidone low dose group (0.5-2.5mg/day).

The most common TEAEs in risperidone lower dose group are: Somnolence (42%), fatigue (18%), abdominal pain (18%), dizziness (16%), nausea (16%), and dyspepsia (16%); Somnolence and fatigue also topped the list of the most common TEAEs in risperidone higher dose group (56% and 30%, respectively), followed by abdominal pain (15%), dizziness (13%), and among others.

Demographic analysis

In response to our request sent through filing communication on Mar. 2, 2007, the sponsor submitted demographic analysis of AEs as part of the response. The following are the findings of Breslow-Day analysis provided by the sponsor:

Age: No significant odds ratio differences in age group analysis (ages 10–12, 13–15, and16–17 year-old) provided the sponsor.

Gender: Odds ratio of "dizziness" seems to be significantly different in risperidone lower dose group (p=0.037), whereas "vomiting" appears significantly more in male subjects of higher dose group (p=0.033). No other significant imbalance of odds ratio between the gender groups observed.

Ethnicity: The sponsor reports that no Native Hawaiian/Other Pacific Islander was enrolled in any study and "some subjects selected multiple categories; these subjects were identified as 'mixed' in the database." Odds ratio of "appetite increased" appears to be significantly different in risperidone higher dose group (p=0.034).

7.1.6 Less Common Adverse Events

The incidence of less common AEs is not included in the submission. The sponsor submitted incidences of 2% in any active treatment group upon our request.

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Table 42. Incidence of Treatment-Emergent Adverse Events with ≥ 2% Incidence in Any Active Treatment Group in Study RIS-BIM-301 (ITT)

AE System Organ Class Adverse Event Preferred Term	PLACEBO (N=58) n (%)	RIS 0.5-2.5 MG (N=50) n (%)	RIS 3-6 MG (N=61) n (%)	ALL RIS (N=111) n (%)
Total no. subjects with adverse events	44 (75.9)	45 (90.0)	58 (95.1)	103 (92.8)
Psychiatric disorders	20 (34.5)	24 (48.0)	45 (73.8)	69 (62.2)
Somnolence	11 (19.0)	21 (42.0)	34 (55.7)	55 (49.5)
Agitation	6 (10.3)	2 (4.0)	7 (11.5)	9 (8.1)
Anxiety	2 (3.4)	0	5 (8.2)	5 (4.5)
Appetite increased	1 (1.7)	2 (4.0)	4 (6.6)	6 (5.4)
Psychosis manic-depressive	3 (5.2)	0	4 (6.6)	4 (3.6)
Suicide attempt	2 (3.4)	1 (2.0)	4 (6.6)	5 (4.5)
Aggressive reaction	3 (5.2)	0	3 (4.9)	3 (2.7)
Insomnia	4 (6.9)	4 (8.0)	3 (4.9)	7 (6.3)
Nervousness	3 (5.2)	1 (2.0)	3 (4.9)	4 (3.6)
Emotional lability	1 (1.7)	1 (2.0)	0	1 (0.9)
Centr & periph nervous system disorders	22 (37.9)	27 (54.0)	34 (55.7)	61 (55.0)
Headache	19 (32.8)	20 (40.0)	23 (37.7)	43 (38.7)
Dizziness	3 (5.2)	8 (16.0)	8 (13.1)	16 (14.4)
Hypertonia	1 (1.7)	2 (4.0)	5 (8.2)	7 (6.3)
Hyperkinesia	1 (1.7)	0	4 (6.6)	4 (3.6)
Extrapyramidal disorder	1 (1.7)	1 (2.0)	3 (4.9)	4 (3.6)
Dystonia	0	3 (6.0)	2 (3.3)	5 (4.5)
Speech disorder	0	1 (2.0)	2 (3.3)	3 (2.7)
Tetany	0	0	2 (3.3)	2 (1.8)
Tremor	0	0	2 (3.3)	2 (1.8)
Cramps legs	0	1 (2.0)	1 (1.6)	2 (1.8)
Vertigo	0	1 (2.0)	0	1 (0.9)
Gastro-intestinal system disorders	14 (24.1)	25 (50.0)	26 (42.6)	51 (45.9)
Abdominal pain	3 (5.2)	9 (18.0)	9 (14.8)	18 (16.2)
Nausea	4 (6.9)	8 (16.0)	8 (13.1)	16 (14.4)
Vomiting	4 (6.9)	6 (12.0)	6 (9.8)	12 (10.8)
Diarrhoea	1 (1.7)	4 (8.0)	4 (6.6)	8 (7.2)
Dyspepsia	2 (3.4)	8 (16.0)	3 (4.9)	11 (9.9)
Saliva increased	1 (1.7)	2 (4.0)	2 (3.3)	4 (3.6)
Constipation	1 (1.7)	2 (4.0)	1 (1.6)	3 (2.7)

Stomatitis	0	1 (2.0)	0	1 (0.9)
Body as a whole - general disorders	13 (20.4)	18 (36.0)	23 (37.7)	41 (36.9)
Fatigue	2 (3.4)	9 (18.0)	18 (29.5)	27 (24.3)
Fever	3 (5.2)	2 (4.0)	2 (3.3)	4 (3.6)
Chest pain	1 (1.7)	2 (4.0)	1 (1.6)	3 (2.7)
Injury	2 (3.4)	3 (6.0)	1 (1.6)	4 (3.6)
Malaise	0	1 (2.0)	1 (1.6)	2 (1.8)
Oedema	0	1 (2.0)	1 (1.6)	2 (1.8)
Allergy	0	1 (2.0)	0	1 (0.9)
Allergy aggravated	0	1 (2.0)	0	1 (0.9)
Back pain	0	2 (4.0)	0	2 (1.8)
Influenza-like symptoms	1 (1.7)	1 (2.0)	0	1 (0.9)
Leg pain	0	2 (4.0)	0	2 (1.8)
Oedema peripheral	0	1 (2.0)	0	1 (0.9)
Wound drainage increased	0	1 (2.0)	0	1 (0.9)
Respiratory system disorders	12 (20.7)	12 (24.0)	17 (27.9)	29 (26.1)
Rhinitis	6 (10.3)	7 (14.0)	8 (13.1)	15 (13.5)
Dyspnoea	0	1 (2.0)	3 (4.9)	4 (3.6)
Coughing	0	2 (4.0)	2 (3.3)	4 (3.6)
Pharyngitis	3 (5.2)	5 (10.0)	2 (3.3)	7 (6.3)
Upper resp tract infection	1 (1.7)	0	2 (3.3)	2 (1.8)
Sinusitis	2 (3.4)	3 (6.0)	1 (1.6)	4 (3.6)
Asthma	1 (1.7)	2 (4.0)	0	2 (1.8)
Bronchospasm	1 (1.7)	2 (4.0)	0	2 (1.8)
Pulmonary congestion	0	1 (2.0)	0	1 (0.9)
Skin and appendages disorders	3 (5.2)	5 (10.0)	7 (11.5)	12 (10.8)
Rash	1 (1.7)	0	4 (6.6)	4 (3.6)
Pruritus	0	1 (2.0)	1 (1.6)	2 (1.8)
Photosensitivity reaction	0	1 (2.0)	0	1 (0.9)
Rash pustular	0	1 (2.0)	0	1 (0.9)
Skin disorder	0	1 (2.0)	0	1 (0.9)

Skin dry	0	2 (4.0)	0	2 (1.8)
Heart rate and rhythm disorders	1 (1.7)	0	6 (9.8)	6 (5.4)
Tachycardia	1 (1.7)	0	3 (4.9)	3 (2.7)
Palpitation	0	0	2 (3.3)	2 (1.8)
Reproductive disorders, female	4 (6.9)	1 (2.0)	4 (6.6)	5 (4.5)
Lactation nonpuerperal	0	1 (2.0)	3 (4.9)	4 (3.6)
Urinary system disorders	0	0	4 (6.6)	4 (3.6)
Urinary incontinence	0	0	3 (4.9)	3 (2.7)
Vision disorders	2 (3.4)	3 (6.0)	4 (6.6)	7 (6.3)
Vision abnormal	0	2 (4.0)	4 (6.6)	6 (5.4)
Conjunctivitis	2 (3.4)	1 (2.0)	0	1 (0.9)
Cardiovascular disorders, general	0	0	3 (4.9)	3 (2.7)
Hypotension postural	0	0	2 (3.3)	2 (1.8)
Metabolic and nutritional disorders	2 (3.4)	1 (2.0)	3 (4.9)	4 (3.6)
Weight increase	1 (1.7)	1 (2.0)	2 (3.3)	3 (2.7)
Hearing and vestibular disorders	0	2 (4.0)	2 (3.3)	4 (3.6)
Ear ache	0	2 (4.0)	1 (1.6)	3 (2.7)
Musculo-skeletal system disorders	2 (3.4)	3 (6.0)	2 (3.3)	5 (4.5)
Arthralgia	2 (3.4)	2 (4.0)	1 (1.6)	3 (2.7)
Skeletal pain	0	1 (2.0)	1 (1.6)	2 (1.8)
Platelet,bleeding & clotting disorders	1 (1.7)	2 (4.0)	2 (3.3)	4 (3.6)
Epistaxis	1 (1.7)	2 (4.0)	2 (3.3)	4 (3.6)
Resistance mechanism disorders	3 (5.2)	2 (4.0)	2 (3.3)	4 (3.6)
Infection viral	0	1 (2.0)	1 (1.6)	2 (1.8)
Infection bacterial	0	1 (2.0)	0	1 (0.9)
Reproductive disorders, male	0	1 (2.0)	0	1 (0.9)
Ejaculation disorder	0	1 (2.0)	0	1 (0.9)
Secondary terms	0	3 (6.0)	0	3 (2.7)
Bite	0	1 (2.0)	0	1 (0.9)
Fall	0	1 (2.0)	0	1 (0.9)
Post-operative pain	0	1 (2.0)	0	1 (0.9)
Surgical intervention	0	1 (2.0)	0	1 (0.9)
Vascular (extracardiac) disorders	1 (1.7)	1 (2.0)	0	1 (0.9)
Flushing	1 (1.7)	1 (2.0)	0	1 (0.9)

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory tests were performed at a central laboratory, According to the protocol, the following laboratory tests are conducted during Study RIS-BIM-301 (see table below): b(4)

Table 43. Clinical Laboratory Tests Performed in Study RIS-BIM-301

Hematology Panel	Serum Chemistry Panel	
white blood cell count	sodium	alkaline phosphatase
differential	potassium	creatine phosphokinase
hemoglobin	chloride	lactic dehydrogenase (LDH)
hematocrit	bicarbonate	uric acid
platelet count	blood urea nitrogen (BUN)	calcium
red blood cell count	creatinine	phosphorus
reticulocytes percent	glucose	albumin
	aspartate aminotransferase (AST)	total protein
	alanine aminotransferase (ALT)	cholesterol
	gamma-glutamyl transferase (GGT)	triglycerides
	bilirubin	prolactin (blinded)
	TSH	thyroxine

Growth hormone was not examined in this study.

Dipstick was used for urinalysis and if the result was clinically significant, test for sediments was performed.

Samples were collected at Screening, Baseline (if Baseline visit was more than 7 days after Screening), and at Endpoint (Day 21, Visit 6).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Study RIS-BIM-301 is the only acute double-blind, placebo controlled study for this indication. Thus, analysis is based on the data from this study only.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Hematology: There were mild decreases of mean hemoglobin, hematocrit, and lymphocytes from baseline to endpoint in risperidone groups compared to those in placebo group. However,

these changes don't seem to be clinically significant. Changes of hematological parameters from baseline to endpoint are presented by the sponsor in the following table.

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Table 44. Hematology - Change from Baseline to Endpoint (RIS-BIM-301: ITT Analysis Set)

	PLACEBO	RIS 0.5-2.5 mg	RIS 3-6 mg
Basophils (%)			
N	50	45	51
Mean baseline (SD)	0.60 (0.341)	0.60 (0.336)	0.58 (0.278)
Mean change (SD)	0.12 (0.456)	0.07 (0.643)	-0.02 (0.375)
Eosinophils (%)			
N	50	45	51
Mean baseline (SD)	2.57 (2.648)	2.54 (2.140)	2.52 (2.579)
Mean change (SD)	0.43 (1.610)	-0.11 (1.739)	0.04 (1.660)
Hematocrit (vol-%)			
N	50	44	51
Mean baseline (SD)	40.96 (3.289)	41.52 (2.992)	40.98 (3.172)
Mean change (SD)	0.30 (4.478)	-1.43 (2.327)	-1.61 (2.515)
Hemoglobin (g/L)			
N	50	45	51
Mean baseline (SD)	136.40 (9.883)	137.27 (11.069)	135.59 (10.427)
Mean change (SD)	2.42 (15.735)	-4.49 (5.570)	-4.18 (6.677)
Lymphocytes (%)			
N	50	45	51
Mean baseline (SD)	36.18 (8.663)	36.46 (9.572)	34.88 (9.886)
Mean change (SD)	1.24 (7.302)	-3.64 (10.612)	-2.23 (8.867)
Monocytes (%)			
N	50	45	51
Mean baseline (SD)	6.14 (1.998)	5.76 (1.706)	5.97 (2.014)
Mean change (SD)	-0.35 (1.605)	0.17 (1.705)	-0.37 (1.905)
Neutrophils (%)			
N	50	45	51
Mean baseline (SD)	54.53 (10.089)	54.64 (10.263)	56.07 (10.958)
Mean change (SD)	-1.45 (7.948)	3.51 (11.622)	2.56 (9.742)
Platelet count (giga/l)			
N	50	45	49
Mean baseline (SD)	294.82 (73.625)	280.64 (57.950)	294.90 (76.956)
Mean change (SD)	10.84 (50.597)	9.31 (39.735)	-5.65 (56.888)
RBC (tera/l)			
N	50	45	51
Mean baseline (SD)	4.83 (0.392)	4.92 (0.387)	4.80 (0.334)
Mean change (SD)	0.10 (0.521)	-0.14 (0.235)	-0.14 (0.245)
Reticulocytes (%)			
N	49	43	50
Mean baseline (SD)	1.70 (0.493)	1.58 (0.445)	1.87 (0.615)
Mean change (SD)	0.06 (0.472)	0.17 (0.367)	0.06 (0.427)
WBC (giga/l)			
N	50	45	51
Mean baseline (SD)	6.69 (1.564)	6.59 (1.977)	7.25 (2.425)
Mean change (SD)	-0.13 (1.351)	0.34 (2.258)	-0.45 (2.036)

N = the number of subjects with both baseline and endpoint values for the parameter;
RBC = red blood cell; RIS = risperidone; SD = standard deviation; WBC = white blood cell
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Clinical Chemistry:

Table 45. Clinical Chemistry Values and Change from Baseline to Endpoint (RIS-BIM-301)

Laboratory Tests	RIS 0.5-2.5 mg		RIS 3-6 mg		Placebo	
	N	Mean/Change	N	Mean/Change	N	Mean/Change
Sodium (mmol/L)	45	140.42/0.07	53	140.49/-0.43	53	140.04/1
Potassium (mmol/L)	45	4.22/0.07	53	4.2/-0.06	53	4.26/-0.07
Bicarbonate (mmol/L)	45	23.84/0.27	53	23.34/-0.09	53	23.66/0.71
Chloride (mmol/L)	45	102.98/0.56	53	103.74/-0.4	53	103.53/0.23
BUN (mmol/L)	45	4.28/0.02	54	4.4/0.12	53	4.55/-0.04
Creatinine (umol/L)	45	58.36/-2.56	54	54.85/0.8	53	53.32/0.17
Glucose (mmol/L)	45	4.94/0.03	54	4.73/0.4	53	4.93/-0.11
Cholesterol (mmol/L)	45	4.37/0.05	54	4.64/0.01	53	4.51/-0.13
Triglycerine	45	1.37/0.03	54	1.39/0.06	53	1.39/0.04
AST (U/L)	43	21.58/1.79	53	21.55/1.11	52	23.27/0.85
ALT (U/L)	45	17.62/4.09	54	16.67/2.93	53	17.51/2.26
Alkaline phosphatase (U/L)	45	201.82/-17.8	54	194.54/-10.8	53	221.7/-5.02
GGT (U/L)	45	15.11/1.42	54	15/0.59	53	15.06/0.59
Total bilirubin (umol/L)	39	8.64/-2.28	46	7.44/0.24	48	8/0.15
Albumin (g/L)	45	44.16/-1.93	54	43.98/-1.20	53	43.23/-0.53
Total protein (g/L)	45	74.31/-1.71	54	75.28/-1.32	53	73.64/-0.53
LDH (U/L)	39	184.39/-8.72	53	198.53/-14.55	50	193.56/3.02
Uric acid (umol/L)	45	291.38/5.53	54	294.15/27.2	53	283.49/9.57
Calcium (mmol/L)	45	2.49/-0.03	54	2.49/-0.01	53	2.47/-0.003
Creatine Kinase (u/L)	44	126.43/-5.39	54	128.37/11.56	53	126.60/10.28
Prolactin (ng/ml)	45	**14.28/40.4**	53	**13.29/61.21**	53	12.50/1.08
Thyroxin (nmol/L)*	49	96.6	61	96.8	58	91.1
TSH (u/L)*	49	1.8	61	1.7	58	1.6

* Only Baseline levels are provided for these two parameters.

There was no significant change from Baseline to Endpoint in urinalysis. The sponsor included TSH and thyroxine levels in the clinical chemistry panel which supposedly to be examined at Screening (not repeated at Baseline if ≤7 days have elapsed since screening values unless found to be clinically abnormal) and endpoint. The sponsor didn't specify or explain why endpoint levels and mean changes in these levels are not provided in the submission.

Except for prolactin level, there were no significant changes of other clinical chemistry parameters from baseline to endpoint in each risperidone treatment group compared with placebo. The magnitude of prolactin level change appears to be dose related: More elevation is seen in the higher dose group. Change in female subjects is slightly higher than that in male subjects (see tables below).

Table 46. Change in Serum Prolactin Level from Baseline to Endpoint

Prolactin (ng/mL)	Placebo	RIS 0.5–2.5 mg	RIS 3–6 mg
Subject Number	53	45	53
Mean baseline (SD)	12.50 (7.929)	14.28 (13.958)	13.29 (11.040)
Mean change (SD)	1.08 (6.789)	40.40 (35.951)	61.21 (41.968)

Table 47. Change in Serum Prolactin Level from Baseline to Endpoint by Gender Groups

Prolactin (ng/mL) Treatment	Placebo	RIS 0.5–2.5 mg	RIS 3–6 mg
N of Male Subjects	26	24	20
Mean baseline (SD)	9.66 (4.636) 0.59	10.70 (9.430) 32.00	7.73 (4.630) 49.56
Mean change (SD)	(6.722)	(22.504)	(23.02
N of Female Subjects	27	21	33
Mean baseline (SD)	15.23 (9.448)	18.37 (17.130)	16.66 (12.422)
Mean change (SD)	1.55 (6.946)	50.01 (45.601)	68.26 (49.106)

There are slight differences comparing each risperidone groups and the placebo group (see table below), but it seems that the trend of elevation is dose related.

Table 48. Change in Serum Glucose Level from Baseline to Endpoint (RIS_BIM-301)

Glucose (mmol/L)	Placebo	RIS-0.5–2.5 mg/day	RIS 3–6 mg/day
Subject Number	53	45	54
Mean baseline (SD)	4.93 (0.534)	4.94 (0.781)	4.73 (0.623)
Mean change (SD)	-0.11 (0.897)	0.03 (0.982)	0.40 (0.844)

7.1.7.3.2 Analyses focused on outliers and shifts from normal to abnormal

Table 49. Hematology - Number of Subjects within Pathologic Limits at Baseline and Outside Post Baseline (RIS-BIM-301: All Subjects Analysis Set)

Lab Test Normal at Baseline	Category	PLACEBO	RIS 0.5-2.5 mg	RIS 3-6 mg
Hematocrit (vol-%)	Below	0/50 (0.0)	1/44 (2.3)	0/51 (0.0)
	Above	1/50 (2.0)	0/44 (0.0)	0/51 (0.0)
Hemoglobin (g/L)	Below	0/50 (0.0)	2/44 (4.5)	0/51 (0.0)
	Above	1/50 (2.0)	0/44 (0.0)	0/51 (0.0)
Platelet count (giga/l)	Below	0/44 (0.0)	0/43 (0.0)	0/46 (0.0)
	Above	1/44 (2.3)	3/43 (7.0)	1/46 (2.2)
RBC (tera/l)	Below	0/50 (0.0)	0/45 (0.0)	0/51 (0.0)
	Above	1/50 (2.0)	0/45 (0.0)	0/51 (0.0)
WBC (giga/l)	Below	0/50 (0.0)	0/45 (0.0)	0/50 (0.0)
	Above	0/50 (0.0)	0/45 (0.0)	0/50 (0.0)

Percentages of laboratory limits subgroups calculated with the number of subjects per lab test normal at baseline as denominator.
A subject may be in more than 1 category.
Abnormality defined as clinically significant abnormal assessment during the treatment phase

There are more subjects in risperidone lower dose group had increased platelet counts than those in placebo group and the risperidone higher dose group. The sponsor explains that "4 of the 5 subjects had adverse events that could have been related to infection or inflammation (vomiting and somnolence in Subject A30015; allergy in Subject A30047; abdominal pain and somnolence in Subject A30298; pharyngitis and rhinitis in Subject A30283)."

Table 50. Clinical Chemistry – Number of Subjects within Laboratory Limits at Baseline and Outside Post Baseline provided by the sponsor (RIS-BIM-301: All Subjects Analysis Set)

	PLACEBO				RIS 0.5-2.5 MG				RIS 3-6 MG			
	Total	LABORATORY LIMITS, n (%)			Total	LABORATORY LIMITS, n (%)			Total	LABORATORY LIMITS, n (%)		
LAB TEST NORMAL AT BASELINE	n	BELOW	WITHIN	ABOVE	n	BELOW	WITHIN	ABOVE	n	BELOW	WITHIN	ABOVE
ALBUMIN (g/l)	46	0	44 (96)	2 (4)	37	0	37 (100)	0	47	0	46 (98)	1 (2)
ALKALINE PHOSPHATASE (U/L)	45	0	43 (96)	2 (4)	40	0	38 (95)	2 (5)	42	0	41 (98)	1 (2)
ALT (SGPT) (U/L)	52	0	48 (92)	4 (8)	44	0	41 (93)	3 (7)	54	0	52 (96)	2 (4)
AST (SGOT) (U/L)	52	0	51 (98)	1 (2)	42	0	41 (98)	1 (2)	53	0	52 (98)	1 (2)
BICARBONATE (mmol/l)	53	0	52 (98)	1 (2)	45	0	43 (96)	2 (4)	53	0	52 (98)	1 (2)
BLOOD UREA NITROGEN (mmol/l)	53	0	52 (98)	1 (2)	45	0	45 (100)	0	54	0	54 (100)	0
CALCIUM (mmol/l)	50	0	46 (92)	4 (8)	42	0	37 (88)	5 (12)	47	0	42 (89)	5 (11)
CHLORIDE (mmol/l)	53	0	53 (100)	0	45	0	45 (100)	0	53	0	53 (100)	0
CHOLESTEROL (mmol/l)	46	0	41 (89)	5 (11)	40	3 (8)	35 (88)	2 (5)	39	0	37 (95)	2 (5)
CREATINE KINASE (U/L)	49	0	46 (94)	3 (6)	44	0	42 (95)	2 (5)	50	0	47 (94)	3 (6)
CREATININE (mmol/l)	53	0	53 (100)	0	44	0	44 (100)	0	53	0	53 (96)	2 (4)
GGT (U/L)	53	0	52 (98)	1 (2)	44	0	43 (98)	1 (2)	54	0	54 (100)	0
GLUCOSE (mmol/l)	53	2 (4)	51 (96)	0	43	1 (2)	42 (98)	0	53	0	52 (98)	1 (2)
LACTATE DEHYDROGENASE (U/L)	49	1 (2)	47 (96)	1 (2)	36	0	36 (100)	0	50	0	49 (98)	1 (2)
PHOSPHORUS (mmol/l)	49	0	47 (96)	2 (4)	43	1 (2)	39 (91)	3 (7)	52	0	51 (98)	1 (2)
POTASSIUM (mmol/l)	53	0	53 (100)	0	45	1 (2)	44 (98)	0	53	0	53 (100)	0
PROLACTIN (ug/l)	44	0	41 (93)	3 (7)	36	0	9 (25)	27 (75)	43	0	5 (12)	38 (88)
SODIUM (mmol/l)	53	0	53 (100)	0	44	0	44 (100)	0	53	0	53 (100)	0
TOTAL BILIRUBIN (mmol/l)	47	0	46 (98)	1 (2)	37	0	37 (100)	0	46	0	45 (98)	1 (2)
TOTAL PROTEIN (g/l)	53	0	53 (100)	0	45	0	45 (100)	0	52	0	50 (96)	2 (4)
TRIGLYCERIDES (mmol/l)	37	0	28 (76)	9 (24)	31	0	22 (71)	9 (29)	38	1 (3)	31 (82)	6 (16)
URIC ACID (mmol/l)	48	0	46 (96)	2 (4)	42	0	41 (98)	1 (2)	49	0	43 (88)	6 (12)

Again, except for prolactin, there are no substantial differences in number of subjects who were within normal limits but became outliers at endpoint between placebo group and the risperidone groups. Shifts are more common in females than in males and in subjects >12 year-old than in those ≤ 12 year-old.

Table 51. Prolactin (ng/mL)--Number of Subjects within Pathological Limits at Baseline and Outside Post Baseline by Age (RIS-BIM-301: All Subjects Analysis Set)

Age Groups	Category	Placebo	RIS 0.5–2.5 mg	RIS 3–6 mg
≤ 12 year-old	Below	0/23 (0.0)	0/15 (0.0)	0/20 (0.0)
	Above	0/23 (0.0)	0/15 (0.0)	3/20 (15.
>12 year-old	Below	0/30 (0.0)	0/30 (0.0)	0/33 (0.0)
	Above	0/30 (0.0)	5/30 (16.7)	10/33 (30.3)

Table 52. Prolactin (ng/mL)--Number of Subjects Within Pathological Limits at Baseline and Outside Post Baseline by Gender (RIS-BIM-301: All Subjects Analysis Set)

Age Groups	Category	Placebo	RIS 0.5–2.5 mg	RIS 3–6 mg
Male	Below	0/26 (0.0)	0/24 (0.0)	0/20 (0.0)
	Above	0/26 (0.0)	0/24(0.0)	1/20 (5.0)
Female	Below	0/27 (0.0)	0/21 (0.0)	0/33 (0.0)
	Above	0/27 (0.0)	5/21 (23.8)	12/33 (36.4)

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

The sponsor did not submit marked laboratory value outliers. Instead, the sponsor submitted "Listing of Subjects within Pathological Limits at Baseline and Outside Post Baseline" for both clinical chemistry and hematology (see page 180 and pages 1322–1329 of Study Report of Study RIS-BIM-301).

7.1.7.4 Additional analyses and explorations

Change of Prolactin level from baseline to endpoint is dose-related. Gender and age also seem to be related to the susceptibility of elevated prolactin level.

7.1.7.5 Special assessments

Other than prolactin level analyzed above, no special assessment for laboratory tests seems to be necessary otherwise.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Blood pressure and pulse, both supine and standing, were measured at each visit. Temperature and respiration rate were measured at Screening and Endpoint.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Data of vital signs are from Study RIS-BIM-301...

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The table below summarizes the mean changes of vital signs from baseline to endpoint. In risperidone treatment group, the pulse rates, both supine and standing, were slightly increased compared to placebo group. Overall, there were no clinically significant changes in mean values of vital signs, whether supine or standing, from baseline to endpoint comparing each treatment group.

Table 53. Mean Changes of Vital Signs from Baseline to Endpoint (RIS-BIM-301, LOCF)

Vital Signs			Placebo		RIS 0.5-2.5mg		RIS 3-6 mg	
			N	Mean/Change	N	Mean/Change	N	Mean/Change
Body Temperature (°F)			51	36.59/-0.01	45	36.61/0.00	55	36.60/+0.01
Pulse Rate (bpm)	Supine		55	79.37/-0.04	49	75.80/+4.80	59	79.17/+4.56
	Standing		56	86.75/+0.09	49	83.08/+4.20	60	86.77/+2.98
Respiratory Rate (times/min)			48	19.33/-0.35	44	19.02/-0.73	51	17.98/+0.57
Blood Pressure	**Systolic** (mmHg)	Supine	56	113.20/-1.61	49	111.22/-1.49	60	110.30/+3.43
		Standing	57	112.75/-0.44	49	110.84/+0.65	60	110.77/+1.20
	Diastolic (mmHg)	Supine	56	67.75/+1.41	49	68.14/-1.57	60	67.45/+1.52
		Standing	57	71.46/-0.53	49	70.76/-0.86	60	71.35/+0.32

7.1.8.3.2 Analyses focused on shifts from normal to abnormal

The criteria for outliers are set by the sponsor as follows:

Pulse Rate: At baseline, Normal = value >65 and <120
- Below = change from baseline ≤-15 & value ≤65
- Above = change from baseline ≥15 & value ≥120

Systolic Blood Pressure: At baseline, Normal = value >90 and <180
- Below = change from baseline ≤-15 & value ≤90
- Above = change from baseline ≥15 & value ≥180

Diastolic Blood Pressure: At baseline, Normal = value >50 and <105
- Below = change from baseline ≤-15 & value ≤50
- Above = change from baseline ≥15 & value ≥105

Table 54. Incidence of Changes Outside of Clinically Important Limits for Subjects with Normal Baseline Values (RIS-BIM-301)

Parameter Abnormality Class			PLACEBO n (%)	RIS 0.5-2.5 mg n (%)	RIS 3-6 mg n (%)
Blood Pressure (mmHg)	**Systolic**	**Supine**	N=54	N=45	N=59
		Below	7 (13)	4 (9)	2 (3)
		Above	0	0	0
		Standing	N=55	N=45	N=59
		Below	2 (4)	2 (4)	3 (5)
		Above	0	0	0
	Diastolic	**Supine**	N=52	N=47	N=58
		Below	2 (4)	4 (9)	0
		Above	1 (2)	0	0
		Standing	N=55	N=47	N=60
		Below	2 (4)	1 (2)	1 (2)
		Above	0	0	1 (2)
Pulse Rate (bpm)		**Supine**	N=47	N=39	N=54
		Below	8 (17)	2 (5)	4 (7)
		Above	1 (2)	0	2 (4)
		Standing	N=49	N=48	N=57
		Below	4 (8)	2 (4)	4 (7)
		Above	1 (2)	2 (4)	8 (14)

*Note: A subject may be in more than 1 abnormality category. Percentages calculated with the number of subjects with normal baseline for the parameter as the denominator.

More subjects with increased *standing* pulse rates (≥ 120 bpm and change ≥ 15 bpm from baseline) in both risperidone treatment groups compared with placebo (4% in lower dose group and 14% in higher dose group versus 2% in placebo); but only in risperidone higher dose group there were more subjects with increased *supine* pulse rate compared to placebo (4% versus 2%). There were also more subjects who had increased pulse rate in standing (14% in higher dose group, 4% in lower dose group) than at supine position (4% in higher dose group, 0 in lower dose group), while no such difference observed within placebo group.

More subjects had blood pressure below the criteria (change from baseline ≤-15 and value ≤90 for systolic or value ≤50 for diastolic) in *standing* in risperidone higher dose group, whether systolic (5% versus 3%) or diastolic (2% versus 0), which happens neither in placebo group nor in risperidone lower dose group.

The sponsor states that most subjects with changes outside of clinically important limits during the study didn't report relevant adverse events concurrently with the abnormal measurement or immediately afterwards, except the following four cases in the risperidone 3-6 mg group.

- Subject A30187 reported dizziness on Day 21 with concurrent increased standing pulse
- Subject A30331 had postural hypotension on Days 14 to 21; there was increased standing pulse rate on Day 14, and decreased standing diastolic blood pressure on Day 21.

- Subject A30067 reported dizziness on Days 8 to 11, and had postural hypotension on Days 10 to 14; on Day 10, there was an isolated increase in standing pulse above clinically important limit.
- Subject A30335 had prolonged QT from Day 7 to Day 14; on Day 10, there was also an isolated decrease in standing pulse.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Abnormality criteria for orthostatic measurements are presented in the following table; a subject was defined as "orthostatic" if all the criteria were met.

Table 55. Potentially Clinically Important Orthostatic Measurements (RIS-BIM-301)

Vital Sign (orthostatic = standing – supine)	Outside predetermined limits if ...
Orthostatic Systolic Blood Pressure (SBP) (mmHg)	≤ -20 mmHg (i.e., drop in SBP of 20 mmHg or more when going from supine to standing position)
Orthostatic Diastolic Blood Pressure (DBP) (mmHg)	≤ -10 mmHg (i.e., drop in DBP 10 mmHg or more when going from supine to standing position)
Orthostatic Pulse Rate (bpm)	≥ 20 bpm (increase 20 bpm or higher)

According to the sponsor, no subject met the above criteria for orthostatic hypotension. (See table below).

Table 56. Orthostatic Parameters - Incidence of Changes Outside of Clinically Important Limits at Any Time Point Post Baseline for Subjects With Normal Baseline Vales (RIS-BIM-301)

Parameter	Placebo		RIS 0.5-2.5 mg		RIS 3-6 mg	
	N	n (%)	N	n (%)	N	n (%)
SBP (stand-sup) ≤-20	55	4 (7)	48	3 (6)	59	5 (8)
DBP (stand-sup) ≤-10	55	8 (15)	46	6 (13)	57	5 (9)
Pulse (stand-sup) ≥20	45	12 (27)	47	14 (30)	51	9 (18)
Orthostacism	55	0	49	0	59	0

Note: Percentages of subgroups calculated with the number of subjects per parameter as denominator
N=Total number of subjects in a subgroup;
n=number of subjects met one of the criteria for orthostacism.

7.1.8.4 Additional analyses and explorations

Most of the subjects (8/11) whose standing pulse rate became above the clinically important limit as defined above were 12 year-old or younger; the only three subjects who had standing pulse above clinically important limit were all in risperidone higher dose group. (See table below.)

Table 57. Vital Sign Outliers by Age Groups (RIS-BIM-301)

Age Group	Vital Sign Parameters Abnormality Class			Placebo n (%)	RIS 0.5-2.5 MG n (%)	RIS 3-6 MG n (%)
≤ 12yo	Systolic BP, mmHg	Supine	Subgroup N	21	16	24
			Below	3 (14)	1 (6)	0
			Above	0	0	0
		Standing	Subgroup N	24	17	23
			Below	2 (8)	0	1 (4)
			Above	0	0	0
	Diastolic BP, mmHg	Supine	Subgroup N	19	18	24
			Below	2 (11)	1 (6)	0
			Above	1 (5)	0	0
		Standing	Subgroup N	22	18	24
			Below	1 (5)	1 (6)	1 (4)
			Above	0	0	0
	Pulse, bpm	Supine	Subgroup N	20	14	21
			Below	2 (10)	0	0
			Above	1 (5)	0	2 (10)
		Standing	Subgroup N	21	17	23
			Below	1 (5)	0	1 (4)
			Above	1 (5)	2 (12)	5 (22)
≥12yo	Systolic BP, mmHg	Supine	Subgroup N	33	29	35
			Below	4 (12)	3 (10)	2 (6)
			Above	0	0	0
		Standing	Subgroup N	31	28	36
			Below	0	2 (7)	2 (6)
			Above	0	0	0
	Diastolic BP, mmHg	Supine	Subgroup N	33	29	34
			Below	0	3 (10)	0
			Above	0	0	0
		Standing	Subgroup N	33	29	36
			Below	1(3)	0	0
			Above	0	0	1 (3)
	Pulse, bmp	Supine	Subgroup N	27	25	33
			Below	6 (22)	2 (8)	4 (12)
			Above	0	0	0
		Standing	Subgroup N	28	31	34
			Below	3 (11)	2 (6)	3 (9)
			Above	0	0	3 (9)

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Digital 12-lead ECG's were recorded at Screening, at Visit 3 (Day 7), and at Visit 6 (Day 21 or early discontinuation). They were reviewed at site by investigator and were read by a cardiologist who was blinded as to study treatment at a central ECG facility Adjustment of QT interval includes QTc Bazett (QTcB), QTc Fridericia (QTcF), and QTcLD (Linear Derived). This review will focus on QT interval analyses based on data from the Fridericia correction as well as the linear-derived model since these adjustments may be more appropriate for drugs that increase the heart rate

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7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Main ECG data is from Study RIS-BIM-301.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Table 58. Change of ECG Parameters and Correct QT from Baseline to Endpoint (Study RIS-BIM-301, ITT Set –LOCF)

ECG Parameter	Placebo		Risperidone 0.5–2.5 mg		Risperidone 3–6mg	
	N=57		N=46		N=58	
Mean Values	**Base**	**Change**	**Base**	**Change**	**Base**	**Change**
HR (bpm)	76.09	-0.89	73.52	+4.33	77.52	+4.17
PR (msec)	135.98	+0.72	141.15	+0.96	140.16	+0.24
QRS (msec)	79.91	+2.67	83.83	-1.24	81.69	-0.69
QT (msec)	365.21	+2.61	367.26	-5.02	363.91	-5.02
QTcF (msec)	392.75	+1.05	390.13	+3.22	394.36	+0.98
QTcLD (msec)	391.32	+1.02	388.50	+2.87	392.76	+0.19

As previous studies show, heart rate was slightly increased in risperidone treated groups. Overall, no remarkable differences of changes from baseline to endpoint are seen in any treatment group or between placebo and risperidone groups.

7.1.9.3.2 Analyses focused on shifts from normal to abnormal

For male subjects, QT interval of 430 or less is considered normal; value of 431-450 ms is considered borderline. For female subjects, QT interval of 450 or less is a normal value; whereas a value of 451–470 is considered borderline. The following table lists criteria for potentially clinically significant ECG parameters by age groups.

Table 59. Potentially Clinically Important Criteria for ECG Parameters (RIS-BIM-301)

ECG parameters		10 to 12 Years		13 to 17 Years	
		Abnormally Low	Abnormally High/Prolonged	Abnormally Low	Abnormally High/Prolonged
Heart rate (bpm)		<55	>130	<50	>130
PR interval (ms)		<90	>170	<90	>200
QRS duration (ms)		<40	>100	<40	>120
QT interval (ms)	Male	--	> 450	--	> 450
	Female	--	> 470	--	> 470

The following table exams the number of individuals who had abnormal value of any ECG parameters at any time point.

Table 60. Incidence of ECG Parameter Values Outside of Clinically Important Limits at Any Time Point Post-Screening for Subjects with Normal Screening Values (Study RIS-BIM-301, ITT Set)

Parameter Value		Placebo n (%)	Risperidone 0.5-2.5mg n (%)	Risperidone 3-6 mg n (%)
Heart rate (bpm)	Total Subject N	57	45	58
	Abnormal low	1 (2)	0	0
	Abnormal high	0	0	0
PR interval (ms)	Total Subject N	57	46	57
	Abnormal low	0	0	0
	Abnormal high	0	0	1 (2)
QRS interval (ms)	Total Subject N	57	44	58
	Abnormal low	0	0	0
	Abnormal high	0	0	1 (2)

Note: A subject may be in more than one abnormality category.

The subject whose HR decreased from 68 bpm at Screening to 49 bpm at Endpoint was in placebo group. There was one subject with increased PR interval (from 164 ms at Screening to 202 ms at Day 7 but returned to normal at Endpoint) and one with increased QRS interval (from 91ms at Screening to 106 ms at Endpoint) -- both were in risperidone higher dose group. No additional adverse events were reported to be associated with these changes in ECG.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

No subject had QTc change of more than 60 ms from Screening to Endpoint according to QTcF and QTcLD. However, there was one subject (A30335) in risperidone higher dose group had prolonged QTcB from 399 ms at Screening to 461 ms on Day 7. It was eventually shorten to 418 ms on Day 14 and 416 ms on Day 21.

No subject dropped out from the study due to abnormal ECG.

7.1.9.4 Additional analyses and explorations

Outliers by age groups are displayed in the following table.

Table 61. Incidence of ECG Parameter Values Outside of Clinically Important Limits at Any Time Point Post-Screening for Subjects with Normal Screening Values by Age Group

	ECG Parameter Value	Placebo n (%)	RIS 0.5-2.5 mg n (%)	RIS 3-6 mg n (%)
Age ≤ 12 year-old	**Heart rate (bpm)**	24	16	23
	Abnormal low	0	0	0
	Abnormal high	0	0	0
	PR interval (ms)	24	16	22
	Abnormal low	0	0	0
	Abnormal high	0	0	0
	QRS interval (ms)	24	14	23
	Abnormal low	0	0	0
	Abnormal high	0	0	1 (4)
Age > 12 year-old	**Heart rate (bpm)**	33	29	35
	Abnormal low	1 (3)	0	0
	Abnormal high	0	0	0
	PR interval (ms)	33	30	35
	Abnormal low	0	0	0
	Abnormal high	0	0	1 (3)
	QRS interval (ms)	33	30	35
	Abnormal low	0	0	0
	Abnormal high	0	0	0

7.1.10 Immunogenicity

Not applicable for this sNDA.

7.1.11 Human Carcinogenicity

No new data is submitted for risperidone.

7.1.12 Special Safety Studies

No special studies for this sNDA.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No data pertaining to discontinuation effects or abuse liability was presented in this sNDA.

7.1.14 Human Reproduction and Pregnancy Data

Not applicable for this sNDA.

7.1.15 Assessment of Effect on Growth

7.1.15.1 Change of Weight, Height, and BMI

Body weight and height measured at Screening, Baseline, Visits 3, 5, and 6 (Days 7, 14, and 21 or early termination).

Weight: Increase in mean weight from baseline to endpoint is observed in both lower and higher doses of risperidone treatment groups compared to placebo group (see table below for change of weight z-score), regardless of age, though there were no apparent differences in the number of subjects with weight increase across the treatment groups.

The sponsor reports that treatment-emergent weight increase was reported as an adverse event in 4 subjects: 3 from risperidone treatment groups (1/50 of risperidone lower dose group and 2/60 of risperidone higher dose group) and 1/58 subjects of the placebo group. Weight gain ranges from 2–12.1 kg. Among the subjects with weight increase, appetite was also increased in 50% of them (one subject in the risperidone 0.5-2.5 mg group, and one subjects in the risperidone 3-6 mg group).

Height: There was no significant difference in mean height between placebo and risperidone treatment groups during the 3-week study, regardless of age. Height z-score is presented in the table below as well.

BMI: Subjects in risperidone treatment group had increased BMI compared to those in placebo group (see table below presented by the sponsor for BMI z-score).

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Table 62. Weight and BMI Z-Scores - Change From Baseline to Endpoint (RIS-BIM-301: ITT Analysis Set)

	PLACEBO	RIS 0.5-2.5 mg	RIS 3-6 mg
Height z score			
Treatment			
N	56	49	60
Mean baseline (SD)	-0.19 (1.107)	-0.05 (1.271)	-0.03 (1.035)
Mean change (SD)	0.03 (0.162)	0.00 (0.199)	-0.03 (0.123)
Weight z score			
Treatment			
N	57	49	60
Mean baseline (SD)	0.65 (1.114)	0.51 (1.022)	0.81 (0.923)
Mean change (SD)	0.03 (0.160)	0.17 (0.215)	0.10 (0.167)
BMI z score			
Treatment			
N	56	49	60
Mean baseline (SD)	0.81 (0.959)	0.61 (1.071)	0.93 (0.874)
Mean change (SD)	0.02 (0.220)	0.19 (0.362)	0.10 (0.198)

N = the number of subjects with both baseline and endpoint values for the parameter;
RIS = risperidone; SD = standard deviation; BMI = body mass index
zscore01a.rtf generated by zscorrun.sas.

The next table presented by the sponsor shows the z-scores of weight and BMI in these two age groups. Z-score changes were slightly more in subjects ≤ 12 years-old than those >12 years old.

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Table 63. Weight and BMI Z-Scores by Age Group - Change From Baseline to Endpoint (RIS-BIM-301: ITT Analysis Set)

Age in Classes: ≤12 years			
Weight z score			
Treatment			
N	24	18	24
Mean baseline (SD)	0.53 (1.185)	0.40 (0.984)	0.67 (0.953)
Mean change (SD)	0.06 (0.179)	0.20 (0.226)	0.14 (0.189)
BMI z score			
Treatment			
N	23	18	24
Mean baseline (SD)	0.64 (0.909)	0.60 (1.089)	0.91 (0.886)
Mean change (SD)	0.08 (0.248)	0.21 (0.451)	0.15 (0.232)
Age in Classes: >12 years			
Weight z score			
Treatment			
N	33	31	36
Mean baseline (SD)	0.74 (1.070)	0.57 (1.054)	0.91 (0.902)
Mean change (SD)	0.00 (0.142)	0.15 (0.211)	0.07 (0.147)
BMI z score			
Treatment			
N	33	31	36
Mean baseline (SD)	0.93 (0.988)	0.61 (1.078)	0.94 (0.878)
Mean change (SD)	-0.01 (0.194)	0.18 (0.307)	0.07 (0.166)

N = the number of subjects with both baseline and endpoint values for the parameter;
RIS = risperidone; SD = standard deviation; BMI = body mass index
zscore01aage.rtf generated by zscorrun.sas.

By Day 7 of the study, four subjects (8%) in risperidone lower dose group and two (3%) in risperidone higher dose group gained weight of more than 7%. No subject in placebo group had weight gain over 7%. By Endpoint, three subjects (5%) in placebo group had weight gain of more than 7%, seven subjects (14%) in risperidone lower dose group and six subjects (10%) in risperidone higher dose group had weight gain of more than 7%.

During the study period, no subject in any treatment group went from the <85th BMI percentile at baseline to the ≥95th BMI percentile at end point. One placebo-treated subject went from the <85th to the 85th-<95th percentile; four subjects in the risperidone lower dose group went from the <85th to the 85th-<95th percentile; Five subjects in the risperidone higher group went from the <85th to the 85th-<95th percentile, and four from the 85th-<95th to the ≥95 percentile. Table below displays the change of BMI percentile ranking from baseline to endpoint in Study RIS-BIM-301.

Table 64. BMI Percentile Rank - Cross-Tabulation at Endpoint versus Baseline (RIS-BIM-301: Intent-to-Treat Analysis Set)

	Treatment Group and Evaluation at Baseline											
	PLACEBO				RIS 0.5-2.5 mg				RIS 3-6 mg			
	<85	85-<95	≥95	Total	<85	85-<95	≥95	Total	<85	85-<95	≥95	Total
BMI percentile Treatment Endpoint												
<85	32	1	0	33	29	0	0	29	28	1	0	29
85-<95	1	8	1	10	4	6	0	10	5	7	1	13
≥95	0	0	13	13	0	0	10	10	0	4	14	18
Total	33	9	14	56	33	6	10	49	33	12	15	60

BMI = body mass index; RIS = risperidone
zscore02a.rtf generated by zscorum.sas.

Despite the changes observed, the impact of risperidone on weight and BMI from a short term treatment of 3 weeks is not likely to be enormous. From previous trials of risperidone treatment for autism, we already learned that weight, height, and BMI were all increased significantly with risperidone treatment. For the similar reason as glucose metabolism, future epidemiology study can also be useful for monitoring the weight change related to risperidone in this patient population.

7.1.15.2 Tanner Staging

Tanner staging was performed at Screening and Endpoint visits. As expected in a short study, there was no shift in Tanner staging, which is a measurement of sexual development, from screening to endpoint in Study RIS-BIM-301, whether by sex or age group.

7.1.16 Overdose Experience

A total of six cases of overdose were reported in 5 literature reports. Dosages ranged from 1mg to 60mg. The Symptoms of overdose reported were tachycardia, dystonia, lethargy, EPS, decreased blood pressure, orthostasis, and delirium (Acri & Henretig, 1998; Cheslik & Erramouspe, 1996; Himstreet & Daya, 1998; Oner et al., 2004; Shea et al., 2004). According to the reports, none of these cases was fatal.

7.1.17 Postmarketing Experience

The sponsor reports that the cumulative exposure to oral risperidone during postmarketing surveillance was estimated as being more than 27 million patient-years. The worldwide exposure in children and adolescents (ages 5-17 years) was estimated as being approximately 1,117,689 patient-years as of August 31, 2006.

To identify all spontaneous reports regarding individuals aged 5-17 years and the number of reports for all other age groups, the sponsor searched the Benefit Risk Management Worldwide Safety Database (SCEPTRE). The proportions of all adverse events reported for risperidone in children and adolescents involving each System Organ Class (SOC) and select Preferred Terms (PTs) within several pre-defined areas of clinical interest were calculated, and compared to the respective proportions in all other age groups.

Overall, incidence of SAEs in postmarketing reports involving children and adolescents was fewer than those of all other age groups (< 1/5 versus 1/3 of case reports). The sponsor reports no new pattern of adverse drug reactions were identified for pediatric over adult populations treated with risperidone on the basis of the cumulative review other than weight gain.

b(4)

In (b) (4), in addition to weight gain, the sponsor found several adverse events displayed disproportional reporting in children and adolescents over other age groups:

1) Serious reports of priapism were reported in a higher proportion of cases in children and adolescents than in other age groups during 2 review cycles, but the sponsor states this disproportionality was not observed in other periods or in the cumulative dataset.

2) Incidence of epistaxis was seen higher in children and adolescents than in other age groups in the 2 most recent 6-month review periods and in the cumulative dataset – a causal association between risperidone and epistaxis in children and adolescents was considered detected, although the mechanism of this effect is not known.

3) A possible increased susceptibility for dyskinesia and ocular manifestations of EPS in children and adolescents treated with risperidone, especially at doses in excess of recommended pediatric doses in the current Reference Safety Information for risperidone was identified during their most recent review period; Nonetheless, the sponsor reports that no disproportionality of reporting has been observed in any individual period or in the cumulative dataset for children and adolescents with regard to tardive dyskinesia or overall extrapyramidal symptoms.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The design of pivotal study and patient enumeration are adequate per the Agency WR.

7.2.1.2 Demographics

Demographic distribution of the pivotal studies is also adequate according to the WR.

7.2.1.3 Extent of exposure (dose/duration)

Extent of exposure is adequate. Please see subsections 5.3 and 6.1.4 for more details.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Other than above mentioned three studies, no other studies were reviewed as part of this sNDA.

7.2.2.2 Postmarketing experience

Please see subsection 7.1.17.

7.2.2.3 Literature

The sponsor reports a comprehensive literature search was conducted covering the period up to August, 31, 2006. The search was performed in 6 phases: An initial search for published information up to May 25, 2000, a second search for published information from May 26, 2000 up to July 31, 2003, a third search for published information from July 31, 2003 up to December 31, 2003, a fourth search for published information from January 1, 2004 up to June 30, 2004, a fifth search for published information from July 1, 2004 up to April 30, 2005 and a sixth search for published information from May 01, 2005 through to August 31, 2006.

The search primarily used the sponsor's literature repository (LMD) and the Medline database. All article sorting, retrieval, translation, assessment, and data extraction were overseen by or performed by [redacted] for the initial search (up to May 25, 2000) and were performed by J&JPRD for the second, third, fourth, fifth and sixth searches (information from May 26, 2000 through August 31, 2006), and jointly by J&JPRD and [redacted] for the sixth search. Only articles containing original clinical data were summarized. The reviews, editorial type publications, and articles on a mixed population of children and adults or young adults only were excluded from assessment. b(4)

A total of 936 articles were identified but only 603 articles were reviewed and categorized after removal of duplicates. Among these, 300 articles contained original clinical data. A total of 169 of these articles were case reports. There were 17 double-blind, placebo-controlled studies and 6 comparative, active-controlled studies in children and adolescents. Additionally, there were 75 open studies and 30 chart reviews. Overall, data were reported for more than 5,400 subjects. Safety results were reported in 206 articles – this is a significant increase compared to the 125

articles previously. Based on the available information, the doses administered ranged from 0.25mg–12 mg/day or 0.01-0.06 mg/kg/day, and the duration of treatment was up to 7 years.

For detailed information on safety reported, please see Section 8.6.

7.2.3 Adequacy of Overall Clinical Experience

The studies met the Agency WR requirements.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There was no special animal and/or in-vitro testing required in the Agency WR.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing of the study is adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The studies conducted fulfill the Agency's WR.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Not applicable as this is not a new drug.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the study design meets the requirement of the FDA WR. However, the marked outlier analysis for both laboratory tests is not provided.

7.2.9 Additional Submissions, Including Safety Update

The sponsor reports the submission of multiple periodic safety reports before this sNDA submission. These periodic reports are not reviewed as this

In addition, the sponsor submitted Safety Update on April 19, 2007. There is not enough time to review these data during this review cycle. They will be reviewed during the next review cycle.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The sponsor presents the list of treatment-emergent common adverse events after comparing with those of adult patients' and lists only those those are at least 5% but also more than those of adults. Such presentation of drug-related adverse events must be corrected. For more details, please see subsection 7.1.5.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Since there is only one pivotal study and one long-term, open-label study and a PK study, no pooling of data was done. Data from individual studies were reviewed separately.

7.4.1.2 Combining data

Data on SAEs, AEs associated with dropouts, and deaths were reviewed in the above mentioned three studies and organized together.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Changes of vital signs, laboratory findings, and ECG as well as adverse events in different dose groups are summarized in Section 7.1.

7.4.2.2 Explorations for time dependency for adverse findings

The sponsor provides information on changes of vital signs, laboratory findings, and ECG. Summaries of these changes from baseline to endpoint are in Section 7.1.7.

7.4.2.3 Explorations for drug-demographic interactions

Drug-demographic interactions are explored in Table 15 of subsection 6.1.4.

7.4.2.4 Explorations for drug-disease interactions

Bipolar I disorder is the only indicated disease for treatment studied. Although the sponsor conducted some analyses with regard to comorbidities of bipolar and other psychiatric diagnosis