CLINICAL REVIEW

Application Type	Supplement NDA's 20272, 20588, 21444
Submission Number	046, 036, 020
Submission Code	SE5
Letter Date	Dec. 21, 2006
Stamp Date	Dec. 22, 2006
PDUFA Goal Date	June 21, 2007
Reviewer Name	June Cai, M.D.
Review Completion Date	June 17, 2007
Established Name	Risperidone
Trade Name	Risperidal®
Therapeutic Class	Antipsychotics
Applicant	Janssen
Priority Designation	P
Formulation	(b) (4) oral solution, Orally disintegrating tablets
Dosing Regimen	(b) (4) 6 mg
Indication	Schizophrenia
Intended Population	Age 13-17 year-old

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend the Division taking an Approvable action for this sNDA (#20272-046) which proposes to use risperidone for the treatment of schizophrenia in adolescents ages 13−17 year-old; however, I recommend that the dosage be limited to risperidone 1−3mg/day.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Postmarketing risk management should include collecting data on tardive dyskinesia, neuroleptic malignant syndrome, 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 bipolar I disorder in children and adolescents (age 10 to 17 year-old), are in response to the Agency WR. The Division has granted the waiver for studying children (age 12 year-old or younger) with schizophrenia.

1.2.3 Other Phase 4 Requests

No new Phase 4 commitment study is required at present.

1.3 Summary of Clinical Findings

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

1.3.1 Brief Overview of Clinical Program

In response to the Agency's Written Request, this submission includes two pivotal efficacy trials (Studies RIS-BIM-302 and RIS-USA-231) on treatment of schizophrenia in adolescents age 13 – 17 year-old. A total of 417 adolescent patients were enrolled in these two studies. 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

Efficacy is demonstrated through the two double-blind, controlled trials: 1) Study RIS-SCH-302 (placebo-controlled study with two risperidone dose groups, 1.5−3mg/day and 4−6mg for 6 weeks), and 2) Study RIS-BIM-231 (using risperidone dose of 0.15−0.6 mg/day as ersatz control compared with higher risperidone dose group 3−6 mg/day for a duration of 8 weeks).

PANSS was the primary endpoint outcome measure in both trials. All risperidone groups, except for the group of ersatz, showed that risperidone is superior to placebo or the ersatz for treatment of adolescent patients with schizophrenia. Moreover, there was no significant difference in effect size between risperidone lower dose group (1−3mg/day) and higher dose group (4−6mg/day) as shown in Study RIS-SCH-302.

1.3.3 Safety

The overall safety evaluation is based on the above mentioned three studies in adolescents with schizophrenia. These include two short term controlled trials (Studies RIS-SCH-302 and RIS-USA-231) up to 6 weeks and 8 weeks, respectively, as well as a six-month open-label study (RIS-USA-234). However, treatment-emergent common adverse event is based on the only placebo-controlled study (Study RIS-SCH-302).

Generally speaking, incidences of adverse events are higher in risperidone higher dose (4–6 mg/day) group than those in lower dose (1–3 mg/day) group, especially extrapyramidal-related symptoms, dizziness, somnolence, and increasing salivation. Significant increase of serum prolactin level is also dose-related.

1.4 Dosing Regimen and Administration

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 13 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: [redacted] (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 proposed indications.

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.

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 and (b) (4) 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.

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 schizophrenia comes from Study RIS-US-231 and Study RIS-SCH-302, both of which are double-blind studies, one is placebo-controlled, and the other ersatz placebo controlled. The main safety data are from both of these studies 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 (a double-blind study that the sponsor conducted for treatment of bipolar 1 disorder in children and adolescents in response to the Agency WR) and RIS-USA-231. There were meetings regarding the Agency's WR for these studies (see section 2.5 for Presubmission Regulatory Issues).

4.2 Tables of Clinical Studies

The following table is provided by the sponsor to display the clinical studies conducted in this clinical development program.

Table 2: Clinical Studies to Fulfill the Pediatric Written Request for Schizophrenia

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 behavioural and psychotic disorders	24 children and adolescents (6-16 years) in equal numbers
Completed Study in Adolescents With Schizophrenia		
Double-Blind, Placebo-Controlled, Parallel-Group, Phase III Study		
RIS-SCH-302[a, b]	Randomized, double-blind, placebo-controlled multicenter 6-week study in adolescents with a DSM-IV diagnosis of schizophrenia and suffering from an acute episode (PANSS total score 60-120) Risperidone 1-3 mg/day Risperidone 4-6 mg/day Placebo	Treated: 160 adolescents with schizophrenia PLA, n=54 RIS 1-3 mg, n=55 RIS 4-6 mg, n=51
Double-Blind, Controlled, Parallel-Group, Phase III Study		
RIS-USA-231[a, b]	Randomized, double-blind, multicenter, 8-week study in adolescents with a DSM-IV diagnosis of schizophrenia[c] and suffering from an acute episode (PANSS total score 60-120) Risperidone 0.15-0.6[d] mg/day Risperidone 1.5-6[d] mg/day	Treated: 279 (257 adolescents with schizophrenia [primary analysis set])[c] RIS 0.15-0.6 mg, n=141 (132 adolescents with schizophrenia) RIS 1.5-6 mg, n=138 (125 adolescents with schizophrenia)
Safety Study		
Long Term Open-Label Study		
RIS-USA-234[a]	Open-label, 6-month, multicenter study in adolescents with schizophrenia. Subjects entered from RIS-USA-231 or RIS-SCH-302 or entered directly[e] Risperidone 2 – 6 mg/day	Analyzed: 297[e] (119 with mode dose ≥3 mg/day and duration ≥180 days) RIS n=297 (including 11 subjects aged ≤12 years old and 4 with schizophreniform disorder)

[a] Included in the Pediatric sNDA for adolescent schizophrenia.
[b] Fulfills the Written Request requirement that at least 50% of patients assigned to active drug must complete to the nominal endpoint of the trial to be considered a completed trial.
[c] The original protocol permitted enrollment of subjects aged ≤12 years and subjects with schizophreniform disorder; these subjects were excluded from enrollment following protocol Amendment 2. The small number of such subjects who had already enrolled (n=22; 19 aged ≤12 years and 7 with schizophreniform disorder) were excluded from the key efficacy and safety assessments.
[d] Minimum-maximum mode doses.
[e] 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

The two individual pivotal studies for this indication have different design and thus will be reviewed separately. For the purpose of better understanding and convenient reading, the review will be incorporated in Section 6 – Integrated Review of Efficacy instead of being in the Appendix.

For safety, all study will be considered, including the PK study RIS-US-160 and RIS-USA-234. Data from the two pivotal studies will be reviewed separately due to the different design.

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

For all studies, the sponsor reports that the studies were conducted consistent with Good Clinical Practices and applicable regulatory requirements despite known instances of nonconformance that were documented and are not considered to have impacted the overall conclusions of this study. Major protocol deviations of pivotal studies were summarized and discussed in the Efficacy Finding section.

4.6 Financial Disclosures

The sponsor reports that there are no disclosable financial arrangements among the investigators listed and the sponsor as defined in 21 CFR 54.2 (a), (b), (c), and (f). From the submission, it seems there is no exception for all studies. In the sponsor's email response to us on Mar. 22, 2007, the sponsor specifies that financial disclosure for all investigators in the two controlled studies is none and 3/6 investigators for the PK study (RIS-USA-160) continues to have no financial interest post one year study completion.

A full list of investigators with number of subjects recruited for Study RIS-SCH-302 can be found in the sponsor's submission of May 1, 2007 (see \\CDSESUB1\N20272\S_046\2007-05-01 in the EDR) and the list for Study RIS-USA-231 can be found on pages 1545 to 1564 of the Study Report.

5 CLINICAL PHARMACOLOGY

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

5.1 Pharmacokinetics

The sponsor reports that correlation of active moiety plasma concentrations at Day 56 (predose) with the efficacy parameters PANSS and CGI was explored graphically. Scatterplots of active moiety plasma concentrations versus PANSS (actual and change from baseline) and CGI show no apparent relationship between the plasma concentrations and any of the assessed parameters or their respective shifts from baseline.

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-HT_2) and D_1, 5-HT_{1A}, 5-HT_{1C}, and 5-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

In the placebo-controlled study (RIS-sCH-302), the two risperidone treatment groups have similar effect size. The mean dose of exposure can be found in subsection 6.1.4 Efficacy Findings (Tables 10 and 11). The following table summarizes the duration of exposure.

Table 3. Summary of Study Treatment Duration (Study RIS-SCH-302: Intent-to-Treat Analysis Set

	----- PLACEBO -----	---- RIS 1-3 mg ---	---- RIS 4-6 mg ---
Total duration, days			
N	54	55	51
Category, n (%)			
1-7	2 (4)	3 (5)	2 (4)
8-14	1 (2)	1 (2)	5 (10)
15-28	9 (17)	4 (7)	1 (2)
29-42	29 (54)	29 (53)	25 (49)
≥43	13 (24)	18 (33)	18 (35)
Mean (SD)	36.50 (9.966)	38.29 (10.837)	37.37 (12.051)
Median	42.00	42.00	42.00
Range	(4.0;48.0)	(3.0;51.0)	(2.0;46.0)
Total Exposure (subject years)	5.4	5.8	5.2

During the fixed dose phase, the median exposure was 28 days for each treatment group and a maximum exposure of 37 days.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Agency WR requests the studies for pediatric population. The indication for this sNDA is schizophrenia in adolescents. The sponsor provides the following background for this indication: "Schizophrenia is a devastating neurodevelopmental disorder with an estimated lifetime adult prevalence of approximately 1.0%. As defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), the essential features of schizophrenia include a mixture of characteristic signs and symptoms, including positive symptoms (delusions, hallucinations), negative symptoms (flat affect, anergy, paucity of speech and thought), and so-called disorganized symptoms (disorganized speech [thought disorder], disorganized

behavior, and poor attention). Although limited data exist, it is estimated that 1 in 10,000 children/adolescents develop full DSM-IV criteria for the diagnosis of schizophrenia worldwide. However, it is recognized that young people often have subthreshold symptomatology well before they meet the formal diagnostic criteria for the disorder. In general, most adolescent patients diagnosed with schizophrenia maintain their diagnosis and their functional outcome is poor, with almost half exhibiting a deteriorating course or minimal improvement. For the majority of patients, including those diagnosed during adolescence, schizophrenia is a recurrent or chronic disorder for which maintenance therapy with psychotropic agents has become the standard of care. Within the pediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents, and the symptoms in this age group are generally similar to those in adults. Schizophrenia has also been described in children <13 years, but it is thought to be uncommon. The phenomenology and diagnostic criteria (DSM-IV) are similar in the adolescent and adult populations; however, the earlier the age of onset the more negative is the impact of the disease on personality and relationship development, cognitive functioning, educational and work attainment, and social functioning. Moreover, adolescent-onset schizophrenia is a life-long illness."

The sponsor also requested waiver for studying this indication in children <13 years of age. The Division has granted this waiver in Feb. 2007.

6.1.1 Methods

The efficacy data are reviewed from the two acute, double-blind, controlled (one placebo-controlled, one using lower dose range as the placebo), and one long term supportive open-label study evaluating safety and efficacy in adolescents treated for up to 6–12 months.

6.1.2 General Discussion of Endpoints

The overall efficacy assessments in the trials of adolescents with schizophrenia include the following:

Table 4. Schedule for Efficacy Assessments in the Studies in Adolescents with Schizophrenia (Studies RIS-SCH-302 and RIS-USA-231)

Scales for Efficacy Assessment*	**RIS-SCH-302**	**RIS-USA-231**
Positive and Negative Syndrome Scale (PANSS)	Screening, Baseline, Weeks 1, 2, 4, 6	Screening, Baseline, Weeks 1, 2, 4, 6, 8
Clinical Global Impression-Severity Scale	Baseline, Weeks 1, 2, 4, 6	Screening, Baseline, Weeks 1, 2, 4, 6, 8
Clinical Global Impression-Improvement Scale	Weeks 1, 2, 4, 6	Weeks 1, 2, 4, 6, 8
Children's Global Assessment Scale	Screening, Week 6	Screening

*PANSS is the primary efficacy variable. No key secondary efficacy variable was defined.

The primary efficacy endpoint is the change in the Positive and Negative Syndrome Scale (PANSS) score from baseline to endpoint for all three studies. This scale was designed to assess

the symptomatic change in the severity of symptoms in adult subjects with schizophrenia and other psychotic disorders. It includes 30 items and provides a total score and 3 subscale scores: The positive subscale (7 items), the negative subscale (7 items), and the general psychopathology subscale (16 items). The severity of each of the 30 items of the PANSS is rated on a scale of 1 (absent) to 7 (extreme). Higher scores represent greater symptom severity.
For children and adolescents with schizophrenia, the Kiddie PANSS was developed. However, the sponsor reports that the Kiddie PANSS had not been validated for use in pediatric schizophrenia at the time these studies were being planned. After noting several irregularities within the Kiddie PANSS and poor acceptance by study investigators, the sponsor chose to use the traditional PANSS (validated in adults) with some adaptations during the interviewing process instead of the Kiddie PANSS for these trials. The adaptations include a) an interview with the parent or guardian in addition to the patient interview; b) a re-ordering of the PANSS questions, leading with less threatening questions to allow the interviewer to build rapport; c) instruction to reword questions as necessary to make them more age-appropriate; and, d) stratification of the interviewees by age range, to provide developmental adjustments for age ranges for each symptom.

The scale was administered on the basis of a semi-structured interview guide by an adequately trained clinician who did not provide psychotherapy or psychoeducation to the subject. Individual subject ratings were made at approximately the same time of day at each visit, and the same person administered the scale at all visits, if possible.

The primary objective for Study RIS-SCH-302 is to determine the efficacy and safety of two dose ranges of risperidone monotherapy (1–3mg/day and 4–6mg/day) versus placebo in the treatment of adolescent schizophrenia.

The primary objective for Study RIS-USA-231 is to evaluate the efficacy and safety of a high-dose risperidone treatment group versus a low-dose risperidone treatment group in adolescents with schizophrenia.

6.1.3 Study Design

The study designs for these two pivotal studies are illustrated in the following figures:

Figure 1. Design of Study RIS-SCH-302

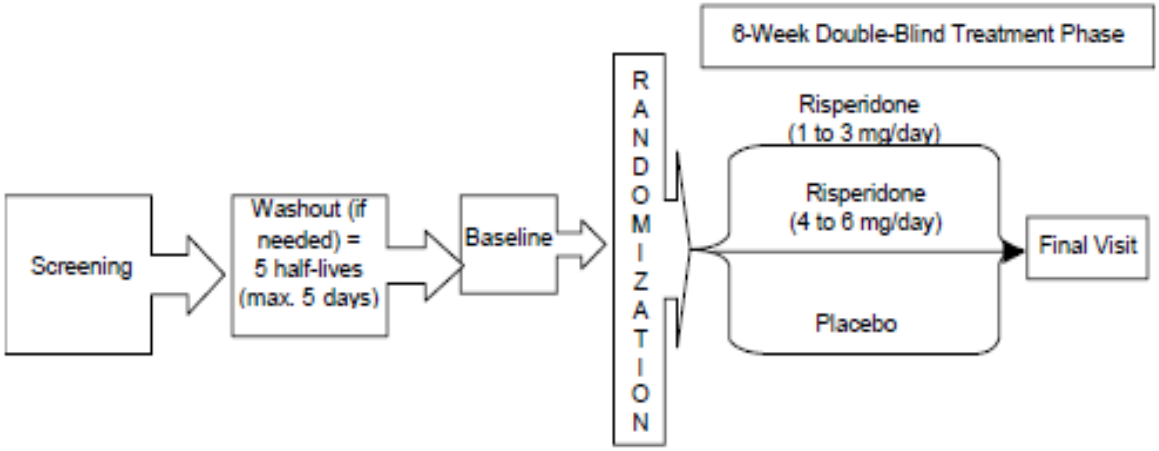
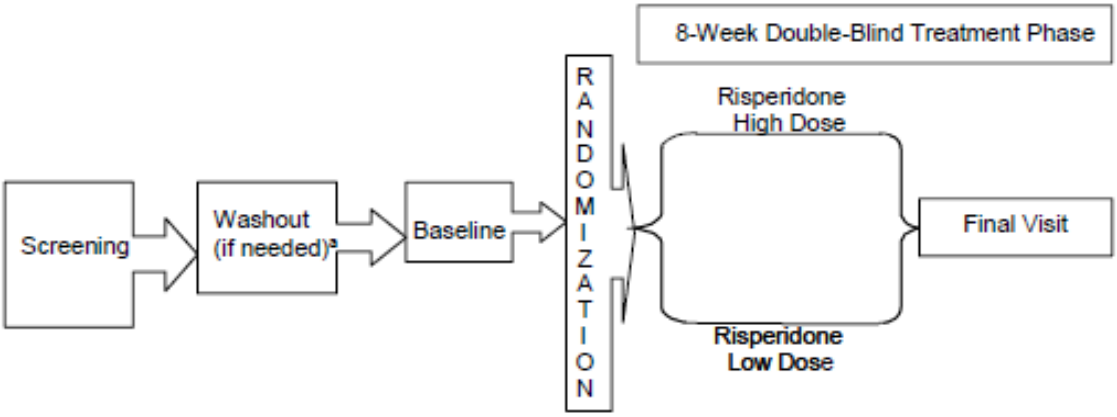

6-Week Double-Blind Treatment Phase
Screening
Washout (if needed) = 5 half-lives (max. 5 days)
Baseline
RANDOMIZATION
Risperidone (1 to 3 mg/day)
Risperidone (4 to 6 mg/day)
Placebo
Final Visit

Table 5. Dose Titration Schedule of Study RIS-SCH-302

Day(s)	Risperidone Dosage Group A[a] (1 to 3 mg/day)	Risperidone Dosage Group B[a] (4 to 6 mg/day)	Notes
1	0.5 mg/day	0.5 mg/day	
2	0.5 mg/day	1 mg/day	Titration could be accelerated or decelerated to target dosage range, if needed
3	0.5 mg/day	2 mg/day	
4	1 mg/day	2 mg/day	
5-6	1 mg/day	3 mg/day	
7	1 mg/day	4 mg/day	Target range achieved
8-14	1 to 3 mg/day	4 to 6 mg/day	Subjects titrated to the maximum tolerated dosage within the target dosage range
15-42	1, 2, or 3 mg/day	4, 5, or 6 mg/day	Maximum tolerated dosage maintained for study duration

[a] A subject should have achieved a minimum dosage of 1 mg/day in dosage group A or 4 mg/day in dosage group B by Day 7. After discussion with the Sponsor, a slower titration rate into the target dosage range was allowed if adverse events emerged. After Day 14, adjustments to the dosage reached by Day 14 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 14 to 42, he or she was withdrawn from the study and could enter the open-label study (RIS-USA-234) if appropriate.

Figure 2. Design of Study RIS-USA-231



Subject Selection

In both studies, subjects were aged between 13 and 17 years, inclusive, with a DSM-IV diagnosis of schizophrenia and suffering from an acute episode (screening and baseline total PANSS score between 60 and 120, inclusive). Subjects were enrolled as either inpatients or outpatients.

The sponsor explains that although in original protocol for Study USA-231, subjects of ≤12 years old were included, they were excluded from enrollment following Amendment 2 and despite these 19 subjects continued the study, they were not included in the main efficacy analyses.

Baseline Characteristics

The majority subjects enrolled in Study RIS-USA-231 were from the U.S. (35%) and Poland (33%).

Overall, the subjects' age and race (the majority were white) are comparable in all treatment groups, but the subjects in Study RIS-USA-231 weighed slightly higher than those in Study RIS-SCH-302 though they are still comparable in each treatment group within each study.

The majority patients in each study were paranoid subtype, followed by subtypes of undifferentiated and disorganized. Though rare, there were catatonic patients in Study RIS-USA-231 compared to Study RIS-SCH-302. About half of all subjects (49%) were hospitalized at Screening.

The baseline characteristics of the two acute efficacy studies are summarized in the following table (see next page).

Additionally, according to the sponsor, in Study RIS-USA-231, only 15% of the subjects had comorbid active psychiatric disorders (such as ADHD, mental retardation, conduct disorder, and sleep disturbances) and 19% had a past history of psychiatric disorders. Over half (66%) of the subjects didn't have psychiatric comorbidities. Active neurologic problems (mainly headache and insomnia) existed in 6% of the subjects. However, in Study RIS-SCH-302, only 55% of the subjects didn't have comorbidities; 40% of subjects had active comorbid psychiatric disorders (most commonly insomnia), and 5% had a past history of other comorbid psychiatric disorders. Active neurologic conditions (predominantly headaches) existed in 4% of the subjects.

Table 6. Demographic and Baseline Disease Characteristics (Studies RIS-SCH-302 and RIS-USA-231)

	RIS-SCH-302 (ITT)			RIS-USA-231 (MITT)	
	Placebo (N=54)	RIS 1-3 mg (N=55)	RIS 4-6 mg (N=51)	RIS 0.15-0.6 mg (N=132)	RIS 1.5-6 mg (N=125)
Sex, n (%)					
Female	19 (35)	25 (45)	14 (27)	52 (39)	60 (48)
Male	35 (65)	30 (55)	37 (73)	80 (61)	65 (52)
Race, n (%)					
White	27 (50)	33 (60)	24 (47)	111 (85)	104 (85)
Non-White	27 (50)	22 (40)	27 (53)	20 (15)	19 (15)
Age in years					
Mean (SD)	15.5 (1.38)	15.7 (1.33)	15.7 (1.29)	15.6 (1.32)	15.6 (1.25)
Median	16.0	16.0	16.0	16.0	16.0
Range	(13;17)	(13;17)	(13;17)	(13;17)	(13;17)
Weight in kilograms					
Mean (SD)	58.5 (20.08)	58.9 (16.56)	58.5 (12.18)	63.9 (11.52)	60.6 (10.47)
Median	52.5	56.0	55.9	63.1	59.9
Range	(36;126)	(37;110)	(36;89)	(31;96)	(36;90)
Weight in classes, n (%)					
<50 kg	24 (44)	19 (35)	11 (22)	11 (8)	18 (14)
≥50 kg	30 (56)	36 (65)	40 (78)	121 (92)	107 (86)
Body Mass Index (kg/m^2)					
Mean (SD)	21.7 (5.68)	21.7 (4.31)	21.4 (3.77)	22.2 (3.39)	21.4 (3.20)
Median	20.4	20.8	20.8	21.9	20.6
Range	(14;38)	(15;34)	(16;35)	(15;30)	(16;32)
Tanner sexual maturity stage, n (%)					
2	3 (6)	0	1 (2)	2 (2)	1 (1)
3	13 (24)	9 (16)	8 (16)	19 (14)	17 (14)
4	24 (44)	31 (56)	27 (53)	51 (39)	50 (40)
5	14 (26)	15 (27)	15 (29)	60 (45)	57 (46)
Diagnosis, n (%)					
Catatonic	0	1 (2)	0	3 (2)	4 (3)
Disorganized	3 (6)	8 (15)	4 (8)	6 (5)	13 (10)
Paranoid	38 (70)	38 (69)	34 (67)	92 (70)	83 (66)
Residual	1 (2)	0	0	7 (5)	0
Undifferentiated	12 (22)	8 (15)	13 (25)	24 (18)	25 (20)
Age at onset of first psychiatric symptom (yrs)					
Mean (SD)	12.6 (3.33)	12.9 (2.75)	13.8 (2.36)	13.7 (2.49)	14.0 (2.13)
Median	13.0	14.0	14.0	14.0	14.0
Range	(2;17)	(4;17)	(6;17)	(4;17)	(4;17)
Age at diagnosis (yrs)					
Mean (SD)	14.8 (1.59)	14.5 (2.62)	14.8 (2.27)	15.3 (1.61)	15.3 (1.30)
Median	15.0	15.0	15.0	16.0	15.0
Range	(11;17)	(4;17)	(6;17)	(7;17)	(12;17)

ITT=intent-to-treat analysis set; MITT=modified intent-to-treat analysis set; n = number of subjects; SD = standard deviation; yrs = years.

Statistic analyses

The primary analysis set for the RIS-SCH-302 study was the intent-to-treat analysis (ITT) set (i.e., all randomized subjects who took at least 1 dose of trial medication). An ITT set was also defined for the RIS-USA-231 study, but a modified intent-to-treat (MITT) analysis set (i.e. those who were younger than 13 years of age were excluded after protocol amendment 2) was the primary analysis set for the efficacy analyses in this trial.

The sponsor further specifies that "the primary analysis was the between-treatment group comparison of the change from baseline at end point of the primary efficacy variable, as assessed by the analysis of covariance (ANCOVA) model. An ANCOVA model including factors for treatment, country and baseline score of the primary efficacy variable was used. In RIS-SCH-302, a step-down closed testing procedure was applied to compare each of the risperidone dosage groups with placebo."

6.1.4 Efficacy Findings

Table 7. Subject Disposition and Discontinuation Reasons (Studies RIS-SCH-302 and RIS-USA-231)

Study		Randomized treatment group	
RIS-SCH-302, n (%)	Placebo	RIS 1-3 mg	RIS 4-6 mg
Randomized	54	55	51
ITT	54	55	51
Completed	36 (67)	45 (82)	44 (86)
Drop outs due to LOE	13 (24)	3 (5)	1 (2)
Drop outs due to AE	2 (4)	3 (5)	4 (8)
Drop outs due to other reasons	3 (6)	4 (7)	2 (4)
RIS-USA-231, n (%)		RIS 0.15-0.6 mg	RIS 1.5-6 mg
Randomized		141	138
ITT		141	138
Completed		87 (62)	97 (70)
Drop outs due to LOE		27 (19)	20 (14)
Drop outs due to AE		6 (4)	8 (6)
Drop outs due to other reasons		21 (15)	13 (9)

AE=adverse event; ITT=intent to treat; LOE=lack of efficacy (insufficient response)

Concomitant medications

Any new psychotherapy or psycho-education as well as most psychotropic medications, including lithium, antiparkinsonian drugs, sedatives, hypnotics, anxiolytics, cholinesterase inhibitors, beta-adrenergic medications, ginko biloba, kava kava, and among others, were prohibited in the RIS-SCH-302 and RIS-USA-231 protocols with the exception of rescue medication (lorazepam or other selected benzodiazepines and non-benzodiazepine sedative hypnotics) for the control of acute agitation and/or insomnia. Propranolol was also an exception for the akathisia. The administration of these medications was also not permitted within 8 hours of efficacy assessments to avoid confounding efficacy results.

In Study RIS-USA-231, although up to 68% subjects were taking other psychotropic medication, esp. olanzapine, haloperidol, and lorazepam, prior to the beginning of the study, and a total of 52% subjects were on lorazepam (42%), zolpidem (11%), hydroxyzine (8%), and diazepam (6%) during the study, only one subject was on other antipsychotics (one in risperidone high dose group). At baseline, three subjects took in each treatment group took lorazepam within 8 hours prior to the assessments; on Day 7, one subject in each treatment group did so. Paracetamol is the second most commonly used medication in the study (19%), followed by antiparkinson drugs (see the next table provided by the sponsor for details). Up to 27% subjects in risperidone higher dose group received medication treatment for EPS symptoms while only 17% subjects in risperidone lower dose group (ersatz placebo) needed such treatment.

Table 8. Concomitant Therapy during Treatment-Therapies with >=5% Incidence in Either Group – MITT (Study RIS-USA-231: Modified Intent-to-Treat Analysis Set)

Analysis Phase: Treatment
In case of recurrent events, subject's first event is used.

ATC Class Who Generic Term	Ris low dose (N=132) n (%)	Ris high dose (N=125) n (%)	Total (N=257) n (%)
Total no. subjects with concomitant medication	94 (71)	99 (79)	193 (75)
Analgesics	33 (25)	25 (20)	58 (23)
Paracetamol	31 (23)	19 (15)	50 (19)
Anti-parkinson drugs	8 (6)	26 (21)	34 (13)
Benzatropine mesilate	2 (2)	7 (6)	9 (4)
Biperiden	3 (2)	8 (6)	11 (4)
Antiinflammatory and antirheumatic products	9 (7)	9 (7)	18 (7)
Ibuprofen	7 (5)	9 (7)	16 (6)
Other gynecologicals	8 (6)	10 (8)	18 (7)
Ibuprofen	7 (5)	9 (7)	16 (6)
Psycholeptics	71 (54)	62 (50)	133 (52)
Diazepam	9 (7)	6 (5)	15 (6)
Hydroxyzine	9 (7)	12 (10)	21 (8)
Lorazepam	56 (42)	51 (41)	107 (42)
Zolpidem	13 (10)	14 (11)	27 (11)
Topical products for joint and muscular pain	9 (7)	10 (8)	19 (7)
Ibuprofen	7 (5)	9 (7)	16 (6)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: A subject may have taken a concomitant medication from more than 1 class. A medication may have been assigned to multiple classes based on its possible rather than actual clinical use.
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In Study RIS-SCH-302, about 75% subjects were treated with other psychotropics, including olanzapine, antidepressants, antiepileptics, and psychostimulants prior to the study. During the study period, still over half of the subjects (59%) received other psychotropics, most frequently lorazepam and trihexyphenidyl that were both permitted per protocol. The table below displays the concomitant therapies that were used in 5% or more subjects in any treatment group.

Table 9. Incidence of Concomitant Therapy during Treatment in ≥5% of Subjects in Any Group (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

ATC Class WHO Generic Term	PLACEBO (N=54) n (%)	RIS 1-3 mg (N=55) n (%)	RIS 4-6 mg (N=51) n (%)	ALL RIS (N=106) n (%)
Total no. subjects with concomitant medication	34 (63)	32 (58)	31 (61)	63 (59)
Psycholeptics	28 (52)	25 (45)	20 (39)	45 (42)
Lorazepam	21 (39)	20 (36)	13 (25)	33 (31)
Zolpidem	7 (13)	9 (16)	5 (10)	14 (13)
Hydroxyzine	5 (9)	4 (7)	2 (4)	6 (6)
Anti-parkinson drugs	6 (11)	9 (16)	17 (33)	26 (25)
Trihexyphenidyl	4 (7)	9 (16)	14 (27)	23 (22)
Analgesics	11 (20)	9 (16)	8 (16)	17 (16)
Paracetamol	10 (19)	6 (11)	8 (16)	14 (13)
Antacids, drugs for treatm.of pept.ulc.and flatul.	3 (6)	4 (7)	2 (4)	6 (6)
Maalox	0	3 (5)	0	3 (3)

Note: Percentages calculated with the number of subjects in each group as denominator. A subject may have taken a concomitant medication from more than 1 class. A medication may have been assigned to multiple classes based on its possible rather than actual clinical use.

There are also 27% subjects in risperidone higher dose group (3-6mg/day) that needed treatment for EPS during the study while only 18% in risperidone lower dose group (1-3mg/day) and 13% in placebo group.

Protocol deviations

In Study RIS-USA-231, 25% subjects in each treatment group had protocol deviations. Most common reasons are concurrent forbidden therapy (14%), wrong dosage (11%), and selection criteria NOS not met (4%).

In Study RIS-SCH-302, about 20% subjects in each treatment group had protocol deviation. Receiving wrong dose was the most common (9% total) reason followed by concurrent forbidden treatment (5% total).

Mean risperidone dosage throughout the study was 2.2mg/day in risperidone lower dose group and 4.6mg/day in risperidone higher dose group; mean dosage after reaching the targeted dose range was 2.8mg/day in lower dose group and 5.6mg/day. (See tables below provided by the sponsor.)

Table 10. Summary of Dosages of Throughout Treatment Phase (Study RIS-SCH-302)

	----- PLACEBO -----	---- RIS 1-3 mg ---	---- RIS 4-6 mg ---
Mode dose (incl days off drug)			
N	54	55	50
Mean (SD)	0.000 (0.0000)	2.573 (0.8017)	5.260 (1.0654)
Median	0.000	3.000	6.000
Range	(0.00;0.00)	(0.50;3.00)	(2.00;6.00)
Mean dose (incl days off drug)			
N	54	55	51
Mean (SD)	0.000 (0.0000)	2.164 (0.5552)	4.562 (1.0259)
Median	0.000	2.449	5.188
Range	(0.00;0.00)	(0.63;2.53)	(0.75;5.29)

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Table 11. Summary of Dosages during Fixed Target Phase (Study RIS-SCH-302)

	----- PLACEBO -----	---- RIS 1-3 mg ---	---- RIS 4-6 mg ---
Mode dose (incl days off drug)			
N	51	50	44
Mean (SD)	0.000 (0.0000)	2.760 (0.5555)	5.545 (0.6973)
Median	0.000	3.000	6.000
Range	(0.00;0.00)	(1.00;3.00)	(4.00;6.00)
Mean dose (incl days off drug)			
N	51	50	44
Mean (SD)	0.000 (0.0000)	2.755 (0.5531)	5.567 (0.6657)
Median	0.000	3.000	6.000
Range	(0.00;0.00)	(1.00;3.00)	(4.00;6.00)

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Efficacy Results

The efficacy results of Studies RIS-SCH-302 and RIS-USA-231 are displayed in the following table submitted by the sponsor.

Table 12. PANSS Total Scores - Change from Baseline to End Point (Studies RIS-SCH-302 and RIS-USA-231)

Study ID		Mean (SD)			Between-group comparison	
Study Treatment (mg/day)	N[a]	Baseline	Endpoint	Change	Diff in LS Mean Changes (95% CI)	p value[b]
RIS-SCH-302						
Placebo	54	93.2 (10.27)	84.4 (16.59)	-8.9 (16.11)	—	—
RIS 1-3	54	95.4 (11.01)	74.1 (17.79)	-21.3 (19.61)	-12.0 (-17.95;-5.99)	<0.001
RIS 4-6	50	93.0 (11.87)	71.8 (18.35)	-21.2 (18.29)	-12.8 (-18.83;-6.71)	<0.001
RIS-USA-231						
RIS 0.15-0.6	131	93.3 (14.14)	80.8 (24.33)	-12.5 (20.32)	—	—
RIS 1.5-6	124	96.4 (15.39)	72.8 (22.52)	-23.6 (22.83)	-10.3 (-15.53;-5.09)	<0.001

[a] N=The number of subjects with both baseline and endpoint measurements (ITT analysis set for RIS-SCH-302, MITT analysis set [Excluding subjects A35259 and A35271] for RIS-USA-231).

[b] p value: Difference in least squares means from ANCOVA model with treatment and country as factors and baseline value as covariate.

CI=confidence interval; LS=least square; SD=standard deviation.

In Study RIS-SCH-302, the risperidone treatment groups are obviously more effective than the placebo group. However, there is no significant difference in effect size seen with two dose ranges.

In Study RIS-USA-231, dose group RIS 1.5–6 mg/day shows significant effect compared to ersatz placebo (dose group RIS 0.15–0.6 mg/day).

Findings in Subgroup Populations

The following tables display efficacy demographic analysis of the two acute double-blind controlled studies.

Table 13. Results of Primary Endpoint in Study RIS-SCH-302 for Sex and Race Subgroups

Demographic Subgroup		PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Sex				
Female	N	19	24	14
	Mean (SD)	-11.6 (12.01)	-22.8 (23.62)	-26.3 (21.40)
	Diff. of LS means (95% CI)		-11.2 (-21.53;-0.88)*	-14.2 (-25.78;-2.52)'
Male	N	35	30	36
	Mean (SD)	-7.4 (17.94)	-20.2 (16.04)	-19.2 (16.85)
	Diff. of LS means (95% CI)		-11.8 (-19.32;-4.29)*	-12.2 (-19.33;-5.09)
Race				
Non-white	N	27	22	27
	Mean (SD)	-15.9 (17.61)	-30.1 (18.77)	-27.8 (21.33)
	Diff. of LS means (95% CI)		-11.1 (-21.39;-0.77)*	-13.4 (-23.18;-3.57)
White	N	27	32	23
	Mean (SD)	-1.9 (10.80)	-15.3 (18.08)	-13.5 (9.58)
	Diff. of LS means (95% CI)		-12.5 (-19.42;-5.65)***	-12.3 (-19.77;-4.77)'

In Study RIS-SCH-302, there seem to be no significant differences in efficacy with different genders or the two race groups and with different dosages in each gender group or each race group.

Table 14. Results of Primary Endpoint for Study RIS-USA-231 in Sex and Race Subgroups

	Change from baseline at Day 56 end point in total PANSS score			
	RIS LOW DOSE		RIS HIGH DOSE	
	N	Mean (SD)	N	Mean (SD) Diff. of LS Means (95% CI)
Sex				
Female	51	-14.5 (19.72)	59	-22.8 (25.88) -8.2 (-16.87;0.53)
Male	80	-11.2 (20.72)	65	-24.3 (19.85) -13.4 (-20.23;-6.55)***
Race#				
Non-White	20	-12.7 (19.16)	19	-30.6 (22.95) -17.0 (-31.76;-2.18)**
White	110	-12.7 (20.45)	103	-22.9 (22.50) -9.4 (-15.02;-3.80)*
Black	20	-12.7 (19.16)	17	-29.9 (24.16) -16.4 (-31.53;-1.23)*

In Study RIS-US-231, risperidone higher dose treatment group shows superior to ersatz placebo group in both gender groups and the efficacy size seems to be comparable between the two gender groups. Similarly, risperidone higher dose treatment group shows to be more effective than the ersatz placebo group in all three race groups the sponsor defined; however, Caucasian group shows the least effect size compared to the other two race groups.

6.1.5 Clinical Microbiology

Not applicable for this submission.

6.1.6 Efficacy Conclusions

The two acute efficacy studies show positive results: Risperidone treatment groups of 1–3mg/day and 4–6mg/day are more effective than placebo group; Risperidone 1.5–6mg/day is more effective than risperidone 0.15–0.6mg/day. The efficacy results have no significant differences in each gender or race groups in both studies except the Caucasian group seems to have the least effect size in Study RIS-USA-231.

Though the sponsor conducted efficacy demographic analysis, the ethnicity/race analysis only consists of two groups: White and Non-white, instead of analyzing based on five ethnic groups according to the WR.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The sponsor included the three above mentioned schizophrenia trials as safety database. Due to the design differences, pooled safety analysis is not performed. Safety data of the PK study (Study RIS-USA-160) are reviewed in the sNDA 20272-047, the application for using risperidone for treatment of bipolar 1 disorder in children and adolescents aged 10-17 years old.

7.1.1 Deaths

There was no treatment-emergent adverse event leading to death in the two controlled studies. However, there was one completed suicide in the open-label long term trial, Study RIS-USA-234. In this six-month open-label trial on children and adolescents with schizophrenia, one subject (#A36124) died from suicide after (b) (6) of open-label treatment. The following is the case summary provided by the sponsor:

"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."

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

Study RIS-SCH-302: The sponsor reports a total of two SAEs in this study, one in each risperidone treatment group and both of which were psychosis that were considered unrelated to the study medication (both happened while they were on risperidone 1mg/day). Subjects were hospitalized and treated with other antipsychotics.

Other two SAEs in this study were in the placebo group: One subject who had appendicitis, bowel motility disorder, peritonitis, and post-operative pain and another developed depression. No unexpected SAEs in this study.

Study RIS-USA-231: A total of nine subjects experienced psychosis and they were considered as serious events. Among them, one subject also had "cerebral oedema" (Subject #A35209) in the lower dose group of risperidone which was reviewed in the sponsor's previous submission on application of risperidone for treatment of irritability of autism and a consultation report on such case from OSE is in DFS. According to the sponsor, the same subject also was coded for suicide attempt for her suicide ideation. The subject withdrew from the study due to these events.

Study RIS-US-234: List of SAEs in this study is displayed in the table below provided by the sponsor.

Table 15. 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.
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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 Aug 21, 2003 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, he 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

Overall, all events that led to drop-out in the two controlled trials and the open-label trial are adverse effects that known to risperidone. Psychosis was the most common reason for discontinuation in all 3 studies.

7.1.3.2 Adverse events associated with dropouts

The next three tables summarize the AEs that associated with dropouts in each study in the clinical program.

Table 16. Adverse events associated with dropouts are summarized in the following table. Incidence of Treatment-Emergent Adverse Events with Action Taken of Permanent Stop (Study RIS-SCH-302, ITT Analysis Set)

AE System Organ Class Adverse Event Preferred Term	Placebo (N=54) n (%)	RIS 1-3 mg (N=55) n (%)	RIS 4-6 mg (N=51) n (%)	ALL RIS (N=106) n (%)
Total no. subjects with perm stop med	2 (4)	3 (5)	4 (8)	7 (7)
Psychiatric disorders	2 (4)	2 (4)	4 (8)	6 (6)
Somnolence	0	0	2 (4)	2 (2)
Anorexia	0	0	1 (2)	1 (1)
Anxiety	0	0	1 (2)	1 (1)
Psychosis	2 (4)	2 (4)	1 (2)	3 (3)
Centr & periph nervous system disorders	0	1 (2)	2 (4)	3 (3)
Ataxia	0	0	1 (2)	1 (1)
Dizziness	0	1 (2)	1 (2)	2 (2)
Cardiovascular disorders, general	0	0	1 (2)	1 (1)
Hypotension	0	0	1 (2)	1 (1)
Heart rate and rhythm disorders	0	0	1 (2)	1 (1)
Palpitation	0	0	1 (2)	1 (1)
Body as a whole - general disorders	1 (2)	0	0	0
Fever	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.

In this placebo-controlled study (RIS-SCH-302), the rate of discontinuation was higher in risperidone higher dose group (8%) than that in the lower dose (5%) and placebo (4%) dose groups. Subject #30064 in the risperidone higher dose group was discontinued from the study as he reportedly had "mild hypotension" and "somnolence."

Table 17. Incidence of Treatment-Emergent Adverse Events with Action Taken of Permanent Stop (Study RIS-SCH-231, ITT Analysis Set)

AE System Organ Class Adverse Event Preferred Term	RIS 0.15-0.6 mg (N=132) n (%)	RIS 1.5-6 mg (N=125) n (%)
Total no. subjects with perm stop med	6 (4.5)	5 (4.0)
Psychiatric disorders	4 (3.0)	3 (2.4)
Psychosis	3 (2.3)	2 (1.6)
Agitation	1 (0.8)	1 (0.8)
Insomnia	0	1 (0.8)
Suicide attempt[a]	1 (0.8)	0
Cardiovascular disorders, general	1 (0.8)	1 (0.8)
ECG abnormal	0	1 (0.8)
Hypertension	1 (0.8)	0
Centr & periph nervous system disorders	1 (0.8)	1 (0.8)
EEG abnormal	0	1 (0.8)
Oedema cerebral	1 (0.8)	0
Respiratory system disorders	0	1 (0.8)
Upper resp tract infection	0	1 (0.8)
Heart rate and rhythm disorders	1 (0.8)	0
Tachycardia	1 (0.8)	0
Liver and biliary system disorders	1 (0.8)	0
SGOT increased	1 (0.8)	0
SGPT increased	1 (0.8)	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events. [a] Verbatim term: suicidal ideation.
EEG= electroencephalogram.

Subject A34447 in Study RIS-USA-231 is a 13-year-old white female, with a diagnosis of paranoid schizophrenia and no other relevant history, was randomly assigned to treatment with high dose risperidone. No prior psychotropic medications were reported. On July 18, 2003 (Day 8 of the study and the day after she received risperidone 2 mg/day, subject's EEG showed abnormal (verbatim term, suspected seizure disorder [pathological changes in EEG]). Study medication was discontinued (last dose on Day 7), and the subject was given treatment with valproic acid 600 mg/day and olanzapine 15 mg/day. The investigator considered the abnormal EEG finding unrelated to the study drug. The subject had not yet recovered from this adverse event at end point. –It seems that the EEG change happened the day after the last dose. Reduced seizure threshold is a known AE of antipsychotics like risperidone.

Insomnia and upper respiratory tract infection are the two additional AEs that led to dropout in the higher dose group.

Subject A34307 is a 15-year-old Caucasian male, with a diagnosis of undifferentiated schizophrenia and no other relevant history. He was randomly assigned to the high-dose risperidone group after 32 days of treatment with risperidone (post-titration dose, 1.5 mg/day).

On [redacted] (b) (6) days after study drug treatment was stopped, the subject experienced increases in delusions and hallucinations and subsequently hospitalized for it two days later (verbatim term, psychotic decompensation). The subject's psychotic symptoms were reported to have eventually resolved on June 24, 2004. He was also reported with other AEs included ECG abnormal, fatigue, fever, headache, and nausea. He received paracetamol for headache, fever, and nausea. Study medication was stopped (last dose, [redacted] (b) (6)) due to the adverse event of ECG abnormal (verbatim term, sinusoidal arrhythmia), which started on November 3, 2003 and was reported to have resolved the same day. ECG results (see below) and the third-party evaluations of this subject's ECG findings were within normal limits at all evaluations:

Table 18. ECG Findings of Subject A34307

ECG parameter	Day –2 Baseline	Day 7 3 Nov 2003	Day 14 7 Nov 2003	Posttreatment 5 Dec 2003
PR interval (ms)	160	150	160	160
QRS interval (ms)	80	80	80	80
QT interval (ms)	360	330	380	320
QTcB (ms)	370	380	370	380
QTcF (ms)	370	360	380	360
QTcLD (ms)	369	370	375	370
Heart rate (bpm)	63	78	58	85

This subject's QTc don't seem to be prolonged.

The subject who had "cerebral oedema" was reviewed in the previous NDA and the case has been reviewed by OSE consultation (see OSE consult for details). No unexpected events in this study other wise.

Table 19. Incidence of Treatment-Emergent Adverse Events with Action Taken of Permanent Stop (Study RIS-USA-234; ITT 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[a]	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 nonpuerperal	0	1 (<1)	1 (<1)

There seem no unexpected adverse events that led to dropouts in this study as well.

7.1.3.3 Other significant adverse events

Somnolence and Fatigue: This analysis will focus on the placebo-controlled trial, Study RIS-SCH-302. Subjects who reported fatigue also reported somnolence in this study. The table below summarizes the incidences of these AEs in each treatment group.

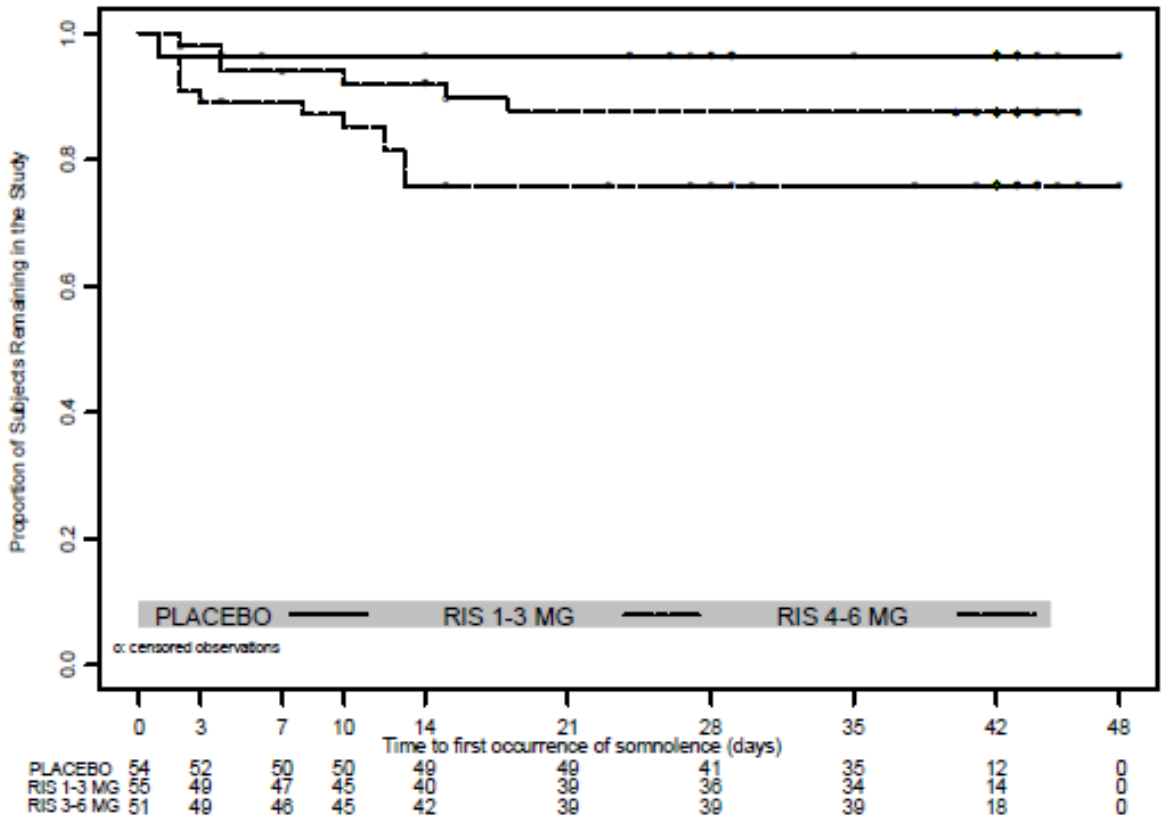
Table 20. Incidence of Treatment-Emergent Somnolence or Fatigue (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

Adverse Event Preferred Term	PLACEBO (N=54) n (%)	RIS 1-3 mg (N=55) n (%)	RIS 4-6 mg (N=51) n (%)
Total no. subjects with somnolence or fatigue	3 (6)	13 (24)	7 (14)
Somnolence	2 (4)	13 (24)	6 (12)
Fatigue	2 (4)	2 (4)	2 (4)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events..

The figure below illustrates the onset of somnolence in this study.

Figure 3. Time to First Occurrence of Somnolence – Kaplan-Meier Curve (Study RIS-SCH-302: Intent-to-Treat Analysis Set)



Subjects on higher doses of risperidone had significantly longer duration of somnolence than those on the lower doses of risperidone (see table below).

Table 21. Number of Days and Percentage of Total Duration with Somnolence (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

	--- PLACEBO --- (N=54)	-- RIS 1-3 mg - (N=55)	-- RIS 4-6 mg - (N=51)
Total days with somnolence			
N	2	13	6
Mean (SD)	3.0 (2.83)	13.3 (10.72)	19.3 (14.64)
Median	3.0	9.0	21.0
Range	(1;5)	(2;31)	(2;39)
% of total duration with somnolence			
N	2	13	6
Mean (SD)	8.1 (4.67)	42.1 (32.72)	57.4 (26.86)
Median	8.1	33.3	64.6
Range	(5;11)	(5;92)	(18;93)

No subjects discontinued the study due to fatigue but two subjects in the risperidone 4-6 mg group discontinued due to adverse events that included somnolence. Subject A30208, a 15-year-old female, discontinued treatment with 4 mg risperidone on Day 11 due to anorexia, ataxia, and somnolence (verbatim: lethargy and sedation). Another subject (A30064) is a 13-year-old male who experienced hypotension starting on Day 4 and somnolence starting on Day 5, while receiving 2 mg risperidone. He discontinued treatment on Day 8 due to these events.

The sponsor reports that the majority of subjects had recovered from adverse events of fatigue or somnolence by final study follow-up

7.1.4 Other Search Strategies

7.1.4.1 Suicide analysis

The sponsor searched any WHO-preferred term containing any of the following text strings: 'suicid', 'overdos', 'injury' or 'aggress'.

According to the sponsor, any verbatim term containing any of the following text strings were also searched: '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'.

Verbatim terms that contained one of the text strings above resulted in terms unrelated to suicidal behavior in any way (e.g., the search for 'gas' found verbatims with 'gastro' or 'gastric'; the search for 'poison' found 'poison ivy'; and so on) were identified as 'false positives' and assigned a score of 99.

Identified cases were categorized using Columbia Suicide Analysis.

The sponsor states no suicide attempt or ideation in the placebo-controlled trial, Study RIS-SCH-302. The sponsor reports that further search reveals two cases in placebo group that were categorized as "injury."

In Study RIS-USA-231, the analysis showed one subject who had suicide attempt in the ersatz placebo group and a total of five cases of "injury": Three in the ersatz placebo group and 2 in risperidone higher dose group. (See next table.)

The subject in ersatz placebo group was Subject A35209 who is a 17 year-old Caucasian female developed cerebral edema, psychosis, and suicide ideation during the study. The case was reported by the sponsor in a Safety Update of a previous sNDA submission. Issue of cerebral edema is also under OSE investigation and monitoring.

Table 22. Incidence of Suicide-Related Adverse Events Based on Columbia Suicide Analysis (STUDY RIS-USA-231: Intent-to-Treat Analysis Set)

Study Phase: TREATMENT

Columbia Score Adverse Event Preferred Term	RIS LOW DOSE (N=141) N (%)	RIS HIGH DOSE (N=138) n (%)
Total no. subjects with suicide-related AE	15 (10.6)	10 (7.2)
03 ACTIONS TOWARDS IMMINENT SUICIDAL BEHAVIOR	1 (0.7)	0
SUICIDE ATTEMPT	1 (0.7)	0
04 SELF-INJURIOUS BEHAVIOR, INTENT UNKNOWN	3 (2.1)	2 (1.4)
AGGRESSIVE REACTION	0	1 (0.7)
INFLICTED INJURY	3 (2.1)	1 (0.7)
08 OTHER: ACCIDENT	10 (7.1)	8 (5.8)
ABRASION NOS	1 (0.7)	0
BURN	1 (0.7)	0
INJURY	8 (5.7)	5 (3.6)
PAIN	0	1 (0.7)
PURPURA	2 (1.4)	2 (1.4)
TOOTH DISORDER	1 (0.7)	0
09 OTHER: PSYCHIATRIC	2 (1.4)	1 (0.7)
AGGRESSIVE REACTION	1 (0.7)	1 (0.7)
INJURY	1 (0.7)	0

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Study RIS-USA-234 is a 6-month open-label extension study. According to the sponsor, "there were 16 reports of adverse events coded to suicide attempt with onset during the open-label study or within 4 days of the last dose of study medication in the study: 2 (5%) of 41 subjects previously treated with placebo and 14 (5%) of 256 subjects previously treated with risperidone. Of the 16 subjects, 7 subjects had suicidal ideation, thoughts or tendencies with no suicide attempt, and 9 subjects attempted suicide, one of which resulted in death. These events were considered serious in 14 subjects and resulted in study discontinuation for 6 subjects."

7.1.4.2 EPS-Related AEs

Rating scales for EPS, including AIMS[1], SAS[2], and BARS[3], were applied at Screening, Baseline, Day 8, 15, 29, and 43 or Endpoint/early termination. Changes of overall scores of these scales from baseline to endpoint are provided by the sponsor in the next three tables.
1) Dyskinetic symptoms were evaluated using the AIMS and mean total severity scores are summarized below:

Table 23. AIMS Total Score - Change From Baseline to End Point (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Total severity score			
Treatment			
N	54	54	50
Mean baseline (SD)	0.61 (1.867)	0.44 (1.586)	0.22 (1.075)
Mean change (SD)	-0.31 (1.398)	0.09 (1.964)	0.16 (1.419)

Note: Higher score indicates worse condition. N is the number of subjects with both baseline and end point values for the parameter.

2) Parkinsonism symptoms were evaluated using the SAS. Mean score changes are summarized below:

Table 24. SAS Total Score - Change From Baseline to End Point (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

Higher Score Indicates Worse Condition	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Total			
Treatment			
N	54	54	50
Mean baseline (SD)	0.05 (0.184)	0.03 (0.095)	0.02 (0.084)
Mean change (SD)	-0.01 (0.087)	0.03 (0.152)	0.10 (0.278)

Note: Higher score indicates worse condition. N is the number of subjects with both baseline and end point values for the parameter.

3) Akathisia symptoms were evaluated using the BARS. The global clinical rating of akathisia is summarized in the following table.

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

Table 25. BARS Global Clinical Rating Frequency Distribution at End Point (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

Parameter Analysis Phase Time Interval Value Description	PLACEBO n (%)	RIS 1-3 mg n (%)	RIS 4-6 mg n (%)
Global clinical rating of akathisia			
Treatment			
Baseline	54	55	51
0	52 (96)	53 (96)	46 (90)
1	1 (2)	1 (2)	4 (8)
2	1 (2)	1 (2)	1 (2)
3	0	0	0
4	0	0	0
5	0	0	0
End Point	54	54	50
0	52 (96)	49 (91)	45 (90)
1	1 (2)	4 (7)	4 (8)
2	1 (2)	1 (2)	1 (2)
3	0	0	0
4	0	0	0
5	0	0	0

Note: Higher score indicates worse condition. Percentages calculated with the number of subjects per time interval as denominator.

Clinically, the sponsor reports that no EPS-related adverse event was considered serious or led to discontinuation from the placebo-controlled study. The table below displays the incidence of treatment-emergent EPS-related AEs by group term.

Table 26. Incidence of Treatment-Emergent EPS-Related Adverse Events by Grouped Term (Study RIS-SCH-302, ITT Analysis Set)

Grouped Term Adverse Event Preferred Term	Placebo (N=54) n (%)	RIS 1–3 mg (N=55) n (%)	RIS 4–6 mg (N=51) n (%)
Total no. subjects with at least one EPS-related adverse event	8 (15)	18 (33)	20 (39)
Dystonia	4 (7)	5 (9)	9 (18)
Hypertonia	4 (7)	3 (5)	7 (14)
Dystonia	0	1 (2)	2 (4)
Oculogyric crisis	0	1 (2)	1 (2)
Parkinsonism	3 (6)	7 (13)	8 (16)
Extrapyramidal disorder	2 (4)	5 (9)	8 (16)
Hypokinesia	1 (2)	2 (4)	0
Akathisia	3 (6)	4 (7)	5 (10)
Hyperkinesia	3 (6)	4 (7)	5 (10)
Tremor	3 (6)	6 (11)	5 (10)
Tremor	3 (6)	6 (11)	5 (10)
Dyskinesia	0	1 (2)	0
Dyskinesia	0	1 (2)	0

The sponsor also reports that no reports of tardive dyskinesia (TD). However, this study is only 6-week long and technically only 5 weeks after target dosage was reached. Thus, by definition, diagnosis of TD wouldn't be able to be made. Not having reports in the study doesn't mean it will not appear if the study lasted longer.

Similarly, the sponsor states no reports of tardive dyskinesia in Study RIS-USA-231. This study lasted 8 weeks only and subjects were given targeted dosage for 7 weeks. In the next table, the sponsor shows the incidence of treatment-emergent EPS-related AEs based on different dosages in this ersatz placebo controlled trial. Most of these symptoms are clearly dose-related.

Table 27. Incidence of Treatment-Emergent EPS-Related Adverse Events by Grouped Term (RIS USA-231, MITT Analysis Set)

	RIS 0.15–0.6 mg			RIS 1.5–6 mg		
Grouped Term Adverse Event Preferred Term	Total (N = 132) n (%)	< 0.35 mg (N=29) n (%)	≥ 0.35 mg (N=103) n (%)	Total (N =125) n (%)	< 3.5 mg (N=37) n (%)	≥ 3.5 mg (N=88) n (%)
Total no. subjects with at least one EPS-related adverse event	13 (9.8)	3 (10.3)	10 (9.7)	41 (32.8)	7 (18.9)	34 (38.6)
Dystonia	8 (6.1)	2 (6.9)	6 (5.8)	23 (18.4)	3 (8.1)	20 (22.7)
Hypertonia	6 (4.5)	2 (6.9)	4 (3.9)	18 (14.4)	2 (5.4)	16 (18.2)
Dystonia	1 (0.8)	0	1 (1.0)	5 (4.0)	1 (2.7)	4 (4.5)
Muscle contractions involuntary	2 (1.5)	0	2 (1.9)	1 (0.8)	0	1 (1.1)
Oculogyric crisis	0	0	0	1 (0.8)	0	1 (1.1)
Tremor	4 (3.0)	1 (3.4)	3 (2.9)	13 (10.4)	1 (2.7)	12 (13.6)
Tremor	4 (3.0)	1 (3.4)	3 (2.9)	13 (10.4)	1 (2.7)	12 (13.6)
Akathisia	2 (1.5)	0	2 (1.9)	11 (8.8)	1 (2.7)	10 (11.4)
Hyperkinesia	2 (1.5)	0	2 (1.9)	11 (8.8)	1 (2.7)	10 (11.4)
Dyskinesia	2 (1.5)	0	2 (1.9)	7 (5.6)	2 (5.4)	5 (5.7)
Dyskinesia	2 (1.5)	0	2 (1.9)	7 (5.6)	2 (5.4)	5 (5.7)
Parkinsonism	0	0	0	5 (4.0)	0	5 (5.7)
Extrapyramidal disorder	0	0	0	5 (4.0)	0	5 (5.7)

The only long-term study lasted over 3 months is an open-label study. Again, the sponsor reports that no incidences of EPS-related AEs were considered serious; however, these AEs did result in 3 dropouts: 2 extrapyramidal disorder and 1 dystonia. A total of 13 (4%) subjects reported dyskinesia. Dose reduction was necessary for 5 subjects and 6 subjects required administration of concomitant therapy. Nonetheless, the sponsor reassures, "Adverse events of dyskinesia were closely examined, and none fit the characteristic profile of tardive dyskinesia."

Increase of incidences of dyskinesia and ocular manifestation of EPS was reported in some of the sponsor's monthly postmarketing reports (see section of Postmarketing Experience), but the sponsor also reports that no disproportionality of tardive dyskinesia or overall EPS in pediatric patients compared to groups of other ages in the cumulative reports.

In the literature search (see subsection 7.1.13 on Literature Search), however, there have been two new cases since last review of sNDA for treatment of irritability associated with autism about 3 years ago, which is 50% increase.

7.1.4.3 Prolactin-Related AEs

Serum prolactin levels are significantly increased in risperidone treatment groups and they are dose-dependent. (See subsection of clinical chemistry for details.)

The sponsor reports that there were no potentially prolactin-related treatment-emergent adverse

events in the placebo-controlled trial (Study RIS-SCH-302). Nevertheless, there are a few cases in the ersatz placebo controlled study and are summarized by the sponsor in the following table.

Table 28. Incidence of Treatment-Emergent Prolactin-Related Adverse Events by Sex – MITT (JNJPRD--TRIAL RIS-USA-231: Modified Intent-to-Treat Analysis Set)

	RIS 0.15–0.6 mg			RIS 1.5–6 mg		
Adverse Event System Organ Class Adverse Event Preferred Term	Total (N=132) n (%)	Female (N=52) n (%)	Male (N=80) n (%)	Total (N=125) n (%)	Female (N=60) n (%)	Male (N=65) n (%)
Total no. subjects with Prolactin-related adverse events	2 (1.5)	1 (1.9)	1 (1.3)	7 (5.6)	5 (8.3)	2 (3.1)
Reproductive disorders, female	1 (0.8)	1 (1.9)	0	5 (4.0)	4 (6.7)	1 (1.5)
Lactation nonpuerperal	1 (0.8)	1 (1.9)	0	3 (2.4)	3 (5.0)	0
Amenorrhoea	0	0	0	1 (0.8)	1 (1.7)	0
Breast pain[a] female	0	0	0	1 (0.8)	0	1 (1.5)
Endocrine disorders	1 (0.8)	0	1 (1.3)	3 (2.4)	1 (1.7)	2 (3.1)
Hyperprolactinaemia	0	0	0	2 (1.6)	1 (1.7)	1 (1.5)
Gynaecomastia	1 (0.8)	0	1 (1.3)	1 (0.8)	0	1 (1.5)

[a]This case was actually reported for a male subject instead of female.

It is unclear whether the incidences were justified by gender. According to the sponsor, none of the potentially prolactin-related adverse events were serious and none led to discontinuation of study treatment. Still, one subject (#A34362) in the risperidone high-dose treatment group had increased prolactin level from a baseline value of 10.03 ng/mL to 92.44 and 97.34 ng/mL at Days 28 and 56 (end point). All cases of amenorrhea, breast pain female, hyperprolactinemia, and gynecomastia and 3/4 cases of lactation nonpuerperal had not resolved at the end of the study. The study drug dosage was adjusted due to lactation nonpuerperal (high-dose group) in 2 subjects and gynecomastia and breast pain in 1 subject.

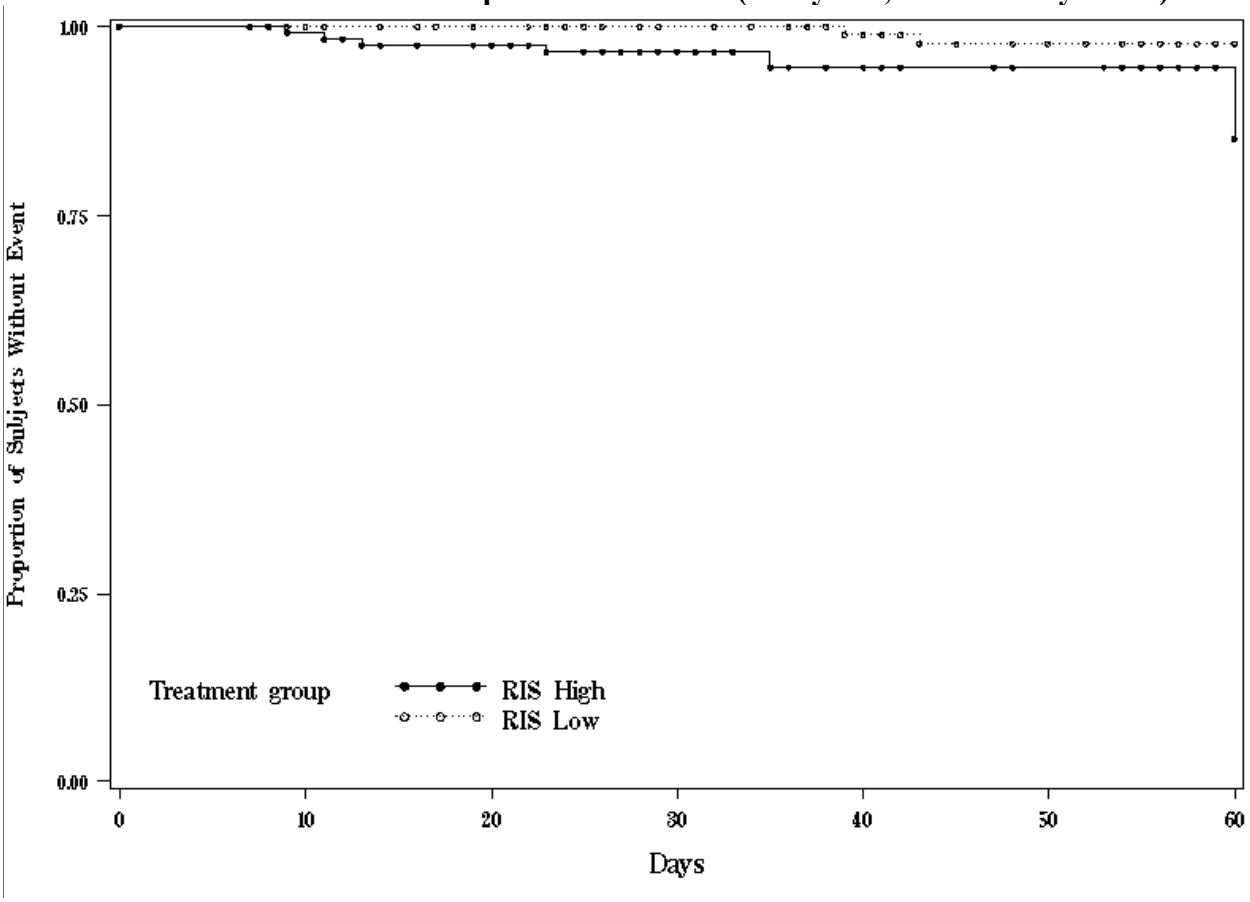
In the following table, the sponsor explored these incidences by artificially selected dosage groups.

Table 29. Incidence of Treatment-Emergent Prolactin-Related Adverse Events by Treatment Subgroups (Study RIS-USA-231, MITT)

AEs System Organ Class Adverse Event Preferred Term	RIS low <0.35mg (N=29) n (%)	RIS low >=0.35mg (N=103) n (%)	RIS high <3.5mg (N=37) n (%)	RIS high >=3.5mg (N=88) n (%)
Total subjects with AEs	1 (3.4)	1 (1.0)	2 (5.4)	5 (5.7)
Reproductive disorders, female	1 (3.4)	0	2 (5.4)	3 (3.4)
Lactation nonpuerperal	1 (3.4)	0	1 (2.7)	2 (2.3)
Amenorrhea	0	0	0	1 (1.1)
Breast pain female	0	0	1 (2.7)	0
Endocrine disorders	0	1 (1.0)	1 (2.7)	2 (2.3)
Hyperprolactinemia	0	0	0	2 (2.3)
Gynecomastia	0	1 (1.0)	1 (2.7)	0

Most of these adverse events started after at least 2 weeks of treatment (see figure x. below).

Figure 4. Time to First Occurrence of Treatment-Emergent, Potentially Prolactin Related Adverse Events – Kaplan-Meier Curve (Study 231, MITT Analysis Set)



7.1.4.4 Glucose-Metabolism

The sponsor reports that there were no glucose metabolism-related treatment-emergent adverse events in the two controlled studies and the 6-month open-label study.

7.1.4.5 Weight Gain and BMI

(See Section 7.1.15 Assessment of Effect on Growth for details.)

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

As stated before that since Study RIS-SCH-302 is a placebo-controlled study while Study RIS-USA-231 is an ersatz-controlled study, review of common adverse events is based on data from RIS-SCH-302.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were collected from the subjects' report (or, when appropriate, from a caregiver, surrogate, or the subject's legally acceptable representative) throughout the study. The sponsor used WHOART as coding dictionary. No significant error or inappropriateness in coding of verbatim to preferred terms of Study RIS-SCH-302.

7.1.5.3 Incidence of common adverse events

The sponsor provides the table (see the next subsection 7.1.5.4) which displays incidences of adverse events that are at least 5% in any treatment group.

7.1.5.4 Common adverse event tables

Table 30. Incidences of Adverse Events that Are ≥ 5% in Any Treatment Group (Study RIS-SCH-302)

Adverse Event System Organ Class Adverse Event Preferred Term	Placebo (N=54) n (%)	RIS 1–3 mg (N=55) n (%)	RIS 4–6 mg (N=51) N (%)	All RIS (N=106) n (%)
Total no. subjects with adverse events	29 (54)	41 (75)	39 (76)	80 (75)
Central and peripheral nervous system disorders	16 (30)	26 (47)	26 (51)	52 (49)
Extrapyramidal disorder	2 (4)	5 (9)	8 (16)	13 (12)
Dizziness	1 (2)	4 (7)	7 (14)	11 (10)
Hypertonia	4 (7)	3 (5)	7 (14)	10 (9)
Headache	10 (19)	7 (13)	5 (10)	12 (11)
Hyperkinesia	3 (6)	4 (7)	5 (10)	9 (8)
Tremor	3 (6)	6 (11)	5 (10)	11 (10)
Psychiatric disorders	12 (22)	21 (38)	15 (29)	36 (34)
Somnolence	2 (4)	13 (24)	6 (12)	19 (18)
Agitation	4 (7)	8 (15)	4 (8)	12 (11)
Insomnia	5 (9)	4 (7)	4 (8)	8 (8)
Anxiety	0	4 (7)	3 (6)	7 (7)
Gastrointestinal system disorders	10 (19)	8 (15)	10 (20)	18 (17)
Saliva increased	1 (2)	0	5 (10)	5 (5)
Nausea	4 (7)	1 (2)	3 (6)	4 (4)
Vomiting	4 (7)	2 (4)	2 (4)	4 (4)
Heart rate and rhythm disorders	3 (6)	3 (5)	4 (8)	7 (7)
Tachycardia	3 (6)	3 (5)	2 (4)	5 (5)
Respiratory system disorders	5 (9)	7 (13)	4 (8)	11 (10)
Pharyngitis	2 (4)	3 (5)	2 (4)	5 (5)

7.1.5.5 Identifying common and drug-related adverse events

Based on the above table, incidences of adverse events that are at least 5% in any treatment group and with rates that are twice of that in placebo group are summarized below:

Table 31. Common Drug-Related Adverse Events in Study RIS-SCH-302

Subject N / Adverse Events	Placebo	RIS 1-3 mg	RIS 4-6 mg	All RIS
	54	55	51	106
Extrapyramidal disorder	2 (4)	5 (9)	8 (16)	13 (12)
Dizziness	1 (2)	4 (7)	7 (14)	11 (10)
Hypertonia	4 (7)	3 (5)	7 (14)	10 (9)
Somnolence	2 (4)	13 (24)	6 (12)	19 (18)
Agitation	4 (7)	8 (15)	4 (8)	12 (11)
Anxiety	0	4 (7)	3 (6)	7 (7)
Saliva Increased	1 (2)	0	5 (10)	5 (5)

7.1.5.6 Additional analyses and explorations

Incidences of extrapyramidal disorder, dizziness, hypertonia, and increased saliva are clearly much higher in the risperidone higher dose group than those in the lower dose group. They are obviously dose dependent. Interestingly, somnolence and agitation are much more common in the risperidone lower dose group. While it is easy to understand decreased agitation with increased dose, the reason for lower incidence of somnolence with increased dose is unclear. Incidences of anxiety are comparable in both treatment groups and are clearly treatment-related.

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 13–15 and16–17 year-old) except for odds ratio of "hyperkinesia" being significantly different in risperidone lower dose group (p=0.049).

Gender: Odds ratio of "dizziness" seems to be significantly different in risperidone lower dose group (p=0.042). No other significant imbalance of odds ratio between the gender groups observed.

Ethnicity: Similarly, odds ratio of "dizziness" appears to be significantly different in risperidone higher dose group (p=0.042) and no other significant imbalance of odds ration among the 5 ethnic groups.

7.1.6 Less Common Adverse Events

Table 32. Incidence of Treatment-Emergent Adverse Events With ≥2% Incidence During Risperidone Open-Label Treatment (JNJPRD--TRIAL RIS-USA-234: Intent-to-Treat Analysis Set)

AE System Organ Class Adverse Event Preferred Term	PLACEBO (N=54) n (%)	RIS 1-3 MG (N=55) n (%)	RIS 4-6 MG (N=51) n (%)	ALL RIS (N=106) n (%)
Total no. subjects with adverse events	29 (53.7)	41 (74.5)	39 (76.5)	80 (75.5)
Centr & periph nervous system disorders	16 (29.6)	26 (47.3)	26 (51.0)	52 (49.1)
Extrapyramidal disorder	2 (3.7)	5 (9.1)	8 (15.7)	13 (12.3)
Dizziness	1 (1.9)	4 (7.3)	7 (13.7)	11 (10.4)
Hypertonia	4 (7.4)	3 (5.5)	7 (13.7)	10 (9.4)
Headache	10 (18.5)	7 (12.7)	5 (9.8)	12 (11.3)
Hyperkinesia	3 (5.6)	4 (7.3)	5 (9.8)	9 (8.5)
Tremor	3 (5.6)	6 (10.9)	5 (9.8)	11 (10.4)
Dystonia	0	1 (1.8)	2 (3.9)	3 (2.8)
Ataxia	0	0	1 (2.0)	1 (0.9)
Oculogyric crisis	0	1 (1.8)	1 (2.0)	2 (1.9)
Hypokinesia	1 (1.9)	2 (3.6)	0	2 (1.9)
Psychiatric disorders	12 (22.2)	21 (38.2)	15 (29.4)	36 (34.0)
Somnolence	2 (3.7)	13 (23.6)	6 (11.8)	19 (17.9)
Agitation	4 (7.4)	8 (14.5)	4 (7.8)	12 (11.3)
Insomnia	5 (9.3)	4 (7.3)	4 (7.8)	8 (7.5)
Anxiety	0	4 (7.3)	3 (5.9)	7 (6.6)
Anorexia	0	1 (1.8)	1 (2.0)	2 (1.9)
Depression	1 (1.9)	0	1 (2.0)	1 (0.9)
Nervousness	0	0	1 (2.0)	1 (0.9)
Psychosis	2 (3.7)	2 (3.6)	1 (2.0)	3 (2.8)
Gastro-intestinal system disorders	10 (18.5)	8 (14.5)	10 (19.6)	18 (17.0)
Saliva increased	1 (1.9)	0	5 (9.8)	5 (4.7)
Nausea	4 (7.4)	1 (1.8)	3 (5.9)	4 (3.8)
Vomiting	4 (7.4)	2 (3.6)	2 (3.9)	4 (3.8)
Dyspepsia	2 (3.7)	2 (3.6)	1 (2.0)	3 (2.8)
Mouth dry	0	1 (1.8)	1 (2.0)	2 (1.9)
Tooth ache	0	0	1 (2.0)	1 (0.9)
Abdominal pain	1 (1.9)	2 (3.6)	0	2 (1.9)
Body as a whole - general disorders	11 (20.4)	7 (12.7)	5 (9.8)	12 (11.3)
Fatigue	2 (3.7)	2 (3.6)	2 (3.9)	4 (3.8)
Fever	1 (1.9)	2 (3.6)	1 (2.0)	3 (2.8)

Hot flushes	0	0	1 (2.0)	1 (0.9)
Lab values abnormal	1 (1.9)	0	1 (2.0)	1 (0.9)
Pain	1 (1.9)	0	1 (2.0)	1 (0.9)
Back pain	1 (1.9)	2 (3.6)	0	2 (1.9)
Heart rate and rhythm disorders	3 (5.6)	3 (5.5)	4 (7.8)	7 (6.6)
Tachycardia	3 (5.6)	3 (5.5)	2 (3.9)	5 (4.7)
Bradycardia	0	0	1 (2.0)	1 (0.9)
Palpitation	0	0	1 (2.0)	1 (0.9)
Respiratory system disorders	5 (9.3)	7 (12.7)	4 (7.8)	11 (10.4)
Pharyngitis	2 (3.7)	3 (5.5)	2 (3.9)	5 (4.7)
Rhinitis	1 (1.9)	2 (3.6)	2 (3.9)	4 (3.8)
Dyspnoea	0	0	1 (2.0)	1 (0.9)
Coughing	1 (1.9)	2 (3.6)	0	2 (1.9)
Upper resp tract infection	0	2 (3.6)	0	2 (1.9)
Skin and appendages disorders	1 (1.9)	2 (3.6)	2 (3.9)	4 (3.8)
Dermatitis	0	0	1 (2.0)	1 (0.9)
Furunculosis	0	0	1 (2.0)	1 (0.9)
Cardiovascular disorders, general	1 (1.9)	1 (1.8)	1 (2.0)	2 (1.9)
Hypotension	0	0	1 (2.0)	1 (0.9)
Platelet,bleeding & clotting disorders	2 (3.7)	0	1 (2.0)	1 (0.9)
Epistaxis	2 (3.7)	0	1 (2.0)	1 (0.9)
Reproductive disorders, male	0	0	1 (2.0)	1 (0.9)
Balanoposthitis	0	0	1 (2.0)	1 (0.9)
Urinary system disorders	1 (1.9)	1 (1.8)	1 (2.0)	2 (1.9)
Face oedema	0	1 (1.8)	1 (2.0)	2 (1.9)
Musculo-skeletal system disorders	2 (3.7)	2 (3.6)	0	2 (1.9)
Myalgia	0	2 (3.6)	0	2 (1.9)

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing includes clinical chemistry panel, hematology, and urinalysis.

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

Review of laboratory testing data is based on the placebo trial, Study RIS-SCH-302.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Hematology

Table 33. Hematology - Change from Baseline to End Point (Study RIS-SCH-302: Intent-to-Treat Analysis Set, per the Sponsor)

	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Basophils (%)			
Treatment			
N	51	50	47
Mean baseline (SD)	0.65 (0.568)	0.49 (0.446)	0.64 (0.544)
Mean change (SD)	-0.07 (0.532)	0.09 (0.537)	-0.02 (0.589)
Eosinophils (%)			
Treatment			
N	51	50	47
Mean baseline (SD)	5.62 (7.232)	3.19 (3.263)	5.21 (6.524)
Mean change (SD)	-0.76 (2.865)	0.54 (3.791)	-0.12 (2.900)
Hematocrit (vol-%)			
Treatment			
N	50	49	45
Mean baseline (SD)	42.42 (5.265)	43.04 (3.851)	44.11 (3.803)
Mean change (SD)	-0.26 (2.841)	-1.00 (4.067)	-1.40 (3.299)
Hemoglobin (g/L)			
Treatment			
N	51	50	47
Mean baseline (SD)	138.24 (17.995)	139.56 (12.115)	142.85 (13.033)
Mean change (SD)	-1.78 (8.312)	-2.64 (13.234)	-3.70 (9.189)
Lymphocytes (%)			
Treatment			
N	51	50	47
Mean baseline (SD)	32.67 (9.241)	29.43 (7.926)	30.30 (8.775)
Mean change (SD)	-1.99 (10.018)	0.40 (10.502)	0.12 (9.296)
Monocytes (%)			
Treatment			
N	51	50	47
Mean baseline (SD)	6.02 (2.242)	5.64 (2.115)	6.07 (1.572)
Mean change (SD)	-0.24 (1.883)	0.10 (2.248)	-0.14 (1.758)

Neutrophils (%)

Treatment			
N	51	50	47
Mean baseline (SD)	55.04 (11.304)	61.05 (8.758)	57.76 (9.829)
Mean change (SD)	3.06 (11.309)	-0.92 (11.688)	0.17 (9.688)

Nonsegm neutrophils (%)

Treatment			
N	21	17	17
Mean baseline (SD)	0.00 (0.000)	0.29 (0.985)	0.00 (0.000)
Mean change (SD)	0.00 (0.000)	-0.29 (0.985)	0.00 (0.000)

Platelet count (giga/l)

Treatment			
N	51	49	47
Mean baseline (SD)	286.96 (66.546)	274.31 (75.358)	280.15 (82.554)
Mean change (SD)	-8.33 (61.846)	1.49 (68.474)	-26.11 (57.274)

RBC (tera/l)

Treatment			
N	51	50	47
Mean baseline (SD)	4.95 (0.668)	4.78 (0.480)	5.07 (0.547)
Mean change (SD)	-0.04 (0.381)	-0.06 (0.356)	-0.12 (0.361)

WBC (giga/l)

Treatment			
N	51	50	47
Mean baseline (SD)	7.15 (2.278)	7.80 (2.763)	7.28 (2.535)
Mean change (SD)	0.16 (2.315)	-0.15 (2.765)	-0.74 (2.180)

Note: N is the number of subjects with both baseline and end point values for the parameter.
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Clinical Chemistry

Table 34. Clinical Chemistry - Change from Baseline to End Point (Study RIS-SCH-302: Intent-to-Treat Analysis Set

	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Albumin (g/L)			
Treatment			
N	53	51	47
Mean baseline (SD)	44.00 (3.913)	45.18 (3.497)	45.15 (3.659)
Mean change (SD)	-0.30 (3.285)	-0.45 (3.300)	-0.87 (3.385)
Alkaline phosphatase (U/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	159.15 (94.918)	126.06 (61.820)	149.56 (87.962)
Mean change (SD)	-1.38 (30.151)	-0.78 (20.983)	-12.17 (24.357)
ALT (SGPT) (U/L)			
Treatment			
N	53	51	47
Mean baseline (SD)	21.42 (14.178)	21.76 (15.070)	21.96 (18.067)
Mean change (SD)	-1.04 (13.752)	1.65 (13.483)	-3.51 (17.213)
AST (SGOT) (U/L)			
Treatment			
N	52	51	47
Mean baseline (SD)	26.10 (10.823)	23.78 (7.682)	25.36 (10.307)
Mean change (SD)	-1.37 (11.771)	0.22 (7.852)	-2.66 (9.494)
Bicarbonate (mmol/L)			
Treatment			
N	53	51	47
Mean baseline (SD)	23.73 (2.264)	23.37 (2.442)	24.17 (2.657)
Mean change (SD)	-1.24 (2.743)	-0.29 (2.945)	-1.12 (2.864)
BUN (mmol/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	3.74 (1.117)	3.71 (1.123)	3.77 (1.119)
Mean change (SD)	-0.22 (1.032)	-0.44 (0.854)	-0.11 (1.169)

Calcium (mmol/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	2.43 (0.145)	2.46 (0.132)	2.47 (0.134)
Mean change (SD)	-0.02 (0.140)	-0.02 (0.109)	-0.04 (0.131)
Chloride (mmol/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	102.60 (2.444)	103.06 (1.984)	102.54 (2.021)
Mean change (SD)	0.87 (2.774)	-0.04 (2.289)	0.98 (2.392)
Cholesterol (mmol/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	4.16 (1.022)	4.20 (1.088)	4.16 (0.788)
Mean change (SD)	-0.09 (0.600)	0.10 (0.777)	-0.11 (0.542)
Creatine kinase (U/L)			
Treatment			
N	53	50	47
Mean baseline (SD)	156.70 (133.459)	140.60 (124.409)	139.09 (102.696)
Mean change (SD)	-12.11 (165.254)	-4.80 (144.497)	-20.60 (83.900)
Creatinine (umol/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	66.64 (13.977)	66.71 (12.727)	69.38 (11.334)
Mean change (SD)	-0.43 (9.031)	-1.37 (7.992)	3.19 (9.762)
FSH (U/L)			
Treatment			
N	17	22	13
Mean baseline (SD)	4.62 (2.771)	5.68 (4.307)	5.64 (2.191)
Mean change (SD)	0.07 (4.109)	-0.18 (3.879)	-0.37 (2.356)

GGT (U/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	16.15 (7.451)	17.75 (9.917)	18.33 (8.845)
Mean change (SD)	-0.43 (4.834)	-0.04 (7.296)	-1.73 (5.530)
Glucose (mmol/L)			
Treatment			
N	53	50	46
Mean baseline (SD)	5.20 (0.673)	5.11 (0.496)	5.03 (0.602)
Mean change (SD)	-0.16 (0.652)	-0.08 (0.744)	0.26 (0.874)
Lactate dehydrogenase (U/L)			
Treatment			
N	50	51	48
Mean baseline (SD)	186.82 (38.933)	171.24 (37.331)	174.85 (45.871)
Mean change (SD)	-2.96 (26.526)	-4.90 (27.910)	-12.83 (29.837)
Luteinizing hormone (U/L)			
Treatment			
N	18	21	12
Mean baseline (SD)	6.96 (10.389)	11.01 (9.171)	7.07 (7.467)
Mean change (SD)	0.99 (13.920)	-1.31 (9.149)	-1.67 (7.156)
Phosphorus (mmol/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	1.32 (0.237)	1.32 (0.253)	1.33 (0.245)
Mean change (SD)	0.02 (0.200)	0.00 (0.251)	0.07 (0.245)
Potassium (mmol/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	4.40 (0.365)	4.41 (0.375)	4.34 (0.329)
Mean change (SD)	-0.11 (0.436)	-0.11 (0.456)	-0.10 (0.329)

	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Prolactin (ng/mL)			
Treatment			
N	50	52	43
Mean baseline (SD)	22.63 (22.766)	29.75 (38.334)	24.13 (22.319)
Mean change (SD)	-5.32 (24.434)	25.65 (34.289)	40.63 (45.611)
Sodium (mmol/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	140.36 (2.442)	141.45 (2.501)	141.44 (2.592)
Mean change (SD)	0.53 (2.715)	-0.14 (3.131)	-0.73 (3.331)
Testosterone (nmol/L)			
Treatment			
N	30	27	29
Mean baseline (SD)	13.43 (5.474)	14.32 (5.591)	15.48 (7.653)
Mean change (SD)	1.08 (5.223)	-0.82 (5.750)	-3.19 (6.988)
Total bilirubin (umol/L)			
Treatment			
N	51	46	47
Mean baseline (SD)	10.96 (6.007)	10.93 (6.668)	10.32 (4.621)
Mean change (SD)	0.10 (4.410)	-0.87 (4.014)	0.04 (4.530)
Total protein (g/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	77.66 (4.871)	77.51 (4.351)	77.92 (5.307)
Mean change (SD)	-1.08 (5.352)	-0.57 (3.936)	-2.25 (5.241)
Triglycerides (mmol/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	1.41 (1.057)	1.45 (0.926)	1.26 (0.766)
Mean change (SD)	-0.19 (0.650)	-0.12 (0.924)	-0.07 (0.746)
Uric acid (umol/L)			
Treatment			
N	53	51	48
Mean baseline (SD)	322.40 (86.408)	314.55 (76.834)	324.88 (75.038)
Mean change (SD)	-2.08 (66.577)	1.96 (49.733)	15.50 (52.398)

Note: N is the number of subjects with both baseline and end point values for the parameter.

Urinalysis

The sponsor reports "no remarkable findings within the urinalysis results."

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 35. Hematology - Percentage of Subjects Within Potentially Clinically Important Limits at Baseline and Outside Post-Baseline (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

Lab Test Normal at Baseline	Category	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Albumin (g/L)	Below	0/53 (0.0)	0/51 (0.0)	0/47 (0.0)
	Above	0/53 (0.0)	0/51 (0.0)	0/47 (0.0)
Alkaline phosphatase (U/L)	Below	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
	Above	0/53 (0.0)	1/51 (2.0)	0/48 (0.0)
ALT (SGPT) (U/L)	Below	0/52 (0.0)	0/50 (0.0)	0/46 (0.0)
	Above	1/52 (1.9)	1/50 (2.0)	3/46 (6.5)
AST (SGOT) (U/L)	Below	0/52 (0.0)	0/51 (0.0)	0/47 (0.0)
	Above	1/52 (1.9)	0/51 (0.0)	2/47 (4.3)
Bicarbonate (mmol/L)	Below	0/53 (0.0)	0/50 (0.0)	0/46 (0.0)
	Above	0/53 (0.0)	0/50 (0.0)	1/46 (2.2)
Blood urea nitrogen (mmol/L)	Below	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
	Above	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
Calcium (mmol/L)	Below	1/53 (1.9)	1/51 (2.0)	0/48 (0.0)
	Above	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
Chloride (mmol/L)	Below	0/53 (0.0)	0/51 (0.0)	1/48 (2.1)
	Above	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
Cholesterol (mmol/L)	Below	4/51 (7.8)	1/49 (2.0)	2/48 (4.2)
	Above	0/51 (0.0)	0/49 (0.0)	0/48 (0.0)
Creatine kinase (U/L)	Below	0/52 (0.0)	0/50 (0.0)	0/46 (0.0)
	Above	1/52 (1.9)	1/50 (2.0)	0/46 (0.0)
Creatinine (umol/L)	Below	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
	Above	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
GGT (U/L)	Below	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
	Above	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
Glucose (mmol/L)	Below	0/53 (0.0)	1/49 (2.0)	0/46 (0.0)
	Above	1/53 (1.9)	1/49 (2.0)	2/46 (4.3)

Lactate dehydrogenase (U/L)	Below	0/50 (0.0)	0/51 (0.0)	0/48 (0.0)
	Above	0/50 (0.0)	0/51 (0.0)	0/48 (0.0)
Phosphorus (mmol/L)	Below	1/53 (1.9)	0/49 (0.0)	0/46 (0.0)
	Above	5/53 (9.4)	2/49 (4.1)	2/46 (4.3)
Potassium (mmol/L)	Below	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
	Above	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
Prolactin (ng/mL)	Below	0/49 (0.0)	0/49 (0.0)	0/42 (0.0)
	Above	1/49 (2.0)	3/49 (6.1)	5/42 (11.9)
Sodium (mmol/L)	Below	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
	Above	0/53 (0.0)	0/51 (0.0)	0/48 (0.0)
Total bilirubin (umol/L)	Below	0/50 (0.0)	0/43 (0.0)	0/47 (0.0)
	Above	2/50 (4.0)	1/43 (2.3)	2/47 (4.3)
Total protein (g/L)	Below	0/52 (0.0)	0/50 (0.0)	0/44 (0.0)
	Above	2/52 (3.8)	1/50 (2.0)	0/44 (0.0)
Triglycerides (mmol/L)	Below	0/47 (0.0)	0/46 (0.0)	0/45 (0.0)
	Above	3/47 (6.4)	3/46 (6.5)	3/45 (6.7)
Uric acid (umol/L)	Below	0/52 (0.0)	0/50 (0.0)	0/48 (0.0)
	Above	1/52 (1.9)	0/50 (0.0)	0/48 (0.0)

Note: Percentages of laboratory limits sub-groups calculated with the number of subjects per lab test normal at baseline as denominator. A subject may appear in more than 1 category.
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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 pages 680−696 of Study Report of Study RIS-SCH-302).

7.1.7.4 Additional analyses and explorations

Although the sponsor conducted some further analyses of these tests, the results will not change the clinical application of this drug. Therefore, these analyses are not reviewed in this review.

7.1.7.5 Special assessments

No special assessments are performed for this sNDA.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs monitoring included supine and standing measure of each subject at each time point and at end point. Change from baseline was calculated and summary statistics are provided. Differences between supine and standing measurements of pulse and blood pressure were calculated for each subject at each time point and at end point as a measure of orthostatic hypotension.

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

Review of vital signs is also focused on the placebo-controlled study, Study RIS-SCH-302.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 36. Mean (+/- SE) Supine Vital Sign Parameters over Time (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

Vital Signs			Placebo		RIS 0.5-2.5mg		RIS 3-6 mg	
			N	Mean/Change	N	Mean/Change	N	Mean/Change
Body Temperature (^{o}F)			54	36.67/-0.02	54	36.71/+0.05	50	36.67/-0.04
Pulse Rate (bpm)	Supine		54	78.26/-0.50	54	75.80/+3.30	50	76.88/-2.20
	Standing		54	85.0/-1.02	54	81.24/+3.17	50	82.52/-1.96
Respiratory Rate (times/min)			54	18.30/-0.07	54	18.15/+0.26	50	17.90/+0.0
Blood Pressure	**Systolic** (mmHg)	Supine	54	115.19/-2.24	54	116.44/-0.83	50	116.16/-3.08
		Standing	54	114.56/-1.28	54	113.91/+0.35	50	115.36/-3.86
	Diastolic (mmHg)	Supine	54	73.07/-1.0	54	73.28/-0.81	50	72.60/-0.52
		Standing	54	74.22/+1.67	54	74.30/-0.67	50	74.66/-1.32

No significant mean changes in vital signs between supine versus standing position in any treatment group.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 37. Table x. Potentially Clinically Important Vital Signs Criteria (Study RIS-SCH-302)

Parameter	Abnormally low	Abnormally high
Pulse (bpm)	A decrease from baseline of ≥15 to a value ≤65	An increase from baseline of ≥15 to a value ≥120
Systolic blood pressure (mmHg)	A decrease from baseline of ≥15 to a value ≤90	An increase from baseline of ≥15 to a value ≥180
Diastolic blood pressure (mmHg)	A decrease from baseline of ≥15 to a value ≤50	An increase from baseline of ≥15 to a value ≥105

Table 38. Table x. Blood Pressure and Pulse - Percentage of Subjects With Normal Baseline Values with Changes Outside of Clinically Important Limits Post-Baseline (Study RIS-SCH-302: Intent-to-Treat Analysis Set

Parameter	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Abnormality Class	n (%)	n (%)	n (%)
Supine Systolic BP, mmHg	53	54	49
Below	0	1 (2)	1 (2)
Normal	53 (100)	53 (98)	48 (98)
Above	0	0	0
Supine Diastolic BP, mmHg	54	54	50
Below	0	0	2 (4)
Normal	54 (100)	54 (100)	48 (96)
Above	0	0	0
Supine pulse, beats/min	48	48	44
Below	0	1 (2)	5 (11)
Normal	48 (100)	47 (98)	39 (89)
Above	0	0	0
Standing Systolic BP, mmHg	51	53	49
Below	0	1 (2)	1 (2)
Normal	51 (100)	52 (98)	48 (98)
Above	0	0	0
Standing Diastolic BP, mmHg	53	54	50
Below	0	0	0
Normal	53 (100)	54 (100)	50 (100)
Above	0	0	0
Standing pulse, beats/min	51	51	49
Below	1 (2)	1 (2)	2 (4)
Normal	49 (96)	48 (94)	47 (96)
Above	1 (2)	2 (4)	0

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Criteria for orthostacism are as follows:

Table 39. Criteria for Orthostacism

Vital Sign (orthostatic = standing minus supine)	Outside predetermined limits if:
Orthostatic SBP (mmHg)	≤ -20 mmHg (i.e., drop of 20 mmHg or more when going from supine to standing position)
Orthostatic DBP (mmHg)	≤ -10 mmHg (i.e., drop of 10 mmHg or more when going from supine to standing position)
Orthostatic pulse (bpm)	≥ 20 bpm (i.e., increase of 20 bpm or more when going from supine to standing position)

Table 40. Vital Signs Orthostatic Parameters - Percentage of Subjects with Normal Baseline Values Outside of Clinically Important Limits Post-Baseline (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

	---------- PLACEBO ---------			-------- RIS 1-3 mg --------			-------- RIS 4-6 mg --------		
	Total	Category, n (%)		Total	Category, n (%)		Total	Category, n (%)	
Parameter	n	Yes	No	n	Yes	No	n	Yes	No
SBP (stand-sup) ≤ -20	53	1 (2)	52 (98)	54	3 (6)	51 (94)	50	2 (4)	48 (96)
DBP (stand-sup) ≤ -10	51	6 (12)	45 (88)	50	6 (12)	44 (88)	49	6 (12)	43 (88)
Pulse (stand-sup) ≥ 20	49	5 (10)	44 (90)	52	8 (15)	44 (85)	48	11 (23)	37 (77)
Orthostatism	54	0	54 (100)	54	0	54 (100)	50	0	50 (100)

Though no subjects met the criteria for orthostatic hypotension, more subjects in the risperidone higher dose group had increases of ≥20 bpm between their standing and supine pulse rates, compared with the risperidone lower dose group (23% vs. 15%) and placebo group (10%).

7.1.8.4 Additional analyses and explorations

No additional analyses and explorations are conducted.

7.1.9 Electrocardiograms (ECGs)

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

According to the sponsor, "digital 12-lead ECG recordings were obtained at each visit and were read at a central ECG facility. An overall reading of the ECG was performed at the ECG central

lab by the interpreting cardiologist." Analyses were conducted for the following measures: Heart rate (HR), PR interval, QRS width, QT interval, QT corrected for HR according to Bazett, Fridericia, and a linear model-based correction.

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

Review of ECG is based on the placebo-controlled study, Study RIS-SCH-302.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Mean changes of ECG parameters, including QT and QTc intervals are presented in the Study Report pages 940 to 946. Though it seems there was a small QT interval increase from baseline to endpoint that is dose dependent, QTcF and other QTc analyses show no significant differences of change.

7.1.9.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

A total of 8 subjects reported tachycardia: 3 subjects in the placebo group, 3 subjects in risperidone lower dose group, and 2 subjects in risperidone higher dose group. Two of them (A30151 and A30119) reported adverse events of tachycardia also related to ECG readings. **Subject A30119** is a 16-year-old female subject in risperidone 1-3 mg group who reported tachycardia (verbatim: ECG abnormality sinus tachycardia) on Day 44, 1 day after receiving her last dose (3 mg). Her supine pulse rate at the end point visit was 88 bpm. No ECG abnormalities or other treatment-emergent adverse events were reported, and no outcome information is available. Subject A30151 of placebo group also reported "ECG abnormal specific" (verbatim: ST segment changes on ECG) which was considered resolved the same day**.**

The criteria for the three QTc analyses are summarized below.

Table 41. Criteria for QTc Value Classification Provided by the Sponsor (Study RIS-SCH-302)

	Normal	Borderline	Prolonged
Males	≤430 ms	431 to 450 ms	>450 ms
Females	≤450 ms	451 to 470 ms	>470 ms

The next table displays the shifts of QT intervals from normal to abnormal throughout the study.

Table 42. Corrected QT Intervals - Percentage of Subjects Within Clinically Important Limits at Screening and Outside Post Screening (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

Parameter	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Value Description	n (%)	n (%)	n (%)
QTcB class	48	52	44
Normal	46 (96)	51 (98)	42 (95)
Borderline	2 (4)	1 (2)	2 (5)
Prolonged	0	0	0
QTcF class	49	53	45
Normal	49 (100)	53 (100)	44 (98)
Borderline	0	0	1 (2)
Prolonged	0	0	0
QTcLD class	49	53	45
Normal	49 (100)	53 (100)	44 (98)
Borderline	0	0	1 (2)
Prolonged	0	0	0

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Table 43. Potentially Clinically Important Criteria for ECG Parameters (Study RIS-SCH-302)

	Abnormally low	Abnormally high
HR (bpm)	<50	>130
PR interval (ms)	<90	>200
QRS interval (ms)	<40	>120

The next table displays the shifts from normal to abnormal throughout the study.

Table 44. ECG Parameters - Percentage of Subjects Within Clinically Important Limits at Screening and Outside Post Screening (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

Parameter Value Description	PLACEBO n (%)	RIS 1-3 mg n (%)	RIS 4-6 mg n (%)
Heart rate (beats/min)	49	52	45
Abn low	0	0	0
Normal	49 (100)	52 (100)	45 (100)
Abn high	0	0	0
PR interval (ms)	50	52	44
Abn low	0	0	0
Normal	50 (100)	52 (100)	44 (100)
Abn high	0	0	0
QRS interval (ms)	50	53	45
Abn low	0	0	0
Normal	50 (100)	53 (100)	45 (100)
Abn high	0	0	0

Corrected QT intervals were also classified as ≥500 ms or <500 ms. Increases from the baseline were classified as change <30 ms, increase 30-60 ms, or increase >60 ms. However, I do not see the result presented by applying these criteria in the Study Report.

7.1.9.4 Additional analyses and explorations

Additional analyses and explorations are not performed.

7.1.10 Immunogenicity

There is no clear evidence of immunogenicity.

7.1.11 Human Carcinogenicity

There is no evidence of human carcinogenicity.

7.1.12 Special Safety Studies

There are no special safety 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 to this sNDA.

7.1.15 Assessment of Effect on Growth

The sponsor provided the mean changes of BMI and weight from Baseline to Endpoint in Study RIS-SCH-302 in the following two tables. Height change is not provided in this study.

Table 45. Body Weight and BMI - Change From Baseline to End Point (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Weight (kg)			
Treatment			
N	54	53	50
Mean baseline (SD)	58.67 (19.984)	59.32 (16.464)	58.70 (12.284)
Mean change (SD)	0.12 (2.037)	1.30 (2.732)	1.50 (1.949)
Body mass index (kg/m²)			
Treatment			
N	54	53	50
Mean baseline (SD)	21.71 (5.617)	21.68 (4.187)	21.45 (3.778)
Mean change (SD)	-0.03 (0.843)	0.36 (0.964)	0.48 (0.713)

N is the number of subjects with both baseline and endpoint values for the parameter.
wt01a.rtf generated by htwtrun.sas.

Table 46. Z-Scores for Body Weight and BMI - Change From Baseline to End Point (JNJPRD--TRIAL RIS-SCH-302: Intent-to-Treat Analysis Set)

	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Weight z score			
Treatment			
N	54	53	50
Mean baseline (SD)	-0.45 (1.826)	-0.31 (1.594)	-0.30 (1.308)
Mean change (SD)	-0.01 (0.263)	0.09 (0.251)	0.12 (0.224)
BMI z score			
Treatment			
N	54	53	50
Mean baseline (SD)	-0.19 (1.634)	-0.02 (1.270)	0.01 (1.011)
Mean change (SD)	0.00 (0.286)	0.08 (0.258)	0.13 (0.233)

N is the number of subjects with both baseline and endpoint values for the parameter.
wt03a.rtf generated by zscorrun.sas.

As in other pediatric studies, this study again shows that both weight gain and BMI increase are dose dependent.

The next table provided by the sponsor displays the incidence of abnormal weigh changes throughout the study, using 7% as categorical criteria.

Table 47. Incidence of Abnormalities for Weight Percent Changes From Baseline (Study RIS-SCH-302: Intent-to-Treat Analysis Set), by the Sponsor

Parameter Analysis Phase Time Interval Value Description	PLACEBO n (%)	RIS 1-3 mg n (%)	RIS 4-6 mg n (%)
Weight (kg)			
Treatment			
Day 15	52	51	48
<-7%	2 (4)	1 (2)	0
≥-7% / ≤+7%	50 (96)	50 (98)	46 (96)
>+7%	0	0	2 (4)
Day 29	50	50	43
<-7%	2 (4)	1 (2)	0
≥-7% / ≤+7%	47 (94)	45 (90)	40 (93)
>+7%	1 (2)	4 (8)	3 (7)
Day 43	35	43	43
<-7%	1 (3)	1 (2)	0
≥-7% / ≤+7%	34 (97)	34 (79)	36 (84)
>+7%	0	8 (19)	7 (16)
End Point	54	53	50
<-7%	2 (4)	1 (2)	0
≥-7% / ≤+7%	51 (94)	44 (83)	42 (84)
>+7%	1 (2)	8 (15)	8 (16)

The following table provided by the sponsor displays the BMI Percentile Rank shift from Baseline to Endpoint.

Table 48. BMI Percentile Rank - Cross-Tabulation of BMI Classes at End Point Versus Baseline (Study RIS-SCH-302: Intent-to-Treat Analysis Set)

	Treatment Group and Evaluation at Baseline											
	---------- PLACEBO ----------				--------- RIS 1-3 mg ---------				--------- RIS 4-6 mg ---------			
	<85	85-<95	≥95	Total	<85	85-<95	≥95	Total	<85	85-<95	≥95	Total
BMI percentile												
Treatment												
End Point												
<85	40	0	0	40	40	0	0	40	43	0	0	43
85-<95	0	6	1	7	3	5	1	9	0	3	0	3
≥95	0	0	7	7	0	0	4	4	0	1	3	4
------	------	------	------	------	------	------	------	------	------	------	------	------
Total	40	6	8	54	43	5	5	53	43	4	3	50

Tanner Staging: There appear no significant changes in Tanner Staging from Baseline to Endpoint in the controlled trials. However, it probably requires longer term studies to evaluate.

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.

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 studies 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

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 (b) (4) 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 (b) (4) 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.

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 clinical studies 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 except for the efficacy demographic analysis of ethnicities/races for which the sponsor only separated the groups into White versus Non-white, instead of five groups as specified in the WR.

The marked outlier analysis for both laboratory tests is not provided.

There was a Case Report Form with handwriting that was very hard to read and find out the gender of the patient. In addition, this particular patient was described as different genders in different places of the submission. – This was discussed in the above (Section 7.1 Integrated Review of Safety).

Otherwise, the data seem to meet the requirement of the Agency WR.

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 marked outlier analysis of laboratory test is not provided in the submission.

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

Most of the review data for safety is from the pivotal studies (RIS-SCH-302 and RIS-USA-231), esp. the placebo-controlled study (RIS-SCH-302) conducted according to FDA WR. However, serious adverse events and deaths as well as drop-outs during adverse events were reviewed from the PK study (RIS-USA-160), pivotal studies, as well as the six-month open-label extension study (RIS-USA-234).

7.4.1.2 Combining data

See above Section 7.4.1.1. Data for safety review were not combined for common adverse events and labs, vital signs, and ECG data analysis.

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

The sponsor provided demographic analysis; however, it was not analyzed based on the five ethnic/race groups according to the Agency WR.

7.4.2.4 Explorations for drug-disease interactions

There is no explorations for drug-disease interactions. Schizophrenia is the only indicated disease for treatment studied. No study regarding subjects with any organ disease or failure is presented.

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interaction studies were done for this submission.

7.4.3 Causality Determination

In this review, adverse events of 5% or more and twice of the incidence of placebo group are considered drug-related.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

(b) (4)

(b) (4)

8.2 Drug-Drug Interactions

To my knowledge, no new drug-drug interaction studies were done for this submission. Also, please see section of Clinical Pharmacology for more details.

8.3 Special Populations

The sponsor didn't have study report on patients with renal or liver or other organ system disease or failure.

8.4 Pediatrics

Due to the rare incidence of schizophrenia in children, the Division has granted waiver for studying this indication in children age 12 year-old.

8.5 Advisory Committee Meeting

No AC meeting has been planned.

8.6 Literature Review

Overall, no deaths were reported in children or adolescents in the literature. Though overdose of risperidone (accidentally or in a suicide attempt) was reported for 6 subjects, none was fatal. Symptoms of overdose are described in Section 7.1.16 Overdose Experiences.

Serious adverse events were reported for 19 subjects, which almost doubled compared to the result reported by the sponsor in the sNDA for treatment of Autism about 3 years ago that included only 10 cases. *Among these new cases, there have been four more cases of Neuroleptic malignant syndrome, two more cases of tardive dyskinesia, two new cases of pancreatitis and one new case of "worsening mitochondrial disorder".* The reported cases are summarized below:

Table 49. Serious Adverse Events Reported in the Literature

Reported SAEs	Number of Subjects
Neuroleptic malignant syndrome	9
tardive dyskinesia	4
acute dystonia	1
probable viral encephalitis*	1
pancreatitis	2
worsening mitochondrial disorder	1

*Characterized by fever, hypertonia, leukocytosis, and elevated creatinine phosphokinase

As mentioned in the previous review, there was a report of toxic carbamazepine level and related serious symptoms observed in 1 subject after initiation of risperidone treatment. However, the sponsor states that a pharmacokinetic drug-interaction study performed by J&JPRD did not show risperidone to have an effect on carbamazepine levels.

Adverse events leading to discontinuation of risperidone were reported in 67 articles. The most frequently reported treatment-limiting adverse events were weight gain (18 articles), EPS (11 articles), prolactin increased (8 articles) and sedation (7 articles).

The adverse events most frequently reported were weight gain (75 articles), sedation (47 articles), and EPS (32 articles). In general, the adverse events reported in the published articles were consistent with the adverse event profile of risperidone or the use of risperidone with various concomitant medications.

8.7 Postmarketing Risk Management Plan

The sponsor did not submit postmarketing risk management plan.

8.8 Other Relevant Materials

Consult from OSE on cerebral edema case and cardiac deaths (Dated May 21, 2007) was reviewed and integrated in the consideration for the decision.

9 OVERALL ASSESSMENT

9.1 Conclusions

The two controlled trials demonstrated that risperidone is effective in adolescents with schizophrenia. (b) (4)

9.2 Recommendation on Regulatory Action

I recommend the Division taking an approvable action for this sNDA application with the dosage (b) (4) 1– 3mg per day.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

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

9.3.2 Required Phase 4 Commitments

This sNDA submission, together with the other sNDA for using risperidone to treat bipolar I disorder in children and adolescents (age 10 to 17 year-old), are in response to the Agency WR. The Division has granted the waiver for studying children (age 12 year-old or younger) with schizophrenia.

9.3.3 Other Phase 4 Requests

No new Phase 4 commitment study is required at present.

9.4 Labeling Review

Labeling review is conducted by Dr. Mitchell Mathis. Please refer to his review for details.

9.5 Comments to Applicant

The sponsor needs to revise the demographic analysis for efficacy using the five ethic/race groups defined by the Agency WR.
In addition, marked outlier analysis for laboratory tests needs to be submitted.

Appendices

9.6 Review of Individual Study Reports

For the convenience of reading, individual studies have been reviewed in Section 6.

9.7 Line-by-Line Labeling Review

Labeling review is reviewed by the Deputy Division Director, Dr. Mitchell Mathis. (Please see his memo for details.)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

June Cai
6/18/2007 11:08:49 AM
MEDICAL OFFICER

Mitchell Mathis
6/18/2007 03:16:54 PM
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