CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

(HFD-120)

Brand Name:	RISPERDAL ®
Generic Name:	Risperidone [ ] b(4)
Drug Category:	Antipsychotic
Sponsor:	Johnson & Johnson
Indication:	Acute Mania of Bipolar Disorder
NDA Numbers:	20-272/SEI-026 & 20-272/SEI-017
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Executive Summary

I. Recommendations

A. Recommendation on Approvability

I recommend that the Division take approvable actions for risperidone, as monotherapy and as adjunctive therapy to mood stabilizers, for the acute of treatment of mania (for up to 3 weeks) in adults with a diagnosis of Bipolar I Disorder.

Risperidone can provide significant benefit in the treatment of acute mania, as demonstrated by the results of the monotherapy and adjunctive therapy trials reviewed herein. Treatment with risperidone can result in rapid (within 3-7 days) and clinically meaningful reductions in severity of each of the critical signs and symptoms of an acute manic episode. Such features include: acute agitation, psychosis, suicidal and dangerous behavior, grossly impaired judgement, grandiosity, impulsivity, risk-taking behavior, and thought disorder. While the two mood stabilizers approved for treatment of acute mania (lithium and valproate) can provide similar benefits for these features, they both have a delayed onset of anti-manic activity (approximately 7-10 days). When used acutely as monotherpy, lithium and valproate often do not treat some critical features of acute mania as quickly or effectively as required. For example, they do not directly treat acute psychotic psychosis and agitation. On the other hand, lithium appears to be effective in treating and preventing suicidal and dangerous behavior. The potential benefits of risperidone in treating acute mania appear to be similar to those of olanzapine, an atypical antipsychotic drug approved for the treatment of acute mania.

The safety and tolerability profile of risperidone treatment (for up to 3 weeks) in subjects with Bipolar Disorder, Acute Manic Episode is acceptable. The profile is quite similar to risperidone's profile in the treatment of schizophrenic patients. Risperidone's safety and tolerability compares reasonably well with those of lithium, valproate, and olanzapine. In the acute mania trials, the most common adverse events associated with risperidone treatment in this population were: extrapyramidal symptoms (EPS), somnolence, akathisia, nausea, dizziness, and abnormal vision. This is consistent with the adverse events reported by schizophrenic subjects treated with risperidone. However, in the mania trials, EPS and akathisia appeared to have been reported with a higher frequency than during the schizophrenia trials.

Treatment with risperidone has been associated with the following serious risks which are listed in the warnings section of labeling: Neuroleptic Malignant Syndrome (NMS), Tardive Dyskinesia (TD) [redacted] The following serious adverse events are labeled as precautions: orthostatic hypotension (associated with dizziness, tachycardia, and syncope), hyperprolactinemia, seizures, dysphagia, [redacted]

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A comparison of the safety profiles of risperidone and the three drugs approved for the

acute treatment of mania is outlined below:

1. Lithium has a relatively narrow therapeutic index. Lithium toxicity can result in renal failure, neurotoxicity, and death. Clinicians must monitor serum lithium levels as well as renal and and thyroid functions, in order to treat safely and effectively. Long-term use of lithium has been associated with renal dysfunction and thyroid dysfunction. Common adverse events include cognitive slowing, sedation, tremor, ataxia, nausea, diarrhea, and polyuria.
2. Valproate treatment has been associated with the following serious events: hepatotoxicity (sometimes severe and fatal); teratogenicity; pancreatitis (sometimes severe and fatal); urea cycle disorders; and thrombocytopenia. Other adverse events include sedation, weight gain, and polycystic ovary syndrome.
3. Olanzapine treatment has been associated with most of the same serious adverse events as risperidone such as: NMS, TD, orthostatic hypotension, seizures, hyperprolactinemia, transaminase elevations, body temperature dysregulation, and dysphagia. Common adverse events reported by Bipolar Disorder subjects in 3-week and 4-week trials included: somnolence, asthenia, dizziness, dry mouth, constipation, dyspepsia, increased appetite, and tremor. Olanzapine has also been associated with EPS, weight gain, and hyperglycemia.

In summary, the safety profile of risperidone compares favorably with those of lithium and valproate; however, there are important differences in safety considerations among the three drugs. The safety and tolerability profile of risperidone closely resembles that of olanzapine.

B. Recommendation on Phase 4 Studies and Risk Management Steps

I recommend that the sponsor conduct the following additional studies as part of the Risperidone-Mania program:

1) An adequate and well-controlled study of risperidone in the treatment of children and adolescents with Bipolar Disorder, Manic Episode. (The sponsor has begun planning a pediatric study of risperidone in mania and has discussed the plan with the Division).
2) A study to assess the longer-term safety of risperidone in the treatment of adults with Bipolar Disorder, Manic episode.
3) A study to assess the potential efficacy of risperidone as continuation and maintenance treatment of Bipolar Disorder.

During long-term safety and efficacy studies, of particular interest would be an assessment of the potential for risperidone to induce mania, exacerbate mania, or accelerate cycling of affective episodes in Bipolar Disorder. Reports from the literature suggest that treatment with risperidone might induce or exacerbate mania in some cases. This could be a drug class effect, since similar reports exist for other atypical antipsychotic medications, and drugs in the class have similar pharmacological profiles. In the trials reviewed herein, treatment with risperidone was temporally associated with acute increases in manic symptoms in some subjects. (The same was true of some subjects treated with placebo). However, in such a short-term trial which involved acutely manic subjects, it is extremely difficult to determine whether risperidone had exacerbated mania in some subjects. Literature suggests that one would need to monitor a large population of Bipolar Disorder patients treated with risperidone for at least 18 months, in order to assess the potential risk of risperidone to induce mania, exacerbate mania, or accelerate cycling of episodes in Bipolar Disorder.

II. Summary of Clinical Findings

A. Brief Overview of the Clinical Program

Risperidone (RISPERDAL) is an atypical antipsychotic drug belonging to the chemical class, benzisoxazole derivatives. The sponsor completed four controlled trials of risperidone in the treatment of acute mania in subjects with Bipolar Disorder. Two were conducted to support a claim for risperidone as monotherapy (RIS-USA-239 and RIS-IND-2), and two were conducted in order to support a claim for risperidone as adjunctive therapy to lithium or valproate (RIS-USA-102 and RIS-INT-46). A total of 894 subjects were randomized and treated: 578 in the monotherapy trials and 306 in the adjunctive therapy trials. Two-hundred and ninety-four (294) subjects received risperidone monotherapy in flexible-doses of 1 to 6 mg/day; 127 received risperidone in flexible-doses of 1 to 6 mg/day with a mood stabilizer (lithium or valproate in RIS-USA-102; lithium, valproate, or carbamazepine in RIS-INT-46); 410 subjects were treated with placebo, and 63 were treated with an active comparator (either haloperidol or valproate). [[ ] For details about the clinical program, refer to Table III.B.1 and Table III.B.2). b(4)

B. Efficacy Review

General Conclusions about Efficacy

The efficacy of risperidone was demonstrated in the acute treatment of mania in subjects with diagnoses of Bipolar I Disorder, Manic or Mixed Episode, (with or without Psychotic Features). Risperidone was efficacious, both as monotherapy and as adjunctive therapy to mood stabilizers (lithium or valproate) as established in three 21-day, well-controlled trials using flexible-dose risperidone in the range of 1-6 mg/day. One pivotal monotherapy trial and one supportive monotherapy trial were positive (RIS-USA-239 and RIS-IND-2, respectively). The pivotal adjunctive therapy trial, (RIS-USA-102) was positive. A second adjunctive therapy trial (RIS-INT-46) did not demonstrate efficacy; however, the results demonstrated a numerical trend toward efficacy.

In summary, the statistical and clinical reviewers verified the results of the sponsor's efficacy analyses. In all trials, the primary outcome measure was the mean change in Young-Mania Rating Scale (YMRS) score between baseline and Day 21. The chosen endpoint is appropriate for the studied indication, and it useful for extrapolating from the study results to the expected benefits for acutely manic patients whom would be treated with risperidone. The YMRS is a well-validated, standard scale used to assess mania, since it addresses the core, clinically important features of mania. The primary analysis was an analysis of covariance (ANCOVA) model, using an LOCF imputation method. The results in the 3 positive studies were statistically significant to a relatively high degree. For both monotherapy studies (USA-239 and IND-2) the p-values were < 0.001. For adjunctive trial USA-102, the p-value was 0.009. In the failed adjunctive therapy study (INT-46) the p-value was 0.089. The magnitude of the estimated treatment effects in each of the three positive studies is clinically meaningful with respect to the treatment of acutely manic patients, especially in such short-term trials. In fact, for each of the positive trials, there was a statistically significant treatment effect for risperidone as early as Day 7. The mean estimated treatment effects persisted and increased throughout the trials.

Results of analyses of secondary outcome measures support the primary efficacy results. In particular, the differential mean change between groups in the Clinical Global Impression-Severity (CGI-S) scores was statistically significant, in favor of risperidone. In addition subgroup analyses demonstrated that the treatment effect of risperidone was consistent, regardless of gender, race, age, baseline severity of illness, presence or absence of psychosis, presence or absence of a mixed manic episode, or particular mood stabilizer used. Since subgroup analyses demonstrated consistent treatment effects, it is difficult to determine whether any predictors of response exist. However, there seem to be some trends toward differential effects among subgroups treated concomitantly with various mood stabilizers.
On the other hand, the sample sizes were too small to permit definitive statistical analysis among such subgroups. At this point, one cannot definitively compare the efficacy of rispridone in mania with other drugs available for the indication. There have been no studies directly comparing risperidone with other approved treatments for acute mania (lithium, valproate, and olanzapine).

It is unlikely that trial exclusions of specific subpopulations would affect the use or potential benefit of risperidone in the expected marketed population. In particular, the protocol excluded: 1) patients with active or recent substance use disorders; and 2) patients who presented with an apparent first episode of mania. It is very likely that both types of patients would be treated with risperidone for acute mania and that the drug would be effective in those subpopulations. Approximately 50-75% of Bipolar Disorder patients have a history of substance abuse. As long as such patients do not suffer from severe hepatic dysfunction, risperidone treatment would be reasonably safe. Furthermore, evidence suggests that bipolar patients who are stabilized with an effective medication regimen are less likely to use substances. Treatment of first-break manic patients is very likely to occur, since they are likely to respond to antipsychotics such as risperidone. Moreover, even if such patients have been misdiagnosed and turn out to have a diagnosis of Schizophrenia or Schizoaffective Disorder, they would likely be treated with an antipsychotic medication such as risperidone.

There were several differences in results between monotherapy trials USA-239 and IND-2. The estimated treatment effect was larger in IND-2 than in USA-239. The difference in least square mean changes in YMRS scores from baseline to endpoint were –12.4 and –5.9, respectively. Moreover, in IND-2, the mean baseline score in the risperidone group was higher (indicating greater severity) than in USA-239 (37.1 vs. 29.1), and the endpoint mean YMRS score in IND-2 was lower (14.5 vs. 18). The mean baseline scores in the placebo groups were nearly identical to those in the risperidone groups of each study. In addition, a higher mean risperidone dose was used in IND-2 than USA-239. The mean modal doses were 5.6 mg and 4.1 mg, respectively. Furthermore, in IND-2, the serum concentrations of the active moiety of risperidone at Week 3 were higher than in USA-239 (47.1 vs. 27.2 ng/mL). When normalized to a 4 mg dose, the concentration remained higher in IND-2 (34.4 vs. 27.4 ng/mL). Since these were flexible-dose studies and separate studies, one cannot draw conclusions about a potential dose-response relationship; however, it is interesting that in IND-2 the mean estimated treatment effect and mean serum concentrations of the active moiety were higher than those in USA-239. In addition, the proportion of discontinuations was unusually low in IND-2 (20%, compared to 51% in USA-

239). Finally, the total dose of lorazepam used in IND-2 was more than 2.5-fold that in USA-239.

The main difference between adjunctive therapy trials was the use of carbamazepine. The pharmacokinetic and pharmacodynamic effects of carbamazepine probably contributed significantly to the failure of the study. Although formal statistical analysis could not be performed for the mood stabilizer subgroups, there were strong trends toward a risperidone treatment effect for both the lithium and valproate groups. In contrast, within the carbamazepine subgroup, an effect favored placebo. Within the placebo group, carbamazepine appeared to have a relatively strong effect, as measured by the change from baseline in YMRS score (-13.3). In the carbamazepine + risperidone group, the mean change was –11.5. Since carbamazepine co-administration can reduce risperidone active moiety concentrations, it is possible that the apparent lack of a risperidone treatment effect was due to this drug interaction.

Treatment Effect Sizes

Calculation of the difference in least square mean change between treatment groups provides an estimate of the risperidone treatment effects in the trials. The estimated treatment effect sizes were similar for monotherapy study USA-239 and adjunctive therapy trial USA-102. The values were -5.9 and –5.1 on the YMRS, respectively, favoring risperidone (compared to placebo). In monotherapy study IND-2, the estimated risperidone effect was considerably larger (-12.4). In USA-102, the estimated treatment effect of haloperidol, compared to placebo, was -4.5, somewhat smaller than the risperidone effect. All of these differences are clinically significant, both in terms of the difference compared to placebo treatment and in the score change on the YMRS.

Another method of estimating the treatment effect involves dividing the mean change in the risperidone by the mean change. Using this method, the estimated risperidone treatment effect size is 2.22 times the effect size of placebo treatment. For IND-2, the estimated treatment effect size is 2.16, and for USA-102, the estimated size of the treatment effect is 1.74, favoring risperidone. The estimated treatment effect of haloperidol compared to placebo is 1.62. It is important to note that the estimates of treatment effect sizes may be biased, especially in studies USA-239 and USA-102, due to the high proportion of discontinuations in these studies (51% in each, compared to 20% in IND-2).

For details concerning efficacy results in all studies, refer to the table in Appendix B

C. Safety Review

Exposures to Study Drug

In summary, treatment with risperidone as monotherapy or as adjunctive therapy to mood stabilizers was reasonably safe and well-tolerated in these 21-day studies in subjects with a Diagnosis of Bipolar I Disorder, Manic or Mixed Episode, with or without Psychotic Features. A total of 894 subjects were treated for a maximum duration of 21 days in these double-blind trials. There were 578 subjects in the monotherapy trials and 306 in the adjunctive therapy trials. Of these, 294 subjects were treated with risperidone as monotherapy in flexible-doses of

1-6 mg/day. In the adjunctive therapy trials, 127 subjects were treated with risperidone in flexible-doses of 1 to 6 mg/day in combination with a mood stabilizer (lithium or valproate in RIS-USA-102; lithium, valproate, or carbamazepine in RIS-INT-46). In the trials, 410 subjects were treated with placebo; and 63 were treated with an active comparator (either haloperidol [53] or valproate [10]). The total risperidone exposure for 421 subjects was 20.5 patient years. In the monotherapy studies, 294 subjects were treated with risperidone for a total of 14.34 patient years. In the adjunctive therapy trials, the risperdone exposure was 6.16 patient years for 127 subjects. The mean doses in monotherapy studies USA-239 and IND-2 were higher (4.1 mg and 5.6 mg) than those in adjunctive trials USA-102 and INT-46 (3.83 and 3.68). In the adjunctive therapy trials, 131 subjects were treated with lithium, and 149 were treated with valproate, and 26 were treated with carbamazepine. Total exposure data for lithium, valproate, and carbamazepine are not available, but some details about mood stabilizer exposure are discussed in the individual study reviews.

Adequacy of Safety Assessments

In these 21-day studies, the safety assessment was adequate and thorough. The types and frequency of safety assessments were clinically appropriate, and the monitoring plan provided for early detection of clinical and laboratory abnormalities and potential adverse events associated with study treatment. In addition, the actions taken for clinical problems that arose, (including discontinuation, medical consultation, and more frequent monitoring), were appropriate.

Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events

There were three deaths in the trials (all in the monotherapy trials). [ ]

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[ ] In Study USA-239, there were 2 deaths in the placebo group. One died from injuries sustained in a motor vehicle accident, and one died due to accidental asphyxiation related to food aspiration and alcohol intoxication.

In the monotherapy trials, 34 subjects had serious adverse events (21 in the risperidone groups and 13 in the placebo groups). In study USA-239, 27 subjects reported SAE; 17 (13%) from the risperidone group and 10(8%) from the placebo group. In study IND-2, SAE were reported by 4(3%) subjects from the risperidone group and 3 (2%) from the placebo group. In the majority of cases in both studies, the SAE appeared to be directly related to the illness under treatment. The most common SAEs were: manic reaction, condition aggravated, increased psychosis, insomnia. In IND-2, two subjects had the SAE, convulsion. Both cases of seizures were related to benzodiazepine withdrawal after using maximal doses of lorazepam in the study. [ ]

[ ] In the adjunctive therapy trials, a total of 14 subjects had SAE. There

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were 4 from the risperidone groups, 6 from the placebo groups, and 4 from the haloperidol group. As in the monotherapy studies, most SAE consisted of psychiatric symptoms. In study USA-102, there was one case of particular note, involving a subject who developed sustained tachycardia, elevated CPK levels and rhabdomyolysis. The subject had been treated with risperidone and lithium. The case had some features consistent with neuroleptic malignant syndrome (NMS),

In the monotherapy trials, a relatively small number of subjects discontinued from the study due to and adverse event (31). Nineteen (19) of these subjects were treated with risperidone, and 12 were treated with placebo. Some of the adverse events were likely related to study drug treatment. The AE which led to discontinuation included: EPS, somnolence, dizziness and tremor, all of which have been associated with risperidone treatment. However, the majority of AE leading to discontinuation were either psychiatric symptoms or medical events which appeared to be unrelated to study treatment. In the adjunctive therapy trials, 19 subjects discontinued due to an adverse event (4 treated with risperidone, 13 treated with placebo, and 2 treated with haloperidol). One of the cases from USA-102 was discussed above (tachycardia, rhabdomyolysis, and CPK elevation).

Commonly Reported Adverse Events

Generally, the types and frequency of adverse events reported were those that would be expected in this population and with risperidone treatment. In monotherapy studies USA-239, IND-2 [ ] [ ] the proportion of the risperidone versus the placebo group reporting adverse events was: (88% vs. 70%); (64% vs. 48%) [ ] respectively. The pattern of adverse events reported was extremely similar among the trials. The most commonly reported adverse events in the risperidone group, (at a greater rate than the placebo group), in descending order, were: extrapyramidal symptoms; somnolence; akathisia; dizziness; nausea; dyspepsia; tremor; agitation; abnormal vision; and hypersalivation.

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In adjunctive trials USA-102 and INT-46, the proportion of the risperidone and placebo groups reporting adverse events was (81% vs. 84%); and (57% vs. 51%). In study USA-102, 91% of the haloperidol group reported adverse events. The most commonly reported adverse events in these trials were: extrapyramidal symptoms, somnolence, dizziness, akathisia, tremor, and hypersalivation. The pattern of adverse events reported was very similar to the pattern in the monotherapy trials.

Particular Adverse Events and Safety Parameters of Interest

Risperidone treatment commonly leads to elevation of serum prolactin levels. In each study, the mean prolactin level increased significantly from baseline in both men and women. Nearly all men and women taking risperidone had abnormally high prolactin levels at endpoint. Elevations ranged from mild (22.67 ng/ml) to a high of 274.9 ng/ml, with the majority of values below 106.65 ng/ml. In USA-239, eight subjects reported adverse events which appeared to be related to hyperprolactinemia. In the other studies, there were no adverse events reported which might have been related to abnormal levels of prolactin.

Risperidone treatment has also been associated with clinically important changes in blood pressure and pulse, including orthostatic hypotension. In fact, in all of the studies, there were cases in which subjects developed clinically important positional increases in heart rate, as well as clinically important positional decreases in systolic and diastolic blood pressure. The proportion of subjects developing at least one of these changes ranged from 14% to 69%, depending on the study. Apparently, very few subjects had changes which met all criteria of orthostatic hypotension. It appears that there were no adverse events reported which correlated with the changes in vital sign parameters.

Since treatment with atypical antipsychotic drugs has been associated with abnormalities in glucose metabolism, such potential abnormalities were a focus of the safety assessment in all studies. In all studies, there were no significant changes in mean glucose levels with risperidone treatment, and there were no mean differences compared to the placebo group. However, increases from baseline in glucose levels were more common in the risperidone group than the placebo group. In each study, there were a small number of subjects in both treatment groups who developed hyperglycemia (usually mild) or glycosuria (mild). The number of such cases was slightly higher in the risperidone group than the placebo. Most did not meet criteria for hyperglycemia

In general, there was an increase in mean weight for the risperidone groups during the 21-day trials. The mean increase (minus the change for the placebo group) was: 1.68 kg, unknown, [ ] [ ] 2.12 kg, and 1.2 kg, respectively, in USA-239, IND-2, [ ] USA-102, and INT-46. One might consider this a potentially significant weight gain in such a short period. b(4)

ECG parameters were studied closely, due to the association of atypical antipsychotic treatment and the risk of electrocardiographic abnormalities, especially prolongation of the QT interval. The sponsor conducted a thorough assessment. There were no significant changes in mean ECG paramters with risperidone treatment. There were no significant differences between treatment groups in ECG parameters. A small number subjects in each treatment group had increases in QTc intervals that were categorized as borderline or prolonged. None of the changes were clinically significant. One subject from the risperidone group had an abnormal QTc value in the "pathologic" range (>500 msec: 517). The event was not associated with clinical signs or symptoms. It was considered possibly related to study treatment. No action was taken, and the event was resolved upon the completion of treatment.

With the exception of prolactin levels (discussed above) there were no clinically meaningful changes from baseline in mean laboratory values in either treatment group. There was no mean change in mean blood glucose level from baseline to Day 21 in the risperidone group.
The vast majority of all laboratory abnormalities were only marginally out of the reference ranges. Some abnormalities had the potential to be clinically significant; however, none of these cases constituted an acutely serious condition. For example, all cases of elevated liver enzymes were relatively mild; none of elevated glucose levels were in a range considered clinically dangerous

Potential for Drug-Drug Interactions and Manageability

Clinically significant drug-drug interactions were observed when ripseridone was co-administered with carbamazepine, valproate, topiramate, or fluoxetine. It is likely that, in clinical practice, these drugs will be used concomitantly with risperidone in some patients with Bipolar Disorder, given the frequent need for polypharmacy in this complex illness. Data from the literature also suggest that co-administration of paroxetine and risperidone can result in increases in risperidone concentrations). Such interactions can lead to either: 1) decreased efficacy of risperidone treatment; 2) or excessive serum concentrations of risperidone, along with an increased risk of adverse effects. Physicians and patients should be informed about these potential interactions which could be clinically significant. Physicians may need to adjust dosages of these medications and/or risperidone if they are co-admistered.

D. Dosing of Risperidone

The risperidone doses and dosing regimen recommended by the sponsor are clinically appropriate and follow from the efficacy and safety results of the trials. The sponsor proposes stable risperidone dosing of approximately 2-6mg/day, both as monotherapy and adjunctive therapy with mood stabilizers. Dosage adjustment, if indicated, should occur within an interval of not less than 24 hours and in dose increments or decrements of 1 mg per day. Since these were flexible-dose and not fixed-dose studies, one cannot draw conclusions about a potential dose-response relationship. Nevertheless, the dosing range used and recommended is reasonable and consistent with previous experience. The range appears to be reasonable given that: 1) similar doses of risperidone were used effectively in studies to treat Schizophrenic subjects; 2) a similar dose range has been used effectively in post-marketing clinical practice to treat psychotic patients; 3) the important clinical features of an acute manic episode in Bipolar Disorder patients overlap considerably with those of an acute psychotic episode in schizo-phrenic patients; and 4) clinicians need to control acute manic symptoms rapidly

. It is possible that at least some manic subjects would have responded to lower doses, if lower doses were used for longer periods. Dose-toxicity relationships were not specifically tested in this study. With a slower titration schedule, some subjects may have had a reduced risk of experiencing adverse effects such as: extrapyramidal symptoms, somnolence, akathisia and lowering of blood pressure, some of which may be dose-related. It would be of particular clinical value to minimize the risk of developing EPS (especially akathisia), since Bipolar Disorder patients generally have a higher risk of developing EPS than schizophrenic patients. Minimizing the risk of akathisia is important because this adverse effect has been associated with completed suicide. Akathisia was reported by 8.2% of risperidone-treated subjects in the monotherapy trials and 6.3% of risperidone-treated subjects in the adjunctive therapy trials. Akathisia may have contributed to the completed suicide in the study.

There is no body of evidence from controlled trials to guide a clinician in the longer-term management of a Bipolar Disorder patient who improves with risperidone treatment. While it is standard practice to use continuation and maintenance treatment beyond an acute episode of mania, currently, there are no data to support the use of risperidone in long-term treatment of Bipolar Disorder. Furthermore, as the sponsor notes, there have been reports that treatment with risperidone and other atypical antipsychotic drugs has been associated with the emergence of

mania. Also, there are no data regarding the potential efficacy of risperidone in preventing episodes of bipolar depression. In fact, there is some concern that risperidone can potentially worsen or induce depressive symptoms. Thus, there is a need to conduct adequate and well-controlled studies of risperidone treatment in the long-term treatment of Bipolar Disorder patients.

D. Special Populations

No studies for this submission were conducted specifically in the elderly, renally impaired, or hepatically impaired subjects with Bipolar Disorder. However, results from previous PK studies of risperidone in some special populations will be discussed below. Potential gender effects were thoroughly and appropriately tested. In contrast, the trials could not adequately assess potential effects of race or ethnicity on the safety and efficacy of risperidone treatment, because there was such a small number of non-Caucasian subjects in the study.

1. **Renal Impairment**: In patients with moderate to severe renal disease, clearance of risperidone and 9-hydroxyrisperidone were decreased by 60% compared to clearance in young healthy subjects. Risperidone doses should be reduced in patients with renal disease.

2. **Hepatic Impairment**: the mean free fraction of risperidone in plasma of subjects with hepatic impairment was increased by about 35% because of the diminished concentration of both albumin and a 1-acid glycoprotein. Risperidone doses should be reduced in patients with liver disease.

3. **Geriatric Patients**: clinical studies of risperidone have not included sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger patients. In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxy-risperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients. Generally, a lower starting dose and a slower titration schedule is recommended for elderly patients, due to the increased frequency of decreased hepatic, renal, and cardiac function and a higher frequency of other comorbid disease and concomitant drug use. Elderly patients have a greater tendency to experience orthostatic hypotension; the risk may be reduced by limiting the initial dose to 0.5 mg BID, followed by careful titration. Monitoring of orthostatic vital signs should be considered in geriatric patients.

4. **Elderly Patients with Dementia:** clinical trial results reveal that elderly subjects with dementia, who are treated with risperidone for psychosis and/or agitation, have an increased risk of cerebrovascular adverse events, including stroke and death. It is currently unclear whether this is a drug class effect. Apparently, no similar signal has been detected in other populations treated with risperidone.

5. **Race and Gender Effects**; no specific PK study was conducted to investigate potential race and gender effects; however, a population PK analysis did not identify important differences in the PK profile of risperidone due to gender or race.

6. **Pregnancy**: there have been no adequate and well-controlled studies of risperidone treatment in pregnant women. Labeling advises that women taking risperidone should inform their physician if they become pregnant or plan to become pregnant. Currently, it appears that there is no specific plan to investigate the effects of risperidone treatment in pregnant women.

   It seems likely that risperidone will be used in some pregnant women with Bipolar Disorder, because the drug may prove to be effective during pregnancy, and the safety profile of risperidone, (when used during pregnancy), may be more acceptable than those of the approved mood stabilizers, lithium and valproate. Both have been associated with risks to the fetus, including teratogenicity. Furthermore, if a pregnant women with

Bipolar Disorder does not receive maintenance treatment for the illness, the risk of exacerbation is high. An alternative approved treatment, olanzapine, appears to carry similar potential benefits and risks if used during pregnancy. Labeling regarding olanzapine use during pregnancy, labor, delivery, and lactation is similar to risperidone labeling.

7. **Labor and Delivery**: The effect of risperidone on labor and delivery in humans is unknown. However, the use of traditional (typical) antipsychotics late in pregnancy has been associated with complications during labor and delivery. This effect appears to be related to extrapyramidal symptoms in the mother and/or the neonate. On the other hand, (depending on dosing), the atypical antipsychotic drugs appear to pose a lower risk of EPS, generally. Thus, if a pregnant woman requires treatment with risperidone, the clinician might consider discontinuing risperidone treatment late in the third trimester.

8. **Nursing Mothers**: Risperidone and 9-hydroxy-risperidone are excreted in human breast milk. Labeling states that women undergoing treatment with risperidone should not breast-feed

9. **Pediatric Use**: the safety and effectiveness of risperidone therapy in children have not been established. However, the sponsor has discussed plans to conduct a trial of risperidone in children and adolescents (ages 10-17) with a diagnosis of Bipolar Disorder, Manic.

Clinical Review

I. Introduction and Background

A. Drug Established and Trade Name; Drug Class; Sponsor's Proposed Indications; Dose Regimens; Age Groups

Risperidone (RISPERDAL ®) is an atypical antipsychotic medication belonging to the chemical class, benzisoxazole derivatives. The sponsor seeks an indication for risperidone in the acute treatment of mania associated with Bipolar I Disorder. Risperidone would be used either as monotherapy or as adjunctive therapy to mood stabilizers that have been approved for the treatment of acute mania (i.e., lithium and valproate). The indication pertains to adult patients ($\geq$ 18 years of age) with a diagnosis of Bipolar Disorder, Manic Episode. For the acute treatment of mania (for up to 3 weeks), the sponsor proposes stable risperidone dosages of approximately 2 to 6 mg per day, either as monotherapy or adjunctive therapy.

B State of Armamentarium for the Indication

Three medications have been approved in the U.S. for the acute treatment of mania associated with Bipolar Disorder: 1) lithium (a mood stabilizer); 2) depakote (an anticonvulsant and mood stabilizer); and 3) olanzapine (an atypical antipsychotic medication). These medications have unique benefits, risks, and limitations in the treatment of Bipolar Disorder.

Lithium
Lithium has a role in: 1) acute treatment of mania; 2) acute treatment of bipolar depression; 3) maintenance treatment of both bipolar mania and bipolar depression; and 4) prophylaxis of bipolar manic and depressive episodes. While one can use lithium effectively as monotherapy in some phases of Bipolar Disorder in some patients, clinicians frequently must use other medications in combination with lithium (for all phases of Bipolar Disorder) in order to provide effective treatment. (Commonly required concomitant medications for the treatment of acute mania include: antipsychotics, benzodiazepines, and other mood stabilizers). Lithium has greatest value in maintenance treatment and prophylaxis of affective episodes. The delayed onset of lithium's antimanic effect (approximately 7 to 10 days) limits its utility in the treatment of acute mania, especially as monotherapy. Moreover, lithium does not adequately treat acute psychotic symptoms or acute agitation, which are common debilitating features of an acute manic episode. Aspects of lithium's safety and tolerability profile also limit its use. For example, lithium has a relatively narrow therapeutic index regarding renal and cognitive function. Long term use of lithium poses the risks of renal dysfunction and thyroid dysfunction. In order to use lithium safely and effectively, one must regularly monitor serum lithium levels, renal function, and thyroid functions. Lithium toxicity can result in cognitive impairment, renal failure, and death. Common adverse events which can limit patients' adherence to lithium therapy include cognitive slowing, sedation, tremor, ataxia, nausea, diarrhea, and polyuria.

Valproate
Valproate can effectively treat acute mania in some patients. As with lithium therapy, valproate monotherapy often does not treat acute mania adequately, and the same classes of concomitant medications used with lithium are required. As with lithium, the onset of antimanic effect is delayed. Furthermore, valproate does not treat psychotic symptoms and often does not treat acute agitation adequately. Valproate is not approved for maintenance therapy mania or for prophylaxis of manic episodes associated with Bipolar Disorder. Similarly, valproate does not effectively treat or prevent depressive episodes of Bipolar Disorder. Risks associated with valproate use include: hepatic dysfunction (sometimes severe, occasionally fatal); pancreatitis; weight gain; and ovarian dysfunction

(polycystic ovary syndrome, irregular menses, amenorrhea). One must monitor liver function and hematologic tests and valproate levels periodically.

Olanzapine
Olanzapine has been approved for the acute treatment of mania associated with Bipolar Disorder, based on two short-term (3 weeks and 4 weeks). Like risperidone, it is categorized as an atypical antipsychotic but is part of a different chemical class). Olanzapine was initially approved for acute and maintenance treatment of schizophrenia. It is used effectively in clinical practice for the treatment of psychotic symptoms, including those associated with acute manic episodes. It is not clear whether olanzapine is efficacious in maintenance treatment or prophylaxis of manic or depressive episodes of Bipolar Disorder. Olanzapine as monotherapy has not been demonstrated to be efficacious in the treatment of acute bipolar depression in clinical trials; however, the combination of olanzapine and fluoxetine has demonstrated efficacy in treating acute depression in Bipolar Disorder.

Advantages of using olanzapine in acute mania include its effectiveness in treating psychotic symptoms, acute agitation, and insomnia. Furthermore, relief of some of these symptoms can begin relatively rapidly. Potential safety and tolerability problems include: extrapyramidal symptoms (akathisia, parkinsonism, dyskinesia, tardive dyskinesia, bradyphrenia, etc.), neuroleptic malignant syndrome, daytime sedation, weight gain, hyperglycemia, and orthostatic hypotension. (All of the above adverse can be associated with treatment with risperidone and other atypical and typical antipsychotic medications).

C. Important Milestones in Product Development

Marketing History
Risperidone has been used extensively in the treatment of schizophrenia and other psychotic conditions since it was first marketed in the U.K. in May 1993. Since December 1993, risperidone has been used extensively in the U.S. for the treatment of schizophrenia. Risperidone is licensed in more than 90 countries for the treatment of schizophrenia. As of May 2002, the cumulative worldwide exposure to risperidone was estimated to be [ ] patient-years. b(4)

Risperidone has been licensed in approximately 15 countries, as adjunctive therapy to mood stabilizers for the acute treatment of mania associated with Bipolar Disorder. (The sponsor Has provided two different lists). The countries include:[ ] Czech Republic,[ ] [ ] Ireland,[ ] Portugal, Spain,[ ] Philippines,[ ]

[ ] b(4)

Sponsor's Discussions with the Division During Program Development
From November 4, 1996 through October 4, 2002 the Division held numerous discussions with the sponsor regarding the development of the Risperidone-Mania program. The Division provided feedback on several drafts of the Phase 3 protocols involving risperidone as mono-therapy and as adjunctive therapy to mood stabilizers (lithium, valproate, and carbama-zepine), in the acute treatment of mania associated with Bipolar I Disorder. The Division informed the

sponsor of the requirements for demonstrating efficacy and for submitting a sufficient application for potential approval. It was agreed that one pivotal trial of risperidone as mono-therapy (USA-239) and one pivotal trial of risperidone as adjunctive therapy to lithium or valproate (USA-102) would be sufficient for filing and for potentially supporting the indication sought.

E. Important Issues with Pharmacologically Related Agents

In general, the drugs categorized as atypical antipsychotics have similar pharmacodynamic profiles, benefits, and safety and tolerability profiles. As with risperidone, treatment with the other atypical antipsychotics (clozapine, olanzapine, quetiapine, ziprasidone, and aripiprazole) have been associated with development of the following adverse events: extrapyramidal symptoms, sedation, orthostatic hypotension, weight gain, and hyperglycemia. Treatment with some of the atypical antipsychotics have been associated with proarrhythmic effects (primarily prolongation of the QTc interval). Ziprasidone may pose a higher risk of QTc prolongation than other antipsychotics. Treatment with quetiapine may be associated with development of cataracts. Risperidone treatment in elderly patients with dementia and agitation/psychosis appears to be associated with an increased risk of cerebrovascular adverse events.

Clozapine differs significantly from the other atypical antipsychotics. It is the only antipsychotic medication demonstrated to be effective in treating previously treatment-resistant schizophrenic patients. Investigators hypothesize that clozapine's unique pharmacologic properties may confer its beneficial effects. Clozapine also has a different safety profile than other atypical antipsychotic drugs. Treatment with clozapine carries the risks of agranulocytosis, myocarditis, and seizures. Like other atypical antipsychotics, clozapine treatment can result in EPS, sedation, weight gain, hyperglycemia, and orthostatic hypotension.

In summary, risperidone and the other atypical antipsychotics, (with the exception of clozapine) appear to have similar potential risks. However, olanzapine is the only atypical antipsychotic that has been approved for the acute treatment of mania.

II. Findings from Statistics, Biopharmaceutics, and Division of Scientific Investigation Consultant Reviews

A. Major Statistical Findings

Mark Rothmann, Ph.D. conducted the statistical review of the risperidone studies. Dr. Rothmans reached the following conclusions:

The two monotherapy trials of risperidone in the acute treatment of mania demonstrated that risperidone treatment had a statistically significant treatment effect compared with placebo. In one of the adjunct therapy trials in acute mania, the superiority of risperidone treatment over placebo was statistically significant. In the other adjunct therapy trial of risperidone in acute mania, there was not a statistically significant treatment effect of risperidone compared to placebo. Due the high proportion of discontinuations in all of the studies which can lead to biased estimates of results, it may be difficult to accurately estimate the size of the treatment effects. (For details, refer to the Efficacy Results section).

B. Biopharmaceuticals Findings

The following is a summary of the review by Andre Jackson, Ph.D. When co-administered with risperidone, topiramate (an anti-convulsant used off-label as a mood stabilizer in Bipolar Disorder) lowers risperidone levels by 30% but does not affect levels of the active metabolite, 9-hydroxy-risperidone. Topiramate caused a 30% decrease in risperidone AUC and Cmax but had no similar effect on the active metabolite which is reported to be equipotent. In effect, the active moiety could be reduced by 15%. It is possible that such an effect may be clinically significant for some patients.

C. Division of Scientific Investigation's Inspection Results

In summary, the findings of the DSI investigations did not affect the interpretation of the efficacy and safety analyses. Ni A. Khin, M.D. conducted investigations at 2 clinical study sites. D. Brown, M.D. was an investigator for studies RIS-USA-239 (monotherapy) and RIS-USA-102 (adjunctive therapy study). Dr. Khin states that that there were "no major objectionable conditions noted" at this site. M. Plopper, MD was an investigator for study RIS-USA-239. Although there were some protocol violations and problems with obtaining informed consent at this site, Dr. Khin notes that the data appear acceptable. Dr. Khin has concluded that the data from these two sites are acceptable for use in support of this supplemental NDA.

II. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

(For details about the pharmacokinetic profile of risperidone, please refer to previous reviews).

Summary of PK Profile

Risperidone is rapidly and well absorbed, and its absorption is unaffected by food intake. The Tmax = 1.0 (0.25 to 3.0) hours, and Cmax = 54.3 (+/- 31) ng/mL. Risperidone is extensively metabolized in the liver by CYP2D6 to the major active metabolite, 9-hydroxy-risperidone, the predominant circulating species which appears to be equipotent with risperidone. Thus, the clinically active moiety is the combination of concentrations of risperidone and

9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxy-risperidone, and risperidone plus 9-hydroxyrisperidone are dose-proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Risperidone and its metabolites are excreted primarily in the urine (70%) and feces (15%). The apparent half-life of risperidone is three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone is about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers.

Risperidone may be subject to two kinds of drug-drug interactions. Inhibitors of the isoenzyme CYP2D6 can interfere with conversion of risperidone to 9-hydroxyrisperidone. Conversely, risperidone may interfere with the metabolism of other drugs metabolized by CYP2D6; however, relatively weak binding of risperidone to the enzyme suggests that such an interaction is not likely to be significant.

A. PK Profile in Subjects with Bipolar Disorder

Plasma concentrations of risperidone and the major active metabolite, 9-hydroxy-risperidone, were measured in subjects with Bipolar Disorder in studies RIS-USA-239, RIS-IND-2, and RIS-INT-46. Plasma concentrations of the active moiety were within the expected concen-tration range, compared with concentrations observed in schizophrenic subjects. (The expected median trough concentrations for schizophrenic subjects given a 4-mg dose were 27 ng/mL for the active moiety and 1.8 ng/mL for risperidone). The sponsor calculated the trough plasma concentrations of the active moiety (actual and normalized to a 4-mg dose) at the end of the 3-week flexible-dose phase. Plasma concentrations observed in RIS-IND-2 were high compared to those in the other trials. On Day 21, the mean active moiety trough concentration was 47.1 ng/mL versus 27.2 ng/mL and 28.2 ng/mL in RIS-USA-239 and RIS-INT-46, respectively. This may have been due to the higher doses given in RIS-IND-2. The mean dose was 5.6 mg, versus 4.1 mg and 3.7 mg in RIS-USA-239 and RIS-INT-46, respectively. After dose-normalization, these differences are less pronounced, based on average and median concentrations.

B. Clinical Drug Interaction Studies with Risperidone

Drug-drug interaction studies of risperidone were conducted in subjects with psychotic disorders, Bipolar I Disorder, and in healthy volunteers treated concomitantly with medications commonly used in the treatment of: 1) Bipolar I Disorder (lithium, valproate, carbamazepine, and topiramate); and 2) other psychiatric illnesses (fluoxetine and amitriptyline). Studies with erythromycin were also conducted. Results are summarized below:

1. **Valproate**: co-administration with risperidone resulted in a 20% increase in valproate Cmax. Such an increase in valproate concentrations could be clinically significant.
2. **Lithium**: concomitant administration with risperidone had no significant effect on the PK profile of lithium.
3. **Carbamazepine**: coadministration of carbamazepine and risperidone resulted in a 50% reduction in plasma concentrations of risperidone and 9-hydroxy-risperidone. This drug interaction is clinically significant.
4. **Topiramate**: coadministration with risperidone resulted in a 30% decrease of risperidone concentration. There was no effect on 9-hydroxyrisperidone concentration. Topiramate co-treatment appears to affect the absorption

and/or distribution of risperidone, without affecting metabolism by CYP450 enzymes. This drug interaction could be clinically significant.

5. **Fluoxetine**: coadministration with risperidone resulted in a 2.5-2.8-fold increase in the plasma concentration of risperidone; the plasma concentration of 9-hydroxy-risperidone was not affected. This drug interaction is clinically significant.
6. **Amitriptyline**: co-administration with risperidone had no significant effect on the pharmacokinetics of risperidone or 9-hydroxy-risperidone.

C. Pharmacokinetics in Special Populations

No studies were conducted specifically in elderly, renally impaired, or hepatically impaired subjects with Bipolar Disorder. The PK profile of risperidone in special populations with other psychiatric disorders has been studied, as outlined below.

1. **Renal Impairment:** in patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite were decreased by 60% compared to young healthy subjects. Risperidone doses should be reduced in patients with renal disease.
2. **Hepatic Impairment:** in patients with hepatic impairment, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and alpha-1-acid glycoprotein. Risperidone doses should be reduced in patients with liver disease.
3. **Geriatric Patients:** in healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients.
4. **Elderly Patients with Dementia:** data from clinical trials in elderly subjects with dementia and agitation and/or psychosis revealed that risperidone treatment was associated with an increased risk of cerebrovascular adverse events, including stroke and death.
5. **Race, Gender, Body Weight Effects:** no specific PK study was conducted to investigate race and gender effects, but a population PK analysis did not reveal important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

A. Pharmacodynamics

No clinical pharmacology studies were performed in subjects with Bipolar Disorder. There were no studies regarding 1) the mechanism of anti-manic action of risperidone; 2) dose selection for the indication; or 3) pharmacological properties related to safety concerns. Risperidone's antipsychotic and antimanic mechanism of action is unknown. Investigators hypothesize that the drug's antipsychotic effect is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other pharmacodynamic effects of risperidone.

III. Description of Clinical Data and Sources

A. Overall Data

The efficacy and safety data from monotherapy studies USA-239 and IND-2 were reviewed in detail. Similarly, efficacy and safety data from adjunctive therapy trials USA-102 and INT-46

were reviewed in detail. [ ] b(4)

[ ] In addition, information from the statistical, biopharmaceutics, and Division of Scientific Investigation reviews was included in this review (please refer to sections II.A-C).

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B. Tables Listing the Clinical Trials Reviewed

TABLE III.B.1. Risperidone Monotherapy in Placebo-Controlled Trials

TRIAL #/ START/STOP DATES	TRIAL DESIGN & OBJECTIVE	STUDY DRUG REGIMEN	DISPOSITION OF SUBJECTS
RIS-USA-239 (US) 11/00-5/02 **Pivotal Study**	Randomized, double-blind, placebo-controlled, parallel group, multicenter, flexible-dose study to assess the anti-manic efficacy and safety of risperidone monotherapy in subjects with Bipolar I Disorder, Manic Episode. Duration: 21 days	**Risperidone:** 3 mg on day 1 2-4 mg on day 2 1-5 mg on day 3 1-6 mg days 4-21 **Placebo**: matching tabs on days 1-21	Screened: 337 Randomized: 262 (78%) Treated: 259 (77%) Risperidone: 134/134 Placebo: 125/128 **Discontinued**: 132 (51%) Risperidone: 59 (44%) Placebo: 73 (58%)
RIS-IND-2	Identical to USA-239:	**Risperidone:** 3 mg on day 1	Screened: 324 Randomized: 291 (90%)

(India) 3/01-12/01 Supportive Study	Randomized, double-blind, placebo-controlled, parallel group, multicenter, flexible-dose study to assess the anti-manic efficacy and safety of risperidone monotherapy in subjects with Bipolar I Disorder, Manic (*or Mixed)* Episode. Duration: 21 days	2-4 mg on day 2 1-5 mg on day 3 1-6 mg days 1-21 **Placebo:** matching tabs days 1-21	Treated: 290 (90%) Risperidone: 146/146 Placebo: 144/145 **Discontinued:** 58 (20%) Risperidone: 16 (11%) Placebo: 42 (29%)
b(4)			

TABLE III.B. 2. Risperidone as Adjunctive Therapy in Placebo-Controlled Trials

TRIAL NO. START/STOP DATES	TRIAL DESIGN & OBJECTIVE	STUDY DRUG REGIMEN	DISPOSITION OF SUBJECTS
RIS-USA-102 10/97-4/99 **Pivotal Study**	Randomized, double-blind, placebo-controlled, parallel group, multi-center, flexible-dose study to assess the anti-manic efficacy and safety of risperidone as adjunctive therapy to mood stabilizers (Lithium or Valproate) in subjects with Bipolar I Disorder, Manic Episode. Double-blind phase: 3 weeks.	**Risperidone + Mood Stabilizer:** 2 mg days 1-2 1-4 mg days 3-4 1-6 mg days 5-21 **Placebo + Mood Stabilizer:** days 1-21 **Haloperidol + Mood Stabilizer:** 4 mg on days 1-2 2-8 mg on days 3-4 2-12 mg on days 5-21	Randomized: 158 Treated: 156 Risperidone: 52/52 Placebo: 52/51 Haldol: 54/53 **Discontinued:** 80 (51%) Risperidone: 22 (42%) Placebo: 29 (57%) Haldol: 29 (55%)
RIS-INT-46 5 countries	Randomized, double-blind, placebo-controlled, parallel group, multi- center, flexible-dose study to assess the anti-manic efficacy and safety of risperidone as	**Risperidone + Mood Stabilizer:** 2 mg on days 1-2 1-4 mg on days 3-4 1-6 mg on days 5-21	Screened: 156 Randomized: 151 (97%) Treated : 150 (99%) Risperidone: 75/75 Placebo: 76/75

10/97-10/99 **Supportive Study**	adjunctive therapy to mood stabilizers (Lithium, Valproate, or Carbamazepine) in subjects with Bipolar I Disorder, Manic or Mixed Episode. Double-blind phase: 3 weeks.	**Placebo + Mood Stablizer:** days 1-21	**Discontinued:** 26 (17%) Risperidone: 12 (16%) Placebo: 14 (19%)

C. Postmarketing Experience

Risperidone Treatment in Psychotic Disorders
As discussed above, risperidone has been used extensively worldwide in the treatment of schizophrenia and other psychotic conditions, since it was first marketed in 1993. Risperidone is licensed in more than 90 countries for the treatment of schizophrenia. As of May 2002, the cumulative worldwide exposure to risperidone was estimated to be [ ] patient-years. b(4)
The Division has extensive data regarding the efficacy and safety of risperidone.

Risperidone Treatment in Acute Mania
Risperidone has been licensed in approximately 15 countries, as adjunctive therapy to mood stabilizers, for the acute treatment of mania associated with Bipolar Disorder. The sponsor has not submitted postmarketing data from international sources.

D. Literature Review

Sponsor's Literature Summary
The sponsor conducted a search of published literature through July 31, 2002, in order to identify publications referring to risperidone in the treatment of mania. Fifty-one articles were retrieved. All of the relevant studies involved open-label treatment with risperidone, and most involved adjunctive treatment with risperidone. Mood stabilizers were the most frequently cited medications co-administered with risperidone; however, other classes of medications were also used. Two publications described concomitant treatment with electro-convulsive therapy. Some publications did not report concomitant medications, and some described trials in which concomitant medication, such as benzodiazepines, could be used as needed. Conclusions about risperidone's efficacy in the treatment of mania were mixed.

IV. Clinical Review Methods

A. Description of How the Review was Conducted

The review was conducted by analyzing each of the four completed studies separately. While the clinical summary, integrated summary of efficacy, and integrated summary of safety were reviewed, the primary review was conducted by analyzing the data from the four individual study reports. All of the following types of data were reviewed: summary discussions, summary tables, individual subject data, and raw data provided by the sponsor. In addition, the review of efficacy was conducted in consultation with the statistical reviewer, Mark Rothmann, Ph.D.

B. Overview of the Materials Consulted for the Review

The primary materials consulted are listed above. Electronically submitted were used.

C. Review of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigation conducted audits at some of the sites involved in the study. A relevant review has been submitted. In addition, several of the individual case report forms were audited at random. There are no apparent problems or deficiencies which would affect the interpretation of the efficacy and safety data.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor states that the studies were conducted in accordance with the "Recommendations Guiding Physicians in Biomedical Research Involving Human Patients" contained in the 1989 version of the Declaration of Helsinki. The sponsor states that the final protocol and all amendments were reviewed and approved by institutional review boards and appropriate ethics committees. The submission includes documentation of appropriate IRB procedures. Generally, it appears that the trials were conducted within accepted guidelines and ethical standards pertaining to research involving human subjects. One study site (105) was disqualified from monotherapy Study USA-239 due to non-compliance with Good Clinical Practice, as was site 210 in monotherapy Study IND-2.

Information Provided for Subjects & Consent Documents
Before any trial-related procedures were done, patients or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation and termination conditions, and risks and benefits of treatment. Patients were informed that they could withdraw from the trial at any time for any reason.

F. Evaluation of Financial Disclosure

The sponsor provided documentation regarding financial disclosure and potential conflict of interest of investigators. There does not appear to be any instances of conflict of interest which affected the conduct or results of the study.

VI. Integrated Review of Efficacy- RIS-USA-239

A. Brief Statement of Conclusions

This study demonstrated the efficacy of risperidone in the acute treatment of mania. For the differential change in YMRS score at Day 21 between the risperidone group and the placebo group at Day 21, there was a statistically significant difference, in favor of risperidone ($p< 0.001$). In addition, there were statistically significant treatment effects at Day 3 ($p< 0.01$) and at Day 7 ($p< 0.001$). The mean baseline YMRS scores were 29.1 and 29.2

in the risperidone and placebo groups, respectively. The mean YMRS scores at Day 21 were 18 and 24.2 in the risperidone and placebo groups, respectively. Thus, the unadjusted mean changes in YMRS scores at Day 21 were –11.1 and –5.0 for the risperidone and placebo groups, respectively. The estimated least squares mean change from baseline to endpoint is -4.8 (a reduction of 4.8 points on the YMRS scale) in the placebo group and -10.6 in the risperidone arm. The estimated difference in the least squares mean change from baseline to endpoint was –5.9 with a corresponding 95% confidence interval of (-8.3, -3.4). Thus, the estimated treatment effect of risperidone compared to placebo treatment is a reduction of –5.9 points on the YMRS scale. Such a reduction in symptomatology in acutely manic patients would clinically meaningful.

The efficacy results for the secondary outcome measures support the conclusion that risperidone was efficacious in this study. In addition, the efficacy of risperidone was demonstrated consistently across all subgroups. Subgroup analyses of efficacy did not reveal any significant differences in efficacy according to gender, age, race, baseline severity of illness, or presence or absence of psychotic symptoms. There were no particular predictors of response in this study. Since this was a flexible-dose study, one cannot draw conclusions about a potential dose-response relationship.

B. General Approach to the Review of Efficacy

The efficacy database and efficacy summaries provided by the sponsor were reviewed in detail.

C. Detailed Review of Trial

C-1 Investigators and Study Sites- USA-239

Study RIS-USA-239 was conducted in the U.S. at 29 sites. (Please refer to **Appendix B** for a full listing of investigators and study sites).

C-2 Objectives of the Study- USA-239

Primary Objective
The primary objective of both trials was to evaluate the efficacy of risperidone monotherapy, relative to placebo, in the treatment of acute mania associated with Bipolar I Disorder. The efficacy of study treatment would be determined by measuring the changes from baseline to the end of treatment (21 days) in Young Mania Rating Scale (YMRS) scores.

Secondary Objectives
The secondary objectives were:
1) To determine whether risperidone is associated with improvement or worsening of

Co-morbid depressive symptoms
2) To estimate the time of onset of maintained anti-manic clinical response to risperidone
3) To evaluate the safety and tolerability of risperidone.
4) To explore relationships between risperidone's pharmacokinetic profile and its efficacy and safety in subjects with acute mania.

C-3 Subject Selection- USA-239

Subjects included were women and men ≥18 years of age who met DSM-IV criteria for Bipolar I Disorder, Most Recent Episode Manic, with or without psychotic symptoms.

Other Key Inclusion Criteria:

1. Female subjects were either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (oral or parenteral hormonal contraceptives; intrauterine device; barrier and spermicide). Female subjects must have had a negative urine pregnancy test at screening and at baseline.
2. Subjects must have been voluntarily hospitalized at the time of enrollment. The primary diagnosis prompting the hospital admission must have been the manic episode that satisfied inclusion criterion.
3. History of > 1 prior documented manic or mixed episodes that required treatment.
4. Manic episodes must not have been caused by somatic antidepressant treatment.
5. Total Young Mania Rating Scale (YMRS) score of > 20 upon screening and at baseline.
6. Total Montgomery-Asberg Depression Rating Scale (MADRS) score < 20 at baseline.

Key Exclusion Criteria:

1. Women who were pregnant or nursing.
2. Met DSM-IV criteria for Schizoaffective Disorder, Rapid Cycling Bipolar Disorder, or Substance Dependence (excluding nicotine or caffeine) in the 3 months prior to entering the study.
3. Total YMRS score at baseline decreased by≥ 25% from the screening score
4. Received treatment with an antidepressant medication or ECT within the 4 weeks prior to screening.
5. Co-morbid medical conditions and concomitant medication use as specified in appendix B.

(Complete Inclusion and Exclusion Criteria for both studies are listed in **Appendix B**).

C-4 Design of the Study- USA-239

This was a 21-Day, randomized, placebo-controlled, double-blind, parallel-group, multicenter trials in initially hospitalized subjects who had a diagnosis of Bipolar I Disorder, Acute Manic Episode. (In IND-2, subjects with mixed manic episodes were also included). Subjects were diagnosed according to DSM-IV criteria, using a structured diagnostic clinical interview. Those who met entry criteria and were receiving anti-manic or other specified psychotropic

drugs or were required to undergo a 3-day washout period before entering a 3-week double-blind treatment phase. For the double-blind treatment phase, subjects were randomly assigned in equal numbers to receive treatment with either risperidone or placebo. Randomized subjects were stratified at baseline according to the presence or absence of psychotic features, (and mixed features in IND-2) and by center. InUSA-239, 134 subjects were randomized to risperidone treatment and 128 were randomized to the placebo treatment. Three patients in the placebo group did not receive treatment. In study IND-2, All of the 145 subjects randomized to risperidone received treatment, and 145 out of 146 subjects randomized to the placebo group received treatment.

During the double-blind treatment phase of both studies, subjects were required to remain hospitalized for a minimum of 7 full days. As of Day 8, subjects could be discharged and followed as outpatients, if they were judged by the investigator to be at no significant risk for suicidal or violent behavior, and if the CGI-Severity score was 3 (mildly ill) or less. Risperidone or placebo was administered orally once daily (in the evening) in a flexible dosage range of 1 to 6 mg. Dosing changes were made for individual subjects according to the efficacy, tolerability, and safety of the study treatments. (Dosing regimens are summarized in the table below). Subjects assigned to risperidone treatment received a single 3 mg dose on Day 1. On Day 2, investigators had the option of adjusting a subject's dose, reducing it to 2 mg or increasing the dose to 4 mg. Beginning on Day 3, the investigator could adjust dosing within the range of 1-5 mg/day. From Day 4 through Day 21 (endpoint), subjects could receive 1-6 mg/day.

Dosing Regimens for Study Drugs

DAY	RISPERIDONE (MG/DAY)	PLACEBO
1	3 mg	Matching tabs
2	2-4 mg	Matching tabs
3	1-5 mg	Matching tabs
4-21	1-6 mg	Matching tabs

Most efficacy and safety assessments were performed on Days 1, 3, 7, 14, and 21, although adverse events and vital signs were assessed more frequently during the inpatient period.

C-5 Outcome Measures- USA-239

Primary Outcome Measure

The primary efficacy measure was the differential change in mean total Young Mania Rating Scale (YMRS) score from baseline to Day 21 between treatment groups (risperidone versus placebo). The YMRS consists of 11 items, with score ranging from 0-60. A higher score represents a greater severity of illness.

Secondary Outcome Measures:

1. Change from baseline in YMRS at secondary time points using observed data
2. Percent of subjects with ≥ 50% reduction in YMRS score
3. Longitudinal analysis of YMRS scores
4. Change from baseline in Clinical Global Impression-Severity (CGI-S)
5. Change from baseline in Global Assessment Scale (GAS
6. Change from baseline in total Positive and Negative Syndrome Scale (PANSS) score
7. Change from baseline in Montgomery Asberg Depression Rating Scale (MADRS) score
8. Onset of maintained response, as measured by change in YMRS score.

C-6 Disposition of Subjects- USA-239

In Study **USA-239,** 78% (262/337) of individuals screened were included and randomized to treatment groups. The most common reasons for exclusion upon screening were:"ineligible to continue trial" and "does not meet inclusion/exclusion criteria." All subjects randomized to the risperidone group (134) received treatment, and 98% (125/128) of subjects randomized to the placebo group received treatment. Fifty-one percent (51%) of subjects discontinued from the 21-day study (58% of the placebo group and 44% of the risperidone group).

C-7 Discontinuations from the Study- USA-239

A high proportion of subjects discontinued from the trial (51%). The proportion was high in both treatment groups (59% of the placebo group and 40% of the risperidone group). The most common reasons for discontinuation from the risperidone group were: insufficient clinical response (14%), withdrew consent (16%), and adverse event (8%). In the placebo group, the most common reasons for discontinuation were "insufficient clinical response (36%), withdrew consent (15%), and adverse event (6%).

C-8 Baseline Demographics and Severity of Illness- USA-239

Baseline Demographics

At baseline of Study USA-239, there were no meaningful differences between treatment groups in demographic variables. The mean age was 38 years in the risperidone group and 40 years in the placebo group. Both groups had a higher percentage of men than women (53% men in the risperidone group and 61% in the placebo group). The majority of subjects were Caucasian (69% in the risperidone group and 75% in the placebo group). African Americans comprised 25% of the risperidone group and 13% of the placebo group. In the risperidone group, 5% were Latino; in the placebo group, 10% were Latino. Subjects classified, as 'other' comprised 2.2% and 2.4% of the risperidone and placebo groups, respectively. There were no significant differences between treatment groups in the following variables: weight, height, and body mass index (BMI).

Baseline Severity of Illness

At baseline, the mean YMRS scores were identical between treatment groups: 29 in Both groups). Similarly, there were no meaningful differences between groups in CGI-S, GAS, total PANSS, and MADRS scores at baseline; the scores were quite similar between treatment groups, as seen in the below. Forty-two percent (42%) of subjects had psychotic symptoms at baseline. A greater proportion of subjects in the placebo group (45%) had psychotic symptoms at baseline compared to the risperidone group (40%).

Baseline Severity of Illness- USA-239

VARIABLE	RISPERID N=134; n (%)	PLACEBO N=124; n (%)
Baseline Total YMRS mean (SE)	29	29.2
Psychotic symptoms At baseline	(40%)	(45%)
Baseline CGI-S, n (%)		
- Mild	2 (1.5)	1 (0.8)
- Moderate	67 (50)	56 (45.2)
- Marked	48 (35.8)	47 (37.9)
- Severe	14 (10.4)	18 (14.5)
- Extremely severe	3 (2.2)	2 (1.6)
Baseline GAS- mean	39.9	38.8
Baseline PANSS-mean	67.1	68.2
Baseline MADRS- mean	9.4	9.5

Bipolar Disorder History- USA-239

For most of the Bipolar Disorder History variables analyzed in USA-239, there were no meaningful differences between treatment groups (see Table 8.3 below). However, for several variables, there appears to be a trend in the placebo group toward greater severity of illness by history; there were higher mean numbers of psychotic episodes per subject and psychiatric hospitalizations per subject for the placebo group, compared to the risperidone group (4.3 versus 1.9 and 7.7 versus 5.7, respectively). There was a trend toward fewer depressive episodes in the placebo group than the risperidone group (5.4 and 7.7, respectively). For the following variables, the treatment groups had nearly identical numbers: number of manic episodes; number of mixed episodes; number of suicide attempts; age of onset of Bipolar Disorder; age at first psychiatric hospitalization; age at first pharmacological treatment; and number of treatment course for substance misuse.

C-9 Treatment Dose and Duration- USA-239

In USA-239, the mean modal dose of risperidone was 4.1 mg. The mean duration of treatment in the risperidone group was 15.6 days. In the placebo group, the mean number of tablets/day was 5.0. The median number of tablets per day was 5.0. The mean duration of treatment in the placebo group was 13.6 (0.65) days.

Treatment Compliance

Treatment compliance was not analyzed in these trials; however, a record was kept of medication dispensed and retrieved by the pharmacist or investigator.

C-10 Concomitant Medications- USA-239

Prohibited Psychotropic Medications

The psychotropic drugs listed below were not permitted during the studies. Subjects must not have used any of these mediations for at least 3 days prior to Day 1 of the study. Prohibited medications included:

1. Lithium, valproate, carbamazepine, lamotrigene, or other anti-convulsants
2. Antipsychotic drugs
3. Benzodiazepines or other anxiolytics (other than lorazepam use, as per protocol)
4. Sedatives and hypnotics
5. Antidepressants
6. Dopaminergic drugs
7. Cholinesterase inhibitors
8. Other psychoactive drugs (St. John's Wort, Kava Kava, gingko, etc)

Permitted Use of Lorazepam- USA-239

Lorazepam use was permitted from Days –3 to 10 for the control of agitation, irritability, restlessness, insomnia, and hostility. Lorazepam treatment was not permitted during the 8 hours prior to a behavioral assessment.

Regimen for Permitted Lorazepam

	DAY	MA DOSE (mg/day)
Washout period	-3-0	8
Treatment phase	1-3	8
	4-7	6
	8-10	4
	11-21	none

Lorazepam use during the 21-day double-blind phase was analyzed according to a number of criteria. (Refer to the table below). While the proportion of subjects treated with lorazepam was

comparable between the risperidone (72%) and placebo (74%) group, the cumulative use of lorazepam in the placebo group was considerably higher than in the placebo group. The total lorazepam dosage used by the placebo group (1,772 mg) was higher than that in the risperidone group (1,364 mg). Similarly, the total lorazepam dose per mITT subject and per subject actually treated with lorazepam were higher in the placebo group compared to the risperidone group (14.2 mg vs.10.2 mg and 19.3 mg vs. 14.1 mg, respectively). Furthermore the total daily dose (over 10 days) of lorazepam for lorazepam-treated subjects was higher in the placebo group than in the risperidone group (1.92 mg vs. 1.43 mg). In addition, the mean and median doses of lorazepam were higher in the placebo group compared to the risperidone group (3 mg versus 2.2 mg and 2.6 mg versus 2.0 mg). On the other hand, the mean and median duration of lorazepam treatment were approximately equal between the two treatment groups (~ 6 days). The difference between groups in mean duration of lorazepam use, as a percentage of the subject's total duration in the study, partially reflects the lower mean duration of study treatment (higher proportion of discontinuations) in the placebo group. In summary, it is unlikely that the level of use of lorazepam use in each treatment group would affect the results of the efficacy analysis. The difference between groups in lorazepam use was not substantial. In fact, the placebo group, on average, used more lorazepam than did the risperidone group. Furthermore, the level of lorazepam use was relatively modest for a population of acutely manic subjects.

Lorazepam Used During the Trial- USA-239

PARAMETERS	PLAC	RIS
Number of subjects (N)	125	134
No. sub treated w/ Lorazepam (n*)	92 (74%)	97 (72%)
Total Lorazepam use (mg)	1772	1364
Total Lorazepam use/N (mg)	14.2	10.2
Total Lorazepam use/n* (mg)	19.3	14.1
Mean (SD) dose (mg)	3.0 (1.6)	2.2 (1.2)
Median dose (mg)	2.6	2.0
Duration of Lorazepam Rx (Days)		
Mean (SD) (Days)	6.2	5.9
Median (Days)	6.0	6.0
Duration of Lorazepam Rx (as percentage of study treatment duration) (%)		
Mean (SD) (%)	62%	46%
Median (%)	60%	38%
Dose per day over Days 1-10 per subject (n*)		
	1.92 mg	1.43 mg

n* = the number of subjects treated with lorazepam

Medication Used to Treat EPS

A higher proportion of subjects in the risperidone group (25%) than the placebo group (14.4%) used medications commonly used to treat extrapyramidal symptoms (EPS). This parallels the

higher proportion of subjects in the risperidone group who reported EPS. In the risperidone group, 25% of subjects were treated with anticholinergic drugs, and 3% were treated with a beta-blocker. In the placebo group, 12% of subjects were treated with anti-cholinergic drugs, and 4% had treatment with a beta-blocker.

Summary of Concomitant Medications Use
Most subjects received concomitant medications during the trial. The proportion of subjects treated with concomitant medications was identical between the risperidone and placebo group (96% in each). Lorazepam was the most commonly used concomitant medication in both groups (81% and 85% of subjects in the risperidone and placebo groups, respectively). Acetominophen was used by 53% and 41% of the risperidone and placebo groups, respectively. Medications for treating EPS (primarily benzatropine), were taken by 22% of subjects in the risperidone group and 11% of the placebo group.

In summary, the use of prohibited medications reported in the trial likely does not affect the results of the primary efficacy analysis. There were only two subjects in the risperidone group whose use of concomitant psychotropic medications had the potential to affect the efficacy results (subject A31222 and A31373). The first subject was treated with clinically significant doses of quetiapine (100 mg for 3 days), valproate (1,175/d x 7 days), as well as extra risperidone (6 mg for 3 days). A separate efficacy analysis was conducted in which these subjects were excluded. The result was identical to the broader analysis of efficacy. The vast majority of instances of "prohibited concomitant medication use" were cases of either: 1) use of medications during the washout period, or 2) medications begun after the subject discon-tinued from or completed the study. Furthermore, the use of prohibited medications was quite similar between the risperidone and placebo groups.

D. Efficacy Results- USA-239

1. Brief Statement about Efficacy Conclusions
Information presented about the efficacy analyses are based on the review performed by Mark Rothmann, Ph.D, Mathematical Statistician, Division of Biometrics, FDA. Please refer to Dr. Rothmann's review for details.

In summary, the statistical reviewer verified the results of the sponsor's analyses of primary and secondary outcome measures. Monotherapy using flexible doses of risperidone (1-6 mg/day) was efficacious in the acute treatment of mania in subjects with a diagnosis of Bipolar Disorder. The primary efficacy endpoint for study RIS-USA-239 was the change from baseline at Day 21 in the YMRS score using a last observation carried forward (LOCF) imputation method. There was a statistically significant difference ($p < 0.001$) in this endpoint between the placebo and risperidone groups (favoring the risperidone group). The estimated least squares mean change from baseline to endpoint is -4.8 (a reduction of 4.8 points on the YMRS scale) in the placebo

group and -10.6 in the risperidone arm. The estimated difference in the least squares mean change from baseline to endpoint was –5.9 with a corresponding 95% confidence interval of (-8.3, -3.4). Thus, the estimated treatment effect of risperidone compared to placebo treatment is a reduction of –5.9 points on the YMRS scale. Such a reduction in symptomatology in acutely manic patients would probably be significant.

Due to the high proportion of subjects who discontinued from the study (56% of the placebo group and 46% of the risperidone group), the estimated mean changes in YMRS scores and the estimated treatment effect may be biased when using the LOCF imputation method and ANCOVA model. However, at Day 3 and at Day 7, (when there were few discontinuations), there were a statistically significant differences ($p<0.01$ and $p<0.001$, respectively) in the change from baseline in YMRS score between the placebo and risperidone groups (favoring the risperidone group).

The secondary endpoints consisted of the changes from baseline to Day 21 in CGI-S, GAS, PANSS and MADRS scores. Except for the MADRS scores, the changes between treatment groups in these endpoints were statistically significant, favoring the risperidone group. In addition, treatment with risperidone was consistently more effective than placebo, as measured by change in YMRS score from baseline at Day 21, regardless of age, gender, race, baseline disease severity score, or the presence or absence of psychotic symptoms at baseline.

2. Sponsor's Statistical Analysis Plan

The intent-to-treat (ITT) population was defined as those randomized subjects who were treated with at least one dose of trial medication (a modified ITT analysis). Some ITT subjects were not included in the efficacy dataset, since they were enrolled at sites which were not in compliance with Good Clinical Practice, or because they did not have both baseline and post-baseline data. Also, some subjects were assigned multiple CRF ID numbers; only data corresponding to the first CRF ID number was used for analysis.

The primary efficacy endpoint was the change from baseline at Day 21 in total YMRS score. The analysis for change in total YMRS was an analysis of covariance (ANCOVA) with a model that included treatment group, investigator, and baseline psychosis as factors and the baseline Value (for YMRS) as a covariate. A similar analysis was performed for secondary outcome measures, CGI-S, GAS, total PANSS, and MADRS, using the baseline values as the sole covariate. A longitudinal analysis of change in YMRS score at Day 3, Weeks 1, 2 and 3 was performed using a mixed effects model with treatment, time, treatment by time, center, and psychosis as factors, and baseline YMRS score as a covariate.

3. Results of the Primary Efficacy Analysis

There was a statistically significant difference ($p< 0.001$) in the primary endpoint between the placebo and risperidone groups (favoring risperidone). The efficacy results are summarized

in the table below. At baseline, the mean YMRS scores were 29.1 in the risperidone group and 29.2 in the placebo group. At endpoint, the mean YMRS scores were 18 and 24.2, respectively. Thus, the change in mean score was –11.1 in the risperidone group and –5 for the placebo group. The estimated least squares mean change from baseline to endpoint is -4.8 (a reduction of 4.8 points on the YMRS scale) in the placebo group and -10.6 in the risperidone group. Finally, the estimated difference in the least squares mean change from baseline to endpoint was –5.9, with a corresponding 95% confidence interval of (-8.3, -3.4), favoring risperidone. Thus, the estimated treatment effect of risperidone compared to placebo treatment is a reduction of –5.9 points on the YMRS scale. Such an effect would be clinically significant for the treatment of acute mania.

Change from Baseline in YMRS Score at Day 21 (LOCF)- USA-239

RX	N	MEAN (SD)			COMPARISON WITH PLACEBO		
		Baseline	Week 3 Endpoint	Change	LSMean Change (SD[a])	Diff in LSM Change (95%CI)	p-value
PLAC	119	29.2 (5.53)	24.2 (11.17)	-5.0 (9.44)	-4.8 (9.52)		
RIS	127	29.1 (5.06)	18.0 (10.66)	-11.1 (10.11)	-10.6 (9.52)	-5.9 (-8.3,-3.4)	<0.001

N: Number of patients with both baseline and post-baseline timepoint measurements.
p-value: Between treatment comparison based on ANCOVA model with treatment, investigator, psychotic feature as factors, and baseline value as covariate.

4. Secondary Efficacy Analysis- USA-239

Although not relevant to proposed labeling, one of the secondary efficacy analyses will be discussed. The sponsor performed a longitudinal analysis of the change from baseline in total YMRS scores at each assessment time-point (Days 3, 7, 14, and 21), based on the LOCF data. As mentioned above, there were significant differences between groups in changes from baseline YMRS scores (LOCF) at Days 3, 7, 14, and 21 ($p<0.001$ for all 4 time points). The treatment effect favored risperidone at each time-point. The between-treatment difference in the mean change in total YMRS score (LOCF) increased from Day 3 to Day 7 and was fairly stable thereafter. Using a Mixed Effects Model, the statistician concluded that the results are consistent with those from the LOCF analysis.

5. Secondary Outcome Measures- USA-239

The secondary efficacy endpoints were: the changes from Baseline at Day 21 in CGI-S, GAS, PANSS, and MADRS scores. To summarize, the outcome measures were positive at Day 21, except for the change in MADRS scores. The other 3 secondary efficacy measures were positive at most of the other time points as well. It is not clear whether the sponsor made adjustments for multiple comparisons in the statistical analysis plan for these secondary outcome measures; however, the analyses indicate that the results had a high degree of statistical significance. Results from the analysis based on observed data were consistent with these results.

6. Clinical Global Impression-Severity of Illness Item (CGI-S)

At Day 21, there was a statistically significant difference in the reduction of CGI-S scores in the risperidone group compared to placebo group ($p<0.001$). There were also statistically significant differences between groups in CGI-S score changes at Days 3, 7, and 14, in favor of risperidone. The analysis is based on an ANCOVA model with treatment, center, psychosis as factors, and baseline CGI-S as a covariate. Results from the analysis based on observed data were consistent with these results made on Day 3.

7. Subgroup and Special Analyses- USA-239

The subgroup variables and categories are defined as follows:

1. Gender (male, female)
2. Race (Caucasian, Hispanic, Black, Oriental, "Other")
3. Age (≤ 22; 23-40; 41-64; ≥ 65 years)
4. Baseline Severity of Illness
   a. Psychotic features at baseline (psychotic, non-psychotic)
   b. YMRS score at baseline (≤ 30; 31-40; ≥ 41).
5. Pharmacokinetic-pharmacodynamic relationships

Subgroup analyses were performed for the change from baseline to Day 21 in total YMRS score. Analyses used an ANCOVA model with treatment, psychosis (except for the subgroup analysis by psychosis) as factors, and baseline total YMRS as a covariate. The between-treatment differences in Least Square Means (LSMeans) and the 95% confidence intervals of the differences were estimated and compared across subgroups. From the subgroup analysis in study USA-239, treatment with risperidone was consistently more effective than placebo, as measured by change in total YMRS score from baseline to Day 2, regardless of age, gender, and the presence or absence of psychosis at baseline. The racial groups other than Caucasian/White were too small in RIS-USA-239 to derive a meaningful conclusion from the subgroup analysis for race. Subgroup analysis by baseline disease severity score showed a significant improvement for all three categories of total YMRS score and greater improvement with greater baseline severity.

a. Gender: Among the 246 patients, 106 (43%) were females and 140 (57%) were males. The between-group differences in mean change from baseline were 7.0 for men and 4.2 for women, both in favor of risperidone. This suggests a consistent effect of risperidone regardless of gender, despite the lack of statistical significance (at the 0.05 level) in the subgroup of women ($p=0.064$). This study was not designed to detect between-group differences within subgroups and is therefore insufficiently powered for such comparisons. More relevant are the between-group differences and how they compare across subgroups.

b. Race

Among the 246 patients, 71%, 20%, 7% and 2% were white, black, Hispanic, and other. Between-group differences in mean change from baseline in the two largest racial groups

were -7.0 in whites and -3.2 in blacks, both in favor of risperidone. The between-group difference for the Hispanic subgroup was –0.9. This suggests the consistent effect of risperidone regardless of race. The estimated effect-size for risperidone, (as measured by the difference in LS means between the risperidone and placebo groups) was lower for the black and Hispanic racial subgroups than for the white racial subgroup. The Difference in LS Means were: -7, -3.2, and –0.9, respectively. Due to the low numbers of black, Hispanic, and "other subjects and the variability in scores within these groups, there was not enough statistical power to formally demonstrate whether the estimated treatment effects were statistically significant in these subgroups. However, one cannot rule out that there was a statistically significant difference. One would need to include larger numbers of subjects from various racial subjects, in order to draw meaningful conclusions about efficacy among certain groups. For the white subgroup, there was a statistically significant difference in the change from baseline to Day 21 in the YMRS score, favoring risperidone ($p<0.001$)

c. Age

In study RIS-USA-239, 10%, 48%, 40% and 2% were in the age groups <23, 23-40, 41-64, and ≥ 65 years, respectively. Between-group differences in mean change from baseline were consistent across the three largest age subgroups. This indicates that risperidone has a similar effect versus placebo regardless of age group.

d. Baseline Severity of Illness (Psychosis & YMRS Score)

For the RIS-USA-239 trial at 3 weeks, risperidone treatment was consistently associated with a greater reduction in total YMRS from baseline when compared with placebo for the two analyses by symptom severity: 1) psychotic features (absent and present); and 2) among subgroups subdivided by baseline mean YMRS scores. Since only 7 subjects had baseline values YMRS scores>40, only descriptive results are given for this subgroup. Results are summarized in Table 56 and Table 57. There were statistically significant treatment effects (favoring risperidone) for subjects with psychotic symptoms ($p<0.05$), as well as for subjects without psychotic symptoms ($p<0.001$). The estimated treatment effects, (calculated by the difference in least square mean) were similar between the risperidone subgroup with psychotic symptoms (-5.2 points on YMRS) and the risperidone subgroup without psychotic symptoms (-5.9). Analysis of potential differences in efficacy among age groups demonstrated that risperidone was efficacious in the "<30" group ($p<0.001$) and in the "31-40" group ($p<0.01$). Due to the small number of subjects over the age of 40 (3), one cannot perform a meaningful analysis for this group. (However, the mean change in YMRS score for this subgroup treated with riperidone was -16.8, while the mean change for the placebo subgroup was +3).

e. Pharmacokinetic-Pharmacodynamic Relationships

There was no apparent relationship between trough plasma concentrations at Day 21 and any

of the efficacy parameters. It should be noted, however, that the sparse sampling approach employed not ideal for thoroughly characterizing potential pharmacokinetic-pharmacodynamic relationships.

8. Efficacy Conclusions- USA-239

In summary, the statistical reviewer verified the results of the sponsor's analyses of primary and secondary outcome measures. Monotherapy using flexible doses of risperidone (1-6 mg/day) was efficacious in the acute treatment of mania in subjects with a diagnosis of Bipolar Disorder. The primary efficacy endpoint for study RIS-USA-239 was the change from baseline at Day 21 in the YMRS score using a last observation carried forward (LOCF) imputation method. There was a statistically significant difference ($p< 0.001$) in this endpoint between the placebo and risperidone groups (favoring the risperidone group). The estimated least squares mean change from baseline to endpoint is -4.8 (a reduction of 4.8 points on the YMRS scale) in the placebo group and -10.6 in the risperidone arm. The estimated difference in the least squares mean change from baseline to endpoint was –5.9 with a corresponding 95% confidence interval of (-8.3, -3.4). Thus, the estimated treatment effect of risperidone compared to placebo treatment is a reduction of –5.9 points on the YMRS scale. The risperidone treatment effect is 2.22 times the effect size of placebo treatment. Such a reduction in symptomatology in acutely manic patients would be clinically significant.

Due to the high proportion of subjects who discontinued from the study (56% of the placebo group and 46% of the risperidone group), the estimated mean changes in YMRS scores and the estimated treatment effect may be biased when using the LOCF imputation method and ANCOVA model. However, at Day 3 and at Day 7 (when there were few discontinuations), there was a statistically significant difference in the change from baseline in YMRS score between the placebo and risperidone groups (favoring risperidone). Results of the secondary endpoint analyses also support the conclusion that risperidone was efficacious for the acute treatment of mania. The secondary endpoints were the mean score changes from baseline to Day 21 in the following rating scales: 1) CGI-S; GAS; and 3) PANSS. The differences at endpoint were statistically significant between treatment groups, favoring placebo. In contrast, the difference in score changes in MADRS scores was not statistically significant. Finally, subgroup analysis demonstrated that treatment with risperidone was consistently more effective than placebo, regardless of age, gender, race, baseline severity of illness, or baseline presence or absence of psychotic symptoms.

The concomitant use of lorazepam would not account for the fact that there was a treatment effect for risperidone. In fact, since the placebo group used more (1.3-fold) lorazepam than the risperidone group, the estimated treatment effect of risperidone might appear slightly higher if adjustments were made for the differential use of lorazepam. On the other hand, the lorazepam

usage in both groups was relatively modest for acutely manic subjects (1.92 mg/day and 1.43 mg/day in the placebo and risperidone groups, respectively, over the first 10 days of the study).

VII. Integrated Review of Safety- USA-239

A. Brief Statement of Conclusions

In this brief (21 days) trial of risperidone in Bipolar Disorder, Manic subjects, risperidone treatment was reasonably safe and well tolerated. There were no unexpected adverse events which might have been attributed to risperidone treatment. The number of subjects treated with risperidone was 134, for 5.78 patient years. The mean modal dose was 4.1 mg. During the trial, there were no deaths in the risperidone group, but there were two deaths in the placebo group. One subject died from injuries sustained in a motor vehicle accident. Another died of accidental asphyxiation related to food aspiration and alcohol intoxication. Serious adverse events were reported for 17(13%) subjects in the risperidone group and 10(8%) in the placebo group. In both groups, the most common SAE was manic reaction (8% of the risperidone group and 5% of the placebo group). SAE which were reported for the risperidone group but not for the placebo group were: agitation (2%), psychosis (1%), suicide attempt (1%), and abnormal thinking (1%). Eight percent (8%) and 6% of subjects in the risperidone and placebo groups, respectively, discontinued from the study due to adverse events. In both groups, the most common adverse event leading to discontinuation was "manic reaction" (3.7% of the risperidone group and 2.4% of the placebo group). Other reasons for discontin-uation from the risperidone group (but not from the placebo group) included: extrapyramidal symptoms (1.4%); somnolence (1%); agitation (1%); hypertensive encephalopathy (1%); dizziness (1%); and paroniria (1%).

Adverse events were reported by 88% of subjects in the risperidone group and 70% in the placebo group. The most commonly reported adverse events in the risperidone group (compared to the placebo group) were: extrapyramidal symptoms (37% vs. 17%); somnolence (28% vs. 7%); akathisia (16% vs. 5%); headache (14% vs.15%); dizziness (11% vs. 9%); nausea (11% 2%); dyspepsia (11% vs. 6%); agitation (8% vs. 6%); manic reaction (8% vs. 6%); abnormal vision (6% vs. 2%); and hypersalivation (5% vs. 1%). Eight subjects reported adverse events which may have been related to hyperprolactinemia. In addition, there were clinically important changes in vital signs which occurred more frequently in the risperidone group than in the placebo group. Clinically important positional increases in heart rate occurred in 69% and 36% of the risperidone and placebo groups, respectively. Significant positional decreases in both diastolic blood pressure and systolic blood pressure occurred in 34% vs. 31% and 15% vs. 11%, respectively. Mean weight increased in the risperidone group (+1.63 kg). The mean weight change in the placebo group was -0.25 kg. Three subjects in the risperidone group and none in the placebo group reported an adverse event of weight increase. Adverse events related to glucose metabolism were reported by 2 subjects in the risperidone group (hyperglycemia and glycosuria) and by one subject in the placebo group (glycosuria).

There were no clinically meaningful changes in mean ECG parameters associated with risperidone treatment, and there were no differences between groups with regard to ECG parameters. No subjects in either treatment group had a QTc >500 ms, regardless of the correction used. A small number of risperidone subjects had QTc intervals that met criteria for being prolonged, and 3% of the risperidone group had a change > 60 msec in QTcLD. There was no change in mean blood glucose level from baseline to endpoint in the risperidone group. Four subjects in each treatment group had post-baseline glucose levels that exceeded criteria for hyperglycemia. The incidence of glucose-related adverse events were 1.5% and 0.8% in the risperidone and placebo groups, respectively.

Concentration-Response & Concentration-Safety Analysis
The relationships between plasma concentrations of the active moiety and both efficacy parameters and certain safety parameters (EPS ratings, heart rate, QT, QTcB, and QTcF intervals) were explored. There were no apparent relationships observed between active moiety plasma concentrations and efficacy and safety parameters.

B. Description of Patient Exposure

Refer to the Conclusions section above.

C. Methods of Safety Review

The safety database and safety results summaries were reviewed in detail.

D. Adequacy of Safety Testing

The safety testing conducted was adequate for the 21-Day trial (please refer to the table below). The parameters and frequency of testing were appropriate for the drug, the population, and the duration of the trial. In addition to standard clinical and laboratory assessments, the sponsor conducted careful assessment of other specific parameters that would be of particular interest during treatment with risperidone or other atypical antipsychotic medications. The following parameters were monitored thoroughly: 1) EPS (with directed ratings), 12-lead ECG (including various interval calculations and corrections), pulse, blood pressure (including potential orthostasis), weight gain, serum glucose (and hemoglobin A-1-C, if glucose was elevated), prolactin levels, potential adverse events related to hyperprolac-tinemia. In addition, pregnancy testing was conducted both at baseline and at Day 21. Furthermore, investigators appeared to provide the appropriate follow-up and treatment, as indicated, for specific adverse events.

Schedule of Safety Assessments:

	SCREEN	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 8	DAY 14	DAY 21
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Body weight		X						X		X	X
ECG		X						X			X
Clin labs, UA	X	X									X
Pregnancy test	X	X									
UDS	X										
Adverse Events			X	X	X	X	X	X	X	X	X
Concom. Meds	X	X	X	X	X	X	X	X	X	X	X
EPS scale		X						X		X	X

E. Summarize Critical Safety Findings and Limitations of Data

E-1 Deaths in Controlled Trial- USA-239

There were 2 deaths in Study RIS-USA-239, (both in the placebo group), which are described below:

1. A 24-year-old man (manic, without psychotic features) discontinued from the trial due to insufficient response, after 6 days of placebo treatment. He died from injuries due to a motor vehicle accident, 20 days after discontinuation from the trial.

2.A 46-year-old man (manic, without psychotic features) withdrew consent 7 days after the start of treatment with placebo. Thirteen days later, he died due to "asphyxia by food bolus," which was associated with acute alcohol intoxication (blood alcohol level 0.20%).

E-2 Serious Adverse Events- USA-239

Serious adverse events occurred in 17 (13%) subjects in the risperidone group and in 10(8%) subject from the placebo group. SAE consisted mainly of psychiatric disorders. The most common SAE in both groups was "manic reaction," which occurred in 8% of subjects in the risperidone group and 5% in the placebo group. Serious adverse events reported for the risperidone but not for the placebo group were: agitation (2%), psychosis (1%), suicide attempt (1%), and abnormal thinking (1%).

The following are risperidone cases:

Hypertensive Encephalopathy: a 46-year-old man discontinued from the trial after 3 days of treatment with risperidone due to the SAE, hypertensive encephalopathy. He had a change in mental status (poorly responsive), and he began vomiting. His blood pressure was 150/118 (supine). On the same day, he had a generalized, tonic-clonic seizure. The patient was hospitalized for medical evaluation and treatment. He discontinued from the study.

Asthma: after 3 days in the study, a 61-year-old woman with a history of asthma required hospitalization, due to an exacerbation of asthma. The event resolved. She discontinued from the study.

Gastroenteritis and Ileus: a 58-year-old man was hospitalized due to 'gastroenteritis." Symptoms included nausea, diarrhea, fever, and headache. He was treated with I.V. antibiotics and fluids. Result of X-ray suggested ileus. He recovered in 2 days and continued in the study.

Suicidal Ideation: 10 days after completing the trial, a 48 y.o. man was hospitalized due to the SAE, pneumonia. Two days later, he had the SAE, suicidal ideation. No other details were provided regarding suicidality, which was resolved 2 days later.

Placebo group:
One subject experienced the serious adverse events of chest pain, bacterial infection, peripheral oedema, and emotional lability for which she was hospitalized. The patient was treated with intravenous antibiotics, and a bone scan was negative. The events resolved after 9 days.

Serious Adverse Events - N (%)- USA-239

	RISP N = 134	PLAC N = 125	RESULTED in DISCONT
Total no. subjects with SAE	17 (13)	10 (8)	R- 10 (8) Pl- 7 (6)
Manic reaction	10 (8)	6 (5)	R- 5 (4) Pl-3 (2)
Agitation	3 (2)	0	Pl- 1 (.8)
Psychosis	1 (.7)	0	Yes
Suicidal ideation	1 (.7)	0	n
Thinking abnormal	1 (.7)	0	n
Depression	0	1 (.8)	Yes
Emotional lability	0	1 (.8)	n
Encephalopathy,	1 (.7)	0	Yes

hypertensive			
Asthma	1 (.7)	0	n
Pneumonia	1 (.7)	0	n
Asphyxia	0	1 (.8)	Yes
Injury, NOS	1 (.7)	1 (.8)	n
Chest pain	0	1 (.8)	n
Edema, peripheral	0	1 (.8)	n
Gastroenteritis	1 (.7)	0	n
GE reflux	0	1 (.8)	n
Infection, bacterial	0	1 (.8)	n
Alcohol problem	0	1 (.8)	n

E-3 Discontinuations Due to Adverse Events- USA-239

Seven (6%) subjects in the placebo group and 10 (8%) subjects in the risperidone group discontinued treatment due to an adverse event. In both groups, the most common adverse event leading to discontinuation was "manic reaction" (2.4% of the placebo group and 3.7% of the risperidone group. Other reasons for discontinuation from the risperidone group (but not from the placebo group) included: EPS (1.4%); somnolence (1%); agitation (1%); hypertensive encephalopathy (1%); dizziness (1%); and paroniria (1%).

Discontinuations Due to Adverse Events- USA-239

	RISP N = 134	PLAC N = 125
DC due to Adverse Events	10 (8)	7 (6)
Manic reaction	5 (4)	3 (2)
Extrapyramidal d/o	2 (1)	0
Somnolence	1 (1)	0
Agitation	1 (1)	0
Paroniria	1 (1)	0
Hypertensive encephalopathy	1 (1)	0
Dizziness	1 (1)	0
Aggressive reaction	0	1 (1)
Anxiety	0	1 (1)
Depression	0	1 (1)

Psychosis	0	2 (2)
Rash, maculopapular	0	1 (1)

E-4 Commonly Reported Adverse Events- USA-239

Adverse events were reported by 88% of subjects in the risperidone group and 70% in the placebo group. The most commonly reported adverse events in the risperidone group (compared to the placebo group) were: extrapyramidal symptoms (37% vs. 17%); somnolence (28% vs. 7%); akathisia (16% vs. 5%); headache (14% vs. 15%); dizziness (11% vs. 9%); nausea (11% 2%); and dyspepsia (11% vs. 6%); agitation (8% vs. 6%); manic reaction (8% vs. 6%); abnormal vision (6% vs. 2%); and hypersalivation (5% vs. 1%).

Other adverse events that were reported by at least twice the proportion as that in the placebo group were: myalgia (5% vs. 2%); fatigue (5% vs. 2%); hypertension (4% vs.1%); impaired concentration (2% vs. 1%); abnormal thinking (2% vs. 0); amnesia (2% vs. 0); paroniria (2% vs. 0); asthenia (2% vs. 1%); heart block (2% vs. 0); lactation, non-puerpural (2% vs. 0); elevated SGOT (2% vs. 0); and ejaculation failure (2% vs. 0)

E-5 Extrapyramidal Symptom- USA-239

A higher proportion of subjects in the risperidone group reported EPS than the placebo group (37 % vs.17%). Akathisia was the most common type, occurring in 18% of risperidone and 6% of placebo patients. Hypertonia was reported by 8% vs. 3% of subjects. The next most common types of EPS were: dystonia (6% vs. 1%); "extrapyramidal disorder" (6% vs. 3%); involuntary muscle contraction (4% vs. 1%); tremor (3% vs. 4%); tetany (2% vs. 1%); tongue paralysis (2% vs. 0); followed by ataxia, dyskinesia, abnormal gait, and hypokinesia (1% vs. 0 for each). There was one discontinuation due to EPS ("tightening in the throat" and "involuntary muscle contraction").

E-6 Potentially Prolactin-related Adverse Events

There were 8 subjects in the risperidone group (6%) and 2 subjects in the placebo group (2%) who experienced potentially prolactin-related adverse events. Two subjects in each group had dysmenorrhea. Other events in the risperidone group were ejaculation failure (2), nonpuerperal lactation (2), and impotence, decreased libido, and sexual dysfunction (1 each). At baseline, 19% (21) of the risperidone group and 14%(15) of placebo group had prolactin levels above the laboratory reference range. For men in the placebo group, the mean prolactin level decreased from baseline (14.13 ng/ml) to endpoint (12.45 ng/ml). For men in the risperidone, the mean prolactin level increased from baseline (13.70 ng/ml) to endpoint (43.54 ng/ml) in the risperidone group. In women, mean prolactin increased from baseline (14.45 ng/ml) to endpoint

(14.64 ng/ml) in the placebo group, and it increased from baseline (19.35 ng/ml) to endpoint (96.12 ng/ml) in the risperidone group.

E-7 Glucose Levels and Adverse Events- USA-239

The proportions of subjects experiencing adverse events related to abnormalities in glucose metabolism were 2(2)% in the risperidone group and (1) 1% glycosuria in the placebo group and. In the risperidone group, one subject with glycosuria had a screening blood glucose level just below normal limits but had no subsequent glucose values outside of normal limits. One subject with hyperglycemia during the trial did not have a known history of diabetes. For this subject blood glucose levels were within normal limits at screening and baseline, but were above clinically important limits at Week 3 (8.7 mmol/L, which does not meet the WHO hyperglycemia criterion for non-fasting samples). In the placebo group, the subject with glycosuria had a blood glucose level of 10.2 mmol/L at baseline, 6.1 mmol/L at Week 1, and 6.9 mmol/L at Week 2

E-8 Vital Signs and Weight

The criteria for "orthostatic hypotension," abnormal vital signs, and significant weight changes are outlined n the tables below. Subjects were considered to have orthostatic hypotension only if they met all 3 criteria outlined in the table below. These parameters are clinically appropriate.

Criteria for "Orthostasis"

VITAL SIGN PARAMETER	ORTHOSTATIC LIMIT (SUPINE – STANDING)
Pulse (bpm)	≤ - 20 bpm
SBP (mmHg)	≥ 20 mmHg
DBP (mmHg)	≥ 10 mmHg

Criteria for "Clinically Important Changes" in Vital Signs

	ABNORMALLY LOW	ABNORMALLY HIGH
Pulse	Decrease ≥ 15 to a pulse ≤ 50	Increase ≥ 15 to a pulse ≥ 100
Systolic B.P	Decrease ≥ 20 to SBP ≤ 90	Increase ≥ 20 to SBP ≥ 180
Diastolic B.P.	Decrease ≥ 15 to DBP ≤ 50	Increase ≥ 15 to DBP ≥ 105
Weight (kg)	Decrease ≥ 7%	Increase > 7%
	Normal Overweight	Obese

BMI	< 25	25-29	≥ 30

Mean Changes in Vital Signs

There were some differences between treatment groups in the mean changes in vital sign parameters. The differences occurred primarily during the first week of treatment. In the risperidone group, the mean pulse (supine and standing) increased slightly from baseline within the first week and at Day 21. Also in the risperidone group, the mean diastolic blood pressure (both supine and standing) decreased slightly compared to baseline during the first week of treatment and by Day 21. Similar pulse and blood pressure changes occurred in the placebo group during the first 4 days. Neither group had significant mean changes in systolic blood pressure.

Individual Changes in Vital Signs

There was no difference between groups in the proportion of subjects meeting criteria for orthostatic hypotension. However, in the risperidone group, there were more cases of "clinically important" changes in supine minus standing systolic and diastolic blood pressures. Similarly, the risperidone group had a greater proportion of clinically important increases in standing minus supine pulse. For the risperidone group, 15% of subjects had clinically important positional changes in SBP, whereas 11% of the placebo group had such changes.
Thirty-four percent (34%) of risperidone subjects had clinically important positional changes in DBP, compared to 31% of the placebo group. Clinically important positional changes in pulse occurred in 69% of risperidone subjects and 36% of placebo subjects.

One subject in the risperidone group, who had a history of hypertension, had the serious adverse event, "hypertensive encephalopathy, which led to discontinuation from the study. Hypertension occurred in three other subjects in the risperidone group and in one subject from the placebo group. Two of these subjects had a history of hypertension. Hypotension occurred in 3 and 0 subjects in the risperidone and placebo groups, respectively. All three cases occurred on Day 2 of treatment and were rated as "mild" adverse events. None of these patients reported having dizziness or other accompanying adverse events. The lowest blood pressure values among these subjects were 72/54 mm Hg.

Weight Changes

There was a statistically significant difference between treatment groups for changes in weight from baseline to Day 21 ($p<0.001$). For the placebo group, the mean change in weight was -0.25 kg; in the risperidone group, the change was +1.63 kg. A weight decrease of ≥7% from baseline to occurred in 1.7% of subjects in the placebo group and in no subjects in the risperidone group. At Day 21 no subjects in the placebo group and 5 subjects (3.9%) in the risperidone group had a ≥7% increase in body weight from baseline. The weight gain for these 5 risperidone subjects ranged from 5.5 kg to 10.4 kg. Two of these subjects met BMI criteria for obesity at baseline (BMI>30) One was overweight at baseline, with a BMI of

26.6 and was obese at endpoint (BMI= 30.2). The other 2 subjects had a normal BMI both at baseline and endpoint. A review of the cases revealed no obvious associations with abnormalities of glucose metabolism. None of the 5 subjects had an adverse event of weight increase. No subject in the placebo group and 3 in the risperidone group had weight gain that was considered clinically significant by the investigator (i.e., had an adverse event of weight gain). For those subjects, weight gain over the 3-week treatment period ranged from 2.3 to 3.7 kg. Based on BMI, two subjects were obese at both baseline and endpoint. Another had a normal BMI at baseline but was overweight at endpoint, after gaining 3.4 kg.

E-9 Electrocardiogram Findings & Cardiac Abnormalities

ECG Parameters and Methods of Analysis

Resting 12-lead electrocardiograms (ECGs) were recorded. Clinically relevant changes that occurred during the trial were recorded as adverse events. Heart rate, along with PR, QRS, QT, QTcB, QTcF, QTcl and QTcLD intervals (msec) were analyzed. The following formulae were used to compute corrected QT intervals:

- Bazett 18,19: QTcB (msec) = QT (msec) * (HR (bpm)/60)1/2
- Fridericia 20: QTcF (msec) = QT(msec) * (HR(bpm)/60)1/3
- Sagie 21: QTcl (msec) = 1000 * QT(sec) + 0.154 * (1 - 60/HR(bpm)
- Linear derived correction factor: QTcLD (msec) = QT (msec)

For QTcB, QTcF, QTcl, and QTcLD, each corrected value was classified as normal, borderline, or prolonged at each timepoint according to the QTcB classification given by the Committee for Proprietary Medical Products (CPMP) of the European Agency for the Evaluation of Medical Products. For change from baseline in heart rate, PR, QRS, QT, QTcB, QTcF, QTcl, and QTcLD intervals, descriptive statistics were used. The number of subjects with values outside the normal limits were summarized at each visit and at endpoint by treatment group. In addition, a cross-tabulation of baseline versus postbaseline values was performed for QTcB, QTcF, QTcl, and QTcLD.

Criteria for "Abnormal ECG Parameters

ECG PARAMETER	ABNORMALLY LOW	ABNORMALLY HIGH
HR	≤ 50	≥ 100
PR interval	-- --	≥ 210 msec
QRS interval	≤ 50 msec	>200 msec
QT interval	≤ 200 msec	>500 msec

Clinically Important Limits for QT Interval per Bazett's Correction

	CLASSIF.	MEN	WOMEN
QTc value	Normal	≤ 430	< 450
	Borderline	431- 450	451- 470
	Prolonged	> 450	> 470
QTc clinically important			
QTc change from baseline	No concern	< 30	
	Concern	30-60	
	Clear concern	> 60	

Mean ECG Changes Over Time

In the risperidone group, most mean changes from baseline to endpoint in ECG parameters were small. In the placebo group, mean heart rate decreased from 74 bpm at baseline to 71 bpm at endpoint. In the risperidone group, mean heart rate increased from 73 at baseline to 75 bpm at endpoint. In the placebo group, the mean PR interval increased from 160 msec to 165 msec at endpoint. In the risperidone group, mean PR interval increased from 162.0 msec at baseline to 162.7 msec at endpoint. In the placebo group, mean uncorrected QT interval increased from 368 msec at baseline to 375 at endpoint. In the risperidone group, the mean uncorrected QT interval decreased from 369 msec at baseline to 366 msec at endpoint. Corrected QT intervals are discussed in more detail below.

Individual ECG Changes

The incidence of ECG parameters outside of clinically important limits at endpoint was generally similar in the placebo and risperidone groups. No subjects in either group had QT values outside the limits. There were 6 subjects in the placebo group and 2 in the risperidone group with prolonged PR intervals. Prolonged QRS intervals were observed in 2 (1.7%) of placebo subjects and 6 (4.8%) of the risperidone subjects.

Abnormal QTc Intervals

No subject in either group at any timepoint had a QTc interval >500 ms, regardless of the correction method used. When the QT interval was corrected using all methods except Bazett's, no subjects in the placebo group and few in the risperidone group had a QTc interval classified as prolonged (i.e.,>450 ms for men or >470 ms for women). Using the Fridericia correction, there were 2 subjects in the risperidone group with prolonged QTc at baseline, and one subject at Week 1. Regardless of the correction used, there were no occurrences of prolonged QTc at Day 21. No subjects in the placebo group had a change >60 msec in QTcF or QTcLD from baseline at Day 21. In the risperidone group, the proportion of subjects with changes >60 msec in QTcF was 3.3% at endpoint; the proportion of subjects with changes >60 msec change in QTcLD was 1.4% at Week 3 and 1.7% at endpoint. None of those changes in the risperidone group resulted in a QTc classified as borderline or prolonged, and none were reported as adverse events. For QTcF, the maximum change for the risperidone group at either timepoint was 84 msec, resulting in a QTcF of 439.69 msec, (within the normal range). For QTcLD, the maximum change in the

risperidone group was 82 msec, resulting in a QTcLD of 382 msec, (within the normal range). The only change in QTcF and QTcLD from normal at baseline to borderline or prolonged at endpoint occurred in the placebo group. In the risperidone group, subjects with QTc classified as borderline or prolonged at baseline had QTc intervals classified as normal at endpoint.

Clinically Significant Cardiac AE

The following ECG abnormalities were considered by the investigator to be clinically significant, (recorded as adverse events): tachycardia (placebo 2, risperidone 4); heart block (placebo 0, risperidone 2); bundle branch block (placebo 0, risperidone 1); myocardial ischemia (placebo 0, risperidone 1); bradycardia (placebo 1, risperidone 0); and QT prolonged (placebo 1, risperidone 0). Other potentially cardiovascular adverse events were: dependent edema (placebo 0, risperidone 1); peripheral edema (placebo 1, risperidone 1); and edema (placebo 0, risperidone 1).

The events for subjects in the risperidone group are described below:

Tachycardia

The proportion of subjects experiencing tachycardia was similar in the treatment groups. The extent of pulse increases among the 4 risperidone subjects with a was minimal. The maximum pulse recorded for any of these subjects was 140 (standing).

1. For that subject, the measurement (140) was recorded at baseline.
2. One subject had an abnormal pulse (104 bpm supine) on one occasion (Day 8) during the trial; ECGs were normal throughout the trial.
3. One subject experienced a maximum standing pulse of 135 bpm on Day 6, increased from a baseline of 84. ECGs were normal throughout. The subject also had the adverse events of vision abnormal (blurry), hypotension, somnolence, and delirium.
4. One subject had a maximum standing pulse of 124 on Day 3, increased from a baseline of 86. Standing pulse was 84 at Week 3. Interpretation of the ECG at baseline included ventricular ectopy, sinus unifocal; this was not listed in the interpretation of the Week 1 ECG. Other adverse events for this subject were blurred vision and hypotension.

Heart Block, ECG Abnormality, and Ischemia

1. Bundle branch block, consisting of widening QRS interval. QRS at baseline was 110 msec, at Week 1 was 120 msec and at Week 3 was 130 ms. All other ECG parameters were normal during the trial. Heart rate per ECG was 82 at baseline and 68 at Week 3. Relevant medical history was unremarkable.

2. Left posterior hemiblock, which occurred 1 day after the last dose of trial medication. The subject had a history of hypertension. He had sinus tachycardia and a prolonged QT on the baseline ECG. Heart rate at baseline was 107 bpm. The Week 3 ECG showed a normal sinus rhythm and left posterior hemiblock. Heart rate was 77. PR and QT intervals were normal, and QRS interval was 90 msec throughout the trial.

3. Left posterior hemiblock- this subject took trial medication (3 mg) for only one day and subsequently withdrew consent. The medical history was unremarkable. Baseline ECG showed normal sinus rhythm, heart rate of 73 bpm and QRS interval of 90 msec. An ECG the following day showed left posterior hemiblock. Heart rate was 75 bpm and QRS interval was 60 ms. The PR interval was 140 ms and QT interval was 380 msec on both occasions

4. "ECG abnormal – LV strain/ischemia", coded to "myocardial ischaemia," 1 day after discontinuing treatment due to insufficient response. The subject received trial medication for only 3 days; the maximum dose administered was 4 mg per day. The subject had hypertension, type II diabetes mellitus, and anemia (at baseline). There was an increase in QT interval from baseline to Week 1 (350 to 370 ms; QTcLD went from 385 to 410). Heart rate per ECG was 80 bpm at baseline and 84 bpm at Week 1.

Edema

1. Edema, dependent ("left ankle swelling"), 20 days after starting treatment. Other adverse events for the subject were goiter, (which was recorded on the same day), and dizziness, and somnolence early in the treatment. The baseline ECG revealed normal sinus rhythm and first degree A-V block. At Week 3, the ECG showed sinus bradycardia as well as first degree A-V block. Vital sign measurements did not show bradycardia; pulse was normal throughout the trial.

2. Edema, peripheral (left leg cellulitis; left and right leg edema), one day after beginning treatment, in a subject who had a h/o hypertension. ECG at baseline and Week 1 showed normal sinus rhythm. The subject discontinued the trial on Day 7 due to insufficient response. At that time, the edema was recorded as not recovered.

3. Edema on Day 12, in a subject who had a history of asthma and "active respiratory congestion" at baseline. The baseline ECG showed T-wave suggestive of ischemia. Other adverse events included dystonia, abnormal vision, and weight increase.

E-10 Clinical Laboratory Findings

Laboratory Parameters Measured:

1. Hematology- the following hematologic parameters were measured at screening, baseline, and Day 21 (or at early discontinuation): hemoglobin, hematocrit, red blood cell count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count. HbA1c was also measured for patients who had serum glucose >250 mg/dL at screening.

1. **Serum Chemistry-** the following laboratory parameters were measured at screening and on Day 21: total cholesterol, total protein, alkaline phosphatase, AST, SGOT, ALT, SGPT, GGT, LDH, total bilirubin, urea, uric acid, creatinine, sodium, potassium, chloride, calcium, albumin, glucose, prolactin. Upon screening, thyroxine (T4), thyroid-stimulating hormone (TSH), and blood alcohol level were measured.

3. Urinalysis: the following were measured at screening and Day 21:
-UA by dipstick for protein, glucose, and occult blood.
-If UA was abnormal, a microscopic exam was performed for WBC, RBC, and casts.
-Urine pregnancy test for women.
-Urine drug screen (only at screening).

Summary of Changes in Laboratory Values

With the exception of prolactin levels (discussed above in section VII.E.6), there were no clinically meaningful differences between baseline and endpoint in mean laboratory values in either treatment group. There was no mean change in mean blood glucose level from baseline to Day 21 in the risperidone group. In the risperidone group 19% of subjects had prolactin levels above the laboratory reference range at baseline, compared to 14% of the placebo group. In men, mean prolactin decreased from baseline (14.13 ng/ml) to endpoint (12.45 ng/ml) in the placebo group, and increased from baseline (13.70 ng/ml) to endpoint (43.54 ng/ml) in the risperidone group. In women, mean prolactin increased from baseline (14.45 ng/ml) to endpoint (14.64 ng/ml) in the placebo group, and increased from baseline (19.35 ng/ml) to endpoint (96.12 ng/ml) in the risperidone group. There were no apparent clinically important differences between treatment groups for urinalysis findings. There were 4 subjects in the risperidone group and no subjects in the placebo group with urinary glucose levels considered abnormally high.

Individual Changes in Clinical Laboratory Values

The most common parameter to change from normal (at baseline) to abnormal was glucose levels. The change was more prevalent in the risperidone group (18%) than in the placebo group (14%). Glucose values below 45 mg/dL and above 121 mg/dL were defined as outside the clinically important limits. (This range pertains to fasting samples). However, in this trial, samples were non-fasting, and values might be expected to exceed the limits considered normal under fasting conditions. In both the placebo and risperidone groups, there were 4 subjects (regardless of baseline values) who had post-baseline glucose concentrations which exceeded normal limits. One these subjects from the risperidone group had a history of diabetes mellitus As discussed above, there were 2 subjects in the risperidone group and one subject in the placebo group who reported glucose-related adverse events.

Individual Clinically Significant Laboratory Abnormalities

The following laboratory findings were reported as adverse events:

1. **Hypercholesterolemia**: in the risperidone group, one subject had hypercholesterolemia at Day 21. At baseline the subject had a normal cholesterol level.
2. **Abnormal liver function tests**:

a. SGOT and SGPT increased. The subject had slightly elevated transaminases at screening (9 and 60 U/L, respectively. The values at Day 7 were 76 and 118 U/L. One week later, the values returned to levels similar to the values at screening.

b. Another subject had elevations of SGOT and SGPT at Week 3 (67 and 167 U/L). The baseline values were normal. One week after termination of treatment, the SGOT was normal, and the SGPT decreased to 76 U/L.

c. One subject had elevated LDH, GGTP, and SGOT. The LDH was normal at screening and at baseline, and it was elevated at Week 3 (258 U/L). The SGOT was abnormal at baseline (61 U/L) and increased to 150 U/L at Week 3; levels returned to normal post-treatment. The SGPT was elevated at baseline (72 U/L), it increased to 78 U/L during the study, and SGPT declined to 48 U/L after the study. The GGT at baseline was 81, 95 at Week 3, and it returned to normal after the treatment period.

d. One subject had elevated SGOT and SGPT at baseline (baseline (92 and 153 U/L, respectively). The SGOT was normal at Week 2, and the SGPT was normal at Week 3. The same subject had a decrease in TSH (from 1.4 at screening to 0.11 mU/L at Week 3. The TSH was normal 12 days after the end of the trial. The free T4 was normal at all timepoints.

3. **Hyperprolactinemia**: in general, most subjects taking risperidone had values outside of normal range at endpoint. Elevations ranged from mild (19.6 ng/ml) to a high of 254.94 ng/ml, with the majority of values below 150 ng/ml. Eight subjects in the risperidone group had other adverse events that were considered related to prolactin levels (discussed above). The subject with the highest endpoint level did not have any potentially prolactin-related adverse events

Subjects with glucose-related adverse events, including the laboratory-related adverse events of glycosuria (1 subject in each treatment group) and hyperglycemia (1 subject in the risperidone group), are discussed above in section VII.E.7.

F. Sponsor's Summary of Safety Update for Ongoing Trials

As of August 13, 2002, more than 300 subjects have been treated in 4 ongoing clinical trials with risperidone. Safety data presented for these studies included serious adverse events reported through August 13, 2002. Overall, no new or unexpected adverse events were reported in these studies. Most adverse events reported for these trials were consistent with symptoms of the psychiatric disorders for which the subject was receiving treatment. Other common adverse events reported were categorized as either CNS, peripheral nervous system, or urinary system disorders.

G. Sponsor's Review of the Literature

A search of databases up to July 31, 2002 was conducted to retrieve publications referring to risperidone and mania. Publications containing original clinical data, (which were not based on trials conducted by the sponsor), were reviewed regarding safety data from all patients, regardless of their diagnosis. The types of safety information reported varied widely in the 315 publications obtained. Safety parameters other than adverse events were reported in few instances. The sponsor states that: "Since not all publications clearly stated the number of patients who were treated with risperidone, the exact number of exposed patients cannot be determined." Adverse events reported in the publications were compared with those reported in the Investigator's Brochure (Risperdal– All Indications, Fourth edition, October 2002). The sponsor concluded that all of the adverse events cited were comparable to those in the Investigator's Brochure, with several exceptions. Six of the 7 cases are described below:

- For three patients treated with risperidone, the reported adverse event was "encephalopathy." In two cases, the presence or absence of concomitant medications or comorbid illness was discussed. The authors did not make attributions about the adverse events. In the third case, encephalopathy was attributed to treatment with valproate. Other concomitant concomitant medications included doxepin, lorazepam, and biperiden.
- One patient treated with risperidone was reported to have neuroleptic malignant syndrome (NMS) and elevated urine myoglobin levels, both of which were diagnosed on the second day of risperidone therapy. Concomitant medication included lithium. The authors attributed causality to risperidone. (Labeling includes NMS in the Warnings section).

- One patient was reported to have "neurotoxicity." Details are not available. The author did not draw a conclusion about the cause(s) of the event and did not discuss potential concomitant medications or comorbid illness.
- One patient was reported to have nephrogenic diabetes insipidus and papilledema. The diabetes insipidus was attributed to the use of lithium. The patient was also treated with oral contraceptive medications.

Reviewer's Comment:
Although "encephalopathy" does not appear in labeling as a potential adverse event, labeling for risperidone does include the following adverse events in the ADVERSE REACTIONS section: delirium, stupor, confusion, aphasia, coma, catatonic reaction, amnesia, and impaired concentration. These adverse events were reported during pre-marketing trials in Schizophrenic subjects.

H. Concentration-Response & Concentration-Safety Analysis

The relationships between active moiety plasma concentrations and safety parameters (EPS ratings, heart rate, QT, QTcB, and QTcF intervals) were explored. There were no apparent relationships observed between active moiety plasma concentrations and efficacy and safety parameters.

STUDY RIS-IND-2

VIII. Integrated Review of Efficacy- IND-2

A. Brief Statement of Conclusions

The efficacy of risperidone as monotherapy was demonstrated in this trial. The difference in YMRS score changes between treatment groups was statistically significant, favoring risperidone ($p<0.001$). The mean decreases from baseline in YMRS score at Day 21 were -22.7 and -10.5 points in the risperidone and placebo groups, respectively. The difference between the risperidone and placebo groups in the change in least-squares means (-12) was statistically significant ($p<0.001$), favoring risperidone. In addition, the differences in change in least square means between the risperidone and placebo groups were statistically significant at Day 3, Day 7, and Day 14 ($p<0.001$ for all analyses), favoring treatment with risperidone. The secondary endpoints consisted of the changes from baseline to Day 21 in CGI-S, GAS, PANSS and MADRS scores. For all analyses, the results were statistically significant; favoring risperidone group. In addition, treatment with risperidone was consistently more effective than placebo, regardless of age, gender, race, baseline severity of illness, or the presence or absence of psychotic symptoms at baseline.

There were several differences in results between monotherapy trials USA-239 and IND-2. The estimated treatment effect was larger in IND-2 than in USA-239. The estimated mean changes in YMRS scores from baseline to endpoint were –12.4 and –5.9, respectively. Moreover, the mean baseline score in the risperidone group was higher (indicating greater severity) than that in USA-239 (37.1 vs. 29.1). Also, the endpoint mean score in IND-2 was lower than that in USA-239 (14.5 vs. 18). The mean baseline scores in the placebo groups were nearly identical to those in the risperidone groups of each study. In addition, higher mean risperidone doses were used in IND-2 than USA-239. The mean modal doses were 5.6 mg and 4.1 mg, respectively. At Week 3, the serum concentrations of the active moiety of risperidone in IND-2 were also higher than in USA-239 (47.1 vs. 27.2 ng/mL). When normalized to a 4 mg dose, the concentration remained higher in IND-2 (34.4 vs. 27.4 ng/mL). There was an uncharacteristically low proportion of subjects who discontinued from the study (20%), compared to 51% in study USA-239. Finally, the total dose of lorazepam used in study IND-2 was approximately 2.5 times the amount of lorazepam used in USA-239.

B. General Approach to the Review of Efficacy

The complete efficacy database and summaries of efficacy results provided by the sponsor were reviewed in detail.

C. Detailed Review of the Trial

C-1 Study Sites and Investigators- IND-2

Study RIS-IND-2 was conducted in India at 8 sites. (Refer to Appendix for a full list of study sites and investigators.

C-2 Subject Selection Criteria- IND-2

In study RIS-IND-2, subjects with a mixed episode were included, in contrast to RIS-USA-239. The other inclusion and exclusion criteria were identical to those in RIS-USA-239. (Refer to section VI.D-2.

C-3 Objectives of the Study- IND-2 (identical to RIS-USA-239)

C-4 Design of the Study- IND-2 (identical to RIS-USA-239)

C-5 Outcome Measures- IND-2 (identical to RIS-USA-239)

C-6 Disposition of Subjects- IND-2

In IND-2, 90% (291/324) of individuals screened were randomized, and 90% (290/324) were treated. All of the 145 subjects randomized to risperidone received treatment, and 99% (145/146) of subjects randomized to the placebo received treatment. In this study, 80% of subjects completed (89% of the risperidone group and 71% of the placebo group).

C-7 Discontinuations- IND-2

In IND-2, only 11% and 29% discontinued from the risperidone and placebo groups, respectively. The most common reasons for discontinuation in were: Insufficient Response, Withdrew Consent, and Adverse Event.

Reasons for Discontinuations- IND-2

	IND-2	
	RISPERID N = 146	PLACEBO N = 144
Completed	130 (89)	102 (71)
Discontinued	16 (11)	42 (29)
Insufficient response	7 (5)	21 (15)
Withdrew consent	1 (.7)	6 (4)
Adverse Event	5 (3)	3 (2)
Lost to follow-up	1 (.7)	10 (7)
Other	2 (1)	2 (1)

C-8 Baseline Demographics & Severity of Illness- IND-2

Baseline Demographics– IND-2

Generally, there were no significant differences in baseline demographics between treatment groups in Study IND-2. However, there was a significantly higher proportion of male subjects versus female subjects in IND-2 (63% versus 37%). In the risperidone group, 69% of subjects were male; in the placebo group, 56% of subjects were male. The mean and median ages in the risperidone and placebo groups were nearly identical. Nearly all subjects were Indian (99% in the risperidone group and 100% in the placebo group). The mean and median weight, height, and body mass index were nearly identical for the 2 treatment groups.

Baseline Severity of Illness-IND-2

In summary, the risperidone and placebo groups were well matched according to baseline severity of illness. The baseline YMRS scores were nearly identical between treatment groups (37 for the risperidone group and 37.4 for the placebo group). The majority of subjects had psychotic symptoms at baseline (60% of the risperidone group and 57% of the placebo group). At baseline only 12 (4%) subjects had a mixed episode (3% and 6% of the risperidone and placebo groups, respectively). Generally, the baseline CGI-severity scores, (subgrouped as mild, moderate, marked, severe, and extremely severe) were similar in the treatment groups. The baseline PANSS and GAS scores were nearly identical between groups, and the baseline MADRS scores were similar between treatment groups.

Baseline Severity of Illness- IND-2

	RISPERID N = 146	PLACEBO N = 144
Baseline Total YMRS- mean	37.0	37.4
-Manic with psychosis	85 (58)	79 (54)
-Manic without psychosis	57 (39)	57 (40)
-Mixed with psychosis	3 (2)	4 (3)
-Mixed without psychosis	1 (1)	4 (3)
Baseline CGI-S, n (%)		
-Mild	0	1 (0.7)
-Moderate	45 (31.0)	41 (28.5)
-Marked	57 (39.3)	51 (35.4)
-Severe	37 (25.5)	47 (32.6)
-Extremely severe	6 (4.1)	4 (2.8)
Baseline PANSS- mean	54.2	54.2
Baseline GAS- mean	35.2	34.6
Baseline MADRS- mean	5.1	5.9

Bipolar Disorder History

The Bipolar Disorder History characteristics were extremely well balanced between treatment groups. The number of manic, mixed, psychotic, and depressive episodes were quite similar between groups. There were no significant differences in any of the parameters assessed. The treatment groups had nearly identical by history number of: manic, mixed, psychotic, depressive episodes.

C-9 Treatment Dose and Duration- Study IND-2

The mean modal dose of risperidone was 5.6 mg. The mean duration of risperidone treatment was 19.9 days. The mean duration of placebo treatment was 17.9 days. The mean number of tablets per subject/day in the placebo group was 5.32.

C-10 Concomitant Medications- IND-2

Permitted & Prohibited Psychotropic Medications- IND-2
These were the same as in USA-239

Lorazepam Use- IND-2
Lorazepam use during the 21-day double-blind phase was analyzed (refer to the table below). In general, higher doses of lorazepam were used in RIS-IND-2 with a longer duration than in RIS-USA- 239. The proportion of subjects treated with lorazepam was comparable between the risperidone (94%) and placebo (95%) treatment groups. In contrast, the total lorazepam dosage used by the placebo group (4,953 mg) was higher than that of the risperidone group (4,435 mg). Similarly, the total lorazepam dosages per mITT subject and per subject treated with lorazepam were higher in the placebo group compared to the risperidone group (34.4 mg versus 30.4 mg and 36.1 mg versus 32.4 mg, respectively). The mean and median doses of lorazepam were also higher in the placebo group compared to the risperidone group (4.4 mg vs. 4.1 mg and 4.4 mg vs. 4.0 mg, respectively). Finally, the mean and median duration of lorazepam treatment was greater in the placebo group than in the risperidone group.

Lorazepam Use During IND-2

	PLAC	RISP
Number of subjects (N)	N=144	N=146
No. subj. treated w/ Lorazepam = n*	n*= 137 (95%)	n*= 137 (94%)
Total Lorazepam dosage (mg)	4952	4435
Total Lorazepam dosage/ N	34	30
Total Lorazepam dosage/ n*	36	32
Mean single dose	4.4	4.1
Median single dose	4.4	4.0
Duration of Lorazepam Rx (Days)		
Mean	8.0	7.5
Median	9.0	8.0
Duration of Lorazepam Rx (as percentage of study treatment duration) %		
Mean	53%	41%
Median	48%	43%

Dose/day (mean) for n*, for 10-day period of permitted lorazepam use	3.61 mg	3.24 mg

General Concomitant Medication Use

The majority of subjects in the trial were treated with concomitant medications. Lorazepam was the most commonly used (94% in the risperidone group and 95% in the placebo group). Medications for the treatment of EPS were used by 38% of the risperidone group and 10% of the placebo group. The most commonly used medications for EPS were anticholinergics (36% and 6% of the risperidone and placebo groups, respectively), followed by antihistamines (11% vs. 2%), and beta-blockers (2% vs. 1%). Other commonly used medications (by approxi-mately 5-10% of subjects): ranitidine, ibuprofen, acetominophen, and amoxicillin. The distribution of use was very similar between groups

D. Efficacy Conclusions

1. Brief Statement of Conclusions

In summary, the statistical reviewer verified the results of the sponsor's analyses of primary and secondary outcome measures. Monotherapy using flexible doses of risperidone (1-6 mg/day) was efficacious in the acute treatment of mania in subjects with a diagnosis of Bipolar Disorder.

The primary efficacy endpoint for study RIS-IND-2 was the change from baseline at Day 21 in the YMRS score using a last observation carried forward (LOCF) imputation method. The mean decreases from baseline in YMRS at Day 21 were -22.7 and -10.5 points in the risperidone and placebo groups, respectively. The difference between the risperidone and placebo groups in the change in least-squares means (LSMeans) was 12 points. The difference was statistically significant ($p<0.001$), favoring risperidone. In addition, the differences in change in least square means between the risperidone and placebo groups were statistically significant at Day 3, Day 7, and Day 14 ($p<0.001$ for all analyses), favoring treatment with risperidone. The secondary endpoints consisted of the changes from baseline to Day 21 in CGI-S, GAS, PANSS and MADRS scores. For all analyses, the results were statistically significant, favoring risperidone group. In addition, treatment with risperidone was consistently more effective than placebo, regardless of age, gender, race, baseline disease severity score, or the presence or absence of psychotic symptoms at baseline.

2. Primary Efficacy Results

There was a statistically significant difference ($p<0.001$) in the primary endpoint between the placebo and risperidone groups, favoring risperidone. The efficacy results for IND-2 are summarized in the table below. At baseline, the mean YMRS scores were 37.1 in the risperidone group and 37.5 in the placebo group. Note that these baseline score were higher than in study USA-239. At endpoint in IND-2, the mean YMRS scores were 14.5 and 26.9, respectively. Thus, the change in mean score was –22.7 in the risperidone group and –10.5 for the placebo group. For both groups, the mean magnitude of change was more than twice that in USA-239, For IND-2, the estimated least squares mean change from baseline to endpoint is –10.8 for the placebo group and –23.2 for the risperidone group. Finally, the estimated difference in the least squares mean change from baseline to endpoint was –12.4, with a corresponding 95% confidence interval of (-15.6, -9.3), favoring risperidone. Thus, the estimated treatment effect of risperidone compared to placebo treatment is a reduction of 12.4 points on the YMRS scale. This estimated treatment effect is more that twice that in USA-239 (5.9). Such a treatment effect would be quite clinically significant for the treatment of acute mania.

The mean decreases from baseline in YMRS at Day 21 were -22.7 and -10.5 points in the risperidone and placebo groups, respectively. The difference between the risperidone and placebo groups in the change in least-squares means (LSMeans) was 12.4 points. The difference was statistically significant ($p<0.001$).

Summary of the Change from Baseline in YMRS at Day 21 (LOCF)- IND-2

RX	N	Baseline Mean (SD)	Day 21/ Endpoint Mean (SD)	Change Mean (SD)	Comparison with Placebo		
					LSMean Change (SD[a])	Diff in LSM Change (95%CI)	p-value
PLAC	142	37.5 (7.93)	26.9 (15.50)	-10.5 (15.47)	-10.8 (13.45)		
RIS	144	37.1 (7.91)	14.5 (12.81)	-22.7 (13.63)	-23.2 (13.45)	-12.4 (-15.6, -9.3)	<0.001

N: Number of patients with both baseline and post-baseline time point measurements.
p value: Between treatment comparison based on ANCOVA model with treatment, investigator, psychotic feature as factors, and baseline value as covariate.
a: Pooled SD based on the ANCOVA model.

3. Secondary Efficacy Analysis- IND-2

The sponsor performed a longitudinal analysis of the change from baseline in YMRS scores at each assessment timepoint (Days 3, 7, 14, and 21), based on the LOCF data. There were significant differences between groups in changes from baseline YMRS scores at Days 7, 14, and 21 ($p<0.001$ for all 4 time points). The treatment effect favored risperidone at each timepoint. The between-treatment difference in the mean change in YMRS score increased from Day 3 to Day 7 and was relatively stable thereafter. Using a Mixed Effects Model, Dr. Rothmann found that the results were consistent with those described above.

4. Secondary Outcome Measures- Study IND-2

The analyses pertained to the changes from baseline to Day 21 in CGI-S, PANSS, GAS, and MADRS scores. In summary, all 4 outcome analyses were positive at Day 21. The p-value was<0.001 for the CGI-S, PANSS, and GAS analyses. The p-value was <0.01 for the analysis of MADRS scores. These measures were positive at most of the other time points. There was no

adjustment for multiple comparisons in the statistical analysis plan for these secondary outcome measures; however, the results appear to demonstrate a high degree of statistical significance.

5. Subgroup Analyses of Efficacy- IND-2

The consistency in the effect of risperidone between subgroups of patients with different demographic backgrounds, baseline disease severity, and other characteristics was analyzed. Subgroup analyses were performed for the change from baseline in YMRS score at Day 21. The effects of treatment with risperidone, were consistent across all subgroups.

Age: Of the 286 subjects, 15%, 56%, 27% and 2% were in the age groups <23, 23-40, 41-64, and ≥ 65 years, respectively. In these three age groups (except for the ≥ 65 years subgroup), the differences in LSMeans and the upper 95% confidence limits were less than zero. This indicated that treatment with risperidone was consistently more effective than placebo regardless of the age of subjects.

Gender: Among the 286 patients, 108 (38%) were women and 178 (62%) were men. In these two subgroups, the differences in LS Means and the upper 95% confidence limits were all less than zero, indicating that treatment with risperidone was consistently more effective than placebo in both subgroups.

Race: Since all subjects except one were classified in the race group "other", an analysis by racial subgroups was not performed.

Presence/absence of psychotic features: Of the 286 subjects, 167 (58%) had psychotic symptoms at baseline and 119 (42%) did not. In both subgroups, the differences in LS Means and the upper 95% confidence limits were less than zero. This indicated that treatment with risperidone was consistently more effective than placebo regardless of presence of psychotic features at baseline.

Manic/mixed episode: Since only 11 (4%) subjects had a mixed episode at baseline, a formal analysis was not performed.

Baseline Severity- YMRS Score

The effectiveness of risperidone as compared with placebo was consistently significant in all subgroups.

The reviewer verified the sponsor's LOCF after three weeks analyses of the change from baseline in total YMRS, CGI-severity, GAS, PANSS and MADRS. Monotherapy with flexible dosing of 1-6 mg/day risperidone was superior to placebo in the treatment of acute manic episodes associated with Bipolar I disorder, as measured by mean change from baseline to endpoint in the total YMRS score, the primary efficacy variable, over a 3-week period.

6. Efficacy Conclusions

In summary, the statistical reviewer verified the results of the sponsor's analyses of primary and secondary outcome measures. Monotherapy using flexible doses of risperidone (1-6 mg/day) was efficacious in the acute treatment of mania in subjects with a diagnosis of Bipolar Disorder. The primary efficacy endpoint for study RIS-IND-2 was the change from baseline at Day 21 in the YMRS score using a last observation carried forward (LOCF) imputation method. The mean decreases from baseline in YMRS at Day 21 were -22.7 and -10.5 points in the risperidone and placebo groups, respectively. The difference between the risperidone and placebo groups in the change in least-squares means (LSMeans) was 12 points. The difference was statistically significant ($p<0.001$), favoring risperidone. In addition, the differences in change in least square means between the risperidone and placebo groups were statistically significant at Day 3, Day 7, and Day 14 ($p<0.001$ for all analyses), favoring treatment with risperidone. The secondary endpoints consisted of the changes from baseline to Day 21 in CGI-S, GAS, PANSS and MADRS scores. For all analyses, the results were statistically significant, favoring risperidone group. In addition, treatment with risperidone was consistently more effective than placebo, regardless of age, gender, race, baseline disease severity score, or the presence or absence of psychotic symptoms at baseline.

IX. Integrated Review of Safety- RIS-IND-2

A. Brief Statement of Conclusions

Safety Conclusions- IND-2

The total number of subjects exposed was 146, for a total of 7.96 subject-years. In this double-blind, flexible-dose trial, the mean risperidone dose was 5.2 mg (mean mode dose was 5.6 mg). There were no deaths reported for this trial. The proportions of proportions of subjects experiencing serious adverse events were similar in the treatment groups: 4 (2.7%) in the risperidone group and 3 (2.1%) in the placebo group. Few subjects in either group discontinued due to adverse events: 5 (3.4%) in the risperidone group and 3 (2.1%) in the placebo group. Adverse events were reported by 64% of the risperidone group and 48% of the placebo group and. The most commonly reported adverse events in the risperidone group were extrapyramidal symptoms (45% in the risperidone group vs. 8% in the placebo group); tremor (10% vs. 1%); headache (6% vs. 3%); insomnia (6% vs. 10%); somnolence (6% vs. 3%); and dystonia (5% vs. 0%).

Prolactin levels increased from baseline to endpoint for subjects in the risperidone group. No potentially prolactin-related clinical adverse events were reported. Among subjects with normal non-fasting glucose levels at baseline, postbaseline abnormalities were more common in the

risperidone group than the placebo group. The changes were small, and most were not consistent with hyperglycemia. Among all subjects, (regardless of glucose levels at baseline), the number of glucose level abnormalities at endpoint was similar between the treatment groups. The incidence of glucose-related adverse events in the risperidone group was 1.4%. Reduced hematocrit, hemoglobin levels, and RBC were more common in the risperidone than in the placebo group. The mean and mean change for these parameters was similar in the placebo and risperidone groups. There were no clinically meaningful differences between groups with regard to vital signs, body weight, and ECG parameters. No subject in either treatment group had a QTc >500 ms, regardless of the correction method used.

B. Methods and Specific Findings of Safety Review

The safety database and the sponsor's summary of safety findings were reviewed. The findings are discussed in the sections below.

D. Adequacy of Safety Testing

The types of safety variables monitored and the methods for conducting safety evaluations were identical to those in Study RIS-USA-239. Safety monitoring was adequate in this study.

E. Summarize Critical Safety Findings and Limitations of Data

Table. Deaths, Serious Adverse Events, and Adverse Events Leading to Discontinuations- IND-2

IND-2	RISPERID N = 146	PLACEBO N =144
Deaths	0	0
SAE	4 (2.7)	4 (2.1)
Discontinuations Due to AE	5 (3.4)	3 (2.1)

E-1 Deaths in Controlled Trials

There were no deaths in Study RIS-IND-2 in either treatment group

E-2 Serious Adverse Events

A relatively low proportion of subjects experienced serious adverse events in study IND-2. Serious adverse events were reported for 4(2.7%) of subjects in the risperidone group and 4(2.1%) of the placebo group. The most common SAE in both groups was "manic reaction," which occurred in one subject in the risperidone group and in two subjects from the placebo group.

The following are brief descriptions of the serious adverse events experienced by subjects treated with risperidone:

1. Cellulitus and abscess of the foot in a subject with diabetes mellitus, which required drainage and antibiotic treatment. The subject remained in the study.
2. Worsening of manic symptoms, which resulted in re-hospitalization.
3. Head injury as the result of an assault, which led to re-hospitalization. The subject recovered without sequelae.
4. Peripheral edema of the lower extremity. The subject remained in the study.

In the placebo group, 4 subjects experienced serious adverse events. Two of the serious adverse events were seizures. One was related to a subdural hygroma, and the other was probably due to withdrawal from lorazepam. One case of seizure led to discontinuation from the study. Two subjects experienced a "manic reaction."

E-3 Discontinuations Due to Adverse Events- IND-2

There were 5 (3)% subjects in the risperidone group and 3 (2%) in the placebo group who discontinued from the study due to an adverse event. These are listed in the table below. Elevated liver enzymes (risperidone group)- Liver enzymes were mildly elevated at screening, increased at baseline and at Week 1 (the last laboratory data available for this subject). The subject discontinued due to this adverse event.

Adverse Events Leading to Discontinuation

	RISPERID N =146	PLACEBO N =144
Any AE leading to DC	5 (3.4)	3 (2.1)
Insomnia	2 (1.4)	1 (.7)
Extrapyramidal d/o	1 (.7)	0
Convulsions	1 (.7)	1 (.7)
Psychosis	0	1 (.7)
Clinical lab abnormality	1 (.7)	0

Risperidone group:

1. Elevated transaminases- the subject had mildly elevated ALT and AST at screening. They were higher at screening (52, 42). At Week 1, the ALT and AST were 281 and 269, respectively. The subject discontinued due to being "uncooperative," even though the reason for discontinuation was coded officially as "elevated liver enzymes." The outcome is unclear.

2. Seizure- this subject had no h/o seizure disorder. Throughout the beginning of the trial,

he was treated with the maximum permitted doses of lorazepam. Near the end of tapering lorazepam treatment, the subject had a seizure. The neurologist diagnosed the condition as benzodiazepine withdrawal.

3 Extrapyramidal Disorder- this subject had persistent EPS. The particular features were not specified. Action taken included reducing the dose of study drug and beginning treatment with diazepam. RIS doses ranged between 4-5 mg after the initial few days of treatment. The subject discontinued on Day 20.

Two other RIS subjects discontinued due to persistent insomnia.

Placebo group:

1. Convulsion- the subject did not have a h/o seizure disorder. He had been taking near maximally permitted doses of lorazepam. He was treated as an outpatient for about 6 days and required rehospitalization for increasing mania and agitation. The subject had a generalized tonic-clonic seizure soon after rehospitalization. Medical evaluation revealed bifrontal subdural hygroma, which was thought to be the cause of the seizure.

2. Psychosis- this subject had psychotic symptoms throughout the study. The symptoms became more acute during the first two weeks of the study.

3. One subject discontinued due to "severe insomnia."

E-4 Commonly Reported Adverse Events

Adverse events were reported by 64% of the risperidone group and 48% of the placebo group and. The most commonly reported adverse events in the risperidone group were: extrapyramidal symptoms (45% in the risperidone group; 8% in the placebo group); tremor (10% vs. 1%); headache (6% vs. 3%); insomnia (6% vs. 10%); somnolence (6% vs. 3%); dystonia (5% vs. 0%); edema (3% vs. 1%)

E-5 Extrapyramidal Symptoms- IND-2

As discussed above, 45% of subjects in the risperidone group reported EPS vs. 8% of the placebo group. Most cases were termed "extrapyramidal disorder." Categorization of the EPS reported during the trial is outlined in the table below.

	RISPERIDONE	PLACEBO
Any Extrapyramidal Sx	66 (45)	11 (8)
"Extrapyramidal d/o"	51 (35)	9 (6)
Tremor	14 (10)	2 (1.4)
Dystonia	7 (5)	0

Occulogyric crisis	2 (1.4)	0
Akathisia	2 (1.4)	0

E-6 Glucose Metabolism- Hyperglycemia and Glycosuria

The proportions of subjects with glucose-related adverse events in this trial were 1.4% (2 subjects) in the risperidone group and none in the placebo group. Both events in the risperidone group were instances of hyperglycemia. Both subjects had baseline glucose levels within the clinically important limits. At Day 21,bone subject who had a history of "diabetes mellitus under control by medication," had a serum glucose level of 153 mg/dL, and the other, who had no prior history of endocrine disorders, had a level of 160.2 mg/dL.

E-7 Vital Signs

In summary, there were no clinically meaningful differences in mean changes between groups with regard to vital signs, body weight, and ECG parameters from baseline to any assessment timepoint in any vital sign parameter.

Specific Changes in Vital Signs

In the risperidone group, there was a higher proportion of subjects (compared to the placebo group) who had clinically important changes in diastolic blood pressure (supine minus standing). This was most pronounced on Day 6, when 6.4% of the risperidone group and 2.2% of the placebo group had a difference between supine and standing values of 10 mmHg or more. At endpoint, the treatment groups had similar degrees of change: 6.3% in the risperidone group and 5.6% in the placebo group and had supine-standing diastolic blood pressure outside of the potentially clinically important limits. For other vital sign parameters, the changes in values were similar between groups.

Individual Clinically Significant Abnormalities

There were more subjects with adverse events of vital sign abnormalities in the placebo group than in the risperidone group: hypertension (placebo- 6; risperidone- 1), hypotension (placebo- 1; risperidone- 0), postural hypotension (placebo 1; risperidone 0).

E-8 Weight

Mean Weights Over Time

Mean weight changes from baseline to endpoint were small and comparable between the two treatment groups. The mean weight change in the placebo group was an increase of 0.07 kg. The mean increase in the risperidone group was 0.06 kg.

Individual Weight Changes
A weight decrease of ≥7% from baseline to endpoint occurred in a similar percentage of subjects in each treatment group. At endpoint, a higher percentage of the placebo group than the risperidone group gained ≥7% of baseline body weight. For none of those was BMI above normal at baseline or endpoint. Of the 4 subjects in the risperidone group, one had a baseline BMI of 12.7 and had a BMI of 13.9 at endpoint. The other 3 patients had BMI values of 19.6, 16.4, and 19.8 at screening/baseline and had BMI values of 22.9, 18.3, and 21.6, respectively, at endpoint, all below the cutoff for "overweight."

Individual Clinically Significant Abnormalities
Weight changes among risperidone-treated subjects were not considered clinically significant by the investigator, (i.e., no patients in the risperidone group had an adverse event of weight change). In the placebo group, two subjects had adverse events of weight increase, and one subject had an adverse event of weight decrease.

Hyperprolactinemia and Related Adverse Events
Prolactin levels increased from baseline to endpoint for subjects in the risperidone group. No potentially prolactin-related adverse events were reported.

E-9 Electrocardiogram Findings

The types of ECG assessments and the methods used for interval corrections were the same as those used in study USA-239.

Mean Values Over Time
Most mean changes from baseline to endpoint for ECG parameters were small and comparable between groups. There was a similar decrease in mean heart rate for both groups (from 83.7 to 78.2 bpm in the placebo group, and from 83.3 to 78 bpm in the risperidone group). The treatment groups had similar increases in uncorrected QT intervals: from 350 to 361 ms at baseline and endpoint, respectively, in the placebo group, and from 349 to 360 ms at baseline and endpoint, respectively, in the risperidone group. There was a slight difference between the groups with respect to change in PR interval. The mean change in the risperidone group was 1.1 ms, whereas the change in the placebo group was –3.7 ms.

Individual ECG Changes
The numbers of ECG measurements meeting criteria for being "clinically important" were generally similar in the placebo and risperidone groups. No subjects in either group had QRS or QT values outside the limits. No subjects in the placebo group and 3 (2.1%) in the risperidone group had elevated PR intervals. Low heart rate occurred in four subjects in the

placebo group (2.9%) and 2 (1.4%) in the risperidone group. Although there was a 9% incidence of elevated heart rate in both groups, this proportion was lower than at baseline (18% in the placebo group, and 14.6% in the risperidone group).

Corrected QT Intervals
No subject in either treatment group at any time-point had a QTc interval >500 ms, regardless of the correction method used. When the QT interval was corrected using all methods except Bazett's, no subjects in either group had a QTc interval classified as prolonged (i.e, >450 ms for males or >470 ms for females. At both Week 3 and endpoint, the proportion of subjects having >60 ms change in QTcF and QTcLD was low and similar between groups. None of those changes in the risperidone group resulted in a corrected QT classified as borderline or prolonged. None were reported as adverse events or were associated with reported symptoms. For QTcF the maximum change in the risperidone group at either time-point was 106 ms, resulting in a QTcF of 413 ms (within the normal range). For QTcLD, the maximum change in the risperidone group was 93 ms, resulting in a QTcLD of 415 ms (within the normal range). The only changes of QTcF and QTcLD from normal at baseline occurred in the placebo group. In both groups, subjects with a QTc classified as borderline at baseline had a QTc classified as normal at endpoint.

Individual Clinically Significant Abnormalities
The number of ECG abnormalities considered by the investigator to be clinically significant was low in both treatment groups. One subject in the placebo group had an adverse event of QT prolonged. One subject in the risperidone group had adverse events of both tachycardia and QT prolonged. The risperidone-treated subject was a 27-year-old man with no history of cardiovascular disorders. His heart rate at screening was 104 bpm, 100 at baseline, and 98 on Day 2. On Day 3 the heart rate was 104 bpm. This was reported as tachycardia, rated moderate and very likely related to drug. No action was taken. As measured on ECG, heart rate on Day 7 was 120 bpm, compared to 98 bpm at baseline. Heart rate at endpoint was 72 bpm, and the outcome was considered to be recovered. Based on the ECG at Day 7, the investigator recorded an adverse event of "QTc prolongation," rated moderate, and very likely related to drug. No action was taken, and the trial medication dose remained unchanged. QTcLD was 408 ms, compared to 371 ms at baseline. At endpoint, the QTcLD was 350 ms and the outcome was considered "recovered."

E-10 Clinical Laboratory Findings

There were no meaningful differences between baseline and endpoint in mean laboratory values in either treatment group, with the exception of increases in prolactin levels. Approximately 20-30% of subjects had prolactin levels above the laboratory reference range

at baseline. In men, mean prolactin decreased from baseline (14.2 ng/ml) to endpoint (10.0 ng/ml) in the placebo group, and increased from baseline (17.5 ng/ml) to endpoint (51.2 ng/ml) in the risperidone group. In women, mean prolactin decreased from baseline (27.85 ng/ml) to endpoint (17.95 ng/ml) in the placebo group, and increased from baseline (23.26 ng/ml) to endpoint (160.7 ng/ml) in the risperidone group. Despite the increase, no potentially prolactin-related adverse events were reported.

A high number of anemic subjects was identified through laboratory testing during the screening period. A large number of subjects in both groups had abnormally low hemoglobin, hematocrit, and RBC values (32%, 18%, and 36%, respectively, in the placebo group and 26%, 13%, and 36%, respectively, in the risperidone group). Anemia is an endemic condition in the region in which the trial is conducted (likely related to diet). There were no clinically important differences between treatment groups for urinalysis findings.

Individual Changes in Laboratory Values

The most common laboratory abnormality was elevated glucose. Although this was most prevalent in the risperidone group (27%), it also occurred in 19% of the placebo group. Glucose values below 45 mg/dL and above 120.6 mg/dL) were defined as outside the clinically important limits (for fasting samples). However, in this trial, samples were non-fasting and would be expected to exceed the limits considered normal under fasting conditions. Similar numbers of subjects in each group (regardless of baseline value) had elevated post-baseline values (5 in the placebo group and 3 in the risperidone group). For most subjects, the extent of the changes were relatively small. Among all subjects in the risperidone group (regardless of baseline value), the maximum post-baseline value observed during the treatment period was 11.4 mmol/L at Week 3, in a subject who had values above the clinically important limits at both screening and baseline (7.9 and 8.1 mmol/L, respectively). This subject, in the risper-idone group, met criteria suggestive of diabetes mellitus. There were two such subjects, both with high baseline values, in the placebo group. As discussed above, there were 2 subjects, both in the risperidone group, with glucose-related adverse events.

Decreased hematocrit, hemoglobin, and RBC, respectively, were noted in 6.5%, 12.8%, and 3.8% of the risperidone-treated subjects who had values within the normal ranges at baseline. In the placebo group, 1.8%, 5.1%, and 0% had decreased hematocrit, hemoglobin, and RBC, respectively. None of these values were considered clinically significant by the investigator, (i.e., none were recorded as an adverse event of anemia). For other parameters, the incidence of post-baseline values outside of the normal range was comparable

Individual Clinically Significant Abnormalities

The following laboratory findings were reported as adverse events:

1. **TSH decreased** (placebo group)- a decrease in TSH from 0.6 mU/L at baseline to 0.1 mU/L at Week 3. (reference range 0.4 – 5). No related clinical symptoms were observed.

2. **Increase in TSH** (risperidone group) from 2.3 mU/L at baseline to 5.9 mU/L at Week 3 Thyroxine was normal and the event was not considered clinically significant

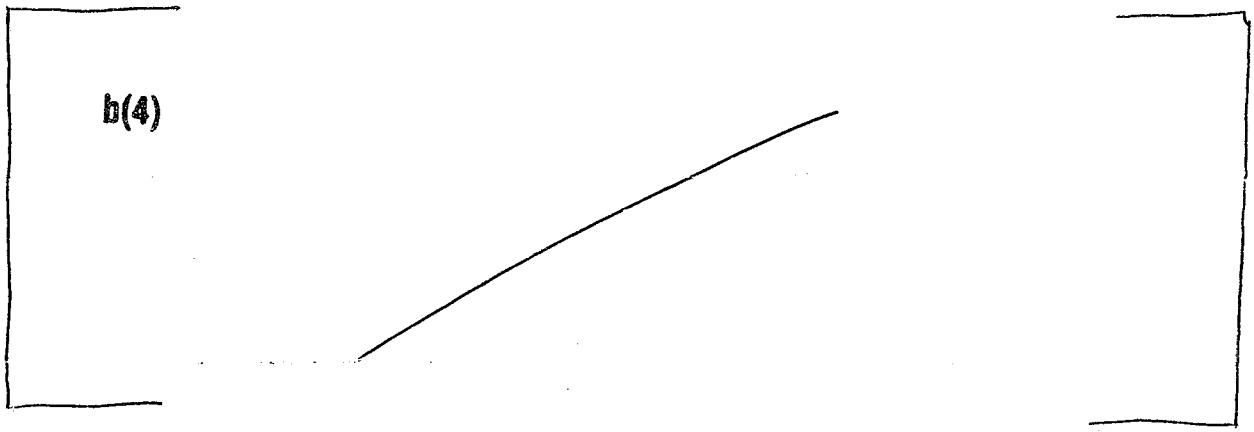
3. **Elevated liver enzymes** (risperidone group)- Liver enzymes were mildly elevated at screening, increased at baseline and at Week 1 (the last laboratory data available for this subject). The subject discontinued due to this adverse event.

4. **Hyperproteinemia** (risperidone group)- the total protein was 78 g/L at screening, 85 g/L at baseline, and 91 g/L at Week 3 (reference range 61-84 g/L. It was not clinically significant.

5. **Thrombocytopenia:** (risperidone group) rated as severe. At baseline, the platelet count was normal (170 giga/L). Platelets were below defined clinically important limits, 26 giga/L, when the patient discontinued the trial at the end of Week 2, due to an adverse event of insomnia. Platelet values had normalized by the time of the next available laboratory data, approximately 3 months later

Concentration-Response & Concentration-Safety Analysis

In this trial, the mean dose-normalized plasma concentrations at Day 21 were higher than those observed in a trial in subjects with Bipolar Disorder who received risperidone as adjunctive therapy (RIS-INT-46). Graphical display of pharmacokinetic-pharmacodynamic relationships was consistent with the differences observed between the risperidone and placebo groups in efficacy and safety parameters. There was no apparent relationship between drug plasma concentration of the active moiety and any of the assessed efficacy and safety parameters or their respective shifts from baseline. However, the design of the present trial did not allow for any specific conclusions on pharmacokinetic-pharmacodynamic relationships.



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Medical Review

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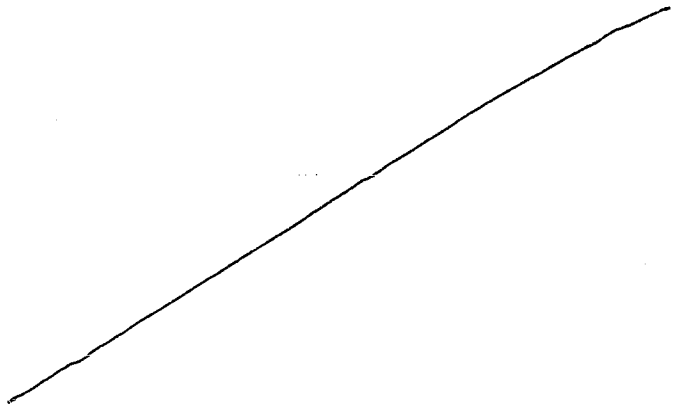

Adjunctive Therapy Studies

Study USA-102

XI. Integrated Review of Efficacy- (Study USA-102)

A. Brief Statement of Conclusions

This trial demonstrated the efficacy of risperidone, as adjunctive therapy to mood stabilizers, in the acute treatment of mania. Subjects were treated with flexible-dose risperidone in the range of 1-6 mg/day, and they had concomitant treatment with either lithium or valproate. There was a statistically significant difference between treatment groups in the change from baseline to endpoint in YMRS score, favoring risperidone (p= 0.009) and haloperidol (P= 0.021) treatment. There were also statistically significant differences in the changes from baseline in YMRS scores at Day 7 (p= 0.031) and at Day 14 (p= 0.022) between the placebo and risperidone groups, favoring risperidone.

At baseline, the mean YMRS score was 28.1 for the placebo group, 27.8 for the risperidone group, and 27.4 for the haloperidol group. At endpoint, the scores were: 19.8, 13.6, and 14.1, in the respective groups. Thus, the mean changes in YMRS score were: -8.2, -14.3, and –13.3, respectively. The estimated least squares mean change from baseline to endpoint was –9.0 in the placebo group, –14.1 in the risperidone group and –13.6 in the haloperidol group. The estimated difference in the least squares mean change from baseline to endpoint was –5.1, with a corresponding 95% confidence interval of (-9.0, -1.3). The estimated difference in LS mean between haloperidol and placebo is –4.5, with a 95% confidence interval of (-8.4,-0.7). Thus, the estimated treatment effect of risperidone, compared to placebo, was a reduction of 5.1 points on the YMRS scale. Such an effect would be clinically significant in the acute treatment of mania. The estimated treatment effect of haloperidol, compared to placebo, was a 4.5 point reduction on the YMRS, which is clinically significant. The risperidone treatment effect was 1.57-fold that of placebo. The haloperidol effect was 1.5 times that of placebo.

Analysis results for secondary efficacy measures support the conclusion that risperidone was efficacious. There was a statistically significant difference at Day 21 (p= 0.002) in the change in CGI scores between groups, favoring risperidone. In addition, subgroup analysis demonstrated a consistent treatment effect of risperidone regardless of: mood stabilizer used; presence or absence of psychotic symptoms at baseline; and 3) diagnosis of manic versus mixed episode at baseline.

B. General Approach to the Review of Efficacy

The full efficacy database and summary of efficacy results provided by the sponsor were reviewed.

C. Detailed Review of the Trial

C-1 Study Sites and Investigators- USA-102

Study USA-102 was conducted at numerous sites in the U.S. (Refer to Appendix – for a full listing of study sites and investigators).

C-2 Selection of Subjects- USA-102

Patients already receiving treatment with lithium or valproate before screening or before randomization could be included in the study. Patients who were not being treated with either lithium or valproate were included as well. All other inclusion and exclusion criteria were identical to those used in the monotherapy studies. (Refer to Appendix B).

C-3 Objectives of the Study- USA-102

The primary objective of the study was to evaluate the efficacy of risperidone plus a mood stabilizer (lithium or valproate) in the acute treatment of mania (for up to 21 days) in adult subjects with Bipolar Disorder.

C-4 Trial Design- USA-102

This was a 21-day, randomized, double-blind, placebo-controlled, parallel-group trial of risperidone as adjunctive therapy to mood stabilizers (lithium or valproate) in the treatment of acute mania. If a subject had not been receiving treatment with either lithium or valproate before randomization, he or she began treatment with one of these mood stabilizers (as open-label treatment) upon randomization. The investigator decided which mood stabilizer to use for an individual subject, depending on the subject's medical history and previous responses to mood stabilizers. Subjects were then randomized to adjunctive treatment with either risperidone, placebo, or haloperidol (used for the purpose of assay sensitivity). Prior to beginning double-blind treatment, subjects were required to undergo a 3-day washout period. During the washout period, antipsychotics, antiparkinson medications, antidepressants, anxiolytics and other centrally acting medications were discontinued with the exceptions of: lithium or valproate; benzodiazepines (flurazepam, temazepam, or oxazepam) or chloral hydrate for treating insomnia; and lorazepam for agitation. subjects who were receiving lithium or valproate at screening could continue treatment or switch to treatment with the other mood stabilizer. Dosing regimens for risperidone, placebo, and haloperidol are illustrated in the table below. Risperidone was dosed flexibly in the range of 1-6 mg/day. Haloperidol was dosed flexibly in the range 2-12 mg/day.

Table. Summary of Daily Administered Doses

Day	Number of tablets	Placebo q.d.	Risperidone q.d.	Haloperidol q.d.
1	2	Placebo	2 mg	4 mg
2	2	Placebo	2 mg	4 mg
3	1 to 4	Placebo	1 mg to 4 mg	2 mg to 8 mg
4	1 to 4	Placebo	1 mg to 4 mg	2 mg to 8 mg
5-21	1 to 6	Placebo	1 mg to 6 mg	2 mg to 12 mg

q.d. = once daily

Subjects remained in the hospital for at least four days of. After Day 4 of treatment, subjects could be discharged from the hospital at the discretion of the investigator. They were permitted to take lorazepam up to 6 mg/day during the washout period and up to 4 mg/day during the first seven days of the double-blind phase. After Day 7, lorazepam was not permitted. Subjects who were discharged on Days 5, 6, or 7 were not allowed to receive lorazepam.

Mood Stabilizer Treatment

During the DB phase, subjects received open-label treatment with either lithium or valproate. The treatment with a mood stabilizer was started as soon as possible after admission to the

hospital. Only one mood stabilizer was permitted. The mood stabilizer could not be switched due to lack of efficacy during the 3-week, DB phase. If a subject experienced an adverse event attributed to the mood stabilizer, the dose was reduced. If the AE persisted, the mood stabilizer could be changed to the other mood stabilizer. Subjects who switched mood stabilizers continued to belong to their original mood stabilizer stratification group for purposes of statistical analysis. A central laboratory measured serum concentrations of lithium or valproate at screening, and on Days 1, 3, 8, 15 and 22, or more frequently if indicated, based upon the judgment of the investigator. The investigator used the serum concentrations to determine the dosing requirements of mood stabilizers for individual patients. Investigators were instructed by the protocol to adjust the dose of mood stabilizer in order to obtain the following serum concentrations:

1. Valproate– trough serum concentration of 50 µg/mL to 120 µg/mL
2. Lithium– 0.6 mEq/L to 1.4 mEq/L (12 hours after the last dose)
3. Carbamazepine – trough serum concentration of 4 µg/mL to 12 µg/mL

Efficacy Assessments
Efficacy assessments and the schedule for assessments were identical to those in the monotherapy studies.

Safety Assessments
The specific efficacy assessments and schedule for assessments were identical to those used in the monotherapy studies.

C-5 Outcome Measures- USA-102

The primary efficacy measure was the change from baseline to Day 21 in YMRS score. The secondary outcome measures were identical to those of the monotherapy studies.

C-6 Disposition of Subjects- USA-102

Of the individuals screened (180), 158 (78%) were randomized. Ninety-nine (99%) of the randomized subjects were treated. There were 52 subjects in the risperidone group, 51 in the placebo group, and 53 in the haloperidol group. Overall, 54% of subjects completed the study (65% if the risperidone group, 51% of the placebo group, and 47% of the haloperidol group).

C-7 Discontinuations from the Study- USA-102

In all three treatment groups, the most common reasons for discontinuation were Withdrew Consent and Insufficient Response. These two reasons for discontinuation accounted for a relatively high proportion of all subjects: 23%, 30%, and 34% of subjects in the risperidone, placebo, and haloperidol groups, respectively. Discontinuations due to adverse events accounted

for 4%, 4%, and 2% of the risperidone, placebo, and haloperidol groups, respectively. Details are presented in the table below.

Reasons for Discontinuations- USA-102

	PLACEB N = 51 N (%)	RISPERID N = 52 N (%)	HALOPER N = 53 N (%)
Completed	26 (51%)	34 (65%)	25 (47%)
Discontinued	25 (49)	18 (35)	28 (53)
Reasons for discontinuation			
• Withdrew consent	10 (20)	9 (17)	15 (28)
• Insufficient response	5 (10)	3 (6)	3 (6)
• Noncompliance	1 (2)	3 (6)	1 (2)
• Adverse event	2 (4)	2 (4)	1 (2)
• Ineligible to contin.	2 (4)	1 (2)	3 (6)
• Lost to follow-up	3 (6)	0	5 (9)
• Other	2 (4)	0	0

C-8 Baseline Demographics and Severity of Illness- USA-102

Baseline Demographics and other Severity of Illness

Overall, 51% of subjects were men, and 49% were women. The median age was 43 years in the placebo group, 41 years in the risperidone group, and 44 years in the haloperidol group. Approximately 78% of subjects in each group were diagnosed as having a manic episode, and 22% a mixed episode. The demographic and baseline characteristics of illness were well balanced among the groups. (Race was not a category under demographic features). The median weights were slightly higher in the risperidone and haloperidol groups, compared to the placebo group (85, 88, and 78 kg, respectively). In summary, the baseline characteristics and severity of illness were evenly distributed among the three treatment groups.

C-9 Concomitant Medications - USA-102

Mood Stabilizers

All subjects were treated concomitantly, in an open-label manner, with a mood stabilizer (either lithium or valproate) at the baseline of treatment. Most subjects in the study were treated with valproate: 111 (71%) received valproate, and 45 (29%) received lithium. Within each treatment group, valproate was used more commonly than lithium, and the proportions of subjects using valproate versus lithium were evenly distributed among the treatment groups. Subjects may have begun treatment with mood stabilizers prior to the baseline of the study; in fact, most subjects (64%) began treatment with mood stabilizers prior to entering the trial. The

proportions of subjects who started mood stabilizers before versus after the beginning of the study were evenly distributed among the treatment groups. Overall,

Distribution of Mood Stabilizer Therapy Use

	PLACEB	RISPERID	HALOPER	TOTAL
Therapy	N=51	N=52	N= 53	N=156
	n (%)	n (%)	N (%)	n (%)
Mood stabilizer at randomization				
- Lithium	14 (28)	14 (27)	17 (32)	45 (29)
- Valproate	37 (72)	38 (73)	36 (68)	111 (71)
Initiation of mood stabilizer				
- Start of trial	20 (39)	17 (33)	19 (36)	56 (36)
- Prior to trial	31 (61)	35 (67)	34 (64)	100 (64)

As discussed above, the investigator decided which mood stabilizer to use for an individual subject, based on appropriate clinical criteria. The protocol that doses were adjusted in order to reach standard serum levels for the individual drug. The mood stabilizer could not be changed according to clinical response; however, it could be changed to the other mood stabilizer, if a subject experienced persistent adverse events attributed to treatment with the mood stabilizer. It is not clear what number of subjects may have been switched to another mood stabilizer. Even if there was a switch, the subject remained categorized in the original mood stabilizer group.

Prohibited Concomitant Therapy

The following medications were **not** allowed during the trial:

1. Antipsychotics other than the trial medication
2. Mood stabilizers other than lithium, valproate, or carbamazepine;
3. Benzodiazepines other than lorazepam, temazepam, oxazepam, or flurazepam;
4. After Day 7, no rescue medication (lorazepam) for agitation was permitted
5. Antiparkinson medication was not permitted at Baseline;
6. Antidepressants were not permitted at entry; (they could be used later in the study).

Permitted Concomitant Medications

1. For sleep only: flurazepam, oxazepam, temazepam (30 mg maximum) and chloral hydrate (1,000 mg maximum)
2. Antidepressants could be initiated during the double-blind phase for clinically significant depression, provided the investigator judged that an antidepressant was unlikely to worsen manic
   symptoms. The HAM-D was to be performed before starting the antidepressant;
3. Lorazepam (up to 6 mg/day) could be taken as rescue medication for agitation during the washout
   phase; lorazepam (up to 4 mg/day) could be taken for agitation during Days 1 to 7;

4. Antiparkinson medication (including propranolol) could be used during the double-blind phase.
5. Medication for medical conditions.

Lorazepam Use During the Trial

During the 21-day trial, 59% of the placebo group, 67% of the risperidone group, and 64% of the haloperidol group used lorazepam at least once. Use of lorazepam was limited to the first 7 days of the double-blind trial. The total lorazepam dose used for those subjects treated with lorazepam was similar among the three treatment groups: 8.7 mg, 10 mg, and 8.5 mg in the placebo, risperidone, and haloperidol groups, respectively. The mean and median single dose of lorazepam were nearly identical across groups. As seen in the table below, the mean and median duration of lorazepam use were both lower than those of the other two groups. For the risperidone group, both the mean total dose per lorazepam-treated subject and the mean total dose per lorazepam-treated per day were slightly higher than those for the other groups. These differences do not appear to be significant, and they are not likely to have affected the results of the efficacy analysis. Furthermore, the total and single doses of lorazepam for all groups are relatively low for a study of acutely manic subjects. This may reflect the fact that all subjects were treated concomitantly with a mood stabilizer.

Lorazepam Use During the Trial- USA-102

	PLAC	RISP	HALOP
Number of subjects (N)	N=51	N=52	N=53
No. subj. treated w/ Lorazepam = n*	30 (59%)	34 (65%)	34 (64%)
Total Lorazepam dosage (mg)	260 mg	339	288
Total Lorazepam dosage/ N	5.1 mg	6.5 mg	5.4 mg
Total Lorazepam dosage/ n*	8.7 mg	10 mg	8.5 mg
Mean single dose	2.1 mg	2.0 mg	2.0 mg
Median single dose	2.0 mg	2.0 mg	2.0 mg
Mean duration of use	4.1 days	3.9 days	4.5 days
Median duration of use	3.0 days	2.5 days	3.5 days
Duration of Lorazepam Rx- as percentage of study treatment duration) %			
Mean	30%	23%	25%
Median	26%	14%	18%
Dose/day (mean) for n* subjects- for period of permitted lorazepam use	1.24 mg/day	1.43 mg/d	1.21mg/day

Medications for Treating EPS

During double-blind treatment, the proportion of subjects in the risperidone group using medications to treat EPS was twice that of the placebo group (17.3% vs. 7.8%). More than twice as many subjects in the haloperidol group (38%) used such medications compared to the risperidone group. All of these subjects were treated with the anticholinergic medication, benztropine. In the haloperidol group, three of the same subjects were also treated with diphenhydramine. One subject in the placebo group had additional treatment with diphenhydramine. None of the subjects was treated with a beta-blocker.

C-10 Trial Medication Exposure During the Double-Blind Phase

Risperidone Exposure

Fifty-two (52) subjects were exposed to risperidone, for a total of 2.65 subject-years.
The mean treatment duration in the risperidone group was 17 days. The median duration was 21 days. The mean risperidone dose was 3.83 mg/day, and the median mode dose was 4 mg/day. The mean and median duration of treatment with placebo was 14.88 and 17 days, respectively. (No PK studies were conducted in this study; thus, potential dose-concentration and concentration-response relationships cannot be assessed).

Haloperidol Exposure

The mean and median duration of treatment with haloperidol was 16.25 and 20 days, respectively. The mean and median haloperidol dose was 6.23/day and 6 mg/day, respectively.

Exposures for Mood Stabilizers

As discussed above, a higher proportion of subjects in each group were treated with valproate than lithium. The proportions were similar among the 3 treatment groups. In general, the mean and median duration of treatment with valproate appeared to be somewhat longer than with lithium. The difference was most pronounced in the haloperidol group. The mean and median doses of lithium were slightly higher in the placebo group than in the other groups.
In contrast, the mean and median doses of valproate were slightly lower in the placebo group than the risperidone and haloperidol groups. It is unlikely that these small differences would have an effect on the efficacy analysis. However, potential differences in serum concentrations of the mood stabilizers among groups could have affected the efficacy results. The mean doses of lithium and valproate that were used are consistent with those typically used in clinical practice.

Mood stabilizer	Placebo	Risperidone	Haloperidol
Lithium	**N =14**	**N=14**	**N=17**
Mean duration (days)	17	18.1	16.1
Median duration (days)	20	21.5	16
Mean dose	1,077 mg	1,052 mg	1,041 mg
Median dose	975 mg	900 mg	929 mg
Valproate	**N=37**	**N=38**	**N=39**
Mean duration (days)	17	19.2	19.6
Median duration (days)	21	22	22
Mean dose	1,312 mg	1,419 mg	1,436 mg
Median dose	1,250 mg	1,437 mg	1,314 mg

Serum Concentrations of Mood Stabilizers During the Study

Serum concentration data were available for some subjects who were treated with lithium or valproate. Data are presented for mean serum levels at baseline and at the end of Week 3. The sponsor has noted that a fairly high proportion of subjects did not reach the targeted therapeutic serum concentrations of mood stabilizer. Data are not available for an analysis

of the outlying subjects; however, the sponsor reports that separate efficacy analyses were performed for: 1) the whole population treated with mood stabilizers; and 2) the subgroup who had reached therapeutic levels of lithium or valproate. The sponsor reports that both efficacy analyses yielded positive results. The clinical and statistical reviewers from the Division did not perform an analysis regarding serum concentrations of mood stabilizers.

Lithium (43 subjects)
At baseline, the mean lithium level was 0.6 mEq/L in the placebo group, 0.7 in the risperidone group, and 0.5 in the haloperidol group. At Week 3, the mean levels were 0.8, 0.7, and 0.7, respectively. The small differences do not appear to be significant. In fact, the mean lithium levels for all groups and for both timepoints are relatively low, especially for the treatment of acute mania. Typically, one aims for a serum lithium level in the range 1.0-1.4 for an acutely manic patient. The study protocol specified that the investigator should adjust dosing so that the subject's lithium level was in the range of 0.6-1.4 mEq/L. However, reasonable doses were used. It must be acknowledged that for such a brief study, it would be relatively difficult to achieve targeted steady-state concentrations. Apparently, there was no guideline regarding the frequency of laboratory testing of drug blood levels.

Valproate (108 subjects)
At baseline, the mean valproate levels were 52.9, 53.4, and 50.1 ug/mL for the placebo, risperidone, and haloperidol groups, respectively. At Week 3, the mean values were higher for each group: 77.3, 65.4, and 76.2, respectively. The small differences among groups are unlikely to be significant. While the baseline valproate levels are near the bottom of the normal range, the Week 3 values are relatively close to those targeted in clinical practice (75-100). The sponsor's suggested range, per protocol, was 50-120 ug/mL.

D. Efficacy Analysis

1. Efficacy Analysis Methods

The intent-to-treat (ITT) analysis set was defined as those randomized subjects who were treated with at least one dose of trial medication. Some ITT subjects may not have been included in the efficacy dataset, either because they were enrolled at sites which were not in compliance with Good Clinical Practice, or they did not have both baseline and post-baseline data. Also, for those subjects with multiple CRF ID numbers, only data from the first CRF ID number were used for the analysis.

The primary efficacy endpoint was the change from baseline at Day 21 in YMRS score. The analysis for change in YMRS was performed using an ANCOVA model that includes treatment group, center, and type of mood stabilizer as factors, and the baseline value (for total YMRS) as a covariate. A similar analysis was performed for CGI-C, BPRS, and HAM-D, using the variable's respective baseline value as the sole covariate.

2. Efficacy Results:

At baseline, the mean YMRS score was 28.1 for the placebo group, 27.8 for the risperidone group, and 27.4 for the haloperidol group. At endpoint, the scores were: 19.8, 13.6, and 14.1, in the respective groups. Thus, the mean changes in YMRS score were: -8.2, -14.3, and –13.3, respectively. The estimated least squares mean change from baseline to endpoint is –9.0 in the placebo group, –14.1 in the risperidone group and –13.6 in the haloperidol group. The estimated difference in the least squares mean change from baseline to endpoint was –5.1, with a corresponding 95% confidence interval of (-9.0, -1.3). The estimated difference in LS mean between haloperidol and placebo is –4.5, with a 95% confidence interval of (-8.4,-0.7). When compared to placebo, there was a statistically significant difference in the change from baseline in YMRS score, favoring risperidone (p= 0.009) and haloperidol (p= 0.021) treatment. There were also statistically significant differences in the changes from baseline in YMRS scores at Day 7 (p= 0.031) and at Day 14 (p= 0.022) between the placebo and risperidone groups, favoring risperidone.

Change from Baseline in YMRS Score in RIS-USA-102 (Day 21-LOCF/endpoint)

			DAY 21/		COMPARISON with PLACEBO		
TREATMT	N	BASELINE MEAN (SD)	ENDPOINT MEAN (SD)	CHANGE MEAN (SD)	LSMean Change (SD[a])	Diff in LSM Change (95%CI)	p-value
PLAC	47	28.1(6.26)	19.8 (11.39)	-8.2 (10.44)	-9.0 (9.36)		
RIS	51	27.8 (5.44)	13.6 (11.26)	-14.3 (9.67)	-14.1 (9.36)	-5.1 (-9.0, -1.3)	0.009
HAL	50	27.4 (6.20)	14.1 (10.48)	-13.3 (9.95)	-13.6 (9.36)	-4.5 (-8.4, -0.7)	0.021

N: Number of patients with both baseline and post-baseline timepoint measurements.
p value: Between treatment comparison based on ANCOVA model with treatment, investigator, type of mood stabilizer as factors and baseline value as covariate.
[a] Pooled SD based on the ANCOVA model

Twenty-two subjects (47%) in the placebo group, fourteen (27%) in the risperidone group, and nineteen (37%) in the haloperidol group discontinued from the study prior to endpoint. Due to the high proportion of discontinuations, the mean change estimates and the difference in mean change estimates may be biased and may be associated with different standard errors than those from using LOCF and the ANCOVA model; thus, the reported p-values may be misleading. However, there was a statistically significant difference between groups (favoring risperidone) in the change from baseline YMRS score at Day 7, when there were few discontinuations. (There were three missing differences in the risperidone group and one missing difference in the placebo group). This result may support the results from the LOCF analysis at Day 21.

3. Secondary Efficacy Analysis

The sponsor performed a longitudinal analysis of the changes in YMRS score between groups at Days 7, and 14. There were statistically significant differences between groups at both timepoints (p= 0.031 at Day 7; p= 0.022 at Day 14).

4. Secondary Outcome Measures

There was a statistically significant difference at Day 21 (p= 0.002) in the change in CGI scores between groups, favoring risperidone. The change in CGI scores for the haloperidol group was also statistically

significantly different at Day 21, compared to placebo (p= 0.003). There was no statistically significant difference between the placebo and risperidone groups in the mean change from Baseline of the total BPRS. Similarly, there was not statistically significant difference in the mean change from baseline in the HAM-D 21-item score at endpoint, between the placebo and risperidone arms.

5. Subgroup Analysis- USA-102

The sponsor and the reviewers did not perform subgroup analyses according to gender, race, and age, due to the relatively small numbers in each subgroup. Analyses were performed according to: 1) mood stabilizer used; 2) presence or absence of psychotic symptoms at baseline; and 3) diagnosis of manic versus mixed episode at baseline. In general, the efficacy results of the analyses described above consistently demonstrated a statistically significant treatment effect, favoring risperidone.

Mood Stabilizer- USA-102

The results for the changes in YMRS scores at endpoint for mood stabilizer subgroups are summarized in the table below. Formal statistical analysis was not performed, due to the small sample sizes. Descriptive statistics suggest that there was a difference between mood stabilizer groups in the magnitude of risperidone treatment effect. Within the VAL subgroup, the mean change in YMRS score for the placebo group was –6.6, and the mean change for the risperidone group was –14.4. Thus, the difference in means was –7.8, favoring risperidone.
In contrast, the mean changes within the LITH subgroup were comparable between the placebo and risperidone groups. The mean changes were –12.5 and –13.8 for the placebo and risperidone groups, respectively. (The results in the haloperidol group were very similar to the results in the risperidone group). The most likely explanation for the apparent difference in risperidone treatment effects between mood stabilizer groups is that lithium provided more benefit in the treatment of mania than did valproate in this study. Within the placebo group, the mean changes in YMRS scores were –6.6 in the VAL group and –12.5 in the LITH group.

Change From Baseline at Day 21 YMRS Score by Type of Mood Stabilizer-USA-102

MOOD STABILIZER	CHANGE FROM BASELINE AT DAY 21 ENDPOINT IN YMRS SCORE					
	Placebo		Risperidone		Haloperidol	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Lithium	13	-12.5 (2.9)	13	-13.8 (2.6)	16	-11.9 (2.4)
Valproate	34	-6.6 (1.7)	38	-14.4 (1.6)	34	-13.9 (1.8)

Presence or Absence of Psychotic Symptoms- USA-102

The results for the 3-week change from baseline in total YMRS (endpoint) in the different psychotic features subgroups are summarized in the table below. Differences between the risperidone and placebo arms in the sample mean changes were similar for the two psychotic features subgroups.

Change in YMRS Scores by Baseline Psychotic Features- USA-102

Psychotic Features	Change from baseline at 3-week endpoint in total YMRS score					
	Placebo		Risperidone		Haloperidol	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Present	20	-9.3 (2.6)	20	-15.4 (2.5)	18	-16.8 (2.4)
Absent	27	-7.5 (1.9)	31	-13.5 (1.6)	32	-11.3 (1.7)

Mixed Episode Versus Manic Episode- USA-102

The results for the 3-week change from baseline in total YMRS (endpoint) in the different bipolar episode subgroups are summarized with descriptive statistics. For those subjects who had manic episodes, the sample mean changes were greater for the risperidone (-14.4) and haloperidol (-13.7) groups than for the placebo (-6.6). For the subjects (11%) who had mixed episodes, the sample mean changes were similar across treatment arms.

Change in YMRS Score by Baseline Bipolar Episode- USA-102

Bipolar Episode	Change from baseline at 3-week endpoint in total YMRS score					
	Placebo		Risperidone		Haloperidol	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Manic	37	-6.6 (1.7)	42	-14.4 (1.5)	38	-13.7 (1.8)
Mixed	10	-14.2 (3.0)	9	-13.6 (3.8)	12	-12.1 (1.8)

6. Efficacy Conclusions- USA-102

The reviewers verified the sponsor's LOCF ANCOVA analyses of the change from baseline in total YMRS, CGI-severity, BPRS and HAM-D. The primary efficacy endpoint for study RIS-USA-102 was the change from baseline at Day 21 in the YMRS score using an LOCF imputation method. This trial demonstrated the efficacy of risperidone, as adjunctive therapy to mood stabilizers, in the acute treatment of mania. Subjects were treated with flexible-dose risperidone in the range of 1-6 mg/day, and they had concomitant treatment with either lithium or valproate. There was a statistically significant difference between treatment groups in the change from baseline to endpoint in YMRS score, favoring risperidone ($p= 0.009$) and haloperidol ($p= 0.021$) treatment. There were also statistically significant differences in the changes from baseline in YMRS scores at Day 7 ($p= 0.031$) and at Day 14 ($p= 0.022$) between the placebo and risperidone groups, favoring risperidone.

At baseline, the mean YMRS score was 28.1 for the placebo group, 27.8 for the risperidone group, and 27.4 for the haloperidol group. At endpoint, the scores were: 19.8, 13.6, and 14.1, in the respective groups. Thus, the mean changes in YMRS score were: -8.2, -14.3, and –13.3, respectively. The estimated least squares mean change from baseline to endpoint was –9.0 in the placebo group, –14.1 in the risperidone group and –13.6 in the haloperidol group. The estimated difference in the least squares mean change from baseline to endpoint was –5.1, with a corresponding 95% confidence interval of (-9.0, -1.3). The estimated difference in LS mean between haloperidol and placebo is –4.5, with a 95% confidence interval of (-8.4,-0.7). Thus, the estimated treatment effect of risperidone, compared to placebo, was a reduction of 5.1 points on the YMRS scale. Such an effect would be clinically significant in the acute treatment of mania. The estimated treatment effect of haloperidol, compared to placebo, was a 4.5 point

reduction on the YMRS, which is clinically significant. The risperidone treatment effect was 1.57-fold that of placebo. The haloperidol effect was 1.5 times that of placebo.

Analysis results for secondary efficacy measures support the conclusion that risperidone was efficacious. There was a statistically significant difference at Day 21 (p= 0.002) in the change in CGI scores between groups, favoring risperidone. In addition, subgroup analysis demonstrated a consistent treatment effect of risperidone regardless of: mood stabilizer used; presence or absence of psychotic symptoms at baseline; and 3) diagnosis of manic versus mixed episode at baseline.

XII. Integrated Review of Safety- USA-102

A. Brief Statement of Conclusions

Risperidone treatment, in combination with either lithium or valproate, was generally reasonably safe and well tolerated. The safety profile of adjunctive therapy was similar to the safety profile of risperidone monotherapy. There were no unexpected safety findings.
In this study, 52 subjects were exposed to risperidone for a total of 2.65 years. The mean modal risperidone dose was 3.83 mg/day. The median duration of risperidone treatment was 17.13 days, compared to 14.9 days for placebos. Fifty-three (53) subjects were treated with haloperidol, 45 subjects were treated with lithium and 111 were treated with valproate. There were no deaths in this trial. Ten subjects experienced serious adverse events: 2 in the risperidone group, 4 in the placebo group, and 4 in the haloperidol group. In the risperidone group, the SAE were: 1) anxiety; and 2) tachycardia. In the placebo group, 3 SAE were manic reactions, and one was an exacerbation of diabetes. The SAE in the haloperidol group were: 2 manic reactions; suicidal ideation with a manic reaction; and EPS/tremor. Discontinuations due to adverse events occurred for 6 subjects: tachycardia and aggressive reaction in the risperidone group; manic reaction and agitation in the placebo group; and fatigue and EPS/tremor in the haloperidol group.

Adverse events were reported by 81% of the risperidone group, 84% of the placebo group, and 91% of the haloperidol group. The most commonly reported AE were: extrapyramidal symptoms (25%, 12%, and 53% of the risperidone, placebo, and haloperidol group, respectively); somnolence (25%, 12%, 30% headache (21%, 24%,15%); dyspepsia (17%,18%,17%); extrapyramidal disorder (14%, 4%, 28%); dizziness (14%, 2%, 8%); hypersalivation (10%, 0, 8%); akathisia (6%, 0, 9%); constipation (6%, 4%, 11%); tremor (4%, 4%, 11%); urinary incontinence (6%, 2%, 2%); increased weight (4%, 2%, 6%); purpura (2%, 6%, 0). The most commonly reported EPS event was "extrapyramidal disorder" (14%, 4%, and 28% of each group respectively). Akathisia was the second most common type of EPS reported in the risperidone group (6%, versus 9% and 0 in the other groups). Hypertonia occurred in 4%, 0, and 4%. Tremor was the second most common EPS in the haloperidol group (11%, compared to 4% in each of the other groups). The following types of EPS were also: hypokinesia (2%, 0, 2%); dyskinesia (0, 2%, 6%); dystonia (0, 2%, 8%); abnormal gait (0, 2%, 4%); involuntary muscle contraction (0, 0, 2%); tetany (0, 2%, 2%); and tongue paralysis (0, 2%, 2%).

There were no adverse events reported which might have been related to changes in prolactin levels. Prolactin levels were not measured in this study. There were no statistically significant mean changes from baseline in vital signs, and there were no statistically significant differences in mean changes among groups. During the double-blind trial, none of the subjects in any group exhibited an abnormal value for blood pressure or pulse (as defined by criteria listed for Study USA-239). There were no reported cases of orthostatic hypotension for any subjects in the trial. The mean changes in weight at Day 21 were + 2.51 kg, + 0.39 kg, and +0.032 kg in the risperidone, placebo, and haloperidol groups, respectively. The weight change in the risperidone group was significantly greater than that of the placebo group ($p<0.001$).

At endpoint, 30 subjects had QTc intervals which were considered either borderline or prolonged. There were 14 cases of prolonged QTc intervals (RIS-4; PLAC-6; HAL-4), and there were 16 cases of borderline QTc (RIS-3; PLAC-6; HAL-7). In addition, one subject from the risperidone group had an abnormal QTc value in the "pathologic" range (>500 msec: 517). The event was not associated with clinical signs or symptoms; it was considered "mild" and possibly related to study treatment. No action was taken, and the AE was resolved upon the completion of treatment. There were no cases of "pathologic" QTc intervals in the placebo or haloperidol groups. The vast majority of all laboratory abnormalities were only marginally out of the reference ranges. Some abnormalities had the potential to be clinically significant; however, none of these cases constituted an acutely serious condition. For example, all cases of elevated liver enzymes were relatively mild; none of elevated glucose levels were in a range considered clinically dangerous. Cases of hyperglycemia occurred in each treatment group

B. Description of Patient Exposure

Discussed above in the statement of conclusions

C. Methods of Safety Review

The full efficacy database and summary of efficacy results provided by the sponsor were reviewed.

D. Adequacy of Safety Testing

The testing was adequate; it was identical in kind and quality to those of the monotherapy studies. Please refer to the analysis section of the Integrated Analysis of Safety for study USA-239.

E. Review of Safety Findings

E-1 Deaths

There were no deaths in the double-blind trial in any treatment group.

E-2 Serious Adverse Events

Serious adverse events were reported by 10 subjects: 2 (4%) in the risperidone group, 4 (8%) in the placebo group, and 4 (8%) in the haloperidol group.

Risperidone group (two subjects; four SAE):
1. **Anxiety**; no action taken; not recovered at endpoint.

2. **Tachycardia; Rhabdomyolysis; creatine phosphokinase (CPK) increased**
   A 59 year-old man was being treated with RIS and LITH. He had a h/o hypertension. He had been treated with lithium before trial for unspecified period. On Day 16 of treatment, he developed sustained tachycardia, for which he was hospitalized. The diagnosis was sinus tachycardia. Two days later, he had elevated CPK (1,593) and was diagnosed as having rhabdomyolysis. He also had an elevated GGTP. The subjects discontinued from the study.

Placebo group (two subjects; two SAE):
1. **Three cases of manic reaction-** one case resolved; 3 did not.
2. **Exacerbation of diabetes** in a subject with history of diabetes mellitus; temporarily stopped study treatment, and the event resolved. The subject was observed to be confused. The serum glucose level was 684. The subject also reported having an episode of falling. The insulin dose was adjusted, and the subject remained in the study. Treated with LITH also.

Haloperidol group (4 subjects; 6 SAE):
1. Two cases of manic reaction- (one treated with VAL; one treated with lithium)
2. Suicidal ideation with manic reaction. No specific action was taken. One day after end of the trial, the subject was re-hospitalized, due to an exacerbation and suicidal ideation.
3. Extrapyramidal disorder (tremor) and Abnormal ECG. (Treated with LITH and HAL). Developed tremor 10 days in to trial. Investigator decreased the haldol dose and treated with Cogentin and propranolol, but tremor persisted and the subject was discontinued from the study. The ECG abnormality resolved, but the EPS had not resolved. The subject also had chest pain, and myocardial infarction was ruled out.

E-3 Discontinuations Due to Adverse Events

Six subjects, (two from each treatment group), reported an adverse event that led to discontinuation from the study.

Risperidone group:
1) Tachycardia. As discussed above, this subject also had rhabdomyolysis and elevated CPK.
2) Aggressive reaction.

Haloperidol group:
1) Fatigue

2) Rule out myocardial infarction; abnormal ECG; tremor: discussed above.

Placebo group: 1) manic reaction; 2) agitation.

E-4 Commonly Reported Adverse Events

Adverse events were reported by 81% of the risperidone group, 84% of the placebo group, and 91% of the haloperidol group. The most commonly reported adverse events (in any group) were: extrapyramidal symptoms (25%, 12%, and 53% of the risperidone, placebo, and haloperidol group, respectively); somnolence (25%, 12%, 30% headache (21%, 24%,15%); dyspepsia (17%,18%,17%); extrapyramidal disorder (14%, 4%, 28%); dizziness (14%, 2%, 8%); hypersalivation (10%, 0, 8%); akathisia (6%, 0, 9%); constipation (6%, 4%, 11%); tremor (4%, 4%, 11%); urinary incontinence (6%, 2%, 2%); increased weight (4%, 2%, 6%); purpura (2%, 6%, 0).

E-6 Adverse Events of Particular Clinical Interest

Extrapyramidal Symptoms (EPS)
In summary, the proportion of subjects in the risperidone group experiencing EPS was considerably higher than that in the placebo group and was significantly lower than that in the haloperidol group. In addition, there was a unique pattern of EPS reported among each group. Such results would be expected, based on pre-marketing and post-marketing experience with risperidone and haloperidol treatment.

As mentioned above, EPS were reported by 25%, 12%, and 53% of the risperidone, placebo, and haloperidol groups, respectively. The most commonly reported EPS event was "extrapyramidal disorder" (14%, 4%, and 28% of each group respectively). Akathisia was the second most common type of EPS reported in the risperidone group (6%, versus 9% and 0 in the other groups). Hypertonia occurred in 4%, 0, and 4%. Tremor was the second most common EPS in the haloperidol group (11%, compared to 4% in each of the other groups). The following types of EPS were also: hypokinesia (2%, 0, 2%); dyskinesia (0, 2%, 6%); dystonia (0, 2%, 8%); abnormal gait (0, 2%, 4%); involuntary muscle contraction (0, 0, 2%); tetany (0, 2%, 2%); and tongue paralysis (0, 2%, 2%).

Prolactin
There were no adverse events reported which might have been related to changes in prolactin levels. Prolactin levels were not measured in this study.

E-7 Vital Signs & Weight

Blood Pressure and Pulse
Among the three treatment groups, the mean systolic blood pressure, diastolic blood pressure, and pulse were very similar. There were no statistically significant mean changes from baseline in vital signs, and there were no statistically significant differences in mean changes among

groups. During the double-blind trial, none of the subjects in any group exhibited an abnormal value for blood pressure or pulse (as defined by criteria listed for Study USA-239). There were no reported cases of orthostatic hypotension for any subjects in the trial.

Weight

At baseline, the mean weights were 87 kg, 83 kg, and 89 kg in the risperidone, placebo, and placebo groups, respectively. The mean changes in weight at Day 21 were + 2.51 kg, + 0.39 kg, and +0.032 kg in the risperidone, placebo, and haloperidol groups, respectively. The weight change in the risperidone group was significantly greater than that of the placebo group ($p<0.001$).

Individual Changes in Weight: weight changes were classified as abnormal of there was a change of at least 7%, compared to the baseline value. In the risperidone group, four subjects (10.5%) had abnormally high weight gains. One subject (2.6%) had an abnormal degree of weight loss. In the placebo group, one subject (4.3%) had an abnormally high weight gain, and no subjects had significant losses of weight. In the haloperidol group, no subjects had abnormal weight gains, and one subject (3.2%) had an abnormal weight loss. Weight change was reported as an adverse event by 2, 1, and 3 subjects in the risperidone, placebo, and haloperidol groups, respectively.

E-8 Electrocardiogram Findings

Among treatment groups, there were small differences in the mean values for ECG intervals; however, these differences were not clinically significant. A number of subjects from all groups had abnormalities in one or more ECG intervals at some point in the trial, including baseline. The proportion of subjects who had abnormal PR or QRS intervals was similar among treatment groups.

Cases of Abnormal QTc at Baseline

Forty subjects had abnormally long QTc intervals at baseline (RIS-14; PLAC-11; HAL-5). Of these 40 cases, 15 were considered "prolonged," and 25 were considered "borderline." One of these subjects from the risperidone group had normalization of the QTc but later had an SAE-tachycardia, considered severe and possibly related to study medication. Study treatment was stopped, and the subject recovered.

Cases of Abnormal QTc at Endpoint

At endpoint, 30 subjects had QTc intervals which were considered either borderline or prolonged. There were 14 cases of prolonged QTc intervals (RIS-4; PLAC-6; HAL-4), and there were 16 cases of borderline QTc (RIS-3; PLAC-6; HAL-7). In addition, one subject from the risperidone group had an abnormal QTc value in the "pathologic" range (>500 msec: 517). The event was not associated with clinical signs or symptoms; it was considered "mild" and possibly related to study treatment. No action was taken, and the AE was resolved upon the completion of treatment. There were no cases of "pathologic" QTc intervals in the placebo or haloperidol groups.

Changes in QTc "of Concern" or of Clear Concern"

A change in QTc from baseline>60 msec is defined as "of clear concern." A change of 30-60 msec is defined as "of concern." One subject from the placebo group had a change in QTc (from 346 to 416) that was of clear concern. After the study, the QTc decreased to 376 msec. The subject had no clinical complications. QTc "changes of concern" occurred in 4, 4, and 3 subjects in the placebo, risperidone, and haloperidol groups, respectively.

E-9 Clinical Laboratory Findings

Mean Changes Over Time

There were no significant mean changes for serum chemistry or hematological parameters. Prolactin levels were not measured in this study.

Individual Laboratory Abnormalities

Many subjects had an abnormal lab value at some point in the study. A significant number of these occurred at baseline and subsequently normalized. Many subjects with abnormal values at baseline did not have subsequent values. Some abnormalities at baseline persisted, but a greater number normalized. The vast majority of all laboratory abnormalities were only marginally out of the reference ranges. In the cases listed below, the parameters were normal at baseline and were abnormal during the study. The abnormalities had the potential to be clinically significant (if they persisted); however, none of these cases constituted an acutely serious condition. For example, all cases of elevated liver enzymes were relatively mild; none of elevated glucose levels were in a range considered clinically dangerous; cases of uricemia, hematuria, leukocytosis, and pyuria were not serious; the case of "low platelet count" was probably not clinically significant (119 K). The case of hyponatremia could have been clinically significant. Several subjects with hyperlipidemia had triglyceride levels > 300.
Of note, cases of hyperglycemia occurred in each treatment group

Abnormal Clinical Laboratory Findings of Potential Clinical Significance- USA-102

Clinical Laboratory Abnormality	Placebo No. of cases	Risperidone No. of cases	Haloperidol No. of cases
Hyperglycemia	3	7	6
Hyperlipidemia	3	4	3
Transiminase elev.	1	6	0
Hypercholesterolemia	0	2	1
Hyperuricemia	1	2	2
Leukocytosis	3	1	0
Hematuria	1	0	2
BUN elevated	1	0	1
Hyponatremia	1	0	0
Thrombocytopenia	1	0	0
Pyuria	1	0	0
Hypochloremia	1	0	0

Study INT-46

XIII. Integrated Review of Efficacy- Study RIS-INT-46

A. Brief Statement of Conclusions

This trial failed to demonstrate efficacy of risperidone in the acute treatment of mania. Although there was an apparent trend toward greater reduction of mean YMRS score in the risperidone group at 21 days (compared to the placebo group), the estimated difference between groups was not statistically significant (p=0.089). Within the lithium and valproate subgroups, there appeared to be potentially meaningful trends toward a treatment effect of risperidone. In contrast, within the carbamazepine subgroup, there was actually a small apparent difference between the treatment groups, favoring placebo. It is possible that important drug interaction effects might have contributed at least partially to the failure of the study. Carbamazepine, when administered with risperidone, can decrease serum concentrations of the active moiety of risperidone by as much as 50%. Thus a potential treatment effect in the RIS + CARB compared to the PLA + CARB effect could be diminished or negated by this drug interaction.

B. General Approach to the Review of Efficacy

The full efficacy database and summary of efficacy results provided by the sponsor were reviewed.

C. Detailed Review of the Trial

C-1 Study Sites and Investigators

Refer to a complete listing in Appendix .

C-2 Subject Selection Criteria

The subject selection criteria were identical to those of study RIS-USA-102

C-3 Objectives of the Study

The primary and secondary objectives were identical to those of study RIS-USA-102

C-4 Study Design

The design of this adjunctive therapy was analogous to that of adjunctive therapy trial USA-102. Differences; one of three mood stabilizers were used in combination with risperidone versus placebo. In contrast to study USA-102, subjects could be treated with carbamazepine (or lithium or valproate). In many countries, valproate had not been approved for treatment of Bipolar Disorder. As a result, a relatively low proportion of subjects in the study were treated with valproate, compared to lithium. In this study, there was not a haloperidol arm.

(For details about the study design, please refer to the Study Design section for Study RIS-USA-102 above.

C-5 Outcome Measures

The primary and secondary outcome measures were identical to those of study RIS-USA-102

C-6 Disposition of Subjects

Of the 157 individuals screened, 151 (97%) were randomized to treatment. All but one randomized subject received treatment (one in the placebo group was not treated). There were 75 subjects in the risperidone group and 76 in the placebo group. The proportion of subjects completing the study was 83%. Sixteen percent (16%) of the risperidone group and 19% of the placebo group discontinued from the study.

C-7 Discontinuations from the Study

Overall, there were relatively few subjects (17%) who discontinued for a study of acute mania. A slightly higher proportion of the placebo group (19%) discontinued, compared to the risperidone group (16%). For the placebo group, the most common reasons for discontinuation were: "withdrew consent" (6.7%); adverse events (4%); and "other" (4%). In the risperidone group, the most common reasons were: lost to follow-up, (4%); insufficient response (2.7%); ineligible to continue (2.7%); and withdrew consent (2.7%). Only one subject in the risperidone group discontinued due to an adverse event.

Reason for Discontinuation	RISP N= 75	PLAC N= 75
Discontinued	12 (16%)	14 (19%)
Adverse Event	1 (1.3)	3 (4)
Ineligible to continue	2 (2.7)	0

Insufficient response	2 (2.7)	1 (1.3)
Lost to follow-up	3 (4)	0
Noncompliance	1 (1.3)	2 (2.7)
Withdrew consent	2 (2.7)	5 (6.7)
Other	1 (1.3)	3 (4)

C-8 Baseline Demographics and Severity of Illness

In study USA-102, 58% of subjects were women and 42% were men. In the placebo group, 58% of subjects were women and 42% were men. In the risperidone group, 59% were women and 41% were men. Thus, the treatment groups were extremely well balanced with respect to gender. Race was not one of the parameters of baseline characteristics. The median age was slightly lower in the risperidone group, compared to the placebo group (38 vs. 42). Median weight and height were virtually identical between groups. Both groups had a higher propor-tion of subjects with a manic episode versus a mixed episode (90% and 94% of the placebo and risperidone groups, respectively). In the risperidone group, the proportion of subjects with psychotic features was greater than that in the placebo group (51% vs. 38%). The placebo group had more subjects categorized as "severe without psychotic features" than did the risperidone group (23% vs. 16%). The proportion of subjects with 'mild severity" of illness was 3% and 4% in the placebo and risperidone groups, respectively. Finally, the proportion of subjects with moderate severity of illness was 36% and 29% in the placebo and risperidone groups, respectively. The baseline YMRS score was 28.3 in the placebo group and 29.4 in the risperidone group. Thus, it appears that the treatment groups are reasonably well balanced regarding severity of illness.

C-9 Concomitant Medications

Mood Stabilizers

Most subjects in RIS-INT-46 were treated with lithium (57%). This was largely due to the fact that valproate was not approved for the treatment of mania in many of the countries in which there were study sites. Valproate was used for 25% of subjects, and carbamazepine was used for 17% of subjects. The proportions of subjects receiving each of the mood stabilizers was very similar between the risperidone and placebo groups: (lithium for 56% vs. 59%; valproate for 25% vs. 25%; and carbamazepine in 19% vs. 16% of subjects). Mood stabilizers were initiated before the trial for 43% of subjects (39% and 47% of the risperidone and placebo groups, respectively. Treatment with mood stabilizers was begun at the start of the trial for 57% of subjects (61% and 53% of the risperidone and placebo groups, respectively). The clinician chose which mood stabilizer to use for the individual subject, depending on the subject's medical history and previous experience with mood stabilizer treatment. The mood stabilizer was used in an open-label manner. The clinician could adjust the dose of mood stabilizer as needed, based on clinical response and targeted serum drug levels. The following serum concentrations were targeted:

1. Valproate: trough serum concentration of 50-125 g/mL;
2. Lithium: 0.6-1.4 mEq/L (12 hours after last dose);
3. Carbamazepine: trough serum concentration of 4-12 g/mL.

As in study USA-102, serum lithium levels were relatively low in both the risperidone and placebo groups: the mean levels at endpoint were 0.63 and 0.75 mEq/L, respectively. For the placebo group, the mean serum valproate concentration at endpoint (97 ug/mL) was well within the range considered therapeutic 50-125). For the risperidone group, the mean serum valproate level was considerably lower (63). The mean serum concentrations of carbama-zepine were relatively low for the treatment of acute mania: 5.7 in the placebo group and 6.3 ug/mL in the risperidone group. There appears to be a trend toward lower mean serum concentrations of lithium and valproate in the risperidone group, compared to the placebo-treated group from Week 1 to endpoint. Such a trend was not apparent in the carbamazepine-treated group. There are at least several potential interpretations regarding the relatively low concentrations of mood stabilizers and the differences between treatment groups: 1) there may have been a beneficial treatment effect from risperidone, such that the risperidone-treated subjects did not require higher doses/concentrations of mood stabilizers; 2) perhaps, investigators were relatively reluctant to maximize the use of mood stabilizers, since this was a study of the effects of risperidone. Investigators may have had concerns about potential confounding effects or potential adverse events; and 3) clinicians often do not maximize the use of mood stabilizers, especially lithium. On the other hand, for such a short trial (21 days), it is difficult to maximize treatment with mood stabilizers.

Lorazepam Use

Unlike the other studies, in INT-46 the protocol did not account for recording lorazepam that might have been used. Therefore, the sponsor could not provide data regarding lorazepam or other benzodiazepine use, and an analogous analysis could not be performed. Available data included the number of subjects who were treated with at least one dose of lorazepam. The majority of subjects had treatment with lorazepam at some point in the study. Lorazepam was used by 63% of the placebo group and by 72% of the risperidone group. There are no data available regarding the total dose of drug used by each group, the mean or median dose, or the mean or median duration of use. Thus, one cannot draw any conclusions about whether or not the use of lorazepam or related drugs could have had an effect on the results of the efficacy analysis.

Medications for the Treatment of Extrapyramidal Symptoms

In the risperidone group, 16% of subjects were treated with medications targeting EPS. In the placebo group, 8% of subjects were treated with such medications. For both groups, nearly all of the medications used were anticholinergic drugs. One subject in the risperidone group was treated with a muscle relaxant, orphenadrine. There are no data available regarding the doses used or the frequency and duration of treatment with these medications.

C-10 Trial Medication Exposure During the Double-Blind Phase

Seventy-five (75) subjects were exposed to risperidone for a total of 3.51 subject-years. The mean modal dose of risperidone was 3.7 mg, the median modal dose was 4 mg, and the range was 1-6 mg. The mean modal number of PLA tablets taken daily during the DB phase was 3.8 tablets (range 2-6). The mean treatment duration of the double-blind phase was 14.7 days (range

1-28 days) for the placebo-treated subjects and 16.7 days (range 2-24 days) for the risperidone-treated subjects. The median treatment duration was 18 days for the placebo group and 21 days for the risperidone group (this seems to have included the 3-day washout phase)

The mean duration of lithium treatment was 16 days (range 2-29 days) in the PLA group and 18 days (range 1-25 days) in the RIS group. For valproate, it was 13 days (range 2-23 days) in the PLA group and 15 days (range 1-24 days) in the RIS group. For carbamazepine, it was 18 days (range 1-23 days) in the PLA group and 18 days (range 3-25 days) in the RIS group.

D. Efficacy Conclusions

This trial failed to demonstrate efficacy of risperidone in the acute treatment of mania. Although there was an apparent trend toward greater reduction of mean YMRS score in the risperidone group at 21 days (compared to the placebo group), the estimated difference between groups was not statistically significant (p=0.089). Within the lithium and valproate subgroups, there appeared to be potentially meaningful trends toward a treatment effect of risperidone. In contrast, within the carbamazepine subgroup, there was actually a small apparent difference between the treatment groups, favoring placebo. It is possible that important drug interaction effects might have contributed at least partially to the failure of the study. Carbamazepine, when administered with risperidone, can decrease serum concentrations of the active moiety of risperidone by as much as 50%. Thus a potential treatment effect in the RIS + CARB compared to the PLA + CARB effect could be diminished or negated by this drug interaction. The descriptive statistics for the efficacy results among mood stabilizer groups support this hypothesis. (Refer to section) On the other hand, In RIS-INT-46, the treatment effect of risperidone (plus lithium or valproate), compared to placebo (plus lithium or valproate) at Day 21 was not statistically significant (p= 0.377).

Primary Efficacy Analysis

The change from baseline in the mean YMRS score after three weeks (the dependent variable) was analyzed using a LOCF imputation method and an ANCOVA model with factors, treatment, country, mood stabilizer, initiation of mood stabilizer and the baseline value of total YMRS score as a covariate. The mean YMRS scores at baseline were 28.3 and 29.3, respectively, for the placebo and risperidone arms. The mean scores at endpoint were 18 vs. 14.9. Thus, the mean reductions in YMRS score at three weeks were -10.3 and -14.5 for the placebo and risperidone groups, respec-tively. The least square mean changes were –9.4 vs. –12.9. Finally, the difference in LS mean was –3.5 (favoring the risperidone group), with a 95% confidence interval of (-7.60, 0.54). The difference between treatment groups in the mean YMRS was not statistically significant (p=0.089). Results are summarized in the text and table below.

Summary of the Change from Baseline in YMRS Score- INT-46

	Placebo			Risperidone			
Time	N	Mean (SE)	Mean change fr. Baseline (SE)	N	Mean (SE)	Mean change fr. Baseline (SE)	p-value[1]
Baseline	73	28.3 □0.7		69	29.3 □0.7		0.364
Week 1	68	21.7 □1.2	6.7 □1.0	67	19.0 □1.2	10.2 □1.1	0.029
Week 2	44	15.4 □1.4	13.3 □1.4	59	16.5 □1.5	12.8 □1.4	0.660
Week 3	33	11.2 □1.7	17.1 □1.8	46	9.7 □1.4	19.9 □1.4	0.377
End point	73	17.9 □1.4	10.3 □1.4	68	14.9 □1.6	14.5 □1.5	0.089

Analysis of Secondary Outcome Measures
There was a statistically significant difference in the change from baseline in total BPRS at Day 21 ($p<0.005$) and Day 7 ($p= 0.012$)

CGI Scores
The results for changes in CGI-Severityscore: there was a statistically significant difference in score changes between the placebo and risperidone groups, favoring risperidone arm at Day 7 ($p= 0.013$) and at Day 21 ($p= 0.019$).

HAM-D Scores
There were no statistically significant differences between the placebo and risperidone groups in the change from baseline in HAM-D scores.

Subgroup Analyses- RIS-INT-46

Efficacy Analysis by Mood Stabilizer
The table below summarizes the results for the changes from baseline in YMRS scores among mood stabilizer subgroups. At the endpoint of the study, the estimates for mean differences between risperidone and placebo groups in the change from baseline in YMRS scores were similar between the lithium and valproate groups. For example, in the lithium subgroup, the estimated mean difference between risperidone and placebo groups was –5.2, favoring risperidone. For the valproate subgroup, the difference was –5.6, favoring risperidone. In contrast, within the carbamazepine subgroup, the estimated difference in YMRS score changes between the risperidone and placebo groups was + 1.8, favoring the placebo group. Since co-administration of carbamazepine and risperidone has been demonstrated to reduce the risperidone active moiety by as much as 50%, it is possible that this drug interaction may have prevented a risperidone treatment effect in the carbamazepine subgroup. Carbamazepine was used by 17% of subjects.

Within the placebo group, lithium appears to have had a significant effect, compared to valproate; the absolute mean change in YMRS score from baseline was much greater for lithium (-11.1. vs. –6.9). Similarly, within the placebo group, there was a large change from baseline for the carbamazepine subgroup.

Change from Baseline in YMRS Score by Type of Mood Stabilizer (RIS-INT-46)

		PLACEBO			RISPERIDONE		
Mood stabilizer	Time	N	Mean ±S.E.	Mean change fr. Baseline ±S.E.	N	Mean ±S.E.	Mean change fr. Baseline ±S.E.
LITH	Baseline	43	28.6		39	29.6	
	Week 1	40	22.0	6.8	38	18.6	10.7
	Week 2	27	15.2	14.1	34	15.4	14.6
	Week 3	21	11.9	17.6	29	11.1	19.2
	Endpoint	43	17.5	**-11.1**	39	13.3	**-16.3**
VAL	Baseline	19	26.9		16	28.2	
	Week 1	17	20.7	6.2	15	18.8	-9.3

	Week 2	7	13.1	-12.9	14	15.1	-12.3
	Week 3	5	5.6	20.0	9	5.4	21.8
	Endpoint	19	20.0	**-6.9**	15	15.6	**-12.5**
CARBAM	Baseline	11	29.5		14	30.1	
	Week 1	11	22.3	-7.2	14	20.4	-9.6
	Week 2	10	17.5 ±2.7	11.2	11	21.7 ±3.7	8.1
	Week 3	7	13.0 ±4.2	13.6	8	9.1 ±3.0	20.4
	Endpoint	11	16.2 ±3.9	**-13.3**	14	18.6 ±4.0	**-11.5**

The timing of initiation of mood stabilizer treatment did not seem to affect the mean difference between risperidone and placebo in the change from baseline in YMRS score. Sixty-one subjects received a mood stabilizer at least 2 weeks prior to beginning trial RIS-INT-46, and 81 initially received a mood stabilizer at the start of the trial. For these two subgroups, there was little difference in the estimates for mean difference between risperidone and placebo in the change from baseline in total YMRS score.

Presence or Absence of Psychotic Symptoms

For study RIS-INT-46, 28 subjects in the placebo arm and 35 in the risperidone arm had psychotic features at baseline (45 vs. 34 did not have psychotic features at baseline). On average, the baseline YMRS scores were about 4 points higher for those with psychotic features. The table below summarizes the results for change from baseline in YMRS score by presence or absence of psychotic features. The estimated mean change from baseline in YMRS score were more similar between the placebo and risperidone arms for those subjects with psychotic features at baseline (-12.2 vs. –15.1) than for those without psychotic features at baseline (–9.2 vs. –13.8).

Change from Baseline in YMRS Score by +/- Psychotic Features at Baseline

		Placebo			Risperidone		
Psychotic features:	**Time**	**N**	**Mean**	**Mean change fr. Baseline**	**N**	**Mean □S.E.**	**Mean change fr. Baseline**
With psychotic features	Baseline	28	30.9		35	31.1	
	Week 1	27	23.2	-7.9	34	20.0	-11.0
	Week 2	19	14.8	-15.5	31	16.9	-14.0
	Week 3	13	8.9	-20.8	25	11.0	-19.9
	Endpoint	28	18.8	**-12.2**	35	16.0	**-15.1**
Without. psychotic features	Baseline	45	26.6		34	27.5	
	Week 1	41	20.8	-5.9	33	18.1	-9.4
	Week 2	25	15.8	-11.6	28	16.1	-11.5
	Week 3	20	12.6	-14.7	21	8.1	-19.9
	Endpoint	45	17.4	**-9.2**	33	13.7	**-13.8**

Manic versus Mixed Episode

At baseline, most subjects (131) had a manic episode, rather than a mixed episode (11).

The placebo group had 7 "mixed" subjects, and the risperidone group had 4. For the "manic" subgroup, the estimates of changes in mean YMRS scores are consistent with results of the primary efficacy analysis: there was an apparent beneficial treatment effect with risperidone, as indicated by the greater reduction of YMRS score in the risperidone group (-14.8 vs. –9.8). In contrast, the magnitude of mean reduction of YMRS score was greater in the placebo group than the risperidone group for the subgroup of "mixed episode" subjects (PLAC- -15.3; RIS- -9.0). Since the numbers of mixed-episode subjects was so small, it is difficult to draw conclusions from these descriptive statistics.

Summary of the Change from Baseline in YMRS Score by Bipolar Episode at Baseline

		Placebo			Risperidone		
Bipolar episode	**Time**	**N**	**Mean**	**Mean change fr. Baseline**	**N**	**Mean**	**Mean change fr. Baseline**
Manic episode	Baseline	66	28.6		65	29.7	
	Week 1	62	22.8	-5.9	63	19.1	-10.5
	Week 2	40	15.7	-13.2	56	16.3	-13.4
	Week 3	31	11.7	-16.9	45	9.8	-19.9
	Endpoint	66	18.8	**- 9.8**	64	14.9	**-14.8**
Mixed episode	Baseline	7	25.4		4	24.3	
	Week 1	6	10.8	-15.2	4	18.8	-5.5
	Week 2	4	13.0	-14.5	3	21.7	-2.7
	Week 3	2	2.5	-20.0	1	5.0	-19.0
	Endpoint	7	10.1	**-15.3**	4	15.3	**-9.0**

Conclusions

This trial failed to demonstrate efficacy of risperidone in the acute treatment of mania. Although there was an apparent trend toward greater reduction of mean YMRS score in the risperidone group at 21 days (compared to the placebo group), the estimated difference between groups was not statistically significant (p=0.089). Within the lithium and valproate subgroups, there appeared to be potentially meaningful trends toward a treatment effect of risperidone. In contrast, within the carbamazepine subgroup, there was actually a small apparent difference between the treatment groups, favoring placebo. It is possible that important drug interaction effects might have contributed at least partially to the failure of the study. Carbamazepine, when administered with risperidone, can decrease serum concentrations of the active moiety of risperidone by as much as 50%. Thus a potential treatment effect in the RIS + CARB compared to the PLA + CARB effect could be diminished or negated by this drug interaction. The descriptive statistics for the efficacy results among mood stabilizer groups support this hypothesis. (Refer to section) On the other hand, In RIS-INT-46, the treatment effect of risperidone (plus lithium or valproate), compared to placebo (plus lithium or valproate) at Day 21 was not statistically significant (p= 0.377).

A subgroup analysis of efficacy according to the presence or absence of psychotic features at baseline indicates that risperidone had a consistent effect, regardless of the presence of absence of psychotic features. In contrast, the subgroup analysis of the manic episode versus mixed episode subjects indicated that the manic group had an apparent risperidone treatment effect, whereas the mixed episode

subgroup had a mean change in YMRS score that suggested a treatment effect for placebo, compared to risperidone. It should be noted that there were only 11 subjects with a mixed episode in the study; thus, it is difficult to draw conclusions from the descriptive statistics for the subgroup.

XIV. Integrated Analysis of Safety- RIS-INT-46

A. Statement of Conclusions

As in the other studies reviewed, treatment with risperidone was reasonably safe and well tolerated. There were no unexpected safety findings, compared with previous exposure to risperidone. In RIS-INT-46, 75 subjects were exposed to risperidone, for a total exposure of 3.5 patient years. The mean modal dose was 3.68 mg/day, and the mean duration of exposure was 16.7 days. The mean duration of treatment with placebo was 14 days. Eighty-six (86) subjects were exposed to lithium, 38 were exposed to valproate, and 26 were exposed to carbamazepine.

There were no deaths in this study. There were 4 serious adverse events (two in each group). One subject treated with risperidone and lithium had the SAE, condition aggravated. Another subject treated with risperidone and lithium had somnolence. Both placebo subjects were treated with lithium; one had the SAE, condition aggravated, and one had suicidal ideation. Thirteen (13) subjects discontinued due to adverse events (2 in the risperidone group, and 11 in the placebo group). Those in the risperidone group were due to condition aggravated and somnolence. Five in the placebo group were related to exacerbations of manic and/or psychotic symptoms. Six were due to medical conditions that did not appear to be related to study treatment. Adverse events were reported 57% of subjects in the risperidone group 51% of subjects in the placebo group. The most commonly reported adverse events in were: Extrapyramidal symptoms (21% in the risperidone group and 8% of the placebo group); headache (9% and 9%); akathisia (7% vs. 0); tremor (5% vs. 1%); insomnia (4% vs. 8%); and nausea (5% vs. 3%). The most common types in the risperidone group were akathisia (7%), tremor (5%), "extrapyramidal disorder" (4%), hypertonia (4%), abnormal gait (3%), and tetany (3%). In the placebo group, the most common EPS were "extrapyramidal disorder" (4%), hypertonia (3%), dyskinesia (1%), and tremor (1%).

There were no reported adverse events which would be consistent with abnormalities in prolactin levels. Prolactin levels were not measured in this study. In the risperidone group, the mean weight increased by 1.7 kg; in the placebo group, the mean weight increased by 0.5 kg. There were no unexpected changes in vital signs. There were a small number of subjects in the risperidone group who had decreases of systolic and diastolic blood pressure. There were no reports of the adverse event, orthostatic hypotension. There no meaningful changes in mean or individual ECG parameters. There was a small number of increases in QT interval which were not clinically significant. There were no changes in mean clinical laboratory parameters during the 21-day trial, and there were no meaningful differences in laboratory values between treatment groups. The majority of abnormal lab values were only nominally outside of the reference ranges; they didn't indicate a serious medical condition, and they were not associated

with clinical signs or symptoms. Hyperglycemia occurred in 5 and 4 subjects in the PLA and RIS groups, respectively. Hypercholesterolemia occurred in 1 and 0, respectively. Hyperlipidemia (1 vs. 3); elevated transaminases (2 vs. 3).

B. Description of Patient Exposure

Refer to the Conclusions section above.

C. Methods of Safety Review

The safety database and summaries of safety findings provided by the sponsor were reviewed in detail

D. Adequacy of Safety Testing

The safety testing was adequate and appropriate for this study (refer to the analogous sections for USA-102 and monotherapy studies USA-239 and IND-2

E. Review of Safety Findings

E-1 Deaths

There were no deaths in either treatment group during the trial.

E-2 Serious Adverse Events

Four serious adverse events were reported during the trial (two in each treatment group).
In the risperidone group, the following were reported:

1. A subject treated with risperidone and lithium had the SAE, condition aggravated at Day 9 of treatment. The subject discontinued from the study and recovered.
2. A subject treated with risperidone and lithium developed the SAE, somnolence at day 3. The dose of study drug was adjusted, and the subject recovered.

The following SAE were reported in the placebo group:

1. A subject treated with placebo and lithium developed the SAE, condition aggravated on the 4th day of study treatment. The subject discontinued and recovered.
2. A subject treated with placebo and lithium had the SAE, 'suicide attempt.' However, the subject had suicidal ideation without any suicidal behavior. The event occurred soon after ending a relationship. The subject discontinued from the study and was considered"not recovered."

E-3 Discontinuations Due to Adverse Events

Thirteen (13) subjects discontinued from the trial due to adverse events. There were 2 from the risperidone group and 11 from the placebo group:

Risperidone group:
1. Condition aggravated. Had been treated with RIS and LITH.
2.Somnolence (RIS and LITH)

Placebo group:
1. Condition aggravated (PLA + LITH)
2. Condition aggravated (PLA + VAL)
3. Agitation (PLA + VAL)
4. Suicidal ideation, without suicidal behavior (PLA + LITH)
5. Constipation
6. Insomnia
7. Orthostasis, dizziness, fall, asthenia, myoclonus, mild renal insufficiency, chronic anemia (VAL)
8. Urticaria. There was no evidence of a generalized hypersensitivity reaction. (PLA + VAL)
9. Hallucination
10. Depression (PLA + LITH)
11. Foot callus

E-4 Commonly Reported Adverse Events

Adverse events were reported 57% of subjects in the risperidone group 51% of subjects in the placebo group. The most commonly reported adverse events in either treatment group were: Extrapyramidal symptoms (21% in the risperidone group and 8% of the placebo group); headache (9% and 9%); akathisia (7% vs. 0); tremor (5% vs. 1%); insomnia (4% vs. 8%); and nausea (5% vs. 3%).

Prolactin-related Adverse Events
No reported adverse events which would be consistent with abnormalities in prolactin levels. Prolactin levels were not measured in this study.

Extrapyramidal Symptoms (EPS)
Eight percent (8%) of the placebo group and 21% of the risperidone group reported having EPS. The most common types in the RIS group were akathisia (7%), tremor (5%), "extrapyramidal disorder" (4%), hypertonia (4%), abnormal gait (3%), and tetany (3%).
In the PLA group, the most common EPS were "extrapyramidal disorder" (4%), hypertonia (3%), dyskinesia (1%), and tremor (1%).

Blood Pressure and Pulse
At baseline, the mean systolic and diastolic blood pressures were not significantly different between treatment groups. However, the mean pulse was significantly higher in the RIS group at baseline (85.1, compared with 80.5 in the PLA group, p = 0.01). During the trial, there were no statistically significant differences between the treatment groups. The number of abnormalities in blood pressure or pulse were very low. The most common abnormalities were observed in systolic blood pressure values at endpoint in the RIS group: three subjects (4.%) had a low SBP (compared with 0 in the

placebo group. At Week 2, the proportion of subjects with low SBP was 3.4% and 2.3% in the RIS and PLA groups, respectively. For DBP in the RIS group, 1.6%, 0, 2.2% and 1.5% had low values at Week 1, Week 2, Week 3, and Endpoint, respectively. None of the PLA subjects had a low DBP at any point in the trial. Pulse in the RIS group was not elevated at any time point. In contrast, 2.3% and 1.4% of PLA subjects had elevated pulse at Week 2 and Endpoint, respectively.

Orthostatic changes
The sponsor did not perform an analysis vital signs with orthostasis as a parameter.

Weight
The mean weight at Baseline was 74.3 kg in the PLA group and 76.5 kg in the RIS group. From baseline to endpoint, there was a mean increase of 1.7 kg the risperidone group and 0.5 kg in the placebo group. The weight increase in the RIS group was statistically significantly larger than in the PLA group (p =0.012 at End point DB, ANOVA). Weight increase was reported as an AE by one subject in the RIS group and one in the PLA group.

Electrocardiogram Findings
There were no significant differences between treatment groups in mean values of ECG parameters. Within groups, there were no significant changes from baseline in mean values of ECG parameters; although, there were small fluctuations in the mean value of ECG parameters during the trial. None of the changes were considered to be clinically significant.

A number of subjects had abnormal values on one or more ECG parameters, but none of the abnormalities were associated with clinical signs or symptoms. The proportion of abnormalities in HR, PR, and QRS intervals was similar between treatment groups at all evaluation points in the trial. Sixteen subjects (5 PLA, 11 RIS) had an abnormal QTcB at baseline (11 borderline, 5 prolonged). At Endpoint, there was one subject in each group with a borderline QTcB. One subject in the PLA group had a prolonged QTcB. Five subjects (1 PLA, 4 RIS) had an abnormal QTcF at baseline (4 borderline, 1 prolonged). There were no abnormal QTcF values during the trial in the RIS group. One placebo-treated subjects had a borderline QTcF at Endpoint.

Clinical Laboratory Findings
There were no changes in mean clinical laboratory parameters during the 21-day trial, and there were no meaningful differences in laboratory values between treatment groups.
There were 36 (5%) placebo and 30 (5%) risperidone subjects who had nonpathological laboratory values before treatment but developed pathological values during treatment.
The majority of these values were only nominally outside of the reference ranges, they didn't indicate a serious medical condition, and they were not associated with clinical signs or symptoms. Hyperglycemia occurred in 5 and 4 subjects in the PLA and RIS groups, respectively. Hypercholesterolemia occurred in 1 and 0, respectively. Hyperlipidemia (1;3); elevated transaminases (2;3).

Cases of liver function test abnormalities in subjects treated with risperidone:
A 43 year-old woman, treated with risperidone, developed an elevation in serum ALT 5.5 times the limit of normal and approximately 9 times her baseline value. The subject also had an

elevation in serum AST which was 2.5 times the normal limit and approximately 2.5 times her baseline value. The abnormalities were noted three weeks after beginning therapy with risperidone. Neither of these elevations were reported as AEs. The subject apparently did not have associated signs or symptoms of hepatic illness. She had been treated with lithium as mood stabilizer. After the trial, the subject continued treatment with risperidone. The liver function tests returned to normal about 3 weeks later.

A 41 year-old man, treated with risperidone and lithium, developed an elevation in serum ALT 4.5 times the normal limit and approximately 6.5 times his baseline value. The abnormality was noted one week after beginning treatment with risperidone, and it accompanied by an elevation in serum AST, which was approximately two times the normal limit and approximately four times his baseline value. Neither of these elevations were reported as AEs. The subject apparently did not have associated signs or symptoms of hepatic illness. After the trial, the subject continued treatment with risperidone. The liver function tests returned to normal about

XV. Dosing, Regimen, and Administration Issues

The sponsor's recommendations about dosing, titration, and administration of risperidone in this indication are reasonable and clinically appropriate. The recommendations follow from the efficacy and safety results of the trials reviewed. Since these were not fixed-dose studies, one cannot draw conclusions about potential dose-response or dose-toxicity relationships. However, flexible dosing in the recommended range (2-6 mg/day) was efficacious and reasonably safe and well tolerated. (For details, please refer to the Executive Summary, Section II.D).

XVI. Use in Special Populations

A. Evaluate Sponsor's Analyses of Gender Effects

The sponsor adequately evaluated potential gender effects on the efficacy and safety of risperidone treatment. There were approximately equal numbers of men and women in the studies, and the sponsor conducted subgroup analyses as indicated.

B. Evaluate Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

It was not possible to critically evaluate potential differences in safety and efficacy in these subjects, due to the relatively small sample sizes of subjects > 50 years old and subjects who were not Caucasian. Descriptive statistics for efficacy analysis suggested that there were no significant differences in efficacy among these subgroups. It would be necessary to have larger sample sizes of these subgroups in order to conduct a formal statistical analysis.

Based on analyses of adverse events by demographic characteristics, baseline disease features, and concomitant medications, there were no trends suggestive of a clinically meaningful increase in adverse events in any subgroup of risperidone-treated patients

C. Pediatric Program

The Division is actively discussing with the sponsor their planned program to study risperidone in children and adolescents with Bipolar Mania.

D. Comment on Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

Although these sub-populations were not studied within the population of Bipolar Disorder, Manic patients, adequate and useful data are available for the use of risperidone in other subjects with hepatic and renal impairment. There have been no studies examining the use of risperidone in pregnant women. Since it is likely that risperidone will be used in pregnant women with Bipolar Disorder, it would be useful to collect data regarding risperidone exposure during pregnancy.

XVII. Conclusions and Recommendations

A. Conclusions

Risperidone can provide significant benefit in the acute treatment of mania, as demonstrated by the results of the monotherapy and adjunctive therapy trials reviewed. Treatment with risperidone can result in relatively rapid and clinically meaningful reductions in severity of each of the critical signs and symptoms of acute mania. Such features include: acute agitation, psychosis, suicidal and dangerous behavior, grossly impaired judgement, grandiosity, impulsivity, risk-taking behavior, and thought disorder. The safety and tolerability profile of risperidone treatment, for up to 3 weeks, in subjects with Bipolar Disorder, Acute Manic or Mixed Episode, with or without Psychotic Features, is acceptable. The profile is quite similar to the safety and tolerability profile or risperidone in the treatment of schizophrenic patients.

Furthermore, the risk/benefit profile of risperidone compares reasonably well with those of the other drugs approved for the acute treatment of mania.

B. Recommendations

I recommend that the Division take approvable actions for risperidone as monotherapy and as adjunctive therapy to mood stabilizers in the acute of treatment of mania (for up to 3 weeks) in adults with a diagnosis of Bipolar I Disorder, Manic or Mixed Episode with or without Psychotic Features.

I recommend that the sponsor conduct the following post-marketing studies as part of the risperidone and mania program:

1. An adequate and well-controlled study of risperidone in the treatment of children and adolescents with Bipolar Disorder, Manic Episode. (The sponsor has begun planning a pediatric study of risperidone in mania and has discussed the plan with the Division).

2. A study to assess the longer-term safety of risperidone in the treatment of adults with Bipolar Disorder, Manic episode.

3. A study to assess the potential efficacy of risperidone as continuation and maintenance treatment of Bipolar Disorder.

XVIII. Appendix

A. Subject Selection Criteria

1. Subject Inclusion Criteria

1. Patients must have been 18 years of age or older.
2 Female patients were either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (oral or parenteral hormonal contraceptives; intrauterine device; barrier and spermicide). Abstinence was not considered an acceptable method.
3. Female patients must have had a negative urine pregnancy test at screening and at baseline.
4. Patients or their legal representatives provided informed consent and signed an informed consent document prior to screening.
5. Patients must have met DSM-IV criteria for Bipolar I Disorder, Most Recent Episode Manic. Other Axis I and II disorders, except those listed in Exclusion Criteria, were allowed. 5* In Study IND-2, subjects could have a mixed episode upon entry.

6. Patients were voluntarily hospitalized at the time of enrollment. The primary diagnosis prompting the hospital admission must have been the manic episode that satisfied inclusion criterion 5 (above).
7. Patients had a history of at least one prior documented manic or mixed episode that required treatment. Such manic episodes must not have been "manic-like" episodes in that they must not have been caused by somatic antidepressant treatment.
8. Patients must have received a total score of at least 20 on the Young Mania Rating Scale (YMRS) at screening and at baseline.
9. Patients must have received at total score of less than or equal to 20 on the Montgomery Asberg Depression Rating Scale (MADRS) at baseline.

2. Exclusion Criteria

1. Patients who met DSM-IV criteria for Schizoaffective Disorder.
2. Patients who met DSM-IV criteria for rapid cycling Bipolar Disorder.
3. Patients who had a known or suspected borderline or antisocial personality disorder.
4. Patients who had a known or suspected history of substance dependence excluding nicotine and caffeine) according to DSM-IV criteria within the three months prior to screening.
5. Patients believed by the investigator to be at significant risk for suicidal or violent behavior during the course of the trial.
6. Female patients who were pregnant or nursing.
7. Patients who had a known or suspected seizure disorder.
8. Patients who had a known or suspected history of other serious, unstable illnesses must have been otherwise healthy on the basis of a physical examination, medical history, electrocardiogram, and the results of blood biochemistry, hematology, and urinalysis tests.
9. Patients were not to be enrolled if their serum ALT or AST tests were greater than twice the upper limit of the central laboratory's reference range. Patients were eligible for enrollment when the results of any other biochemistry, hematology, or urinalysis tests were not within the central laboratory's reference ranges only when the investigator judged the deviations not to be clinically noteworthy.
10. Patients who had hypo- or hyperthyroidism, unless stabilized on appropriate medication for at least 3 months prior to screening (a normal TSH was required prior to randomization).
11. Patients whose YMRS total score at baseline decreased by 25% or more from their screening score.
12. Patients who had received an antidepressant medication or electroconvulsive therapy within the 4 weeks prior to screening.
13. Antidepressant medications included known antidepressants used for other indications (e.g., anxiety
14. disorders, sleep disturbance, smoking cessation) as well as St. John's Wort.
15. Patients who had a history of neuroleptic malignant syndrome (NMS)or similar encephalopathic syndrome.
16. Patients who, by history, had received within 3 days prior to baseline, any psychotropic medication prohibited in the Concomitant Therapy section of the protocol. Exceptions were to be permitted for such patients and they were to be allowed to enroll (no sooner than the following day and with the concurrence of the sponsor) when the investigator determined that their symptoms were much worse compared with screening.
17. Patients who were receiving antiparkinsonian drugs or beta-adrenergic blockers at baseline.
18. Patients who had received cocaine, phencyclidine, amphetamine,
19. methylphenidate, pemoline, an opioid, or a hallucinogen within 3 days prior to baseline, as evidenced by history or as suggested by a positive urine drug screen (UDS).
20. Patients who had been intoxicated with alcohol within 3 days prior to baseline, as evidenced by history or as suggested by a blood alcohol level (BAL) of greater than or equal to 100 mg/dL at screening. Exceptions were to be permitted for such patients and they were to be allowed to enroll (no sooner than the following day and with the concurrence of the sponsor) if the investigator determined that their symptoms were much worse compared with screening.
21. Patients who had received clozapine within 1 month prior to screening.
22. Patients who had received a depot antipsychotic within one treatment cycle prior to screening.
23. Patients who had a known or suspected history of hypersensitivity or intolerance to risperidone.
24. Patients who had a history of a poor anti-manic response to an antipsychotic drug which was used as the sole anti-manic agent.

25. Patients who had a known or suspected history of severe drug allergy or hypersensitivity.
26. Patients who had previously participated in this trial.
27. Patients who had participated in any investigational drug trial within 3 months prior to screening.
28. Patients who had an anticipated life expectancy of ≤ 6 months.

Study Withdrawal Criteria
Patients may be withdrawn from the trial if:

1. A serious adverse event occurs
2. They receive or require concomitant therapy not allowed by the protocol;
3. Their YMRS total score increases by > 50% over the baseline value.

Subjects must have been withdrawn from the trial if, at any time:
1. They withdrew their consent;
2. Investigator considers it in the best interest of the subject that he/she be withdrawn;
3. Randomization code is broken;
4. Pregnancy occurs.
5. Investigator believes a subject to be at significant risk for suicidal or violent behavior.
6. Subject meets DSM-IV criteria for a major depressive episode.

Appendix B.

Summary of the Change from Baseline in Total YMRS Score at Day 21

STUDY/ TREATMEN	N	BASELINE MEAN (SD	WEEK 3/ ENDPOINT MEAN (SD)	CHANGE MEAN (SD)	COMPARISON WITH PLACEBO		
					LSMean Change (SD[a])	Diff in LSM Change (95%CI)	p-value
RIS-USA-239							
Placebo	119	29.2 (5.53)	24.2 (11.17)	-5.0 (9.44)	-4.8 (9.52)		
Risperidor	127	29.1 (5.06)	18.0 (10.66)	-11.1 (10.11)	-10.6 (9.52)	-5.9 (-8.3,-3.4)	< 0.001
RIS-IND-2							
Placebo	142	37.5 (7.93)	26.9 (15.50)	-10.5 (15.47)	-10.8 (13.45)		
Risperidor	144	37.1 (7.91)	14.5 (12.81)	-22.7 (13.63)	-23.2 (13.45)	-12.4 (-15.6, -9.3)	<0.001
RIS-USA-102							
Placebo	47	28.1(6.26)	19.8 (11.39)	-8.2 (10.44)	-9.0 (9.36)		
Risperidor	51	27.8 (5.44)	13.6 (11.26)	-14.3 (9.67)	-14.1 (9.36)	-5.1 (-9.0, -1.3)	0.009
Haloperid	50	27.4 (6.20)	14.1 (10.48)	-13.3 (9.95)	-13.6 (9.36)	-4.5 (-8.4, -0.7)	0.021
RIS-INT-46							

Placebo	73	28.3 (5.61)	18.0 (12.26)	-10.3 (11.80)	-9.4 (12.07)		
Risperidor	68	29.4 (6.09)	14.9 (12.94)	-14.5 (12.64)	-12.9 (12.07)	-3.5 (-7.6, 0.5)	0.089

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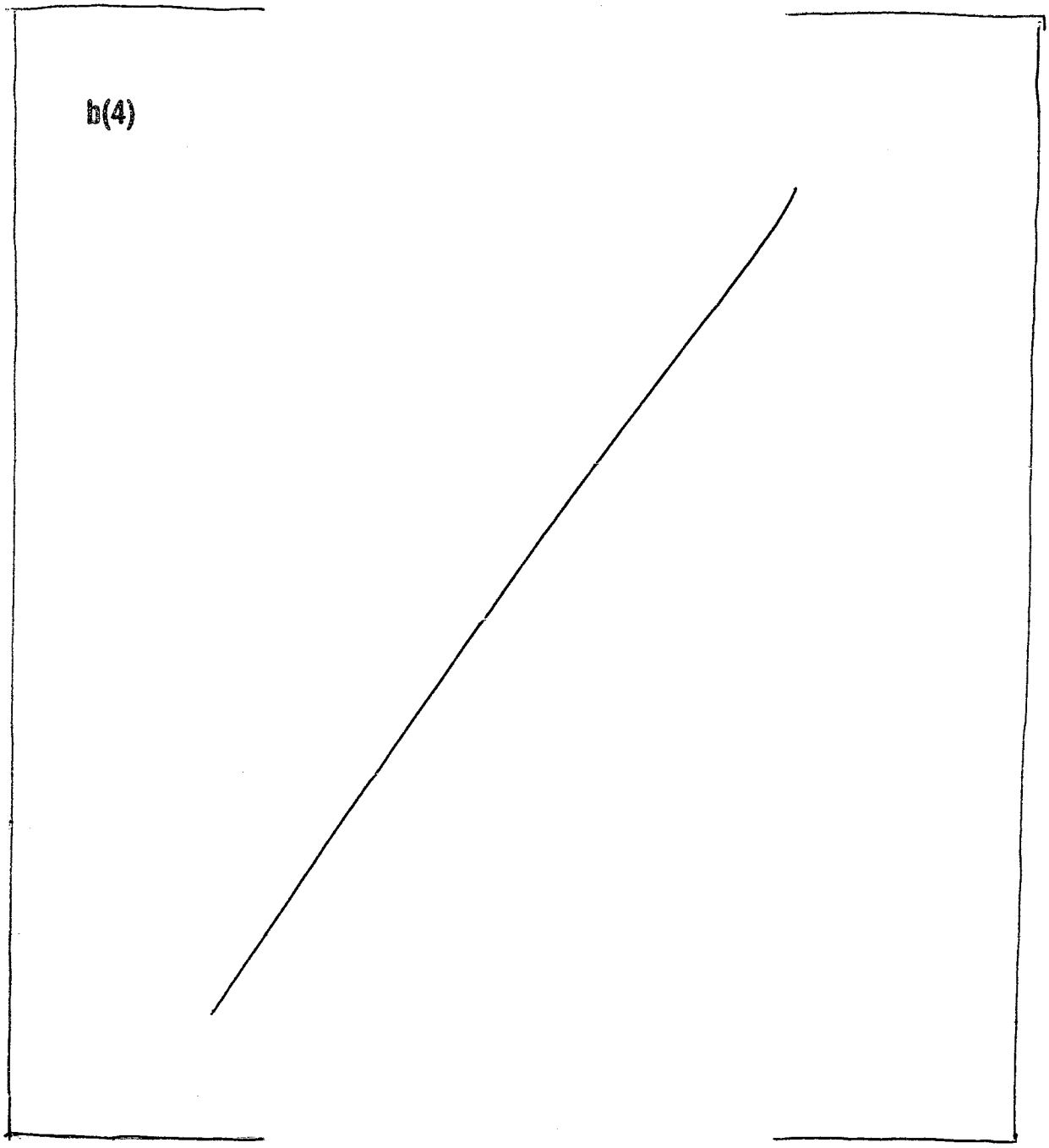

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_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

CLINICAL REVIEW

Clinical Review Section

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Robert Levin, M.D., August 12, 2003
FDA, CDER, ODE1, DNDP, HFD-120

Cc: NDA
T Laughren
P Andreason
R Levin
D Bates

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/s/

Robert Levin
8/13/03 10:56:30 AM
MEDICAL OFFICER

Thomas Laughren
9/12/03 08:24:15 AM
MEDICAL OFFICER
I agree that these supplements are now approvable; see memo to file for more detailed comments.--TPL