CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-346

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA:	21-346
Sponsor:	Janssen
Clock Date:	8/31/01

Drug Name

Generic Name	Risperidone Long Acting Injection
Trade Name	Risperdal CONSTA

Drug Characterization

Pharmacological Category:	Benzisoxazole derivative
Proposed Indication:	Schizophrenia
NDA Classification:	3-S
Dosage Forms, Strengths, and Routes of Administration:	Injection 25mg, 37.5mg and 50mg

Reviewer Information
Clinical Reviewer: Earl D. Hearst, M.D.
Review Completion Date: 10/01/03

EXECUTIVE SUMMARY:

The sponsor has provided a summary of published and unpublished literature that makes a persuasive case for the usefulness and need of Risperdal Consta. The safety data updated in this submission is similar to that of the original NDA for Risperdal Consta. No new pattern of events was uncovered that would alter the risk/benefit profile of Risperdal Consta as pesented in the original NDA. From a clinical viewpoint I recommend that Risperdal Consta be approved.

I. REVIEW:

BACKGROUND

Johnson & Johnson Pharmaceutical Research & Development (J&JPRD), submitted a New Drug Application for RISPERDAL CONSTA (NDA 21-346), a long-acting injection formulation of risperidone, in the treatment of schizophrenia on August 31, 2001.

The Division of Neuropharmacological Drug Products (DNDP) notified J&JPRD on June 28, 2002 that the application for RISPERDAL CONSTA was not approvable under Section 505(d) of the Act and 21 CFR 314.125(b). Three Pharmacology/Toxicology deficiencies were cited in the letter as the primary factors influencing the decision by the Division to not approve NDA 21-346: (1) differences in the tumor profiles in the 24-month carcinogenicity studies with RISPERDAL CONSTA and RISPERDAL tablets; (2) no reproductive toxicology studies with RISPERDAL CONSTA; and (3) no data to support that impurities — were qualified in the oral nonclinical studies. The Division elaborated further by concluding, "These findings would preclude approval of this application in the absence of any demonstration of a clinical advantage of this product".

J&JPRD met with DNDP on July 26, 2002 to discuss plans to address each of the pharmacology/toxicology issues cited in the Action Letter and to initiate discussion regarding the clinical benefit of RISPERDAL CONSTA J&JPRD again met with DNDP on February 25, 2003 to discuss plans for the complete response to the Action Letter. Three main topics were discussed at the meeting: (1) the potential clinical benefit of a long-acting intramuscular (IM) formulation of an atypical antipsychotic; (2) nonclinical studies that would be submitted in the complete response to address pharmacology/toxicology issues raised in the Action Letter; and (3) plans to conduct an embryofetal toxicity study with RISPERDAL CONSTA.

Following a presentation of the potential clinical benefit of RISPERDAL CONSTA, the Division agreed that there is a potential clinical benefit of a depot atypical antipsychotic and suggested that the complete response should contain a detailed review of the existing data for IM depot and oral formulations that make a compelling argument for improved compliance and

decreased relapse of psychotic symptoms with depot antipsychotics. The Division further agreed to consider approving RISPERDAL CONSTA without a complete resolution of the carcinogenicity findings in rat if the data demonstrate that the IM depot formulation provides clinical benefit. J&JPRD provided a list of nonclinical studies that would be included in the complete response to address the pharmacology/toxicology deficiencies cited in the Action Letter. In addition to these studies, the Division requested summary and individual data listings for the incidence of adrenomedullary findings (including adrenal pheochromocytoma) from the oral carcinogenicity study in rat. The Division noted that if J&JPRD proposed strain or substrain differences as an explanation for the differences in tumor profiles between the oral and IM depot studies, it would be important to provide data by which to compare the relevance of each strain or substrain for assessing human risk.

At the February 25, 2003 meeting, the Division stated their position that the complete study report for the IM depot embryofetal developmental toxicity study should be submitted to NDA 21-346 prior to approval. However, the Division agreed to consider the potential for a clinical benefit when making a decision as to the need for the embryofetal developmental toxicity study prior to approval. The Division further agreed to continue discussions related to the design of the embryofetal toxicity study at a later time.

At a teleconference held on March 25, 2003 with J&JPRD and Dr. Lois Freed, Pharmacology/Toxicology Reviewer for DNDP, the following agreements were reached on the design of the embryofetal toxicity study:

•Dr. Freed agreed that the 80 mg/kg dose was too high because it impairs mating, and suggested that J&JPRD consider a dose between 20 mg/kg and 80 mg/kg. An additional dose-ranging study will be conducted to evaluate possible higher doses than 20 mg/kg.

•A third dose (below 20 mg/kg) group will be added to the study.

•An oral treatment group is required to provide a reference to the previous study with RISPERDAL tablets (NDA 20-272). In addition to agreements reached on the design of the study, J&JPRD agreed to include a proposal in the complete response regarding the timing of the submission of the embryofetal toxicity study.

Organization of the Response to the Action Letter

This document contains the responses from J&JPRD to issues identified by DNDP in the Action Letter, dated June 29, 2002, for RISPERDAL CONSTA, (NDA 21-346, submitted August 31, 2001). The organization

and content of the response reflect recommendations made by the Division at meeting held on February 25, 2003 and at a teleconference held on March 25, 2003.

Clinical response:

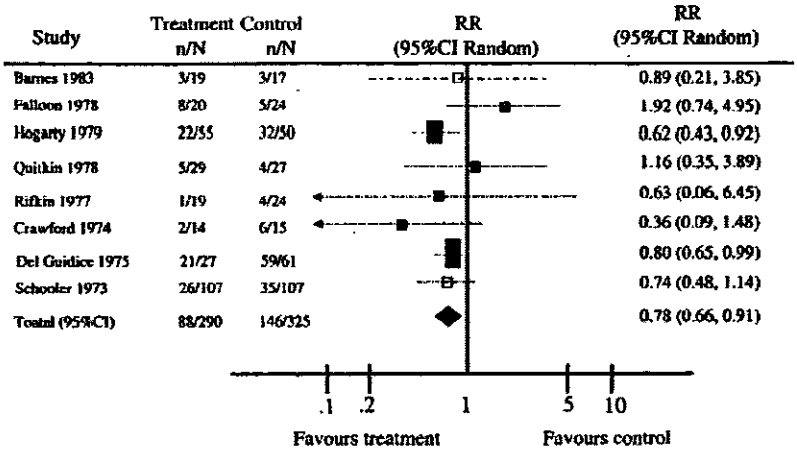
We have previously acknowledged a clinical need for a long acting injectable form of risperidone. We asked the sponsor to summarize and provide documentation to support this belief. The sponsor supplies 64 research papers supporting their position. There are reference links to refer the reader to the literature papers that support the following points. I have included the references in the appendix to this review. Several papers are summarized below.

Mentschel, Leucht, and Kane have recently completed an unpublished meta-analysis involving studies of at least 10 months in duration comparing long-acting vs oral antipsychotics. Overall relapse rates on oral medications were 45% compared with 30% on depots, with an absolute risk reduction of 14% and a relative risk reduction of 32% (p=0.002). See studies below:

Table: At least 10 months studies comparing depot antipsychotics with oral antipsychotics in outpatients with schizophrenia

Study	Method	Participants	Interventions
Barnes 1983	Randomised, double-blind, 1 year.	Schizophrenia (PSE), N=36, mean age 49yrs, sex: 12M, 18F.	1. Fluphenazine decanoate 25mg/IM biweekly. 2. Pimozide dose 6mg/day
Parkes 1978	Randomised, double-blind, 20 months.	Schizophrenia (Schneider's criteria), all stabilized prior study entry, N=44, mean age 39 years, sex: 20M, 24F.	1. Fluphenazine decanoate 25mg/IM fortnightly (majority of patients). 2. Pimozide, mean 8mg/day (majority of patients)
Hogarty 1979	Randomised, double-blind, 24 months.	Schizophrenia, N=103, mean age 34 years, sex: 46M, 54F.	1. Fluphenazine decanoate mean 25mg biweekly. 2. Oral fluphenazine mean = 10mg/day
Quitkin 1978	Randomised, double-blind, 1 year.	Schizophrenia (RDC), all stabilized before study entry, N=60, age: 17-40 years, sex: 41M, 19F.	1. Fluphenazine decanoate modal dose range 0.5-1ml biweekly, range 0.5 – 3.75 ml biweekly. 2. Penfluridol oral weekly, range 20- 160 mg, modal dose 60 – 80 mg weekly.
Rifkin 1977	Randomised, double-blind, one year.	Schizophrenia (Kraepelinian criteria), all stable, N= 73.	1.Fluphenazine decanoate: mean 0.5ml biweekly. 2. Fluphenazine oral mean 5mg 3. Placebo.
Schooler 1980	Randomised, double-blind, one year.	Schizophrenia, N=260 – of these 214 entered the maintenance phase, mean age 29 years, Sex: 170M, 120F.	1. Fluphenazine decanoate mean 34.2mg/fld 3 weekly. 2. Fluphenazine oral mean 24.8mg
Crawford 1974	Double-blind, 40 weeks	Schizophrenia (according to the criteria of Forrest and Hay), N = 97 – of these 31 entered the trial, age between 20 and 65 years, sex: 9M, 22F	1. Fluphenazine decanoate 2. Trifluoperazine hydrochloride
Del Guidice 1975	Randomised, 23 months	Schizophrenia, N = 88 male patients, age between 20 and 50 years old	1. Fluphenazine hydrochloride mean 21.7 mg/day 2. Fluphenazine hydrochloride + Placebo i.m., mean 21.7 mg/ day 3. Fluphenazine enanthate + Placebo oral; after 6 weeks 25 mg FE biweekly

Conclusion: When only long-term, outpatient studies are considered there is evidence that depot antipsychotics prevent psychotic relapses more effectively than oral antipsychotics.



Test for heterogeneity chi-square=6.54 df=7 p=0.48
Test for overall effect z=3.06 p=0.002

Reviews of adherence suggest nonadherence rates of 26% with depot medication and nonadherence rates of 40 to 50% with oral medication. The use of long-acting injectable antipsychotics appears to increase adherence by between 10 and 40%. See below.

Young, Zonana and Shepler, Bull Am Acad Psy Law 1986 This paper compared 5 studies with depot medication to 23 studies of oral meds regarding adherence.

John L. Young, MD; Howard V. Zonana, MD; and Lynn Shepler, MD

Risk of relapse and recidivism makes the failure to take antipsychotic medication as prescribed a significant issue in forensic psychiatry. This question may arise in such contexts as the setting of bail, plea bargaining, the insanity defense, and sentencing. We have reviewed the literature on medication noncompliance in schizophrenia and present here the results, organized by topics relevant for the work of forensic mental health experts.

Reported rates of noncompliance vary widely, reflecting major differences in the populations studied and the methods used as well as the complexities involved in defining noncompliant behavior. A noncompliance rate of 50 percent has been attributed globally to chronic patients, both medical and psychiatric.

The tendency of significant factors to interact precludes a simple typology of noncompliance. However, environmental security and supportiveness correlate positively with adherence; whereas anxiety, paranoia, grandiosity, depression, and side effects correlate negatively.

Clinicians' assessments of whether medication is being taken have proven to be unreliable. Although monitoring by chemical measurement, particularly a radioreceptor assay for urine samples, can be useful, depot injection ensures that prescribed medication is being taken. Less invasive means of promoting compliance are described; psychodynamic and ethical issues to be considered in the monitoring and promotion of compliance over extended time periods are presented.

We also probe the link between medication noncompliance and behavioral relapse. The time between default and relapse is most often measured in weeks. Whether due to medication withdrawal or not, the relapse pattern of each individual tends to repeat, allowing its recognition before recidivism occurs. Restarting medication at this stage, especially with a dosage increase, is usually effective.

In sum, the forensic mental health expert can now readily use a large and diverse literature to assist with a variety of significant issues.

Remington and Adams, Can. J. Psy, 1995 See below.

Conclusions

Our understanding of depot neuroleptics has progressed considerably over the years, and a number of conclusions can be drawn from the current body of evidence.

1. Depot neuroleptics represent an effective but likely underutilized alternative to oral agents, particularly in the United States.
2. Depot neuroleptics offer distinct advantages associated with bioavailability and duration of action. Yet, they also have disadvantages such as dose titration.
3. Relapse rates are diminished with depot as compared to oral neuroleptics, but not to the extent that might be anticipated.
4. Depot neuroleptics are not a panacea. They do not ensure compliance, although they do permit better documentation of noncompliance in a way that can help distinguish it from treatment resistance.
5. Depots appear equally effective in terms of clinical response, and they do not appear to have a greater risk of side-effects.
6. The conversion from oral to depot neuroleptics is not well established for any of the depot neuroleptics, and is influenced, at least in part, by the recent trend towards lower neuroleptic doses.
7. Plasma levels for depots correlate better with dose than with clinical response or side-effects.

In the face of diminishing health care dollars, deinstitutionalization and greater emphasis on outpatient programs, depot neuroleptics are likely to take on a more important role in the long-term treatment of schizophrenia. To this end, we need to expand our knowledge of depot neuroleptics, particularly in terms of pharmacokinetics, dosing and clinical demographics. In light of the development of newer oral neuroleptics with atypical features, it will also be important to pursue the development of depots which can offer these same clinical advantages.

Cramer and Rosenheck, Psychiatric Services 1998

Objective: The authors reviewed research on medication compliance in psychiatric treatment and compared compliance rates with compliance rates in treatment of physical disorders. **Methods:** MEDLINE was used to locate reports in the literature on medication compliance in psychiatric treatment for the years 1975 through 1996. These reports and studies cited in the reports were reviewed to determine the methods used to assess compliance and the compliance rates reported. Ten reports describing assessment methods and including medication compliance rates for antidepressant medication and 24 reports for antipsychotic medication were selected. They were compared with 13 reports that used microelectronic monitoring to assess medication compliance of patients with a range of nonpsychiatric disorders. **Results:** Studies of psychiatric patients used various methods of estimating medication compliance, including interviews with patients, clinicians' judgment, and pill counts, but overall showed low rates of compliance. Patients receiving antipsychotics took an average of 59 percent of the recommended amount of the medications, with a range from 24 to 90 percent. Patients receiving antidepressants took 65 percent of the recommended amount, with a range from 40 to 90 percent. The mean compliance rate for patients with physical disorders was 76 percent, with a range from 60 to 92 percent, although the microelectronic monitoring showed frequent omission of doses and discontinuation of medication. **Conclusions:** Compliance with medication regimens among patients with psychiatric disorders may be lower than among patients with physical disorders. However, the difference may be largely attributable to the methods used for estimating compliance. The findings suggest the need for new and improved methods for monitoring compliance and increasing patients' compliance with pharmacotherapy. (*Psychiatric Services* 49:196–201, 1998)

A recent unpublished meta-analysis found a 23% risk of relapse with first-generation medications compared with a 15% risk with second- generation medications (p=0.0001), Kane, JM et al

Abstract:

Objective: The objective was to perform a systematic review and meta-analysis of the potential of the new generation antipsychotic drugs (NA) to improve adherence and decrease relapse rates in patients with schizophrenia.

Method: Randomized, controlled trials comparing NA with placebo and/or conventional antipsychotics were identified. Data on relapse, general treatment failure and drop-outs due to adverse events were extracted, and combined in a meta-analysis. Results: Few trials were available for each individual drug, therefore NA were analyzed as a group in an explorative manner. The analysis of six placebo comparisons, involving a total of 983 patients, clearly demonstrated that NA are effective for relapse prevention. Eleven studies with a total of 2032 patients provided comparative data on relapse/treatment failure for new and conventional antipsychotics. The analysis revealed a modest but statistically significant reduction in relapse rates and overall treatment failure with the new drugs. Whether this advantage was partly mediated by improved adherence to treatment remains unclear. No significant superiority in terms of fewer dropouts due to adverse events was found. Furthermore, a number of methodological problems were identified. Conclusions: Overall, the currently available data suggest a potential for the new drugs to reduce relapse rates. Methodological issues to be addressed in future trials include the choice of comparator, appropriate dosage, the application of clinically-relevant relapse criteria, monitoring of adherence, and the minimization of drop-outs.

Correll, Leucht, and Kane have recently completed an unpublished meta-analysis indicating a clinically and statistically significant reduction in the risk of TD utilizing second-generation as compared with first-generation antipsychotics. Mean annual risk of TD for SGA=.91% vs. 6.2% for Haldol used as comparator in 3 studies. See below.

Abstract

Background: Based on lower rates of acute extrapyramidal side effects compared to first generation antipsychotics (FGAs) and preliminary data, second generation antipsychotics (SGAs) are expected to also cause less tardive dyskinesia (TD). **Methods:** Systematic review of studies with SGAs lasting ≥1 year and reporting on new cases of TD or dyskinesia. **Results:** In nine studies, 2,105 patients received treatment with risperidone (3 studies, n=571), olanzapine (2 studies n=610), quetiapine (2 studies, n=386), amisulpride (1 study, n=331) or ziprasidone (1 study, n=207) for a weighted mean of 269 days. Study designs were double-blind and randomized (n=3), open-label extensions of double-blind randomized trials (n=4), and open-label (n=2). Of the four trials that had a comparator (all in adults with schizophrenia-spectrum disorders), three used haloperidol (n=408) and one placebo (n=71). Five studies included adults (n=1419, mean age: 37 years), one a mixed population (n=207, mean age: 50 years), and three exclusively patients ≥54 years (n=479; mean age: 78 years). The weighted mean annual incidence of TD for SGAs was 0.91% (range: 0-2.1%) in adults, 6.8% in the mixed population, and 5.8% (range: 2.6-13.4%) in the elderly, compared to 5.3% (range: 4.1-7.4%) in adults treated with haloperidol. **Conclusions:** Results from nine long-term studies support the notion that SGAs have a reduced risk for TD compared to FGAs. However, more carefully designed studies, ideally beyond one year and comparing different SGAs in FGA-naïve patients, are needed to estimate the true risk. It would not appear premature for clinicians to consider these findings in making long-term treatment decisions.

I have reviewed all the papers and agree that the following sponsor supplied conclusions are a fair presentation of the literature.

Relapse in schizophrenia is serious. Relapse is characterized not only by decreased social and vocational functioning and increased caregiver burden, but also by homelessness, self-harm (including suicide), and aggressive or violent behavior. Moreover, patients with frequent relapse may accumulate morbidity in the form of residual or persistent symptoms and decrements in function from their premorbid status.

60% to 75% of patients with schizophrenia relapse within 1 to 2 years without antipsychotic medication. The nonadherence rate with oral medications in schizophrenia is on average 42%.

Continuous medication reduces the risk of relapse to 20 to 30%.

Patients without gaps in medication therapy have 2 to 4 times less risk of rehospitalization.

Patients with a =30-day gap in medication therapy have >4 times the risk of suicide attempts.

Depot antipsychotic treatment, a method of attaining continuous medication, has been shown to reduce relapse rates and rehospitalization to a significant degree compared with treatment using oral antipsychotics.

Only first-generation antipsychotics (haloperidol and fluphenazine) are available in depot formulations for those patients who can benefit from treatment with a long-acting injectable antipsychotic.

Risperidone long-acting injectable has been shown to be an effective and well-tolerated antipsychotic medication in both short- and long-term treatment.

They conclude that Risperidone is the only second-generation antipsychotic with a long-acting injectable form in late-stage development, and therefore represents a unique and significant addition to the treatment armamentarium of schizophrenia and an important means for improving treatment outcomes.

It is my belief that Risperdal Consta would be a useful addition for the treatment of schizophrenia and persuasive data has been provided by the sponsor.

SAFETY DATA:

This submission reports safety information for RISPERDAL CONSTA from 15 May 2001 to 18 March 2003, as requested by the Division of Neuropharmacological Drug Products in a communication on 18 March 2003.

ORGANIZATION AND DATA SOURCES

Johnson and Johnson Pharmaceutical Research and Development (J&JPRD) provides the requested safety information in this submission. The information is organized as follows (i.e., completed J&JPRD clinical studies and ongoing J&JPRD sponsored clinical studies, other clinical research studies [medical affairs and others], postmarketing experience, and worldwide literature. The studies and other source information that contribute to this safety response are shown in Table 1 along with the number of patients exposed to RISPERDAL CONSTA and the design of the study, if applicable.

Table 1: Sources of Safety Information

Study Number	Design	Number of RISPERDAL CONSTA -treated Patients
Completed J&JPRD Studies		
RIS-INT-62	Randomized, open-label comparison to olanzapine;1 year treatment (3-month analysis endpoint)	309
RIS-USA-259	Open-label, switching from oral neuroleptic;3 month treatment	141
RIS-INT-85	Open-label, switching from typical depot neuroleptic; 3 month treatment	166
Ongoing J&JPRD Studies		
RIS-INT-63	Open label extension of RIS-INT-61 and RIS-INT-57	806 [a]
RIS-INT-80	Open label extension of RIS-INT-62 and RIS-INT-85	212 [b]
RIS-USA-196	Open label extension of RIS-USA-121	242 [a]
RIS-USA-265	Open label extension of RIS-USA-259	75 [b]
Total J&JPRD Studies		**1664** [c]
Other Clinical Research Studies [d]	Varied	NA
Postmarketing Population	NA	NA
Worldwide Literature	NA	NA

[a] Data for RIS-INT-63 and RIS-USA-196 are cumulative from the clinical databases as of 18 March 2003
[b] Data for RIS-INT-80 and RIS-USA-265 are cumulative from the clinical databases as of 16 March 2003
[c] Sum of patients in RIS-INT-62, RIS-INT-63, RIS-INT-85, RIS-USA-196, and RIS-USA-259. Patients in RIS-INT-80 and RIS-USA-265 are already included in the RIS-INT-62, RIS-INT-85, and RIS-USA-259 totals.
[d] Sponsored by Janssen-Cilag Medical Affairs Europe, Janssen Pharmaceutica Medical Affairs USA, and Others

J&JPRD studies

The safety information provided in this document from the J&JPRD clinical

studies completed after the 4-month Safety Update Report was derived from the finalized/locked clinical databases.

The safety information for the ongoing extension studies came from the pharmacovigilance database (CIOMS Narrative/line listings) for RISPERDAL CONSTA up to 25 March 2003. In addition, some specific analyses (i.e., exposure and discontinuations due to adverse events) for the ongoing extension studies were determined from the unlocked clinical databases as of 16-18 March 2003 to provide the requested information. Therefore, the safety information from the ongoing studies is limited as of the cutoff date and as these studies are not finalized, is subject to potential future alterations.

Other non-IND clinical research studies

The safety data for this section was derived from a search of the pharmacovigilance database that excluded all J&JPRD studies and all events unrelated to a clinical study. The majority of these studies were sponsored by Janssen-Cilag Medical Affairs Europe and Janssen Pharmaceutica, Medical Affairs Division in USA. As with all pharmacovigilance data, this information might be subject to change and is not as complete as the data derived from locked clinical databases. Exposure calculations included these types of studies as well as two J&JPRD sponsored studies (RIS-JPN-16 and RIS-SIV-101) that are being conducted in Japan.

Clinical studies

Since the submission of the 4-month Safety Update Report of 4 December, 2001 (cutoff date 15 May 2001), three Phase 3 clinical studies were completed (RIS-INT-85, RIS-USA-259 and RIS-INT-62). In addition, 4 Phase 3 open-label extension studies (RIS-INT-63, RIS-USA-196, RIS-INT-80, and RIS-USA-265) are ongoing and provide up to 3 years of clinical safety information. Two of the ongoing studies are extensions of the Phase 3 studies described in NDA 21-346 submission for RISPERDAL CONSTA. Study RIS-USA-196 is the extension of RIS-USA-121; RIS-INT-63 is the extension of RIS-INT-61, and RIS-INT-57. Data from these two open-label extension studies until the cutoff date of 15 May 2001 were presented in the 4-month Safety Update.

Estimate of Exposure to RISPERDAL CONSTA (Clinical Studies)

Table 14 summarizes patient-years of exposure in the studies conducted since the ISS plus the ongoing extension studies. In total, 1664 patients have been treated with RISPERDAL CONSTA in these studies for a total exposure of 749456 days or 2053.30 patient-years.

Table 14: Patient-years of Exposure on RISPERDAL CONSTA: Ongoing Studies or Studies Completed after 15 May 2001

Study	Number Of Patients	Total Exposure, Days	Patient-years of Exposure
All studies [a]	**1664[e]**	**749456**	**2053.30**
INT-62	309	79851	218.77
INT-63 [c]	806	543779	1489.81
INT-80 [b,d]	212	40096	109.85
INT-85	166	11227	30.76
USA-196 [c]	242	52889	144.90
USA-259	141	8823	24.17
USA-265 [b,d]	74	12791	35.04

[a] INT-62, INT-85, and USA-259 are completed studies. INT-63, INT-80, USA-196, and USA-265 are ongoing.

[b] INT-80 is the extension study of INT-62 and INT-85. USA-265 is the extension study of USA-259.

[c] Data for INT-63 and USA-196 are cumulative from the clinical databases as of 18 March 2003

[d] Data for INT-80 and USA-265 are cumulative from the clinical databases as of 16 March 2003

[e] Sum of patients in INT-62, INT-63, INT-85, USA-196, and USA-259. Patients in INT-80 and USA-265 are already included in the INT-62, INT-85, and USA-259 totals.

Total exposure in the pooled, multiple-dose studies included in the ISS was 230546 patient-days or 631.63 patient-years in 1499 patients. The multiple-dose studies included in the ISS were: RIS-USA-121, RIS-INT-61, RIS-INT-57, RIS-INT-31, RIS-INT-32, RIS-SWE-17. RIS-INT-63 is the extension study of RIS-INT-61 and RIS-INT-57. RIS-USA-196 is the extension study of RIS-USA-121. The total number of patients treated with RISPERDAL CONSTA in clinical studies can be determined by adding the following to 1499:

•The number of RISPERDAL CONSTA-treated patients in INT-62, INT-85, and USA-259 (309 + 166 + 141 = 616).

•The number of patients in the placebo arm of USA-121 who entered USA-196 (59).

•The number of patients in the RISPERDAL oral arm of INT-61 who entered INT-63 (203).

This gives a total of 1499 + 616 + 59 +203 = 2377 RISPERDAL CONSTA-treated patients with 230546 + 749456 = 980002 total days of exposure or 2684.94 patient-years of exposure to RISPERDAL CONSTA based on clinical study databases as of 18 March 2003.

Completed Clinical Studies Data

Deaths (Completed Clinical Studies)

There were 2 patients who died in the completed RISPERDAL CONSTA clinical studies since the 4-month Safety Update Report (Table 2). Both deaths occurred in the RISPERDAL CONSTA group in the one year comparative study RIS-INT-62. In this study 6 patients died in the comparative olanzapine group. Only the RISPERDAL CONSTA treated patients will be described here.

Table 2: Patients Who Died During the Completed Clinical Studies (RIS-INT-62, RIS-USA-259, RIS-INT-85)

Study	Placebo depot	RISPERDAL CONSTA n/N (%)
RIS-INT-62 [a] (1 year)	–	2/309 (0.6)
RIS-INT-62 (3 months)	–	0/309[b] (0)
RIS-USA-259	–	0/141 (0)
RIS-INT-85	–	0/166 (0)
Total (3 months)	–	0/616 (0)
Pooled NDA completed studies[c] (3 months)	1/107 (1.0)	6/1499 (0.4)

[a] Includes events over the entire period

[b] The total number of patients (309) does not include 9 patients who were only treated with oral risperidone and who discontinued during the run-in period. Those 9 patients did not receive RISPERDAL CONSTA™.

[c] The completed repeated-dose studies in the original NDA that were pooled for the 3-month endpoint (RIS-USA-121, RIS-INT-57, RIS-INT-61, RIS-INT-31, RIS-SWE-17, RIS-INT-32)

Neither of the deaths in the RISPERDAL CONSTA group were considered related to study medication (Table 3) nor did they occur by the 3-month endpoint (Table 2). No patients died in either RIS-USA-259 or RIS-INT-85. Both patients, who died in RIS-INT-62, were women. One patient (CRF ID A30074, 50-years-old), who had been administered RISPERDAL CONSTA 50 mg/biweekly with 21 injections, was hospitalized for "weight loss" and "dysphagia", and was diagnosed with "esophageal carcinoma". She

subsequently died from the esophageal cancer. Patient CRF ID A30074 (55-years-old), who had received 16 injections of 50 mg/biweekly RISPERDAL CONSTA died ("accident") in a fire. Both causes of death were considered by the investigator not to be related to study medication.

Table 3: Cause and Relatedness of Deaths in the Completed Studies (RIS-INT-62, RIS-USA-259, RIS-INT-85)

Patient ID Number	Study	Age (years)	Sex	Cause of Death		Relatedness[a] to Study Drug
				Preferred Term	Description	
A30074	RIS-INT-62	55	F	Esophageal carcinoma	Esophageal cancer	Not related
A30776	RIS-INT-62	50	F	Death	Accident	Not related

[a] Relatedness as reported by the investigator and confirmed by the sponsor.

Serious Adverse Events (Completed Clinical Studies)

There was a similar incidence of serious adverse events reported with RISPERDAL CONSTA in the Phase 3 completed clinical studies compared to that reported with RISPERDAL CONSTA and placebo treatment in the ISS of the NDA (Table 4). SAEs are mainly psychiatric in nature with no unusual pattern to the occasional medical SAE.

Table 4: Patients With Serious Adverse Events During the Completed Clinical Studies (RIS-INT-62, RIS-USA-259, RIS-INT-85)

Study	Placebo n/N (%)	RISPERDAL CONSTA n/N (%)
RIS-INT-62 (1 year)[a]	--	78/309 (25.2)
RIS-INT-62 (3 months)	--	41/309[b] (13.3)
RIS-USA-259	--	22/141 (15.6)
RIS-INT-85	--	14/166 (8.4)
Total (3 months)	--	**77/616 (12.5)**
Pooled NDA completed studies[c] (3 months)	**25/107 (23.4)**	**177/1499 (11.8)**

[a] Includes events over the entire period

[b] The total number of patients (309) does not include 9 patients who were only treated with oral risperidone and who discontinued during the run-in period. Those 9 patients did not receive RISPERDAL CONSTA™.

[c] The completed repeated-dose studies in the original NDA that were pooled for the 3-month endpoint (RIS-USA-121, RIS-INT-57, RIS-INT-61, RIS-INT-31, RIS-SWE-17, RIS-INT-32)

A higher incidence of SAEs in the psychiatric disorder category was noted in the RIS-INT- 62. Two patients (RIS-INT-62) died due to a serious adverse event and 12 patients discontinued treatment due to a serious adverse event. In addition, narratives for all serious adverse events for these studies are provided and I have reviewed these.

Table 5: Serious Adverse Events in 2 or More Patients in any Study (Completed Clinical Studies)

Adverse event Preferred term	RISPERDAL CONSTA RIS-INT-62[a] (N = 309) n/N (%)	RISPERDAL CONSTA RIS-INT-85 (N = 166) n/N (%)	RISPERDAL CONSTA RIS-USA-259 (N = 141) n/N (%)
Any Serious Adverse Event	**78 (25.2)**	**14 (8.4)**	**22 (15.6)**
Psychiatric disorders			
Psychosis	44 (14.2)	9 (5.4)	9 (6.4)
Suicide attempt	17 (5.5)	1 (0.6)	0
Anxiety	7 (2.3)	1 (0.6)	0
Injury	6 (1.9)	0	0
Drug abuse	4 (1.3)	0	0
Agitation	3 (1.0)	2 (1.2)	3 (2.1)
Depression	3 (1.0)	0	0
Alcohol problem	2 (0.6)	0	0
Depression aggravated	2 (0.6)	0	1 (0.7)
Insomnia	2 (0.6)	3 (1.8)	0
Manic reaction	2 (0.6)	0	0
Medication error	2 (0.6)	0	0
Paranoid reaction	2 (0.6)	1 (0.6)	1 (0.7)

[a] Includes events over the entire study period

Serious Adverse Events of Potential Clinical Interest
RIS-INT-62

In RIS-INT-62, the serious adverse events of potential clinical interests were tardive dyskinesia (1), hyperglycaemia (2), convulsions (1), and myocardial

infarction (1). These events are briefly summarized here by the sponsor. None of these patients died as a consequence of the serious adverse event.

Tardive Dyskinesia
Patient CRF ID A30317 [age 44 yrs], had the serious adverse event of "dyskinesia tardive". She had a known history of experiencing tardive dyskinesia. Her starting study dose was RISPERDAL CONSTA 25 mg biweekly and she completed the study on a dose of RISPERDAL CONSTA 50 mg biweekly. The event was considered severe by the investigator and reported as doubtfully related to study medication. The event resolved without change to the trial medication and she completed RIS-INT-62 on a dose of RISPERDAL CONSTA that was higher than her beginning study dose.

Hyperglycemia

Patient (CRF ID #A30358) [age 49 yrs], had several episodes of "hyperglycemia" that were reported as serious adverse events. This patient had a history of insulin dependent diabetes. He recovered from the first episode but the second episode had no stop date reported. The first event was considered severe by the investigator and reported as not related to study medication. The second event was considered severe by the investigator and possibly related to study medication due to the high elevation of glucose levels following an injection of RISPERDAL CONSTA.

RIS-USA-259

Adverse events of clinical interest described below are diabetes mellitus and ketosis (both in same patient) and chest pain occurring in 1 patient.

Diabetes Mellitus and Ketosis

Patient CRF ID #A30322, [age 81yrs], had the serious adverse event of "NIDDM and "diabetic ketoacidosis". The patient had concomitant disorders that included hypertension, prostatic cancer and chronic obstructive pulmonary disease. The event of "diabetic ketoacidosis" resolved and was considered moderately severe by the investigator and not related to study medication. The serious adverse event of "NIDDM" did not resolve and was considered mild and not related to study medication. The patient completed the study.

Chest Pain

Patient CRF ID #A30358, [age 50 yrs], had the serious adverse event of "chest pain". A cardiologist was consulted and ruled out cardiac problems. The investigator considered the serious adverse event to be moderate in severity and not related to study medication. The patient discontinued the study due to the serious adverse event.

RIS-INT-85

In this study 2 patients permanently discontinued treatment as a result of a serious adverse event. There was one serious adverse event of potential clinical interest, hyperglycemia, from RIS-INT-85.

Patient CRF ID #A30272, age 50, had several episodes "hyperglycemia" that were considered serious adverse events. The first episode was at study entry when the patient was found to have the concomitant disorder of Diabetes Mellitus. This was considered moderate in severity and not related to study medication. The second serious adverse event of "hyperglycemia" was considered severe and not related to the study medication by the investigator. Insulin therapy was initiated and the patient completed the study without further problems.

Adverse Events Leading to Discontinuation (Completed Clinical Studies)

There were generally few discontinuations due to adverse events reported with RISPERDAL CONSTA in the completed studies (Table 6) compared to placebo treatment or RISPERDAL CONSTA treatment reported in the ISS of the original NDA. For the completed studies, data from 616 patients treated with RISPERDAL CONSTA for up to 1 year are included. Overall only 2.3% of the patients discontinued the trials prematurely due to an adverse event. This figure is compared to the 5.3% from the 3–month endpoint pooled data and the 12.1% from the placebo group from the original NDA.

Table 6: Patients With Adverse Events Leading to Discontinuation in the Completed Clinical Studies (RIS-INT-62, RIS-USA-259, RIS-INT-85)

Study	Placebo n/N (%)	RISPERDAL CONSTA n/N (%)
RIS-INT-62 (1 year)[a]	-	9/309[b] (2.9)
RIS-INT-62 (3 months)	-	7/309[b] (2.3)
RIS-USA-259	-	5/141 (3.5)
RIS-INT-85	-	2/166 (1.2)
Total (3 months)	-	**14/616 (2.3)**
Pooled NDA completed studies[c] (3 months)	**13/107 (12.1)**	**79/1499 (5.3)**

[a] Includes events over the entire study period

[b] The value 309 represents patients during this period who were treated with RISPERDAL CONSTA™ An additional 9 patient entered the run-in period but did not receive RISPERDAL CONSTA™.

[c] The completed repeated-dose studies in the original NDA that were pooled for the 3-month endpoint (RIS-USA-121, RIS-INT-57, RIS-INT-61, RIS-INT-31, RIS-SWE-17, RIS-INT-32)

The most common adverse events leading to discontinuation in all three completed studies were in the Psychiatric Disorders group. Suicide attempt, depression, agitation and anxiety were the major reasons for patients discontinuing due to Psychiatric Disorders in RIS-INT-62. Suicide attempt and depression occurred in 2 or more patients and led to discontinuation whereas agitation and anxiety occurred in 1 patient each. In RIS-USA-259, the most common psychiatric adverse events that led to discontinuation were agitation, dreaming abnormal, drug dependence and insomnia. Agitation was the only adverse event that occurred in more than 1 patient and also led to discontinuation. In RIS-INT-85, the most common psychiatric adverse events that led to discontinuations were psychosis and suicide attempt in 1 patient each. There were no other events that led to discontinuation in RIS-INT-85. In RIS-USA-259 besides Psychiatric Disorders leading to discontinuations were Body as a Whole-General Disorders, chest pain.

In RIS-INT-62 aside from the psychiatric disorders other adverse events that occurred but only once each were injury, abnormal coordination; hyperglycemia, weight increase; lactation nonpuerperal, menstrual disorder; myocardial infarction and spinal cord injury.

There were 2 patients from RIS-INT-62 that had serious adverse events leading to death. I reviewed these 2 narratives for the patients.

Ongoing Extension Clinical Studies
(Data Available as of 18 March 2003)

This section reports on all currently ongoing open-label extension studies (RIS-INT-63, RIS-INT-80, RIS-USA-196, and RIS-USA-265) conducted by J&JPRD. These studies include follow up data on patients over a period up to 3 years after completion of the preceding studies. The number of patients treated in these studies and the date of the first treated patient are provided in the table below.

RIS-USA-265 74 14 Nov 2001

Date for the Ongoing Extension Studies

Study	Number of Patients Treated	First Patient Visit
RIS-INT-63	806	4 Feb 2000
RIS-INT-80	212	22 Oct 2001
RIS-USA-196	242	21 Dec 1999
RIS-USA-265	74	14 Nov 2001

Deaths (Ongoing Extension Studies)

There were 14 patients who died during or within 30 days following discontinuation of treatment in the ongoing extension studies (RIS-INT-63, RIS-INT-80, RIS-USA-196, and RIS-USA-265) with RISPERDAL CONSTA(Table 8).

Table 8: Patients Who Died During the Ongoing Extension Studies (RIS-INT-63, RIS-INT-80, RIS-USA-196, and RIS-USA-265)

Study	RISPERDAL CONSTA n/N (%)
RIS-INT-63	11/806 (1.4)
RIS-INT-80	0/212 (0)
RIS-USA-196	2/242 (0.8)
RIS-USA-265	1/74 (1.4)
Total (> 3 months to 4 years, extension)	**14/1334 (1.0)**
Total (3 month- completed studies post 4-month update)[a]	**0/616 (0)**
Pooled NDA completed studies[b] (3 months)	**6/1499 (0.4)**

[a] from Table 2 (RIS-INT-62 3-month endpoint, RIS-USA-259, RIS-INT-85)
[b] The completed repeated-dose studies in the original NDA that were pooled for the 3-month endpoint (RIS-USA-121, RIS-INT-57, RIS-INT-61, RIS-INT-31, RIS-SWE-17, RIS-INT-32)

There were 11 deaths in RIS-INT-63; no deaths in RIS-INT-80; 2 deaths in RIS-USA-196 and 1 death in RIS-USA-265 (Table 9). The percentage of patients who died in the ongoing extension studies as of the cutoff date of 15 March 2003 (1.0%) was higher than the pooled 3-month data from the original NDA (0.4%) and from the studies completed since the 4-month Safety Update (0 %) (Table 8).

As the 4-month Safety Update summarized the data from the two extension studies (RIS-INT-63 and RIS-USA-196) up to 15 May 2001 and the data reviewed here for the ongoing extension studies included all events from the beginning of these studies. There are some patient reported in this summary who were described previously. Five of the 11 deaths in RIS-INT-63 and one of the two deaths in RIS-USA-196 were included in the 4-Month Safety Update totals (Table 9).

Of the 14 cases there were 3 cases of suicide, 2 cause unknown, 2 bowel perforations, 1 myocardial infarction, 1 car accident, 1 choked on food, 1 cerebral infarction, 1 breast cancer, 1 pulmonary cancer and 1 cardiac failure. All deaths, regardless of cause, were reported by the investigator as not related or doubtfully related to study medication. A review of these deaths revealed no clinically significant trends. Complete narrative information for the patients who died are provided and I have reviewed these.

Table 9: Cause and Relatedness of Deaths During the Ongoing Extension Studies

DSS Number	Study	Age (years)	Sex	Cause of Death		Causality[a] to RISPERDAL CONSTA
				Preferred Term	Description	
EMADSS2001001896 (A31217)[b]	INT-63	38	M	Accidental injury	Collided with a car, brain death	Not related
EMADSS2002003778	INT-63	75	F	Asphyxia	Choked on food, rarely chewed before swallowing	Not related
EMADSS2001001326 (A31212)[b]	INT-63	74	F	Cerebral infarction	Cerebral infarction, Hx. of atherosclerosis	Not related
EMADSS2002004191	INT-63	37	M	Death	Assumed suicide	Not related
NSADSS2002047322	USA-265	63	M	Death	Cause unknown, Hx. of COPD and Pneumonia	Not related
NSADSS2002036717	INT-63	46	M	Myocardial infarction	Myocardial infarction, Hx of DM	Not related
NSADSS2002035527	INT-63	51	F	Suicide attempt, Hepatic Neoplasms malignant, Pulmonary carcinoma, Cholelithiasis, Neoplasm, malignant aggravated	Breast cancer	Not related
NSADSS2003002731	INT-63	62	M	Pulmonary carcinoma, brain metastases	Primary lung cancer with brain metastasis	Not related

DSS Number	Study	Age (years)	Sex	Cause of Death		Causality[a] to RISPERDAL CONSTA
				Preferred Term	Description	
EMADSS2001001637 (A30787)[b]	INT-63	26	M	Suicide Psychotic reaction NOS	Suicide	Not related
NSADSS2000002985 (A30183)[b]	USA-196	52	M	Bowel perforation and peritonitis	Adenocarcinoma, perforation of colon	Doubtful[c]
NSADSS2001022329	USA-196	44	F	Bowel perforation, abdominal pain , nausea and diarrhea	Perforation of colon	Doubtful
JRFBEL2000002674 (A30847)[b]	INT-63	63	M	Heart failure Lower Resp, Tract infection, dyspnea	Heart failure	Doubtful
EMADSS2001004122	INT-63	50	M	Sudden death	Cause unknown, chronic low grade anemia and lung changes	Doubtful
JRFBEL2000002382 (A30548)[b]	INT-63	46	M	Suicide	Suicide	Doubtful

[a] Causality to RISPERDAL CONSTA™ was evaluated by the sponsor's medical officer based on the information available from the CIOMS line listings (Attachment 23)
[b] Deaths also reported in the 4-month Safety Update.

Serious Adverse Events (Ongoing Extension Studies)

The majority of the serious adverse events reported in the pharmacovigilance database with RISPERDAL CONSTA (Table 10) in the 4 Phase 3 ongoing extension studies were of the Psychiatric Disorders type. Those serious adverse events that occurred 10 or more times (Table 11) were also reported in the 4-month Safety Update. The remainder of the events occurred at a lower frequency (less than 10) and often occurred only once or twice. The serious adverse events

were grouped according to the most representative reaction term used in the CIOMS forms. Those of potential clinical interest based on the known safety profile of risperidone are summarized below by body system. Narrative information for all serious adverse events is provided and I have reviewed these.

Table 10: Frequency of Serious Adverse Events During the Ongoing Extension Studies (RIS-INT-63, RIS-INT-80, RIS-USA-196, and RIS-USA-265)

Study	RISPERDAL CONSTA Number of Serious Adverse Events
Total	**677**
RIS-INT-63	383
RIS-INT-80	53
RIS-USA-196	198
RIS-USA-265	43

Note: Number of serious adverse events are listed rather than number of patients as derived from the CIOMS listing (Attachment 24).

Table 11: Serious Adverse Events >= 10 Events During the Ongoing Extension Studies (RIS-INT-63, RIS-INT-80, RIS-USA-196, and RIS-USA-265)

Reaction (Serious Adverse Event)	Number of events
Any serious adverse event	**677**
Serious adverse event ≥ 10	**366**
Suicidal ideation	65
Anxiety	50
Depressed state	42
Condition aggravated	40
Hallucination	31
Psychosis	28
Insomnia	21
Delusion	19
ADE NOS	18
Drug abuse	15
Agitation	14
Paranoia aggravated	13
Aggressive reaction	10

Note: Number of serious adverse events are listed rather than number of patients as derived from the CIOMS listing (Attachment 22 and Attachment 24).

Serious Adverse Events of Potential Clinical Interest

SAEs are mainly psychiatric in nature with no unusual pattern to the occasional medical SAE. The serious adverse events of potential clinical interest for the

ongoing extension studies were cerebral infarction (1 patient), cerebral ischemia (1) chest pain (1), diabetes mellitus (4), diabetes mellitus aggravated (1), hyperglycemia (3), hypoglycemia (1) tardive dyskinesia (1), stroke (1), and facial paralysis (1). Brief sponsor summaries are provided for selected cases of interest below.

Cerebral Infarction

Patient EMADSS2002006816, age 58 yrs, was found unconscious and was hospitalized. The investigator confirmed the diagnosis of a severe infarction of the basal ganglion resulting in right hemiparesis and coma. No action was taken regarding study medication. The event was reported by the investigator as serious and not related to study drug. She was discharged from the hospital not yet recovered from the insult of "cerebral infarction". No information was available regarding history of preexisting risk factors. Her medical history reported only of having had a hysterectomy (date unknown).

Cerebral Ischemia

Patient NSADSS2002031484, an 81-year-old male had the serious adverse events of "hypertension and cerebral ischemia". This patient has a medical history of hypertension, Diabetes Mellitus, hypercholesterolemia, extrapyramidal symptoms, and cancer of the prostrate. He was on multiple concomitant medications including goserelin, insulin, benzatropine mesylate, carbamazepine, clonidine, propranolol hydrochloride, bicalutamide and pravastatin sodium. No action was taken regarding study medication. The investigator reported both events as serious and not related to RISPERDAL CONSTA. The patient recovered without sequelae.

Stroke

Patient NSADSS2002004882, 41-yr-old man, had the serious adverse event of "stroke". The patient had a history of heavy smoking. The serious adverse event of "stroke" was reported by the investigator as serious and not related to study medication but more likely related to his history of heavy smoking. Study medication was permanently stopped. The patient recovered with the sequelae of very mild dysphagia.

Patient EMADSS2001001326, age 74, who died due to "cerebral stroke" had a history of tuberculosis, left anterior hemiblock, abdominal aortic aneurysm, and atherosclerosis.

Facial Paralysis

Patient EMADSS2001005081, age 54 yrs had the serious adverse event of "paralysis facial". She was hospitalized due to acute paralysis of the left facial

nerve of uncertain etiology. A computerized tomography scan was negative. Blood pressure and ECG were normal. She spontaneously recovered within hours. The event was reported by the investigator as serious and doubtfully related to study medication.

Chest Pain

Patient EMADSS2002001260, age 37 yrs had the serious adverse event of "chest pain". The possibility of a cardiac infarction was excluded. The patient was discharged from the hospital without sequelae. No action was taken with study medication and the patient completed the study. The event was reported by the investigator as serious and possibly related to study drug. This patient, with a recent history of bronchitis, experienced chest pain for which a cardiac origin was excluded.

Diabetes Mellitus

Four patients had the serious adverse event of "Diabetes Mellitus". A fifth patient had the event of "Diabetes Mellitus aggravated". This patient had a history of diabetes and was treated with oral hyperglycemics. One of the patient's with Diabetes Mellitus had a history of insulin dependant diabetes. In two patients, no preexisting hyperglycemia was known from the medical history. One patient carried the risk factors of obesity and hypertension, for the other 2 patients, hyperglycemia was discovered subsequent to hospitalization for additional events.

Patient EMADSS2002005609, age 51 yrs had a history of obesity (grade II) and insulin dependent diabetes for 7 years. She was hospitalized for more intensive diabetic therapy. No action was taken regarding study medication. The adverse event of "Diabetes Mellitus" was reported by the investigator as serious and not related to study drug.

Patient NSADSS2002022117, age 35 years had the serious adverse event of "Diabetes Mellitus". He had a history of concomitant medications specifically for hypertension and was obese. Almost 5 months after starting on RISPERDAL CONSTA, he developed an abnormal glucose level. No action was taken regarding study medication. He subsequently developed diabetic ketone acidosis relating to the new onset of diabetes. He was hospitalized, treated and discharged recovered with sequelae. The adverse event of "Diabetes Mellitus" was reported by the investigator as being serious and possibly related to RISPERDAL CONSTA. In this obese patient, hyperglycemia was reported for the first time 529.days after the start of the trial treatment.

Patient EMADSS2001005081, age 49 yrs had the serious adverse event of "Diabetes Mellitus". While hospitalized for a fractured femur it was discovered

he had an elevated glucose level and subsequently was diagnosed with having "Diabetes Mellitus". The adverse event of "Diabetes Mellitus" was reported by the investigator as serious and not related to study drug. The paucity of data for this case does not allow a complete assessment by the sponsor. It is unclear if the glucose levels were obtained under fasted conditions nor what the exact levels were. In addition, it is unknown what the outcome of the adverse event was.

Patient NSADSS2001026174, age 49 yrs was hospitalized for the serious adverse event of "depression aggravated". While hospitalized, the patient was diagnosed with new onset of "Diabetes Mellitus". No change was made to trial medication. She was treated with oral medications and discharged improved. The investigator reported the events as serious and not related to study medication. In this patient, hyperglycemia was reported for the first time 442 days after the start of the trial treatment. As the trial medication was not interrupted (i.e., no de-challenge took place), it is difficult to assess in this patient, if a causal relationship exists between the trial treatment that had been ongoing for more than 14 months at the time of event, and the reported adverse event.

Patient JRFUSA2000003662, age 51 yrs had the serious adverse event of "Diabetes Mellitus aggravated". From what was reported it appears that he has a history of diabetes and is being treated with the concomitant medication of metformin hydrochloride. He was hospitalized for the additional serious adverse events of "hallucination auditory, shaking, paranoid reaction, and suicidal tendency". His unstable glucose levels were considered to be an exacerbation of the diabetes. The patient was reported as recovered. The investigator reported the events as serious and doubtfully related to RISPERDAL CONSTA with the aggravation of the diabetes due to the hyperglycemia. The sponsor concurs with the investigator's opinion.

Hyperglycemia

Three patients had the serious adverse event of hyperglycemia. Two patients have a medical history of Diabetes Mellitus and the other did not.

Patient EMADSS20020000688, a 65 year-old female had the serious adverse event of "hyperglycemia". Her medical history included anxiety, palpitations, Diabetes Mellitus, and hypertension. She was on many concomitant medications to help treat the various concomitant disorders. These medications included acetylsalicylic acid, potassium chloride, furosemide, candesartan cilexetil, metformin hydrochloride, propranolol hydrochloride, hydrozyzine hydrochloride, zopiclone and orphenadrine hydrochloride. She recovered from this event. It was reported that the event was serious and doubtfully related to RISPERDAL CONSTA.

Patient NSADSS2002022494 age 46 yrs, experienced the serious adverse event of "hyperglycemia". This patient had a medical history of mental retardation, and insulin dependent diabetes mellitus. He had the event 890 days after the start of the trial treatment. The patient was seen in the emergency room, where he was treated (not specified) and sent home. No action was taken regarding study medication. The investigator reported the event as not related to RISPERDAL CONSTA. Given the patient's medical history, the sponsor concurs with the investigator's opinion.

Patient NSADSS2001030616, age 37 yrs had the serious adverse event of "hyperglycemia" on Day 708 of the study. The patient went to the hospital not feeling well and was hospitalized for the event of "hyperglycemia". He was treated with an insulin infusion and started on Humulin N insulin (dosages unknown). No action was taken regarding study medication. The investigator reported the event as serious and doubtfully related to RISPERDAL CONSTA. The patient's clinical status remains unchanged. No other date is available. The paucity of data on this case does not allow a complete assessment by the sponsor. In addition, it is not known what the outcome of the adverse event was.

Patient NSADSS2002040836, age 63 yrs had the serious adverse event of "hypoglycemia". This patient's medical history included Adult Onset Diabetes Mellitus, anemia, tardive dyskinesia, akathisia, insomnia, vasculitis, hypertension, and hypothyroidism. The patient is on multiple concomitant medications. He was unable to be aroused from sleep by his caregiver and was transported to the hospital. He was admitted with a diagnosis of unstable diabetes-hypoglycemia. No action was taken regarding study medication. The patient recovered without sequelae. The investigator reported the event of "hypoglycemia" as serious and not related to RISPERDAL CONSTA. Given the patient's medical history, the sponsor concurs with the investigator's opinion.

Dyskinesia Tardive

Patient NSADSS200103864, age 42 yrs had the serious adverse event of "Dyskinesia Tardive" while being hospitalized for the serious adverse events of "depression aggravated, suicidal tendency and condition aggravated". He was treated with lorazepam, switched to clonazepam (0.5 mg b.i.d.) that was increased to a t.i.d dosing schedule. Several days after this increase of clonazepam he experienced the event of "Dyskinesia Tardive". He received 2 mg oral risperidone and 75 mg /biweekly RISPERDAL CONSTA at the time of the event. The serious adverse event of Dyskinesia Tardive" was reported by the investigator as serious and not related to study medication. Given that the adverse event of tardive dyskinesia disappeared without change in the treatment with RISPERDAL CONSTA and 2 mg of oral risperidone, and was not reported again when the total dose of oral risperidone was increased to

4 mg, the sponsor supports the assessment of the investigator.

Adverse Events Leading to Discontinuation (Ongoing Extension Studies)

A total of 114 patients from the ongoing extension studies discontinued treatment due to an adverse event (Table 12). The overall incidence of 8.5% of the extension studies that had an exposure ranging from 3 months up to 3 years was higher than for the 3-month pooled data from the NDA (5.3%) and the 3-month data from the recently completed studies (2.3%). This higher incidence of discontinuation was expected from the longer exposure period of the ongoing studies.

Table 12: Patients With Adverse Events Leading to Discontinuation During the Ongoing Extension Studies (RIS-INT-63, RIS-INT-80, RIS-USA-196, RIS-USA-265)

Study	RISPERDAL CONSTA[a] n/N (%)
RIS-INT-63	69/806 (8.6)
RIS-INT-80	5/212 (2.4)
RIS-USA-196	38/242 (15.7)
RIS-USA-265	7/74 (9.5)
Total (> 3 months to 4 years, extensions)	**119/1334 (8.9)**
Total (3 month- completed studies post 4-month update)[b]	**14/616 (2.3)**
Pooled NDA completed studies[c] (3 months)	**79/1499 (5.3)**

[a] These values were calculated from the listing of adverse events leading to discontinuation of treatment (permanent stop) from the clinical database that was not locked at the time of the analysis, 18 March 2003 (Attachment 25, Attachment 26, Attachment 27, and Attachment 28).

[b] Total was from Table 6.

[c] The completed repeated-dose studies in the original NDA that were pooled for the 3-month endpoint (RIS-USA-121, RIS-INT-57, RIS-INT-61, RIS-INT-31, RIS-SWE-17, RIS-INT-32)

The number of patients discontining due to adverse events appears to be higher in RIS-USA-196 compared to the other trials, however, the type of events leading to discontinuation was similar among the trials being mainly in the Psychiatric Disorders group. As previously described in the 4-month Safety

Update, the higher percentage of patients with adverse events leading to discontinuation may be attributed to the lower stability of patients entering study RIS-USA-196 from RIS-USA-121 compared to the patients from RIS-INT-61 and RIS-INT-57 who entered RIS-INT-63.

OTHER NON-IND CLINICAL RESEARCH STUDIES (MEDICAL AFFAIRS DATA AVAILABLE AS OF 18 MARCH 2003)

Patient safety information from studies conducted by the Medical Affairs Department of Janssen Pharmaceutica and other sources was obtained from the worldwide pharmacovigilance database (CIOMS line listings) up to 18 March 2003. This information included deaths and serious adverse events reported during this period. Also included in this summary are events and exposure for two J&JPRD studies (RIS-JPN-16 and RIS-SIV-101). Similar analysis methods were used as in the ongoing extension studies.

Estimate of Exposure to RISPERDAL CONSTA (Other Non-IND Clinical Research Studies)

Table 17 summarizes exposure to RISPERDAL CONSTA during the Clinical Research Studies up to 28 February 2003. This cutoff date was chosen due to the 14 day period between injections according to the dose administration instructions for the marketed product. This cutoff date would then account for the events occurring 14 days following the last injection or up to 15 March 2003. Exposure estimates were derived by summing the total number of injections. The number of patient-days of treatment was calculated as number of injections times 14 days. The number of patient-years of treatment was calculated as patient-days divided by 365.

Table 17: Other Clinical Research Studies RISPERDAL CONSTA Exposure to 28 Feburary 2003

Region	Injections dispensed
EMEA (Aug 2002 to Feb 2003)	8,530
United States (2 May 2002 to 28 Feb 2003)	780
Japan (to 28 Feb 2003)	33
Total packs supplied (= injections given)	**9,343**
Patient days (packs x 14 days per pack)	130,802
Patient years of treatment (patient days/365)	**358**

Deaths (Other Non-IND Clinical Research Studies)

There were 12 patients who died in the medical affairs studies (Table 15). Ten deaths, regardless of cause, were reported by the investigator as being not related or doubtfully related to study medication. Two deaths were reported by the investigator to be possibly related to study medication. Of these 2 patients, one patient (EMADSS2003000055) was reported as a suicide attempt. He had made several suicide attempts prior to his death. His last suicide attempt resulted in his suffering brain death. The other patient (EMADSS2003000769) was reported as being unstable before his switch to RISPERDAL CONSTA. He experienced a manic episode 18 days prior to his committing suicide. The patient was administered his second injection of RISPERDAL CONSTA on the same day that he had the manic episode. He had another dose of risperidone 5 days prior to his committing suicide by hanging.

The other 10 deaths were the result of either a concomitant medical disorder or possibly related to a prior medical history. A review of these deaths revealed no clinically significant trends (Table 15). Narratives are provided and I have reviewed these.

Table 15: Cause and Relatedness of Deaths During the Medical Affairs Studies

DSS Number	Age (yr)	Sex	Cause of Death		Causality [a] to RISPERDAL CONSTA
			Preferred Term	Description	
NSADSS2001029200	43	M	Accidental overdose	Accidental overdose of alcohol and prescription drugs	Not related
EMADSS2003001175	45	M	Pneumonia	Pneumonia	Not related
EMADSS2002007181	49	M	Gastrointestinal tract bleed NOS, esophageal varices	Gastrointestinal tract bleed from esophageal varices	Not related
EMADSS2002005005	57	M	Neoplasm malignant aggravated	Carcinoma of left lung with metastases to liver, lungs, and adrenal glands	Not related
EMADSS2002005174	63	M	Myocardial infarction	Cardiac infarction and severe arteriocoronary sclerosis	Not related
EMADSS2002004741	69	M	Drowning	Drowning, Hx. of severe arteriosclerosis	Not related
EMADSS2003001813	79	F	Heart failure	Decompensated cardiac insufficiency, 3 yr. Hx of refusing cardiac medications	Not related
EMADSS2002005614	27	F	Heart failure	Poisoning (poison not identifiable) or acute heart failure	Doubtful
EMADSS2002005883	55	M	Sudden Death, Atherosclerosis	Severe coronary atherosclerosis	Doubtful
EMADSS2003000602	65	M	Pericardial effusion, embolism pulmonary, cardiac arrest	Pericardial effusion, pulmonary embolism, and asystole	Doubtful
EMADSS2003000055	28	M	Suicide attempt	Suicide attempt	Possible
EMADSS2003000769	52	M	Suicide	Suicide	Possible
			Manic reaction		

[a] Causality to RISPERDAL CONSTA™ was evaluated by the sponsor's medical officer based on the information available from the CIOMS line listings (Attachment 32).

Serious Adverse Events (Other Non- IND Clinical Research Studies)

The majority of the serious adverse events reported in the pharmacovigilance database for RISPERDAL CONSTA in the medical affairs studies were of the Psychiatric Disorders type. Those serious adverse events that occurred 5 or more times were also reported in the 4-month safety update (Table 16). The serious adverse events were grouped according to the most representative

reaction term used in the CIOMS line listing. The remainder of the events occurred at a lower frequency (equal to or less than 5 occurrences) and often occurred only once or twice. Narrative information for all serious adverse events is provided and I have reviewed these.

Table 16: Serious Adverse Events Occurring >5 Times During the Clinical Research Studies

Reaction Term[a]	N
Total serious adverse events	**242**
Suicide attempt	31
Condition aggravated	27
Anxiety	25
Agitation	12
Respiratory Disorders[b]	10
Depression	9
Drug abuse	8
Insomnia	8
Aggressiveness	7
Extrapyramidal disorder	6

[a] The reaction terms shown include other reaction terms that could have been coded together.

[b] The reaction term respiratory disorders was not used in the CIOMS forms but included such serious adverse events as bronchitis, pneumonia, and low respiratory infection as well as asthma.

Serious Adverse Events of Potential Clinical Interest

SAEs are mainly psychiatric in nature with no unusual pattern to the occasional medical SAE. The following serious adverse events of potential clinical interest were identified as convulsions (n = 4), stroke (n = 2), angina or chest pain (n = 2), atrial flutter (n = 1), myocardial infarction (n = 1), pulmonary embolism (n= 1), facial paralysis (n = 1), enuresis/fecal incontinence (n = 1), and blood sugar increased (n = 1). These are briefly described here by the sponsor and more details are provided in formatted narratives which I have reviewed.

Convulsions

Of the 4 reported serious adverse events of convulsions, 2 serious adverse events were reported for the same patient (EMADSS2002004108, age unknown and EMADSS2002005154, 49-year-old woman). At the time of the first event, she also had hyponatremia. She had a history of thrombosis in the left hemisphere. She discontinued treatment after the second event, although the investigator considered the event to be doubtfully related to the study medication.

Two patients with reported grand mal seizures both had a history of alcohol abuse. One of the patients (EMADSS2002003504, 31-year-old man) had a history of convulsions prior to study start, and the other patient

(EMADSS2003000772, 70-year-old man) had brain lesions due to a previous fall. In the first case, the investigator considered the adverse event very likely related to the study treatment and discontinued the study medication. In the second case, the investigator thought the event doubtfully related to the study medication. The sponsor has provided brief summaries below.

Stroke

One serious adverse event of stroke, in a 56-year-old man (EMADSS2003001147), and 1 of possible stroke, in a 40-year-old woman (EMADSS2002004569), were noted in the database. In the first patient no apparent risk factors were present. The second patient had concomitant insulin, indicating that she probably suffered from diabetes. In both cases, the investigator considered the serious adverse event as doubtfully related to study medication. However, no firm conclusions can be drawn on the relationship to study medication given the limited data available for these 2 cases
The other serious adverse events of potential clinical interest, for which only 1 report was made, are atrial flutter (n = 1), myocardial infarction (n = 1), pulmonary embolism (n= 1), facial paralysis (n = 1), enuresis/fecal incontinence (n = 1), and blood sugar increased (n = 1) and are briefly summarized below with additional information provided in narrative which I have reviewed.

For most of the serious adverse event of potential clinical interest that occurred once, there was either a doubtful relationship between treatment with RISPERDAL CONSTA and the event, as well as no adjustment was required in study medication (angina EMADSS2002007040(0), chest pain EMADSS2002001260, myocardial infarction EMADSS2002003212(0), pulmonary embolism EMADSS2003000602(0), and facial paralysis EMADSS2001005081). The serious adverse event of atrial flutter EMADSS2002006707(0) did not require a change in study medication and the patient received concomitant medication and recovered with sequelae. Of the other events of potential clinical interest, the serious adverse event of blood sugar increase NSADSS2002045104(0), the patient had a history of alcohol abuse and diabetes; and for an additional patient, enuresis/fecal incontinence EMADSS2003000746(0) occurred during the period before risperidone was released to an effective plasma level and this patient recovered from the adverse event during the period of peak plasma level.

Adverse Events Leading to Discontinuation (Other Non-IND Clinical Research Studies)

Information about discontinuations due to adverse events is not available for the Non-IND Studies.

POSTMARKETING EXPERIENCE

RISPERDAL CONSTA was first registered in the United Kingdom for the treatment of schizophrenia on August 2002. Spontaneously reported patient information for deaths and serious adverse events that occurred during the postmarketing period to 15 March 2003 were obtained from the sponsor's pharmacovigilance database. These patient reports were reviewed by the sponsor's Drug Safety and Surveillance medical officer. These events are summarized in the following sections.

Estimate of Exposure to RISPERDAL CONSTA (Postmarketing Period)

Table 20 summarizes postmarketing exposure to RISPERDAL CONSTA from the approval date in each country up to 28 February 2003. This cutoff date was chosen due to the 14 day period between injections according to the dose administration instructions for the marketed product. This cutoff date would then account for the events occurring 14 days following the last injection i.e., up to 15 March 2003. Exposure estimates were derived by adding the total number of packs sold with the assumption that a pack was equivalent to an injection received. The number of patient-days of treatment was calculated as number of packs times 14 days. The number of patient-years of treatment was calculated as patient-days divided by 365.

Table 20: Postmarketing RISPERDAL CONSTA Exposure to 28 Feburary 2003

Country	**Packs Sold**
United Kingdom	
Germany	
Austria	
Switzerland	
Denmark	
Total packs supplied (= injections given)	
Patient days (packs x 14 days per pack)	
Patient years of treatment (patient days/365)	

Worldwide Approval of RISPERDAL CONSTA (April 23, 2003)

	COUNTRY	DATE OF APPROVAL
1	Germany	25 April 2002
2	Mexico	11 June 2002
3	Switzerland	26 June 2002
4	Austria	8 August 2002
5	United Kingdom	8 August 2002
6	New Zealand	15 August 2002
7	Netherlands	8 October 2002
8	Iceland	28 October 2002
9	Ireland	17 December 2002
10	Denmark	23 December 2002
11	Israel	31 December 2002
12	Korea	8 January 2003
13	Lithuania	29 January 2003
14	Finland	5 February 2003
15	Spain	11 February 2003
16	Czech Republic	19 February 2003
17	Hungary	5 March 2003
18	Argentina	13 March 2003
19	Australia	26 March 2003
20	Colombia	9 April 2003
21	Estonia	4 April 2003
22	Norway 23 April 2003	

Deaths (Postmarketing Period)

The sponsor's pharmacovigilance database was searched up to 15 March 2003 for spontaneous reports of death occurring while a patient was receiving RISPERDAL CONSTA during treatment in areas where the medication was approved for use. A total of 12 reports of death were identified in the search of the postmarketing events. All were reported by health care professionals. The majority of patients were elderly or had medical or psychiatric histories that could have contributed to their death. A minority of cases lacked comprehensive information, thus hindering a definitive conclusion. All deaths are summarized in Table 18 and the text below. Detailed narratives for these patients are provided which I have reviewed.

Review of the 12 reports of death in the Worldwide Safety Database revealed no emerging trends. In four of the six deaths that occurred in the age group over 55, viable medical rationales were offered for the cause of death. Causality per the reporting physician was deemed "not related" in three of the deaths and was not provided in the fourth.

Table 18: Cause and Relatedness of Deaths During the Postmarketing Period up to 15 March 2003 Where Approved

DSS Number	Age (years)	Sex	Preferred Term	Cause of Death	Causality[a] to RISPERDAL CONSTA
EMADSS2002006519	88	M	Death	Possibly from pneumonia. Also suffering from vascular dementia and Chronic Obstructive Pulmonary Disease	Not related
EMADSS2002006612	71	F	Ileus	Ileus, died postopeatively	Not related
EMADSS2002007131	62	F	Bronchitis	Bronchitis. Found at home dead in bed	Not related
EMADSS2003001376	50	M	Suicide	Suicide by hanging	Not related
EMADSS2002006954	32	F	Lower respiratory tract infection	Lower respiratory tract infection. Also suffered asthma and unconfirmed hypertension and cardiomyopathy	Not related (probably)
EMADSS2003002280	Unknown	M	Hepatic failure	Hepatic failure. No more information provided	Not related
EMADSS2003001179	50	M	Pulmonary embolism, deep venous thrombosis, psychosis aggravated	Pulmonary embolism due to deep venous thrombosis shown on autopsy	Doubtful
EMADSS2003000476	Unknown[b]	F	Cardiac arrest, convulsions grand mal	Cardiac arrest following grand mal seizure	Possible
EMADSS2003001006	68	F	Sudden death	Cause not confirmed	Possible[c]
EMADSS2003001939	76	F	Cardiac arrest	Cardiac arrest at bus stop, Unsuccessful resuscitation attempts, possible untreated hypertension	Possible[c]
EMADSS2003002060	66	M	Stroke	CVA	Possible[c]
EMADSS2003000555	48	F	Death, Aggressive reaction	Aggressive reaction	Possible

[a] Causality recorded in the table is the assessment of the DSS medical officer. RISPERDAL CONSTA™ was evaluated by the DSS department based on the sponsor's policy by which all spontaneous reports are considered "possibly related". The assessment in this table for causality will, therefore, not always agree with the initial reported relationship to treatment.

[b] Although the patient's age was unknown, the physician referred to her as elderly.

[c] Causality for this event is pending receipt of further follow-up information.

Serious Adverse Events (Postmarketing Period)

The sponsor's pharmacovigilance database was searched up to 15 March 2003 for spontaneous reports of serious events occurring while a patient was receiving RISPERDAL CONSTAduring treatment in areas where the medication was approved for use. A total of 66 patients with serious adverse events (including deaths) were identified in the pharmacovigilance database CIOMS narrative/line listings. Of these 66 patients, 7 patients participating in sponsored studies were inadvertently included. Of the remaining 59 patients, 47 had non-fatal outcomes. The primary events for patients with non-fatal outcome are summarized in Table 19.

Table 19: Number of Patients With Non-fatal Serious Adverse Events During the Postmarketing Period

Primary SAE (also included SAE)	**Number of Patients[a]**
Condition aggravated (Psychosis aggravated, lack of efficacy)	9
Extrapyramidal disorder (Dystonia, dyskinesia tardive)	9
Convulsions (Convulsions aggravated, seizures cerebral)	5
Aggressiveness (Aggressive reaction, anger)	3
Electrolyte abnormality (Hyponatremia)	3
Allergic reaction	2
Exanthema	2
Asthma aggravated	1
Coma	1
Drug abuse-illicit	1
Galactorrhea	1
Hypersalivation	1
Injection site pain	1
Lipase, amylase increased	1
Mental deterioration	1
Oculogyric crisis	1
Priapism	1
Purpura thrombocytopenic	1
Steven's-Johnson syndrome	1
Stroke	1
Suicide attempt	1
Temperature elevation	0

The most common serious adverse events reported in the postmarketing period were providied; e.g., "Condition (Schizophrenia) Aggravated" including Psychosis Aggravated or Exacerbation of Psychotic Symptoms (12 occurrences), and "Extrapyramidal Symptoms" including Extrapyramidal Disorders, Parkinsonism, Dyskinesia, Dystonia, and Akathisia (12 occurrences). I have reviewed the narratives for all SAEs in this category.

Serious Adverse Events of Potential Clinical Interest

Those serious adverse events of potential clinical interest are briefly described Below by the sponsor. None of these events, after review by the sponsor's Drug Safety and Surveliance medical officer, were found to be related to treatment with RISPERDAL CONSTA.

Coma

In one patient (EMADSS2002005713, age unknown) serious adverse events of coma, increased serum potassium levels and rhabdomyolysis were reported. This patient may have been more susceptible to developing rhabdomyolysis secondary to the elevated potassium levels. It is known that high levels of potassium can interfere with muscle innervation and function. Regarding the event of coma, no definitive conclusion can be made since this patient had not other data reported. The patient recovered from all of these events.

Convulsions

There were 8 patients with serious adverse events of convulsions, convulsions aggravated, or seizures cerebral. One of the reports occurred in a patient with a history of epilepsy. Case EMADSS2002006197, describes a 61-year-old patient whose seizures were controlled with carbamazepine, which was administered during treatment with RISPERDAL CONSTA. This patient also had psychosis aggravated. He also received concomitant medication of paroxetine, lorazepam, and haloperidol. Due to the multiple concomitant medications, a definitive relationship between risperidone and the events cannot be made. Two patients had substance abuse or dependence histories: EMADSS2002007265, age in early 20's had a history of drug abuse; EMADSS2002007041, age 31, had a history of cannabis dependence and alcohol abuse. For these two patients, not enough data are available to determine if a causal relationship exists between RISPERDAL CONSTA and the serious adverse events. In 3 of the cases of convulsions, hyponatremia was also noted. The report for 1 of these 3 patients (EMADSS2003001745) included coma, convulsions, hyponatremia, and electrolyte imbalance. This patient recovered from the convulsions and coma. Information regarding the sodium and other electrolytes is pending. Since this patient recovered without sequelae, the ionic imbalances may have predisposed the patient to convulsions and coma more than there being a relationship between these event and

RISPERDAL CONSTA treatment. The report for a patient with seizures cerebral, hyponatremia and hematemesis (EMADSS2002008062, age 45) suggested Syndrome of Inappropriate Antidiuretic Hormone as a cause. However, the patient recovered once a fluid restriction was imposed. The other patient (EMADSS2003001417, age unknown) was noted to have drunk a lot of water a few weeks prior to the convulsion.

Case EMADSS2002006665, age 51, had no known medical history – ECG, urea, and electrolytes were all normal at the time of the convulsion. Given the paucity of the data available, no conclusion can be made regarding the relationship of the event and RISPERDAL CONSTA. One of the patients with convulsions (EMDADSS2003000476) died of cardiac arrest and is discussed under Deaths. The paucity of data on this patient hinders a definitive conclusion about the relationship between the serious adverse event and RISPERDAL CONSTA.

Stroke

There were 2 patients with serious adverse events of stroke. One case was fatal (EMADSS2003002060) and is described under Deaths. Given the lack of data on this patient, it is not possible to comprehensively assess the contribution of the administration of RISPERDAL CONSTA. The other patient (EMADSS2002006815, age 52) experienced a stroke 44 days after initiation of treatment with RISPERDAL CONSTA; the report lists the treatment as ongoing. Concomitant medication included procyclidine and flupentixol decanoate. The physician reported the patient as not yet recovered and the event as doubtfully related to RISPERDAL CONSTA. No other data was available.

Steven's Johnson Syndrome

The patient with Steven's Johnson Syndrome (EMADSS2002006705, age 19) had elevated mycoplasm titres. This patient was re-exposed to RISPERDAL CONSTA without experiencing any adverse reaction.

Allergic Reaction

One patient, a health care provider who when preparing an injection of RISPERDAL CONSTA accidently spilled solvent on her hand developed an allergic reaction (EMADSS2003000965, age 30). This individual had a history of similar allergic reactions to lamb and beef. It was reported that there was a possibility she reacted to the protein in the solvent. The sponsor disagrees with the reporter's conclusion in that the diluent does not contain proteins.

Exanthema

Two patients had the serious adverse events of exanthema. One patient was on the concurrent medications of valproate and oral risperidone and RISPERDAL

CONSTA (EMADSS2003000076, age 45). The patient was re-challenged with the valproate and oral risperidone without the recurrence of exanthema, leaving the RISPERDAL CONSTA suspect. The patient recovered. The other patient who developed exanthema (EMADSS2003001359, age 54) did not have enough reported data to determine a temporal relationship between the event and RISPERDAL CONSTA.

LITERATURE SEARCH

The update literature search regarding risperidone long-acting injection use by patients was undertaken by Johnson & Johnson Pharmaceutical Research & Development, L.L.C., formerly known as Janssen Research Foundation (the Sponsor). Seven commercial literature databases were searched for original clinical research, in any language, referring to risperidone long-acting injection, covering the period from 1 August 2002 through 19 March 2003.
The searches were conducted by Nancy Marchuk, scientific information specialist in the Research Information Services Department of the Sponsor, using the search terms "risperidone" along with the following in the bibliographic reference and abstract, when available: "depot or long acting or intramuscular or microsphere".

The following commercial databases were searched; dates, including last update, are shown in parentheses:

•MEDLINE(R) (1966-2003/Mar W3);
•PsycINFO(R) (1887-2003/Mar W3);
•EMBASE (1974-2003/Mar W2);
•Biosis Previews(R) (1969-2003/Mar W2);
•ToxFile (1965-2002/Dec W4);
•SciSearch (R) (1990-2003/Mar W2);
•Pascal (1973-2003/Mar W2).

In addition, searches were conducted in the Sponsor's Literature Management and Documentation system (LMD). This is an archive repository for published product literature and internal and external research reports on the Sponsor's products. The documents are generated by the Sponsor and other sources. Publications are collected from screening of journals, proceedings, abstract books, and commercial databases.

Only publications (journal articles, published abstracts or posters, letters to the editor) containing original clinical data that were not based on studies conducted by the Sponsor, were included in this summary. Non-English publications were professionally translated into English prior to summarization. The data of each of those publications was extracted into a spreadsheet. Publications were reviewed for safety data occurring during treatment with risperidone long-acting injection, from all patients regardless of diagnosis.

Adverse events (AEs) were those events identified in the article as 'adverse events', 'adverse effects', 'side effects', 'adverse drug effects', or similar. All events reported in the articles were summarized as 'adverse events', without any attribution of intensity or relationship to study medication. Some authors reported all AEs, while others reported only the most common AEs. These were all treated the same way for summary purposes. Serious adverse events (SAEs) were those that were identified in the article as 'serious' or those that were reported to result in death or hospitalization. AEs, SAEs, and other safety information such as vital signs and laboratory findings were included as reported in the publications.

OVERVIEW OF THE LITERATURE SEARCH

A total of 104 articles were located as a result of the combined literature searches. After removal of 44 duplicates, this was reduced to 61 unique publications. Reviews, editorials, publications describing the same datasets or previously published data, publications based on Sponsor trials and those containing no data on risperidone-treated patients were not summarized.

LITERATURE SAFETY RESULTS

The sponsor lists the references for the 61 articles but does not supply the papers for my review. I have reviewed the tittles to these articles and find nothing of unusual interest. The sponsor warrants the following conclusions in Italics based on the literature search.

"The level of safety information reported, including the number of patients in the studies, varied widely among articles. Many articles gave no safety information, or the information was in a format that could not be extracted or summarized effectively. Since not all publications clearly stated the number of patients who were treated with risperidone, or the specific diagnosis for each patient, the exact number of exposed patients and patients with a particular diagnosis could not be determined.

Adverse events about which specific information was provided were compared against those reported in the Investigator's Brochure for Risperidal - All Indications, fourth edition, dated October 2002. All adverse events were comparable to those reported in the Investigator's Brochure. In conclusion, no unexpected adverse events were reported. All adverse events observed in the literature were qualitatively similar to those reported in the Investigator's Brochure."

SUMMARY OF EVENTS OF INTEREST

I have searched for the following adverse events of interest in this submission. The following table displays the events of Hyperglycemia, Diabetes, and Stroke.

	Hyperglcemia	Diabetes	Stroke
Completed Trials	2	1	0
Ongoing Trials	3	5	3
Non-IND Trails	0	0	1
Postmarketing	0	0	2

SUMMARY AND CONCLUSION

I believe the sponsor has presented evidence that there is a need for a long acting depot injection form of Risperdal.

The safety data presented in the submission is similar to that of the original NDA for Risperdal Consta. No new events were uncovered that would alter the risk/benefit profile of Risperdal Consta as discussed in the original NDA. SAEs are mainly psychiatric in nature with no unusual pattern to the occasional medical SAE. If the preclinical findings are acceptable I believe the clinical safety of Risperdal Consta is currently adequate.

From a clinical viewpoint I recommend that Risperdal Consta be approved. Biopharm has prepared some recommendations and labeling changes. My labeling comments remain unchanged from the original review.

Earl D Hearst, M.D.
HFD-120

CC:laughren, hearst, andreason, hardeman

APPENDIX

APPEARS THIS WAY
ON ORIGINAL

TABLE OF STUDIES

Table of Studies

J&JPRD Sponsored Studies for the Safety Response

Study/Phase	Dosing regimen	Treatment duration	Study Design	Number of patients (Schizophrenia/schizoaffective)
Completed after 4-month Safety Update (Phase 3, Repeated-dose Studies)				
RIS-INT-62 (Phase 3) The objective of the study is to confirm the non-inferiority of risperidone depot microspheres to olanzapine tablets (efficacy and safety, Weeks 1-13) and to document long-term safety and efficacy (Weeks 14-53).	Run-in: RIS oral 2 mg, 4 mg, or 6 mg OR oral olanzapine beginning with 5 mg and titrated to best dose with increments of 5 mg up to 20 mg. Treatment: Administration of RIS depot microspheres 25 mg or 50 mg every 2 weeks OR once daily olanzapine tablets 5 mg, 10 mg, 15 mg, or 20 mg. For RIS depot patients, supplementation with RIS oral 2 mg during first 3 weeks after first injection. For RIS depot patients, supplementation with RIS oral (up to 4 mg) at discretion of the investigator during trial.	1 week 53 weeks	Open-label, randomized, multicenter, comparative (International)	560[1] 363[2]
RIS-USA-259 (Phase 3b) The objective of the study is to examine safety and efficacy when switching from oral neuroleptics (other than risperidone) to risperidone depot microspheres.	Run-in: Treatment with current oral neuroleptics (haloperidol, quetiapine fumarate, olanzapine) Treatment: Administration of RIS depot microspheres 25 mg, 37.5 mg, or 50 mg every 2 weeks. The first injection is 25 mg; dose may be increased by increments of 12.5 mg to a maximum of 50 mg. Patients continue on current oral antipsychotic medication for 3 weeks after first injection. Supplementation with RIS oral 1 mg after Week 3, in case of exacerbation of psychotic symptoms.	4 weeks 12 weeks	Open-label, multicenter (United States)	141/141/0)

Study/Phase	Dosing regimen	Treatment duration	Study Design	Number of patients (Schizophrenic/schizoaffective)
Completed after 4-month Safety Update (Phase 3, Repeated-dose Studies)				
RIS-INT-65 (Phase 3b) The objective of the study is to examine safety and efficacy when switching from typical depot neuroleptics to risperidone depot microspheres.	Run-in: Treatment with current conventional depot neuroleptics (haloperidol decanoate, fluperitrol decanoate, fluphenazine, zuclopenthixol decanoate) Treatment: Administration of RIS depot microspheres 25 mg, 37.5 mg, or 50 mg every 2 weeks. The first injection is 25 mg; dose may be increased by increments of 12.5 mg to a maximum of 50 mg. Supplementation with RIS oral 1 mg, in case of exacerbation of psychotic symptoms.	2 cycles 12 weeks	Open-label, multicenter (International)	166 (166/0)

Study/Phase	Dosing regimen	Treatment duration	Study Design	Number of patients (Schizophrenic/schizoaffective)
Ongoing Extension Studies (Phase 3, Repeated-dose)				
RIS-USA-196 (Phase 3) (Open-label extension of study RIS-USA-121) The objective of the study is to examine the long-term safety of risperidone depot microspheres.	Administration of RIS depot microspheres 25 mg, 50 mg, or 75 mg every 2 weeks. Patients were titrated to a best dose of 25 mg, 50 mg, or 75 mg. The first injection is 25 mg; dose may be increased by 25 mg every 2 weeks to a maximum dose of 75 mg. Supplementation with RIS oral 2 mg during first 3 weeks after first injection. Supplementation with RIS oral at discretion of the investigator during trial.	Minimum of 1 year	Open-label, multicenter (United States)	271 (249/22)

Study/Phase	Dosing regimen	Treatment duration	Study Design	Number of patients (Schizophrenic/schizoaffective)
Ongoing Extension Studies (Phase 3, Repeated-dose)				
RIS-INT-63 (Phase 3) (Open label extension of studies RIS-INT-61 and RIS-INT-57) The objective of the study is to examine the long-term safety of risperidone depot microspheres.	Administration of RIS depot microspheres 25 mg, 50 mg, or 75 mg every 2 weeks. Patients were titrated to a best dose of 25 mg, 50 mg, or 75 mg. Dose may be increased by 25 mg every 2 weeks to a maximum dose of 75 mg All patients from RIS-INT-61 received double-blind oral medication during the first 3 weeks of treatment. Patients who were treated with placebo tablets and risperidone depot microspheres during RIS-INT-61 continued to receive placebo tablets, while patients treated with risperidone tablets and placebo depot received 2 mg, 4 mg, or 6 mg risperidone tablets according to their previous medication schedules during the first 3 weeks of the extension trial. Patients from RIS-INT-57 continued on the same dose of risperidone depot microspheres as during the last 3 months of RIS-INT-57. Supplementation with RIS oral (up to 4 mg) at discretion of the investigator during trial.	Minimum of 1 year	Open-label, multicenter (International)	779 (717/62)

Study/Phase	Dosing regimen	Treatment duration	Study Design	Number of patients (Schizophrenic/schizoaffective)
Ongoing Extension Studies (Phase 3, Repeated-dose)				
RIS-INT-80 (Phase 3) (Open-label extension of trials RIS-INT-62 and RIS-INT-85) The objective of the trial is to document the long-term safety of 25, 37.5, and 50 mg risperidone depot microspheres given every 2 weeks to subjects with schizophrenia or schizoaffective disorder.	Administration of RIS depot microspheres 25, 37.5, or 50 mg every 2 weeks. Subjects who have completed the RIS depot microspheres arm of the RIS-INT-62 trial or have completed the RIS-INT-85 trial will continue on the same dosage as, or one that is 12.5 mg lower or higher than, the last injection at the end of the previous trial. During RIS-INT-80 the dosage of RIS depot microspheres may be increased or decreased by 12.5-mg increments at the discretion of the investigator to a maximum dosage of 50 mg. Only those patients who received 75 mg in the RIS-INT-62 trial will be allowed to continue on this dosage; however, an attempt is to be made to decrease the dosage in these subjects to 50 mg within 3 months after Protocol Amendment 2 was approved ("as soon as clinically indicated" was removed with Amendment 2). Throughout the trial a maximum of 4 mg/d oral RIS may be administered as a supplement to the RIS depot microspheres injections at the discretion of the investigator if clinically needed.	1 to 2 years (or <2 years in specific countries if registered and commercially available)	Open-label, multicenter (International)	up to 440 up to 280 (schizophrenic or schizoaffective) from RIS-INT-62 up to 160 (schizophrenic) from RIS-INT-85

Study/Phase	Dosing regimen	Treatment duration	Study Design	Number of patients (Schizophrenic/schizoaffective)
Ongoing Extension Studies (Phase 3, Repeated-dose)				
RIS-USA-265 (Phase 3) (Open-label extension of trial RIS-USA-259) The primary objective of the trial is to document the long-term safety of 25, 37.5, and 50 mg risperidone depot microspheres given every 2 weeks in patients diagnosed with schizophrenia. A secondary objective is to evaluate efficacy in subjects with schizophrenia who were previously treated with an oral antipsychotic as measured by Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI).	Administration of RIS depot microspheres 25, 37.5, or 50 mg every 2 weeks Subjects who have completed the RIS-USA-259 trial will continue on the same dosage as the last injection at the end of RIS-USA-259. The maximum dosage is 50 mg. During RIS-USA-265 the dosage of RIS depot microspheres may be increased or decreased by 12.5-mg increments by the investigator. Throughout the trial oral RIS may be administered as a supplement to the RIS depot injections at the discretion of the investigator if clinically needed.	at least 1 year	Open-label, multicenter	up to 120 (schizophrenic)

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/s/

Earl Hearst
10/1/03 03:59:23 PM
MEDICAL OFFICER

Thomas Laughren
10/24/03 08:04:03 AM
MEDICAL OFFICER
I agree that this NDA is approvable; see memo to file for more detailed comments.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA: 21-346
Sponsor: Janssen
Clock Date: 8/31/01

Drug Name

Generic Name: Risperidone Long Acting Injection
Trade Name: Risperdal Consta

Drug Characterization

Pharmacological Category: Benzisoxazole derivative
Proposed Indication: Schizophrenia
NDA Classification: 3-S
Dosage Forms, Strengths, and Routes of Administration:
Injection 25mg, 37.5mg and 50mg

Reviewer Information

Clinical Reviewer: Earl D. Hearst, M.D.
Review Completion Date: 5/13/02

Table of Contents

Clinical Review for NDA 21-346

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Risperdal Consta is both efficacious and safe and is approvable.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Consideration can be given to a relapse prevention trial and a pediatric program for phase IV commitments.

No trials with risperidone depot microspheres have been conducted in children younger than 18 years of age. At the pre-NDA meeting for risperidone depot microspheres (April 20, 2001), the Division acknowledged its commitment to respond to study proposals provided in the May 5, 2000 submission. Based on the ongoing nature of these discussions, JRF is requesting a deferral of the commitment to submit a pediatric clinical proposal until discussions with the Division are complete.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The research and development program for risperidone depot microspheres in the treatment of schizophrenia was conducted globally and included a total of 13 trials:

_ Phase 1 and 2 trials (10 trials) - 9 international and 1 US;
_ Phase 3 trials (3 trials) - 2 international and 1 US; and,
_ Ongoing trials (4 trials) - 2 Phase 3 extensions trials, 1 Phase 3 international trial, and 1 Phase 2 international trial.

B. Efficacy

The primary analysis was of the change from baseline in total PANSS at Endpoint in study RIS-USA-121. The change in each risperidone depot group was significantly better than in the placebo group (p _ 0.002). Mean change from baseline was numerically the best in the risperidone depot 50 mg group (average improvement of 8.7 points), followed by the risperidone depot 25 mg and risperidone depot 75 mg groups.

C. Safety

The safety review reveals no new or unusual events and is similar in nature to the pattern seen in existing labeling for Risperdal. These trials included adult and elderly patients, in in- or out-patient populations with schizophrenia or schizoaffective disorder. The incidences and types of serious adverse events were lower and comparable between the 25-mg and 50-mg treatment groups, compared with the 75-mg group. Mean intensity of injection site pain was mild and diminished from first to last injection in all treatment groups. There were no clinically relevant mean changes from baseline to endpoint in laboratory values, vital signs, or ECG parameters for any patients treated with risperidone depot microspheres. In general, no clinically relevant differences in adverse event profiles were found for gender, race, or body mass index. Risperidone depot microspheres were safe and well tolerated in elderly patients (> 65 yrs). There were no clinically relevant differences in the safety profiles of non-elderly and elderly patients.

D. Dosing

Dosing recommendations are derived primarily from one study. RIS_USA_121 was the only double blind fixed dose study. Risperidone depot microspheres were found to be effective in the treatment of patients with schizophrenia over a dose range of 25, 50 and 75 mg when administered every 2 weeks as IM injections. The change from baseline in total PANSS at endpoint with risperidone depot 75 mg was not superior to that of the 50-mg group when compared with placebo. Therefore, it was concluded that the 75-mg dose of risperidone depot did not provide additional benefit over the 50-mg dose. Overall, adverse events within the central and peripheral nervous system disorders occurred with a higher incidence with 50 mg and 75 mg of risperidone depot while the incidence was lower with 25 mg of

risperidone depot and placebo, and comparable between these latter two groups. Among the expected adverse events, EPS and potentially prolactin-related adverse events occurred in a higher percentage of patients with increasing dose levels of risperidone depot. JRF intends to market dosage strengths of 25 mg, 37.5 mg, and 50 mg risperidone depot microspheres.

E. Special Populations

As discussed at the pre-NDA meeting (April 20, 2001), pharmacokinetic, efficacy, and safety data from 57 elderly patients ($\geq$ 65 years old) treated for up to 12 months with risperidone depot microspheres are provided in this submission.

No trials with risperidone depot microspheres have been conducted in children younger than 18 years of age (see Pediatric Use/Certification Statement). At the pre-NDA meeting for risperidone depot microspheres (April 20, 2001), the Division acknowledged its commitment to respond to study proposals provided in the May 5, 2000 submission. Based on the ongoing nature of these discussions, JRF is requesting a deferral of the commitment to submit a pediatric clinical proposal until discussions with the Division are complete.

There are no safety or efficacy differences in special populations such as age, gender or race (see special populations in review). There are special population dosing precautions listed in the dosing section to follow.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Risperidone is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1, 2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido [1,2-a]pyrimidin-4-one. Its molecular formula is C23H27FN4O2 and its molecular weight is 410.49.

The proposed tradename for the new formulation of risperidone,

RISPERDAL CONSTA _ (risperidone) Long-Acting Injection, has been submitted under the IND to the Office of Post-marketing Drug Risk Assessment for review and approval (Serial No. 042, August 13, 2001). JRF intends to market dosage strengths of 25 mg, 37.5 mg, and 50 mg risperidone depot microspheres

B. State of Armamentarium for Indication(s)

Risperdal is approved in oral dosage for schizophrenia. There are other depot antipsychotic medications already approved for schizophrenia.

C. Important Milestones in Product Development

Milestones reached with the FDA regarding the clinical development program for risperidone depot microspheres include the following:

_ Trial designs

Placebo-controlled trial (RIS-USA-121): At the End-of-Phase 2 (EOP-2) meeting on 13 April 1999, the FDA indicated that a single, placebo-controlled study with assay sensitivity would be sufficient to support the submission of an NDA for risperidone depot microspheres. The FDA further stated that the trial design of RIS-USA-121 would be considered a test of the clinical use of risperidone depot microspheres. The final protocol for RIS-USA-121 included an oral supplementation period for the first 3 weeks after the first injection. Patients randomized to receive 25 mg, 50 mg, or 75 mg risperidone depot microspheres were to receive 2mg, 4 mg, or 6 mg, respectively, of oral risperidone once daily during this period; patients randomized to the placebo depot microspheres treatment group were given placebo tablets. The oral supplementation period was designed to ensure that adequate plasma concentrations of risperidone were maintained during the initial zero-order release period and until the main release of risperidone from the depot microspheres had begun.

Non-inferiority, controlled trial (RIS-INT-61): At the EOP-2 meeting (13 April 1999), the FDA stated that although the trial design of the non-inferiority study requested by the CPMP does not allow for the detection of false positives, data from this trial could be used to support safety and dosing recommendations for risperidone depot microspheres. At the pre-NDA meeting (20 April 2001), the Division indicated that efficacy data from this trial could be included in the NDA, but could not be used to

support efficacy in the label.

Indications

Based on correspondence from the FDA dated 21 January 2000, the protocol for RIS-USA-121 was amended (Amendment 2, 25 February 2000) to exclude patients with schizoaffective disorder as well as patients with violent or suicidal tendencies from entering the trial. Baseline characteristics, and efficacy and safety data for patients with schizoaffective disorder who had entered RIS-USA-121 prior to this amendment are presented in the ISE and ISS; however, no treatment comparisons were made for these patients. (Efficacy and safety data from schizoaffective patients enrolled in the open-label trial, RIS-INT-57, are also presented).

Special populations

At the EOP-2 meeting (13 April 1999), the FDA agreed that data from approximately 50 elderly ($\geq$65 years old) patients enrolled in the open-label trial, RIS-INT-57, would be sufficient to evaluate the pharmacokinetic and safety profile in elderly patients. The FDA further stated that no separate efficacy trial in elderly patients would be required.

At the pre-NDA meeting (20 April 2001), the difference in dosing recommendations for the elderly in the label for oral risperidone and in the proposed label text for risperidone depot microspheres was noted. The Division indicated that the dosing recommendations for the elderly will be determined during the review of the NDA and will depend on the similarity or differences in the pharmacokinetic profiles of nonelderly and elderly patients.

Extent of exposure

The Division agreed that the number of patients enrolled in RIS-INT-57, the open-label, 12-month safety trial (579 patients treated for approximately 6 months, and 361 patients treated for approximately 1 year),

Statistical analysis plans

Per agreement at the EOP-2 meeting, the primary efficacy analysis set for RIS-USA-121 was comprised of intent-to-treat

patients with schizophrenia. For efficacy analysis, intent-to-treat patients included all randomized patients with at least 1 depot injection and at least 1 postbaseline PANSS assessment.

Amendment 2 for RIS-USA-121 (25 February 2000) also specified additional longitudinal data analyses to address the issue of treatment discontinuations due to inefficacy, as well as to analyze the time of, and the reason for, dropouts. These revisions to the planned statistical analyses were in response to the FDA's concern that 12 weeks of placebo treatment in poorly controlled patients with schizophrenia would result in a high rate of dropouts (correspondence dated 21 January 2000). The statistical analysis plans for the Phase 3 studies, the ISE, and the ISS were approved at the pre-NDA meeting (20 April 2001).

Analysis of QT data

ECGs were centrally read by [redacted] in the Phase 3 studies. Per the statistical analysis plan, three correction factors were applied to the analysis of QT data, using Bazett's formula, Fridericia's formula, and the linear formula according to Sagie et al. As recommended by the FDA (pre-NDA meeting, 20 April 2001), an additional linear correction factor (QTcL-2) was applied to the QT data.

Dose proportionality

At the pre-NDA meeting (20 April 2001), the FDA agreed that if dose proportionality of 25, 50, and 75 mg of risperidone depot microspheres was established in pharmacokinetic trials, pharmacokinetic and safety data from a single-dose trial, RIS-INT-72, would be sufficient to support the recommended use of the intermediate dose of 37.5 mg [redacted]

Bioequivalence of formulations

At the EOP-2 meeting (13 April 1999), the FDA requested that bioequivalence be shown between oral and depot formulations, and between Phase 1-2 and Phase 3 (to-be-marketed) formulations. At the pre-NDA meeting (20 April 2001), the Division agreed that the biopharmaceutical approach to be used in the NDA was acceptable. Early fluctuations in plasma levels of the active moiety (sum of unchanged risperidone and the metabolite, 9-hydroxy-risperidone) were observed during the first week after injection in a small number of patients in Phase 1-2 studies; these plasma concentrations were less than those associated with

8 mg oral risperidone. The potential cause for the early drug release was examined in animal studies and was attributed to an inflammatory response at the injection site. The incidence of early drug release was predicted to be very low in Phase 3 trials due to an improved diluent and a smaller injection needle used in the Phase 3 studies. The proposed pharmacokinetic sampling scheme (Days 1, 4, and 7 after the injection) to assess plasma concentrations in Phase 3 studies was considered acceptable by the FDA to allow review of the early drug release phenomenon (EOP-2 meeting, 13 April 1999; pre-NDA meeting, 20 April 2001).

Nonclinical toxicology

At the pre-NDA meeting (20 April 2001), the FDA agreed that issues related to the toxicology requirements for the NDA raised at the EOP-2 meeting (13 April 1999), including the protocol for the 24-month carcinogenicity study, had been successfully addressed. An agreement was also reached at the pre-NDA meeting that the NDA would include information to evaluate the potential reproductive toxicity of the polymer and its degradation products.

D. Other Relevant Information

Risperidone depot microspheres is not yet commercially available.

E. Important Issues with Pharmacologically Related Agents

Below is a list of INDs and NDAs filed to the Agency for RISPERDAL (risperidone) for the treatment of the manifestations of psychotic disorders (e.g. schizophrenia):

IND/NDA Number	Dosage Form	Date Filed	Date Approved
NDA 20-272	Tablets	April 15, 1992	December 29, 1993
NDA 20-588	Oral Solution	June 2, 1995	June 19, 1996
IND 31,931	Tablets	August 9, 1988	n/a
IND 52,982	Microspheres Injection	March 18, 1997	n/a

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Nonclinical toxicology studies conducted with risperidone depot microspheres include tolerance studies in several species, primary irritation studies in the rabbit, repeated-dose toxicity studies in the rat and dog, and the 24-month carcinogenicity study in the rat (EDMS-BEBE-2644186). In addition, an Ames reverse mutation study with risperidone depot microspheres is provided (EDMS-BEBE-2893737). Supportive evidence of the nonclinical pharmacokinetics and toxicology of oral risperidone may be found in the original NDA (20-272) and in the Pharmacology, Toxicology, and Pharmacokinetic Summaries for oral risperidone that are included in this NDA.

The microspheres are comprised of 7525 polyactide-co-glycolide (PLG), a biodegradable biomedical copolymer that has been extensively used in internal surgical devices. After injection, the microspheres are hydrolyzed into two endogenous components: lactic acid and glycolic acid (hydroxyacetic acid). A microspheres vehicle control group was included in repeated-dose toxicology studies and in the 24-month carcinogenicity study (see Toxicology Summary and EDMS-BEBE-2644186, respectively).

A separate report summarizing studies conducted with the microspheres vehicle is also provided (EDMS-BEBE-2810462). Information from reproductive and metabolism studies with the copolymer used in the microspheres is available to the Division in the — for — —. Ethicon, the sponsor for the — — is a wholly owned subsidiary of the Johnson & Johnson (J&J) Corporation. Ethicon has provided a letter authorizing the Division to reference the — on the behalf of JRF, which is also a wholly owned subsidiary of the J&J Corporation.

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III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

There are no nonclinical pharmacology studies included in this NDA. The sponsor has provided pharmacokinetic information reproduced below in italics.

The pharmacokinetics of risperidone depot microspheres were assessed by monitoring of plasma levels in a clinical long-term safety study. Fifty seven (57) elderly patients (_65 years) were recruited and received every 2 weeks intramuscular injections of risperidone depot microspheres (25, 50 or 75 mg) for a period of at least 6 months and up to 1 year.

Bioequivalence was demonstrated between the tablet and depot microspheres formulations of risperidone (RIS-INT-32), and between the Phase 1/2 and Phase 3 (to-be-marketed) formulations of risperidone depot microspheres (RIS-INT-54).

Per agreement at the pre-NDA meeting (April 20, 2001), no formal bioequivalence trial was performed with the to-be-marketed formulation, which is the same as that used in Phase 3 trials. Plasma concentrations from approximately 1250 patients treated with risperidone depot microspheres in Phase 3 trials are provided in the individual clinical trial reports (RIS-USA-121; RIS-INT-61; RIS-INT-57) and in the Clinical Pharmacokinetics Summary.

Per agreement at the pre-NDA meeting (April 20, 2001), pharmacokinetic data to assess potential early drug release (plasma concentrations on Days 1, 4, and 7 after the injection of risperidone depot microspheres) are provided for two Phase 1 trials (RIS-INT-54; RIS-INT-72) and for three Phase 3 trials (RIS-USA-121; RIS-INT-61; RIS-INT-57) in which the to-be-marketed formulation was used.

The pharmacokinetics of risperidone depot microspheres have been examined in patients with schizophrenia or schizoaffective disorder. The release profile of a single risperidone depot microspheres injection consists of a small initial release within the first 24 hours (<1% of the dose), followed by a lag time of about 3 weeks with hardly any release of drug from

the depot. Therapeutic plasma concentrations are reached 3 to 4 weeks after injection, are maintained for 2 weeks (through 6 weeks after injection), and subside by 7 weeks after injection.

Sustained, therapeutic plasma drug concentrations are reached when risperidone depot microspheres is injected every 2 weeks. Therapeutic concentrations emerge from Week 3 onward after the first injection. Oral supplementation during 3 weeks after the first IM injection guarantees a smooth transition from oral risperidone to depot risperidone, with stable plasma concentrations from the first week onwards. Injections of risperidone depot microspheres every 2 weeks (25-75 mg) results in equivalent plasma exposure (AUC, Cav, Cmin) but lower peak to trough fluctuations compared to oral tablets (2-6 mg) administered once daily.

The pharmacokinetics of risperidone depot microspheres after single or repeated injection (every 2 weeks) were dose-proportional from 25 to 75 mg. The pharmacokinetics of the intermediate doses (37.5 and 62.5 mg) were evaluated after single injection and found to be dose-proportional to the 50 mg reference, based on dose-normalized Cmax and AUC.

Active moiety plasma levels were comparable between risperidone oral and depot treatment for all dose levels (2, 4 and 6 mg versus 25, 50 and 75 mg) during the 12-week duration of a non-inferiority trial. Plasma levels of active moiety remained stable after long-term use (1 year) of risperidone depot microspheres, indicating that no accumulation was associated with prolonged use up to 24 injections administered once every 2 weeks.

No formal pharmacokinetic interaction studies were performed with risperidone depot microspheres.

The pharmacokinetics of risperidone depot microspheres were not studied in patients with renal and hepatic impairment.

B. Pharmacodynamics

There are no nonclinical pharmacology studies included in this NDA. No clinical pharmacology trials were performed with risperidone depot microspheres.

IV. Description of Clinical Data and Sources

A. Overall Data

Data for this submission is derived exclusively from the clinical development program. The research and development program for risperidone depot microspheres in the treatment of schizophrenia was conducted globally and included a total of 13 trials:

_ Phase 1 and 2 trials (10 trials) - 9 international and 1 US;
_ Phase 3 trials (3 trials) - 2 international and 1 US; and,
_ Ongoing trials (4 trials) - 2 Phase 3 extensions trials, 1 Phase 3 international trial, and 1 Phase 2 international trial.

B. Tables Listing the Clinical Trials

Table 11: Overview of the clinical trials in patients supporting the NDA for risperidone depot microspheres

Trial	Study Phase	Primary objective(s) (schizophrenia/ schizoaffective/other)	Risperidone depot microspheres dose (risperidone tablet)	Treatment duration	Number of patients
Single-dose trials					
Pooled, single-dose trials					
RIS-BEL-34	1	Pharmacokinetic	50 mg	1 injection	8 (8/0/0)
RIS-INT-25	1	Pharmacokinetic	50 mg	1 injection	9 (9/0/0)
RIS-INT-38	1	Pharmacokinetic	100 mg	1 injection	9 (9/0/0)
RIS-NED-13	1	Pharmacokinetic	25 mg	1 injection	8 (8/0/0)
RIS-USA-111	1	Pharmacokinetic	25 mg	1 injection	8 (6/2/0)
RIS-INT-54	1	Pharmacokinetic	25, 50, 75 mg	1 injection	56 (52/4/0)
Total					**98 (92/6/0)**
Single, intermediate-dose trial					
RIS-INT-72	1	Pharmacokinetic	37.5, 50, 62.5 mg	1 injection	**76 (76/0/0)**
Pooled, repeated-dose trials (3-month endpoint)					
RIS-INT-31	1	Pharmacokinetic	25, 50, 75 mg	16 weeks	28 (28/0/0)
RIS-SWE-17	1	Pharmacokinetic	25, 50, 75 mg	16 weeks	13 (13/0/0)
RIS-INT-32	2	Pharmacokinetic	25, 50, 75 mg	15 weeks	82 (68/8/6) Efficacy, safety, pharmacokinetic,
RIS-USA-121	3	(placebo-controlled) Efficacy, safety, pharmacokinetic	25, 50, 75 mg	12 weeks	439 (400/39/0)

RIS-INT-61	3	(noninferiority with risperidone tablet)	25, 50, 75 mg (2, 4, 6 mg)	12 weeks	640 (640/0/0)
RIS-INT-57	3	Long-term safety, efficacy, pharmacokinetic	25, 50, 75 mg	50 weeks	725 (615/110/0)
Total					**1927 (1764/157/6)**
		Ongoing Trials			
RIS-JPN-16	2	Pharmacokinetic (single-dose)	25, 50, 75 mg	1 injection	24[a)] 9 [b)]
RIS-INT-62	3	Efficacy and safety (non-inferiority with olanzapine tablet)	25, 50, 75 mg (5, 10, 15, 20 mg)	1 year	537[a)] 228[b)]
RIS-INT-63	3	Long-term safety (extension of RIS-INT-61, RIS-INT-57)	25, 50, 75 mg	1 year	855[a)] 798[b)]
RIS-USA-196	3	Long-term safety (extension of RIS-USA-121)	25, 50, 75 mg	1 year	348[a)] 273[b)]

a) Planned enrollment.

b) Number of patients treated as of 30 April 2001

C. Postmarketing Experience

Risperidone depot microspheres is not yet commercially available.

D. Literature Review

Commercial literature databases were searched for clinical and nonclinical original research, in any language, referring to risperidone depot microspheres. The searches were conducted by Nancy Marchuk, a scientific information specialist in the Research Information Services Department of Janssen Pharmaceutica, using the search terms "risperidone" along with "depot" or "microspheres" or "intramuscularly" in the bibliographic reference and abstract, when available. As the target cut-off date was March 31, 2001, the last search was conducted in April 2001. The following commercial databases were

searched; dates, including last update, are shown in parentheses: Medline (1966-2001/May W5), Aidsline (1980-2000/Dec), Cancerlit (1975-2001/Mar), HealthSTAR (1975-2000/Dec), Toxline (1965-2000/Dec), Derwent Drug File (1983-2001/May W3), PsycINFO (1887-2001/May W2), EMBASE (1974-2001/May W1), and SciSearch (1974-2001/May W2).

In addition, searches were conducted in Janssen Research Foundation's (JRF) Literature Management and Documentation system (LMD). This is an archive repository for published product literature and internal and external research reports on JRF products. The documents are generated by JRF and other sources. Publications are collected from screening of journals, proceedings, abstract books, and commercial databases.

The only documents describing original research with risperidone depot microspheres that were found in these searches were items based on research conducted by JRF. Therefore, there is no new relevant data from the literature.

V. Clinical Review Methods

A. How the Review was Conducted

I will review RIS-USA-121 (the only double-blind placebo controlled phase III trial) in detail and the other two phase III studies briefly. The safety update will be integrated with the pre-existing database for purposes of presenting deaths, serious adverse events and adverse events leading to dropout.

B. Overview of Materials Consulted in Review

This submission is provided in 65 volumes hard copy and electronically in the EDR with 13 electronic additions. There is a 12 volume safety updated provided in hard copy and electronically. Electronic images of 507 CRFs have been provided for patients who died, experienced a serious adverse event, or discontinued treatment due to an adverse event. SAS datasets have been provided for the individual Phase 3 clinical trials (RIS-USA-121, RIS-INT-57, and RIS-INT-61) and for the integrated safety data. Pharmacokinetic datasets from all clinical trials are also provided. The sponsor provided several tables at my suggestion which integrated safety events which although presented in many separate places were not previously collected in any single table.

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

DSI received a consult request for clinical site inspection from the Review Division (HFD-120) dated October 3, 2001. Inspection assignment was issued on October 22, 2001 for 3 domestic sites, Drs. Lowy, Lauriello and Brown. Their conclusion follows:

"Although some deficiencies were noted in the areas of protocol violations and minor deficiencies in drug accountability, the data from these 3 sites appear acceptable for use in support of this NDA."

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The final protocol and any amendments were reviewed and approved by independent Ethics Committees or by appropriately constituted institutional review boards (IRBs) according to specifications outlined in the US Code of Federal Regulations (CFR). The trial was conducted in accordance with the principles of Good Clinical Practice as outlined in 21 CFR Parts 50, 56, and 312 and the Declaration of Helsinki and its subsequent revisions.

E. Evaluation of Financial Disclosure

Financial disclosure information is provided for all studies that were ongoing or started after February 2, 1999. For the placebo-controlled trial conducted in the U.S. (RIS-USA-121), due diligence was exercised to obtain financial certification/disclosure information from all participants who signed Form 1572. For international trials, due diligence was exercised to obtain financial certification/disclosure information from all investigators and sub-investigators.

Form 3454 is provided for study participants who had no financial information to disclose (Attachment 1 of Form 3454) or for whom due diligence was exercised but complete financial certification/disclosure information was not received (Attachment 2 of Form 3454). Form 3455 is submitted for each study participant who met the criteria of having financial information to disclose. I have reviewed this data and find it to be acceptable.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

RIS-USA-121 is a clearly positive study and the statistical review conducted by Sharon Yan, Ph.D. is in agreement with this conclusion.

B. General Approach to Review of the Efficacy of the Drug

This Integrated Summary of Efficacy contains the results from three Phase III clinical trials in which patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (2 international, RIS-INT-61 and RIS-INT-57; and 1 US, RIS-USA-121). These trials included a total of 1804 patients (1655 patients with schizophrenia /149 patients with schizoaffective disorder) who received an injection of risperidone depot microspheres every 2 weeks at 25 mg, 50 mg, or 75 mg/dose. The 3 trials are listed below.

RIS-USA-121: a placebo-controlled trial that provides the basis for the claim of effectiveness of risperidone depot microspheres for the treatment of schizophrenia.

RIS-INT-61: a controlled, non-inferiority trial comparing risperidone depot microspheres to risperidone oral tablet. This trial was conducted to satisfy CPMP requirements for an European filing.

RIS-INT-57: an open-label, non-randomized, one-year trial. This trial was conducted to satisfy requirements for long-term dosing.

As of the data cutoff date of April 30, 2001, efficacy data supporting this NDA were derived from 1655 patients with schizophrenia; safety data were derived from a total of 2101 patients (1932 patients with schizophrenia, 163 patients with schizoaffective disorder, and 6 patients with schizophreniform disorder). Of these patients, 1499 patients received risperidone depot microspheres in repeated-dose trials, corresponding to approximately 543 patient-years of exposure.

I will present tables describing the data base after which I will review RIS-USA-121 in detail and the other two studies briefly.

Table 1: Overview of the Phase 3 clinical trials supporting the NDA for risperidone depot microspheres

Trial	Primary Objective(s)	Risperidone Depot Microspheres Dose (Risperidone Tablet Dose)	Treatment duration	Number of Randomized Patients with Injection (Schizophrenic/ Schizoaffective)
RIS-USA-121	Efficacy, safety, pharmacokinetic, (placebo-controlled)	25, 50, 75 mg	12 weeks	439 (400/39)
RIS-INT-61	Efficacy, safety, pharmacokinetic (non-inferiority with risperidone tablet)	25, 50, 75 mg (2, 4, 6 mg)	12 weeks	640 (640/0)
RIS-INT-57	Long-term safety, efficacy, pharmacokinetic	25, 50, 75 mg	50 weeks	725 (615/110)
Total				1804 (1655/149)

Source: Clinical Research Reports for RIS-USA-121, RIS-INT-61 and RIS-INT-57.

Table 2: Dosing regimen and treatment duration *RIS-USA-121, RIS-INT-61, RIS-INT-57*

Trial	Dosing regimen	Treatment duration	Blinding
RIS-USA-121 Run-in:	RIS oral: 2 mg for 4 days and 4 mg for 3 days	1 week	Open
Treatment:	Biweekly administration of RIS depot 25 mg, 50 mg, or 75 mg supplemented with RIS oral 2 mg 4 mg, or 6 mg daily, respectively, for 3 weeks	12 weeks (6 injections)	Double-blind
RIS-INT-61 Run-in:	2 weeks of RIS oral 2 mg, 4 mg, or 6 mg daily while other antipsychotic medication was tapered to discontinuation. 2 weeks of adjusting treatment to optimal RIS oral dose and 4 weeks of treatment with optimal dose RIS oral 2, 4 or 6 mg.	8 weeks	Open
Treatment:	Biweekly administration of RIS depot 25 mg, 50 mg, or 75 mg supplemented with RIS oral at final run-in dose for first 3 weeks or biweekly placebo depot with once daily RIS oral dosing of 2 mg, 4 mg, or 6 mg: 2 mg oral → 25 mg depot 4 mg oral → 50 mg depot 6 mg oral → 75 mg depot	12 weeks (6 injections)	Double-blind
RIS-INT-57 Run-in:	RIS oral 6 mg daily while other antipsychotic medication was tapered to discontinuation (no run-in for patients already taking risperidone)	2 weeks	Open
Treatment:	Biweekly administration of RIS depot 25 mg, 50 mg, or 75 mg (adjusting to optimal depot dose at scheduled visits) supplemented with: • Mandatory RIS oral 1 mg to 6 mg for Weeks 1 to 2, • optional RIS oral 1 mg to 6 mg for Week 3, • temporary RIS oral 1 mg to 6 mg from Weeks 4 to 52	1 year (50 weeks) (25 injections)	Open

Source: Clinical Research Reports for RIS-USA-121, RIS-INT-61 and RIS-INT-57.

Across the risperidone depot treatment groups in the randomized double-blind trials (RIS-USA-121 and RIS-INT-61), there was no difference in the percentage of patients discontinuing for any reason (see Table 3 below). There was a higher percentage of patients who discontinued in the US trial (RIS-USA-121 at approximately 52%) than in the international trial (RIS-INT-61 at 20.5%, 17.5% and 21.9% with risperidone depot 25 mg, 50 mg, and 75 mg). In the long-term trial, RIS-INT-57, there was a mode dose-related increase in the percent of patients who discontinued due to any reason (25 mg at 23.3%, 50 mg at 30.7%, and 75 mg at 43.8%).

The primary reasons for discontinuation across all three trials was adverse event, insufficient response, and withdrawal of consent. The percent of patients discontinuing due to adverse events and withdrawal of consent was generally higher with higher risperidone depot doses. Conversely, in RIS-USA-121, the percentage of patients who discontinued due to insufficient response decreased with higher doses of risperidone depot (25 mg at 22.2%, 50 mg at 14.6%, and 75 mg at 12.0%) (Table 3).

Table 3: Reasons for discontinuation of trial medication: n (%) of patients with schizophrenia who completed run-in *RIS-USA-121, RIS-INT-61, RIS-INT-57*

Trial termination reason	Placebo Depot	RIS depot 25 mg	RIS depot 50 mg	RIS depot 75 mg	RIS oral (2 to 6 mg)
Number with injection					
USA-121	98	99	103	100	--
INT-61	--	88	126	105	321
INT-57	--	120	228	267	--
Discontinued for any reason					
USA-121	67 (68.4%)	51 (51.5%)	53 (51.5%)	52 (52.0%)	--
INT-61	--	18 (20.5%)	22 (17.5%)	23 (21.9%)	50 (15.6%)
INT-57	--	28 (23.3%)	70 (30.7%)	117 (43.8%)	--
Adverse event					
USA-121	12 (12.2%)	11 (11.1%)	12 (11.7%)	14 (14.0%)	--
INT-61	--	3 (3.4%)	8 (6.3%)	7 (6.7%)	15 (4.7%)
INT-57	--	5 (4.2%)	13 (5.7%)	12 (4.5%)	--
Death					
USA-121	1 (1.0%)	0	0	0	--
INT-61	--	0	0	0	1 (0.3%)
INT-57	--	2 (1.7%)	2 (0.9%)	2 (0.7%)	--
Insufficient response					
USA-121	29 (29.6%)	22 (22.2%)	15 (14.6%)	12 (12.0%)	--
INT-61	--	3 (3.4%)	1 (0.8%)	8 (7.6%)	8 (2.5%)
INT-57	--	2 (1.7%)	7 (3.1%)	39 (14.6%)	--
Withdrew consent					
USA-121	10 (10.2%)	7 (7.1%)	13 (12.6%)	11 (11.0%)	--
INT-61	--	4 (4.5%)	8 (6.3%)	5 (4.8%)	13 (4.0%)
INT-57	--	14 (11.7%)	31 (13.6%)	43 (16.1%)	--
Other reasons (including: ineligible to continue, lost to follow-up, non-compliant, 'other')					
USA-121	15 (15.3%)	11 (11.1%)	13 (12.6%)	15 (15.0%)	--
INT-61	--	8 (9.1%)	5 (4.0%)	3 (2.9%)	13 (4.0%)
INT-57	--	5 (4.2%)	17 (7.5%)	21 (7.9%)	--

Source: Table SUB.7 USA121, Table SUB.9 INT61, Table SUB.9B INT61, Table SUB.4A INT57

Table 4: **Demographic and other baseline characteristics: n (%) (all treatment groups pooled; patients with schizophrenia) *RIS-USA-121, RIS-INT-61, RIS-INT-57***

Characteristics	RIS-USA-121 (N = 400)	RIS-INT-61 (N = 640)	RIS-INT-57 (N = 615)
Sex, n (%)			
Female	100 (25.0%)	226 (35.3%)	193 (31.4%)
Male	300 (75.0%)	414 (64.7%)	422 (68.6%)
Age (years)			
Mean (SE)	37.7 (0.49)	40.0 (0.44)	42.0 (0.57)
Range	18 – 55	18 – 66	18 - 84
Race, n (%)			
Black	167 (41.8%)	35 (5.5%)	15 (2.4%)
White	166 (41.5%)	562 (87.8%)	564 (91.7%)
Hispanic	45 (11.3%)	1 (0.2%)	5 (0.8%)
Oriental	11 (2.8%)	16 (2.5%)	11 (1.8%)
Other	11 (2.8%)	26 (4.1%)	20 (3.3%)
Body Mass Index (kg/m^2)	n=395	n=632	n=608
Mean (SE)	29.0 (0.36)	27.2 (0.24)	27.4 (0.21)
Range	17 – 61	15 – 56	14.5 - 48.5
Weight (kg)	n=396	n=634	n=608
Mean (SE)	86.9 (1.03)	80.4 (0.71)	81.3 (0.72)
Range	49 –159	43 –166	40 -155

Source: Table SUB.11 USA121, Table SUB.14 INT61, Table SUB.7A INT57

Table 5: Demographic data for elderly (≥65 years) patients with injection *RIS-INT-57*

	RIS depot 25 mg n=27	RIS depot 50 mg N=21	RIS depot 75 mg N=9	All treatments N=57
Sex, n (%)				
Female	18 (66.7%)	9 (42.9%)	3 (33.3%)	30 (52.6%)
Male	9 (33.3%)	12 (57.1%)	6 (66.7%)	27 (47.4%)
Race, n (%)[a]				
Caucasian	27 (100%)	21(100%)	9(100%)	57 (100%)
Age, years				
Mean (SE)	72.0 (1.06)	70.3 (1.12)	68.8 (0.91)	70.9 (0.68)
Range	(65; 84)	(65; 80)	(65; 72)	(65; 84)
Weight, kg				
Mean (SE)	67.76 (2.985)	64.51 (2.530)	81.78 (8.107)	68.78 (2.211)
Range	(46; 106)	(43.8; 95)	(43; 129)	(43; 129)
Body mass index				
Mean (SE)	26.48 (1.061)	23.37 (0.775)	28.46 (2.068)	25.65 (0.697)
Range	(17.7; 41.4)	(16.1; 29.0)	(19.9; 39.8)	(16; 41.4)

Source: Table SUB.9 INT57

Table 6: Stratification: n (%) (patients with schizophrenia)
RIS-USA-121 and RIS-INT-61

RIS-USA-121				
Stratification group	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
PANSS at randomization				
≤80	47 (48.0%)	45 (45.5%)	45 (43.7%)	47 (47.0%)
>80	51 (52.0%)	54 (54.5%)	58 (56.3%)	53 (53.0%)
Hospitalization status at randomization				
Inpatient	47 (48.0%)	49 (49.5%)	49 (47.6%)	50 (50.0%)
Outpatient	51 (52.0%)	50 (50.5%)	54 (52.4%)	50 (50.0%)

RIS-INT-61		
	RIS oral N= 274[a]	RIS depot N= 268[a]
PANSS total at randomization		
<60	71 (25.9%)	80 (29.9%)
≥60	203 (74.1%)	188 (70.1%)
ESRS total at randomization		
0-1	81 (29.6%)	95 (35.4%)
>1	193 (70.4%)	173 (64.6%)
Use of depot neuroleptics in 6 months prior to screening		
Yes	112 (40.9%)	104 (38.8%)
No	162 (59.1%)	164 (61.2%)
Optimal run-in dose		
2 mg	73 (26.6%)	72 (26.9%)
4 mg	110 (40.1%)	109 (40.7%)
6 mg	91 (33.2%)	87 (32.5%)

Source: Table SUB.2 USA121, Table SUB.3 INT61
a: Table based on IVRS source. Four patients had no data available in the IVRS source.

The baseline disease characteristics were similar across the three trials for the distribution of schizophrenia types. Most patients were of the paranoid type with undifferentiated schizophrenia as the second most prevalent form. The age at onset was also similar with the appearance of schizophrenia during the second decade of life, however patients were on average 6 to 8 years older in RIS-INT-61 compared to RIS-USA-121 for age of onset. Number of previous hospitalizations were not substantially different between RIS-USA-121 and RIS-INT-61.

Table 7: Baseline disease characteristics (patients with schizophrenia) *RIS-USA-121, RIS-INT-61, RIS-INT-57*

	RIS-USA121				RIS-INT61		RIS-INT57
Characteristics	Placebo depot N = 98	RIS depot 25 mg N = 99	RIS depot 50 mg N = 103	RIS depot 75 mg N = 100	RIS oral N= 277	RIS depot N= 269	RIS depot N=615
Schizophrenia type[a]							
Catatonic (295.2)	0	0	1 (1.0%)	0	1 (0.4%)	2 (0.7%)	3 (0.5%)
Disorganized (295.1)	2 (2.0%)	2 (2.0%)	6 (5.8%)	3 (3.0%)	17 (6.1%)	13 (4.8%)	33 (5.4%)
Paranoid (295.3)	78 (79.6%)	76 (76.8%)	74 (71.8%)	74 (74.0%)	169 (61.0%)	166 (61.7%)	382 (62.1%)
Residual (295.6)	0	0	0	0	42 (15.2%)	41 (15.2%)	99 (16.1%)
Undifferentiated (295.9)	18 (18.4%)	21 (21.2%)	22 (21.4%)	23 (23.0%)	48 (17.3%)	47 (17.5%)	96 (15.6%)
Unspecified	--	--	--	--	--	--	2 (0.3%)
Age at onset,	n=91	n=97	n=100	n=97	n=275	n=264	
Mean (SE) Range	22.0 (0.66) (9-42)	22.8 (0.76) (8-44)	21.4 (0.7) (7-42)	20.3 (0.63) (9-43)	29.1 (0.59) (9-62)	28.8 (0.58) (14-61)	--
Age at first hospitalization	n=89	n=91	n=94	n=94			
Mean (SE) Range	24.4 (0.8) (14-47)	25.1 (0.93) (0-47)	23.3 (0.79) (8-45)	23.2 (0.91) (0-50)	--	--	--
Number of previous hospitalizations	n=89	n=96	n=101	n=94	n=271	n=263	
Median (range)	4 (0-28)	3.5 (0-99)	4 (0-50)	4 (0-63)	3 (0-94)	3 (0-36)	--

Source: Table SUB.13 USA121, Table SUB.18 INT61, Table SUB.10 INT57
-- Data not collected
a: As defined in DSM-IV

I will end this sections with a table of trial design and dosing for all studies.

Table 13: Trial design and dosing schedule

Study	Dosing regimen	Treatment duration	Trial Design
Single-dose			
RIS-BEL-34	RIS depot 50 mg	Single injection + 8-week follow-up	Open-label, multicenter
RIS-ENT-23	RIS depot 50 mg	Single injection + 10-week follow-up	Open-label, multicenter
RIS-ENT-38	RIS depot 100 mg	Single injection + 10-week follow-up	Open-label, single-center
RIS-NED-33	RIS depot 25 mg	Single injection + 8-week follow-up	Open-label, single-center
RIS-USA-111	RIS depot 25 mg	Single injection + 8-week follow-up	Open-label, single-center
RIS-INT-54 Part I: Part II:	RIS depot 25 mg, 50 mg, or 75 mg (Bridging study between the 125-g production process and the 20-kg production process used in the Phase 3 studies)	Two single injections in Part I and Part II (27 weeks) Single injection + 15-week follow-up/washout Single injection + 12-week follow-up	Open-label, Multicenter
RIS-INT-72	RIS depot 37.5 mg, 50 mg, or 62.5 mg	Single injection + 12 week follow-up	Open-label, parallel-group, multicenter
Repeated-dose			
RIS-INT-33	Administration of RIS depot 25 mg, 50 mg, or 75 every 2 weeks	10 weeks (5 injections) + 7-week follow-up	Open-label, parallel-group, multicenter
RIS-SWE-13	Administration of RIS depot 25 mg, 50 mg, or 75 mg every 2 weeks; injections given on Days 1, 15, 29, 43, and 57.	10 weeks (5 injections) + 7-week follow-up	Open-label, parallel-group, multicenter
RIS-INT-32 Run-in:	Prior to entry, patients were required to be on oral RIS 2 mg, 4 mg, or 6 mg daily for at least 4 weeks	4 week	Open-label

Study	Dosing regimen	Treatment duration	Trial Design
Treatment:	Administration of RIS depot 25 mg, 50 mg, or 75 mg every 2 weeks following once daily oral dosing of 2-mg, 4-mg, or 6-mg risperidone tablets for 1 week. Exploratory oral supplementation (2 mg, 4 mg, or 6 mg during Weeks 1 to 3 and 1 mg, 2 mg, or 3 mg during Weeks 4 and 5) also was evaluated.	10 weeks (5 injections) + 5-week follow-up	Open-label, parallel-group, multicenter
RIS-USA-121			
Run-in:	RIS oral: 2 mg for 4 days and 4 mg for 3 days	1 week	Open-label
Treatment:	Administration of RIS depot 25 mg, 50 mg, or 75 mg every 2 weeks and supplemented with RIS oral 2 mg, 4 mg, or 6 mg daily, respectively, for 3 weeks	12 weeks (6 injections)	Randomized, double-blind, placebo-controlled, parallel-group, multicenter
RIS-INT-68			
Run-in:	2 weeks of RIS oral 2 mg, 4 mg, or 6 mg daily while other antipsychotic medication was tapered to discontinuation 2 weeks of adjusting treatment to optimal RIS oral dose 4 weeks of treatment with optimal dose RIS oral	8 weeks	Open-label
Treatment:	Administration of RIS depot 25mg, 50 mg, or 75 mg every 2 weeks and supplemented with RIS oral at final run-in dose for first 3 weeks or placebo depot every 2 weeks with once daily RIS oral dosing of 2 mg, 4 mg, or 6 mg	12 weeks (6 injections)	Randomized, double-blind, double-dummy, multicenter
RIS-INT-57			
Run-in:	RIS oral 6 mg daily while other antipsychotic medication was tapered to discontinuation	2 weeks	Open-label
Treatment:	Administration of RIS depot 25 mg, 50 mg, or 75 mg (adjusting for optimal depot dose at scheduled visits) every 2 weeks and supplemented with – Mandatory RIS oral 1 mg to 6 mg for Weeks 1 to 2 – Optional RIS oral 1 mg to 6 mg for Week 3 – Temporary RIS oral 1 mg to 6 mg from Weeks 4 to 50	1 year (50 weeks) (25 injections)	Open-label, multicenter

Source: Individual Clinical Research Reports

C. Detailed Review of Trials by Indication

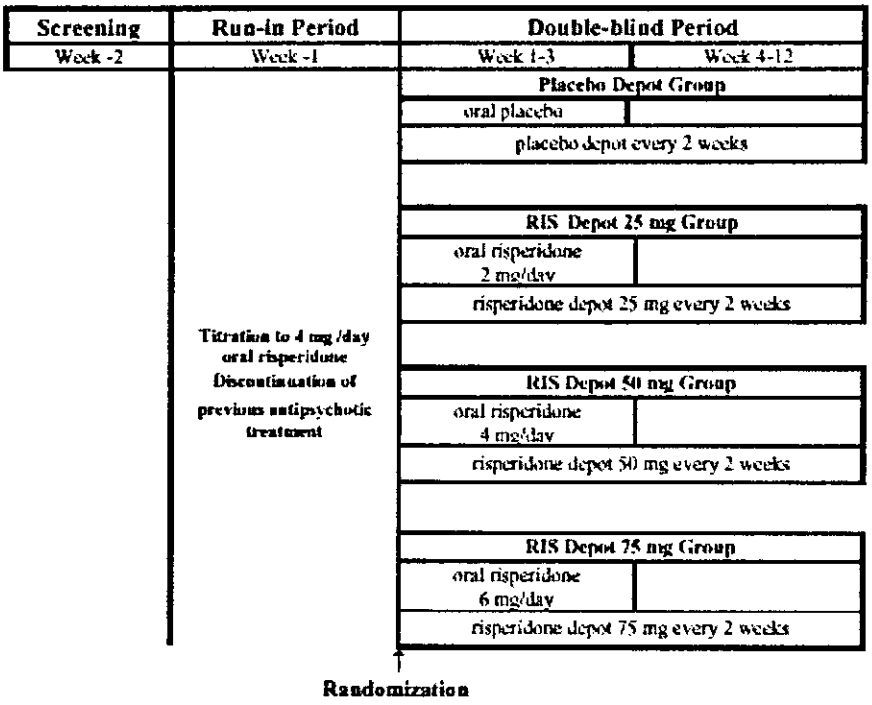
RIS-USA-121

Investigators
Principal Investigator:
Samuel J. Keith, M.D.
Professor and Chairman
Department of Psychiatry
2400 Tucker NE
Albuquerque, NM 87131-5326

This was a multicenter, randomized, double-blind, parallel group trial. In total 416 patients with schizophrenia were to be included, 104 in each treatment group. Subjects were either inpatients or outpatients. Efficacy and safety assessments were performed at baseline and thereafter biweekly (every 2 weeks). For the purposes of this trial, baseline was defined as Day 1/Visit 3, the randomization visit timepoint.

The total trial duration was 14 weeks, consisting of a 1-week screening period, a 1-week period (run-in) during which patients were discontinued from other neuroleptics and started on oral risperidone (up to 4 mg/day) and a 12-week double-blind period during which patients received an injection of placebo, 25, 50, or 75 mg risperidone depot microspheres every 2 weeks. In addition, during the first 3 weeks of double-blind treatment, patients received placebo, 2, 4, or 6 mg of oral risperidone per day.

Figure 1: Trial design



Indication / objectives: Schizophrenia / Primary objective: To compare the efficacy of risperidone depot microspheres 25 mg, 50 mg, or 75 mg with placebo depot on the symptoms of schizophrenia over a 12-week period. The study was powered to demonstrate a statistically significant difference from placebo depot for at least one dose of risperidone depot microspheres on change from baseline to endpoint in total PANSS. Secondary objectives: To document the safety and effects on quality of life of risperidone depot in patients with schizophrenia treated for up to 12 weeks and to assess steady-state plasma concentrations.

Trial design: Multicenter, randomized, double-blind, parallel-group study

Main inclusion criteria:

_ Age between 18 and 55, inclusive;

_ Diagnosis of schizophrenia according to the DSM IV criteria (295.10, 295.20, 295.30, 295.60, 295.90); (amendment on 25 February 2000 after trial start date excluded patients with schizoaffective disorder)

_ Baseline Positive and Negative Syndrome Scale (PANSS) score of _ 60 and _ 120 (1-7 scoring);

_ Patient and, when appointed, patient's guardian or legal representative, had signed the informed consent form;
_ Patient was otherwise healthy on the basis of a pre-trial physical examination, medical history, electrocardiogram and the results of blood biochemistry, hematology tests and a urinalysis performed within a week of the start of the open risperidone run-in period. If the results of the biochemistry or hematology tests or the urinalysis testing were not within the laboratory's reference ranges, the patient could have been included only on condition that the investigator judged that the deviations were not clinically significant. This was clearly recorded in the source documents and in the CRF as a pre-existing condition. A negative urine pregnancy test, if the patient was a female of childbearing potential, prior to the run in phase.

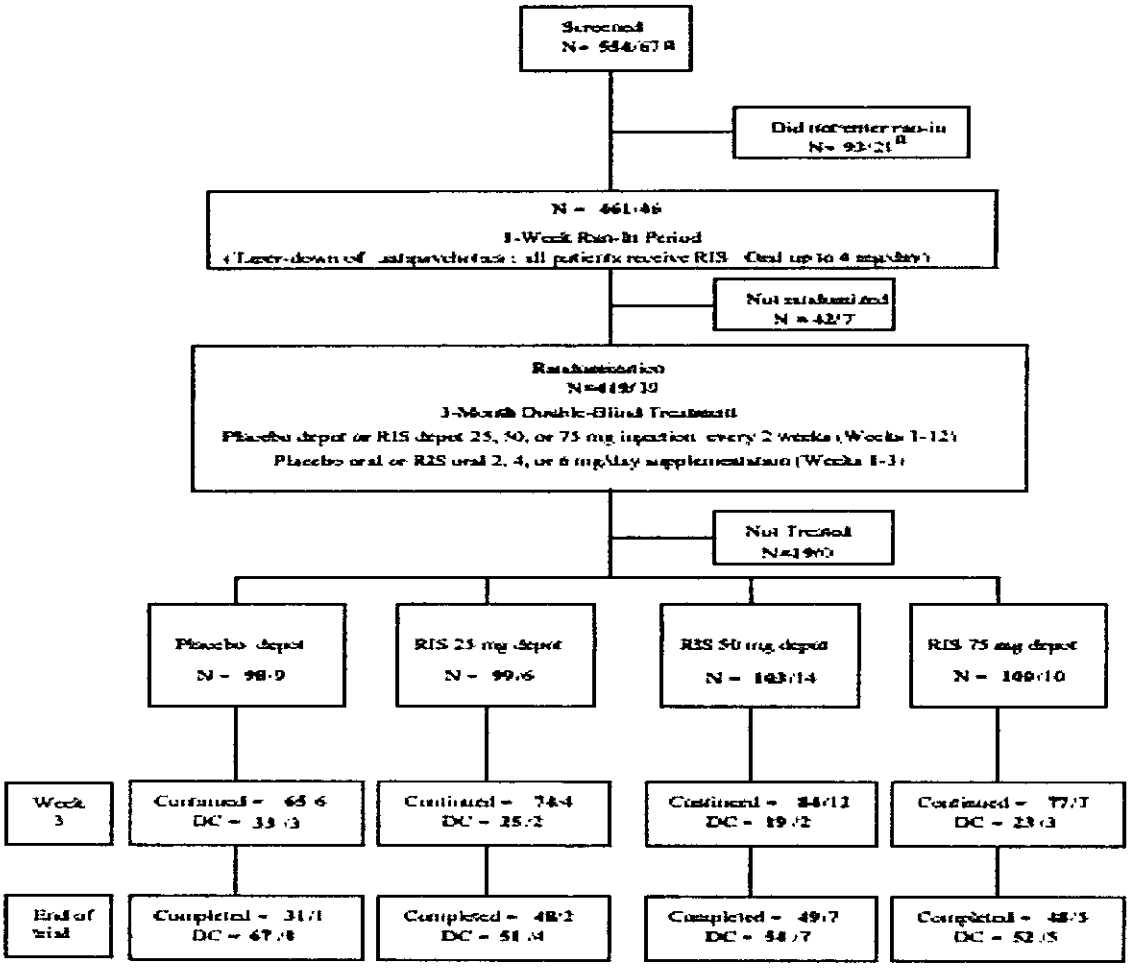
Main exclusion criteria:

_ Patients currently receiving treatment with a depot antipsychotic (last injection within 120 days of screening);
_ A DSM IV Axis I diagnosis other than schizophrenia;
_ DSM IV diagnosis of substance dependence within 3 months prior to the screening visit (Visit 1) was exclusionary, but nicotine and caffeine dependencies were not exclusionary;
_ Tardive dyskinesia, if present, was associated with more than mild symptomatology in the opinion of the investigator.
_ History of neuroleptic malignant syndrome;
_ Documented organic disease of the central nervous system including, but not limited to stroke, tumor, Parkinson's Disease, Alzheimer's Disease, Huntington's Disease, history of brain trauma resulting in significant impairment, chronic infection, neurosyphilis; Acute, unstable and/or significant and untreated medical illness (e.g., infection, unstable diabetes, uncontrolled hypertension, unstable angina);
_Current seizure disorder requiring medication;
_A clinically significant ECG abnormality in the opinion of the investigator;
_Pregnant or breast-feeding female;
_Female patient of childbearing potential without adequate contraception. Adequate contraception included: abstinence, oral contraceptives, intrauterine devices, barrier method (diaphragm or condom) plus spermicide, Norplant™ or Depo Provera™;
_Use of disallowed concomitant therapy;
_Patients who had received new antidepressant drug treatment for depression or who had received different dosages of their current antidepressant drug treatment in the three months preceding the run-in period;
Participation in an investigational drug trial in the 30 days prior to the run-in period;

_Known sensitivity or intolerance to risperidone;
_Patients known to be unresponsive to risperidone;
_Patients known to be refractory to typical neuroleptics;
_History of severe drug allergy or hypersensitivity;
_
Patients at risk for violent behavior against other individuals;
_Patients with current suicidal ideation.

There was a total of 621 patients who entered this trial (Figure 2). A total of 554 were patients with schizophrenia and 67 were patients for whom schizoaffective disorder or no diagnosis was recorded on the CRF page. Of the total of 554 patients with schizophrenia who entered the trial, 461 entered the run-in period. The remaining 93 patients failed screening for the following reasons: subject ineligible to continue (49 patients); subject withdrew consent (31); subject lost to follow-up (8); and other (5) . Sixty-one (61) patients with schizophrenia who entered the run-in period discontinued before entering the double-blind depot treatment period, due to adverse event (8), insufficient response (1), other (5), being ineligible to continue (5), lost to follow-up (8), non-compliance (6), and withdrawal of consent (28). A total of 67 patients with schizoaffective disorder (55) or a missing diagnosis (12) entered the trial. Of these 67 patients, 46 (all with schizoaffective disorder) entered the run-in period and 21 (including the 12 with missing diagnosis) patients failed screening for the following reasons: subject ineligible to continue (13 patients); subject withdrew consent (7); and other (1). Of the 46 patients, 7 discontinued during the run-in period (adverse event in 1 patient, ineligible to continue in 3, lost to follow-up in 1, and withdrawal of consent in 2). The remaining 39 were randomized to double-blind treatment.

Figure 2. Patient disposition



Reasons for discontinuations can be seen in table 10 below.

Table 10: Reasons for discontinuation of trial medication during double-blind: n (%) (patients with schizophrenia)

Trial termination reason	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Discontinued for any reason	67 (68.4%)	51 (51.5%)	53 (51.5%)	52 (52.0%)
Adverse event	12 (12.2%)	11 (11.1%)	12 (11.7%)	14 (14.0%)
Death	1 (1.0%)	0	0	0
Insufficient response	29 (29.6%)	22 (22.2%)	15 (14.6%)	12 (12.0%)
Other	5 (5.1%)	6 (6.1%)	4 (3.9%)	4 (4.0%)
Ineligible to continue the trial	0	3 (3.0%)	3 (2.9%)	2 (2.0%)
Lost to follow-up	6 (6.1%)	2 (2.0%)	3 (2.9%)	6 (6.0%)
Non-compliant	4 (4.1%)	0	3 (2.9%)	3 (3.0%)
Withdrew consent	10 (10.2%)	7 (7.1%)	13 (12.6%)	11 (11.0%)

Source: Table.SUB.7 USA121

One additional RIS depot 50 mg patient terminated the trial due to insufficient response. The termination visit came more than 49 days after the patient's last injection, so this patient does not appear in this table.

In patients with schizophrenia, demographic characteristics were generally balanced among the treatment groups for age, race, and BMI (Table 12). Mean age was approximately 35 to 40 years of age (18-55). Most patients were racially black or white. The mean BMI was 29 with a range of 17-61 among the treatment groups. There was a higher percentage of women in the risperidone depot 25 mg and 75 mg groups than in the placebo depot or risperidone depot 50 mg groups (p=0.025 for overall treatment group comparison. Baseline disease characteristics, concomitant medications and study drug exposure are provided in tables 14,17,18 and 19.

Table 12: Demographic and other baseline characteristics (patients with schizophrenia)

Characteristics	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Sex n (%)				
Female	18 (18.4%)	31 (31.3%)	19 (18.4%)	32 (32.0%)
Male	80 (81.6%)	68 (68.7%)	84 (81.6%)	68 (68.0%)
Age (years)				
Mean (SE)	37.7 (0.95)	38.9 (0.99)	36.2 (0.93)	38.1 (1.06)
Range	18 – 54	18 – 55	19 - 55	18 - 55
Race, n (%)				
Black	37 (37.8%)	41 (41.4%)	40 (38.8%)	49 (49.0%)
Caucasian	45 (45.9%)	37 (37.4%)	45 (43.7%)	39 (39.0%)
Hispanic	12 (12.2%)	13 (13.1%)	11 (10.7%)	9 (9.0%)
Oriental	1 (1.0%)	5 (5.1%)	4 (3.9%)	1 (1.0%)
Other	3 (3.1%)	3 (3.0%)	3 (2.9%)	2 (2.0%)
Body Mass Index (kg/m^2)	n=94	n=99	n=102	n=100
Mean (SE)	27.8 (0.62)	30.2 (0.79)	28.5 (0.63)	29.6 (0.76)
Range	18 – 49	17 – 59	18 - 48	19 – 61
Weight (kg)	n=95	n=99	n=102	n=100
Mean (SE)	83.6 (1.72)	88.4 (2.04)	87.4 (2.17)	88.2 (2.25)
Range	56 –138	54 –159	49 -159	49 – 153
Height (cm)	n=98	n=99	n=102	n=100
Mean (SE)	174.15 (0.945)	171.82 (0.998)	174.71 (0.925)	172.9 (0.98)
Range	152.4 – 195.6	144.8 - 195.6	149.9 - 198.1	147.3 - 193

Source: Table SUB.11 USA121

Table 14: Baseline disease characteristics (patients with schizophrenia)

Characteristics	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Schizophrenia type				
Catatonic (295.2)	0	0	1 (1.0%)	0
Disorganized (295.1)	2 (2.0%)	2 (2.0%)	6 (5.8%)	3 (3.0%)
Paranoid (295.3)	78 (79.6%)	76 (76.8%)	74 (71.8%)	74 (74.0%)
Undifferentiated (295.9)	18 (18.4%)	21 (21.2%)	22 (21.4%)	23 (23.0%)
Age at onset,	n=91	n=97	n=100	n=97
Mean (SE);	22.0 (0.66)	22.8 (0.76)	21.4 (0.7)	20.3 (0.63)
Range	(9-42)	(8-44)	(7-42)	(9-43)
Age at first hospitalization,	n=89	n=91	n=94	n=94
Mean (SE);	24.4 (0.8)	25.1 (0.93)	23.3 (0.79)	23.2 (0.91)
Range	(14-47)	(0-47)	(8-45)	(0-50)
Number of previous hospitalizations	n=89	n=96	n=101	n=94
Median (range)	4 (0-28)	3.5 (0-99)	4 (0-50)	4 (0-63)

Source: Table SUB.13 USA121

Table 17: ATC classes for concomitant medications in ≥10% of patients in any group during run-in: n (%) (patients with schizophrenia)

ATC class	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Any concomitant therapy	83 (84.7%)	88 (88.9%)	92 (89.3%)	92 (92.0%)
Analgesics	25 (25.5%)	29 (29.3%)	22 (21.4%)	26 (26.0%)
Antacids, drugs for treatm.of pept.ulc.and flatul.	14 (14.3%)	16 (16.2%)	15 (14.6%)	19 (19.0%)
Anti-Parkinson drugs	18 (18.4%)	29 (29.3%)	29 (28.2%)	20 (20.0%)
Antiepileptics[a]	15 (15.3%)	13 (13.1%)	13 (12.6%)	11 (11.0%)
Antihistamines for systemic use	8 (8.2%)	10 (10.1%)	4 (3.9%)	7 (7.0%)
Antiinflammatory and antirheumatic products	6 (6.1%)	10 (10.1%)	7 (6.8%)	8 (8.0%)
Laxatives	3 (3.1%)	10 (10.1%)	7 (6.8%)	9 (9.0%)
Psychoanaleptics	14 (14.3%)	22 (22.2%)	24 (23.3%)	23 (23.0%)
Psycholeptics	80 (81.6%)	80 (80.8%)	87 (84.5%)	80 (80.0%)
Stomatological preparations	11 (11.2%)	9 (9.1%)	6 (5.8%)	7 (7.0%)
Vitamins	11 (11.2%)	14 (14.1%)	10 (9.7%)	19 (19.0%)

Source: Table SUB.16 USA121

a: Concomitant medication included in the antiepileptic ATC class included: carbamazepine, clonazepam, gabapentin, and valproate. These medications could have been used in the treatment of non-epileptic conditions and may not reflect the occurrence of epilepsy in patients in this trial.

One patient may have taken concomitant medication from more than one class. Table is ordered alphabetically by ATC class. A medication may have been assigned to multiple classes based on its possible rather than actual clinical use.

Table 18: ATC classes for concomitant medications in ≥10% of patients in any group during double-blind treatment: n (%) (patients with schizophrenia)

ATC class	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Any concomitant therapy	80 (81.6%)	84 (84.8%)	89 (86.4%)	88 (88.0%)
Analgesics	30 (30.6%)	36 (36.4%)	34 (33.0%)	34 (34.0%)
Antacids, peptic ulcer and flatulance medication	13 (13.3%)	17 (17.2%)	16 (15.5%)	22 (22.0%)
Anti-Parkinson drugs	13 (13.3%)	12 (12.1%)	24 (23.3%)	23 (23.0%)
Antibacterials for systemic use	3 (3.1%)	8 (8.1%)	7 (6.8%)	13 (13.0%)
Antihistamines for systemic use	3 (3.1%)	6 (6.1%)	14 (13.6%)	8 (8.0%)
Antiinflammatory and antirheumatic products	10 (10.2%)	14 (14.1%)	10 (9.7%)	18 (18.0%)
Antipruritics including antihistamine, anesthetic	4 (4.1%)	3 (3.0%)	13 (12.6%)	6 (6.0%)
Beta blocking agents	3 (3.1%)	5 (5.1%)	3 (2.9%)	10 (10.0%)
Cough and cold preparations	2 (2.0%)	6 (6.1%)	2 (1.9%)	10 (10.0%)
Laxatives	4 (4.1%)	11 (11.1%)	8 (7.8%)	14 (14.0%)
Ophthalmologicals	8 (8.2%)	7 (7.1%)	6 (5.8%)	13 (13.0%)
Other gynecologicals	10 (10.2%)	13 (13.1%)	9 (8.7%)	14 (14.0%)
Psychoanaleptics	12 (12.2%)	15 (15.2%)	18 (17.5%)	20 (20.0%)
Psycholeptics	50 (51.0%)	43 (43.4%)	46 (44.7%)	57 (57.0%)
Stomatological preparations	14 (14.3%)	11 (11.1%)	9 (8.7%)	13 (13.0%)
Topical products for joint and muscular pain	10 (10.2%)	13 (13.1%)	9 (8.7%)	14 (14.0%)
Vitamins	14 (14.3%)	15 (15.2%)	10 (9.7%)	20 (20.0%)

Source: Table SUB.17 USA121

One patient may have taken concomitant medication from more than one class. Table is ordered alphabetically by ATC class. A medication may have been assigned to multiple classes based on its possible rather than actual clinical use.

Table 19: Exposure to trial medication during double-blind treatment – all randomized with injection: n(%) (patients with schizophrenia)

Exposure	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Number of depot injections				
1	30 (30.6%)	21 (21.2%)	18 (17.5%)	21 (21.0%)
2	14 (14.3%)	13 (13.1%)	14 (13.6%)	13 (13.0%)
3	6 (6.1%)	8 (8.1%)	10 (9.7%)	8 (8.0%)
4	9 (9.2%)	6 (6.1%)	11 (10.7%)	8 (8.0%)
5	6 (6.1%)	0	0	1 (1.0%)
6	33 (33.7%)	51 (51.5%)	50 (48.5%)	49 (49.0%)
Oral exposure duration[a] (days)				
1-13	23 (23.5%)	14 (14.1%)	15 (14.6%)	15 (15.0%)
14-27	75 (76.5%)	83 (83.8%)	87 (84.5%)	82 (82.0%)
28-41	0	2 (2.0%)	1 (1.0%)	3 (3.0%)

Source: Table SUB.18 and 21 USA121

a: Oral treatment during the supplementation period was placebo, 2 mg, 4 mg, and 6 mg for the placebo depot, RIS depot 25 mg, 50 mg, and 75 mg groups.

DOSE TIMING

From the second injection on, injections were administered within the protocol-specified three-day window (i.e., within 11 to 17 days since the previous injection) for at least 92% of the patients in each group. Average time between injections was less than 11 days for one risperidone depot 50 mg patient and more than 17 days for two risperidone depot 50 mg patients (Table 20).

Table 20: The time between injections: n(%) (patients with schizophrenia)

Average time between injections (days)	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Number with ≥2 injections	68	78	85	79
<11	0	0	1 (1.2%)	0
11-17	68 (100.0%)	78 (100.0%)	82 (96.5%)	79 (100.0%)
>17	0	0	2 (2.4%)	0
Mean (SE) (days)	14.08 (0.077)	14.06 (0.085)	14.2 (0.154)	14.05 (0.081)

Source: Table SUB.20 USA121

Plasma concentrations are steady from day 8 and are listed below in table 21.

Table 21: Plasma concentrations of active moiety (ng/mL; mean ± SD) at each timepoint and for each treatment group and dose level

Visit (Day) Treatment	3 (1)	4 (8)	5(15)	6 (22)	7 (29)	8 (33)	10 (43)	12 (57)	13 (61)	15 (71)	17/EP (85)
Placebo depot - N	102	91	70	66	56	52	50	36	34	33	30
Active moiety	25.3±19.3	2.08±6.46	1.04±2.82	0.40±0.98	0.15±0.30	0.10±0.19	1.75±8.19	0.44±1.95	0.17±0.56	0.04±0.14	2.84±8.93
25 mg depot - N	100	86	79	73	64	63	58	53	49	48	45
Active moiety	28.7±21.1	20.9±14.7	21.5±20.0	22.4±18.6	11.7±7.66	17.1±8.83	18.1±11.5	17.5±8.81	20.6±11.9	17.0±8.34	18.7±9.23
50 mg depot - N	114	102	93	89	78	70	67	58	56	55	45
Active moiety	28.6±24.5	34.1±24.3	30.3±21.1	35.2±23.1	25.3±15.0	39.8±25.0	33.5±18.4	37.0±19.8	37.9±24.0	34.0±19.1	35.5±18.7
75 mg depot - N	104	92	82	75	72	69	63	54	54	53	47
Active moiety	27.1±20.7	49.0±35.1	55.3±44.6	63.3±42.0	34.9±16.9	56.5±25.8	48.6±27.1	46.9±25.1	56.3±28.3	47.5±22.7	44.7±20.6

Source: Table PK.1 USA121

Of the 102 subjects treated with placebo depot who had pharmacokinetic blood draws, only 5 subjects exhibited drug levels greater than 1 ng/mL during any one of the depot injection visits (Visit 6-15).

Mean and SD values may not match Table PK.1 due rounding were rounded. If 5 was in the second decimal place the value was rounded up.

Efficacy

The primary analysis was of the change from baseline in total PANSS at endpoint. These results are summarized in Table 22. The change in each risperidone depot group was significantly better than in the placebo group (p _ 0.002). Mean change from baseline was numerically the best in the risperidone depot 50 mg group (average improvement of 8.7 points), followed by the risperidone depot 25 mg and risperidone depot 75 mg groups.

Table 22: Total PANSS score – mean and mean change from baseline at endpoint (patients with schizophrenia)

	Placebo depot		RIS depot 25 mg		RIS depot 50 mg		RIS depot 75 mg	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Baseline	92	82.0 (1.54)	93	81.7 (1.32)	98	82.3 (1.41)	87	80.1 (1.53)
Endpoint	92	84.5 (2.12)	93	75.6 (2.35)	98	73.6 (2.03)	87	74.5 (2.31)
Change from baseline to endpoint: Mean Least squares mean	92	2.5 (1.73) 2.6	93	-6.1 (2.08) -6.2	98	-8.7 (1.55) -8.5	87	-5.6 (1.88) -7.4
Between-group diff on LS means (RIS - Placebo) and 95% CI				-8.8 (-14.9, -2.7)		-11.1 (-17.1, -5.1)		-10.0 (-16.2, -3.8)
p-value[a] (comparison with placebo on change)				0.002		<0.001		<0.001

Source: Tables PANSS.1, PANSS.4 USA121

a: ANCOVA model including treatment, investigator, baseline value. Pairwise comparisons of least squares means by Dunnett's test.

Positive and Negative symptoms were significant also in table 23.

Table 23: PANSS Positive and Negative Symptoms subscales - mean and mean change from baseline at endpoint (patients with schizophrenia)

	Placebo depot		RIS depot 25 mg		RIS depot 50 mg		RIS depot 75 mg	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Positive symptoms								
Baseline	92	24.5 (0.57)	93	25.2 (0.53)	98	24.9 (0.55)	87	24.5 (0.65)
Endpoint	92	24.8 (0.79)	93	23.0 (0.81)	98	21.6 (0.66)	87	22.5 (0.85)
Change from baseline to endpoint: Mean Least squares mean	92	0.3 (0.65) -0.2	93	-2.2 (0.67) -2.3	98	-3.4 (0.51) -3.5	87	-2.0 (0.67) -3.0
Betw-group diff on LS means (RIS - Placebo) and 95% CI				-2.1 (-4.2, -0.03)		-3.4 (-5.4, -1.3)		-2.9 (-5.0, -0.7)
p-value[a] (comparison with placebo on change)				0.046		<0.001		0.005
Negative symptoms								
Baseline	92	20.0 (0.63)	93	20.2 (0.59)	98	20.1 (0.62)	87	19.0 (0.51)
Endpoint	92	20.5 (0.62)	93	17.4 (0.67)	98	18.5 (0.66)	87	17.9 (0.63)
Change from baseline to endpoint: Mean Least squares mean	92	0.4 (0.44) 0.9	93	-2.8 (0.62) -2.4	98	-1.5 (0.56) -1.2	87	-1.1 (0.60) -1.2
Betw-group diff on LS means (RIS - Placebo) and 95% CI				-3.3 (-5.0, -1.6)		-2.1 (-3.8, -0.4)		-2.0 (-3.8, -0.3)
p-value[a] (comparison with placebo on change)				<0.001		0.011		0.018

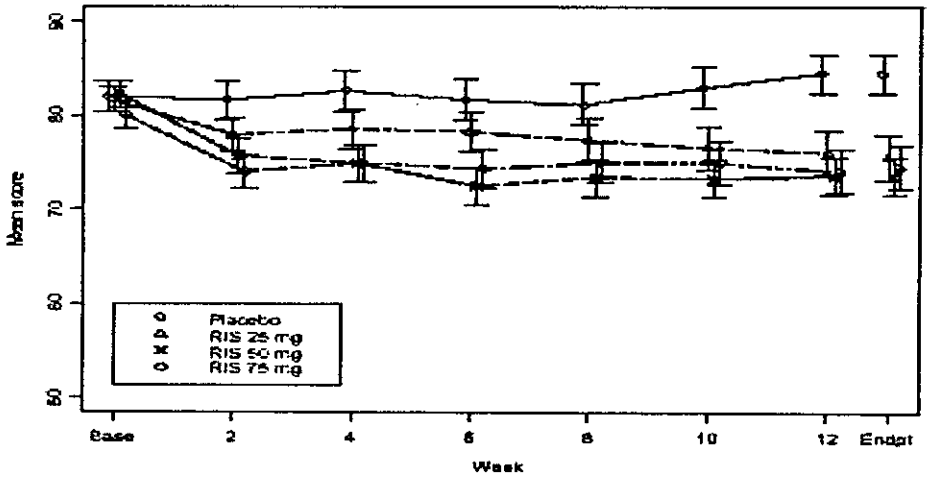
Source: Table PANSS.1 and PANSS.4 USA121

A: ANCOVA model including treatment, investigator, baseline value. Pairwise comparisons of least squares means by Dunnett's test.

PANSS assessments were scheduled for every two weeks. Total PANSS by treatment group over time is plotted in Figure 5.

Figure 5: **Total PANSS score over time– mean (±SE) (patients with schizophrenia)**

LOCF



Observed case

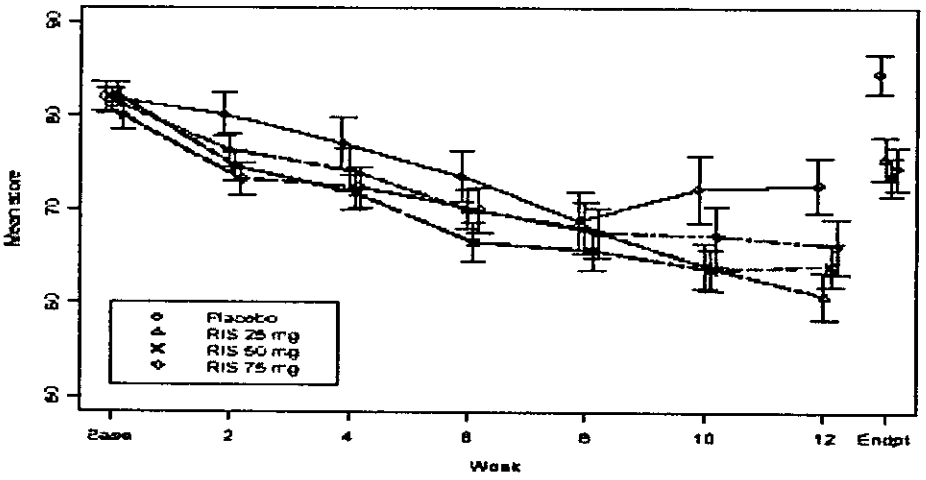


Table 26: Clinical Global Impression (CGI)-mean and mean change from baseline at endpoint (patients with schizophrenia)

	Placebo depot		RIS depot 25 mg		RIS depot 50 mg		RIS depot 75 mg	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Baseline	91	3.1 (0.08)	93	3.1 (0.08)	96	3.1 (0.07)	87	3.1 (0.10)
Endpoint	91	3.3 (0.12)	93	2.8 (0.12)	96	2.7 (0.10)	87	2.7 (0.12)
Change from baseline to endpoint	91	0.2 (0.11)	93	-0.3 (0.09)	96	-0.3 (0.08)	87	-0.3 (0.11)
p-value[a] (comparison with placebo on change)				<0.001		<0.001		<0.001

Source: Table CGI.3 USA121

a ANCOVA model including treatment, investigator, baseline value and PANSS stratification (IVRS). Pairwise comparisons of least squares means by Dunnett's test.

The change (table 26) in each risperidone depot group at endpoint was significantly better than in the placebo group ($p<0.001$). In an LOCF analysis by timepoint, change from baseline in the risperidone depot 50 mg and 75 mg groups was significantly better than the placebo group at every timepoint from Week 2 to Week 12 ($p \_ 0.035$. Change in the risperidone depot 25 mg group was significantly better than the placebo group at every timepoint ($p \_ 0.028$) except Weeks 5, 7, and 8 ($p \_ 0.11$).

D. Efficacy Conclusions

Risperidone depot microspheres appear to be effective in the treatment of patients with schizophrenia over a dose range of 25, 50 and 75 mg when administered every 2 weeks as IM injections. Efficacy was demonstrated by the significantly improved total PANSS score for all risperidone dose groups when compared to placebo depot treatment. In addition to the primary efficacy parameter, the effect was also shown in all secondary efficacy parameters: positive and negative PANSS subscales, percent of clinical improvement in total PANSS score, CGI, and CGI-C that were significantly improved with risperidone depot when compared to placebo. The change from baseline in total PANSS at endpoint with risperidone depot 75 mg was not superior to that of the 50-mg group when compared with placebo.

Safety for RIS-USA-121

I will include the safety review of this trial at this point in the review because it is the only double-blind placebo controlled trial available to compare study drug against placebo for safety events. Deaths, SAEs and adverse events leading to dropout will be summarized in the safety update section for the entire database.

Adverse events for RIS-USS-121

During the double-blind period, there were no differences in the overall incidence of adverse events reported by patients with schizophrenia across groups [81 (82.7%), 79 (79.8%), 86 (83.5%), and 82 (82.0%) placebo depot group, and risperidone depot 25 mg, 50 mg, or 75 mg treatment] (see Table 35 below). The most frequently reported adverse events occurring in greater than 5% of patients with schizophrenia in any group were in the psychiatric disorders, central and peripheral nervous system disorders, gastrointestinal disorders, body as a whole disorders, respiratory system disorders, metabolic and nutritional disorders, and heart rate and rhythm disorders system-organ classes (Table 35).

For psychiatric disorders and heart rate and rhythm disorders class, the incidence of adverse events was higher in the placebo depot group than the risperidone depot groups. Adverse events that occurred in at least 15% of patients were in the psychiatric disorders class (agitation, insomnia, anxiety, and psychosis (Table 35). For the events of agitation, insomnia, and anxiety, there was no consistent pattern of occurrence among treatment groups. Somnolence and the related adverse event of fatigue were reported in a higher percentage of patients in all risperidone treatment groups compared with placebo.

For central and peripheral nervous system disorders, the overall incidence of adverse events was higher in the risperidone 50 mg and 75 mg groups (Table 35). In particular, extrapyramidal disorder, hyperkinesia, hypertonia, headache, and dizziness occurred in a higher percentage of patients treated in at least one risperidone depot group compared with placebo depot.

For gastrointestinal disorders, the incidence was higher overall in the risperidone depot treatment group and included adverse events that occurred in > 5% of patients (dyspepsia and constipation) (Table 35). For the other adverse events, there was no apparent pattern between groups.

For the remaining body classes (body as a whole, respiratory system, and metabolic and nutritional disorders), there were no apparent between-group patterns except for weight increase that occurred in a higher percentage of patients with risperidone depot treatment than with placebo (Table 35).

Table 35: Treatment-emergent adverse events in ≥5% of patients in any treatment group during the double-blind period: n (%) (patients with schizophrenia)

WHO system-organ class WHO-preferred term	Placebo depot N = 98	RIS depot 25 mg N = 99	RIS depot 50 mg N = 103	RIS depot 75 mg N = 100
Any adverse event	81 (82.7%)	79 (79.8%)	86 (83.5%)	82 (82.0%)
Psychiatric disorders	*59 (60.2%)*	*52 (52.5%)*	*44 (42.7%)*	*51 (51.0%)*
Agitation	24 (24.5%)	15 (15.2%)	11 (10.7%)	20 (20.0%)
Insomnia	14 (14.3%)	16 (16.2%)	13 (12.6%)	16 (16.0%)
Anxiety	15 (15.3%)	7 (7.1%)	6 (5.8%)	14 (14.0%)
Psychosis	23 (23.5%)	15 (15.2%)	10 (9.7%)	12 (12.0%)
Somnolence	3 (3.1%)	5 (5.1%)	6 (5.8%)	10 (10.0%)
Hallucination	5 (5.1%)	7 (7.1%)	6 (5.8%)	5 (5.0%)
Nervousness	5 (5.1%)	2 (2.0%)	2 (1.9%)	2 (2.0%)
Central & peripheral nervous system disorders	*28 (28.6%)*	*28 (28.3%)*	*52 (50.5%)*	*49 (49.0%)*
Headache	12 (12.2%)	15 (15.2%)	23 (22.3%)	21 (21.0%)
Extrapyramidal disorder	3 (3.1%)	4 (4.0%)	8 (7.8%)	10 (10.0%)
Hyperkinesia	4 (4.1%)	2 (2.0%)	9 (8.7%)	10 (10.0%)
Hypertonia	5 (5.1%)	4 (4.0%)	5 (4.9%)	10 (10.0%)
Dizziness	6 (6.1%)	8 (8.1%)	11 (10.7%)	8 (8.0%)
Gastro-intestinal system disorders	*14 (14.3%)*	*31 (31.3%)*	*33 (32.0%)*	*29 (29.0%)*
Dyspepsia	2 (2.0%)	7 (7.1%)	7 (6.8%)	9 (9.0%)
Nausea	5 (5.1%)	3 (3.0%)	4 (3.9%)	9 (9.0%)
Constipation	1 (1.0%)	5 (5.1%)	7 (6.8%)	7 (7.0%)
Vomiting	6 (6.1%)	4 (4.0%)	3 (2.9%)	4 (4.0%)
Diarrhea	3 (3.1%)	5 (5.1%)	1 (1.0%)	2 (2.0%)
Mouth dry	1 (1.0%)	0	7 (6.8%)	2 (2.0%)
Saliva increased	1 (1.0%)	6 (6.1%)	2 (1.9%)	1 (1.0%)
Body as a whole - general disorders	*18 (18.4%)*	*20 (20.2%)*	*23 (22.3%)*	*18 (18.0%)*
Pain	4 (4.1%)	10 (10.1%)	3 (2.9%)	4 (4.0%)
Fatigue	0	3 (3.0%)	7 (6.8%)	3 (3.0%)
Injury	6 (6.1%)	0	2 (1.9%)	3 (3.0%)
Respiratory system disorders	*14 (14.3%)*	*22 (22.2%)*	*9 (8.7%)*	*18 (18.0%)*
Rhinitis	8 (8.2%)	14 (14.1%)	4 (3.9%)	7 (7.0%)
Coughing	4 (4.1%)	5 (5.1%)	2 (1.9%)	5 (5.0%)
Metabolic and nutritional disorders	*5 (5.1%)*	*10 (10.1%)*	*7 (6.8%)*	*6 (6.0%)*
Weight increase	2 (2.0%)	5 (5.1%)	4 (3.9%)	4 (4.0%)
Heart rate and rhythm disorders	*12 (12.2%)*	*3 (3.0%)*	*6 (5.8%)*	*2 (2.0%)*
Tachycardia	6 (6.1%)	1 (1.0%)	4 (3.9%)	1 (1.0%)

Source: Table AE.3.1USA121

Patients may have had more than one adverse event.

Adverse events reported any time during treatment or within 49 days of end of treatment were included.

Incidence was based on the number of patients, not the number of events.

Table 36: Treatment emergent adverse events during the first 3 weeks of the double-blind period in ≥5% of patients in any treatment group: n (%) (patients with schizophrenia)

WHO system-organ class WHO-preferred term	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Any adverse event	61 (62.2%)	57 (57.6%)	72 (69.9%)	66 (66.0%)
Psychiatric disorders	*43 (43.9%)*	*37 (37.4%)*	*34 (33.0%)*	*36 (36.0%)*
Agitation	19 (19.4%)	9 (9.1%)	7 (6.8%)	14 (14.0%)
Insomnia	10 (10.2%)	10 (10.1%)	10 (9.7%)	11 (11.0%)
Anxiety	11 (11.2%)	4 (4.0%)	5 (4.9%)	8 (8.0%)
Psychosis	15 (15.3%)	13 (13.1%)	7 (6.8%)	7 (7.0%)
Central & peripheral nervous system disorders	*18 (18.4%)*	*22 (22.2%)*	*39 (37.9%)*	*32 (32.0%)*
Headache	6 (6.1%)	12 (12.1%)	17 (16.5%)	11 (11.0%)
Hypertonia	5 (5.1%)	2 (2.0%)	3 (2.9%)	8 (8.0%)
Hyperkinesia	2 (2.0%)	1 (1.0%)	9 (8.7%)	7 (7.0%)
Dizziness	3 (3.1%)	4 (4.0%)	6 (5.8%)	6 (6.0%)
Extrapyramidal disorder	2 (2.0%)	4 (4.0%)	4 (3.9%)	6 (6.0%)
Gastro-intestinal system disorders	*11 (11.2%)*	*18 (18.2%)*	*20 (19.4%)*	*19 (19.0%)*
Dyspepsia	2 (2.0%)	5 (5.1%)	7 (6.8%)	8 (8.0%)
Constipation	1 (1.0%)	4 (4.0%)	5 (4.9%)	6 (6.0%)
Nausea	4 (4.1%)	3 (3.0%)	2 (1.9%)	5 (5.0%)
Respiratory system disorders	*6 (6.1%)*	*9 (9.1%)*	*3 (2.9%)*	*12 (12.0%)*
Rhinitis	4 (4.1%)	7 (7.1%)	1 (1.0%)	4 (4.0%)
Body as a whole - general disorders	*11 (11.2%)*	*13 (13.1%)*	*10 (9.7%)*	*8 (8.0%)*
Injury	5 (5.1%)	0	0	2 (2.0%)
Pain	2 (2.0%)	7 (7.1%)	2 (1.9%)	2 (2.0%)

Source: Table AE.2.1USA121

Patients may have had more than one adverse event.

Adverse events reported any time during treatment or within 49 days of end of treatment were included.

Incidence was based on the number of patients, not the number of events.

Table 37: Treatment-emergent adverse events during Weeks 4-12 of the double-blind period in ≥5% of patients in any treatment group: n (%) (patients with schizophrenia)

WHO system-organ class WHO-preferred term	Placebo depot (N = 54)	RIS depot 25 mg (N = 65)	RIS depot 50 mg (N = 71)	RIS depot 75 mg (N = 66)
Any adverse event	43 (79.6%)	45 (69.2%)	49 (69.0%)	51 (77.3%)
Central & peripheral nervous system disorders	*15 (27.8%)*	*9 (13.8%)*	*21 (29.6%)*	*27 (40.9%)*
Headache	7 (13.0%)	4 (6.2%)	6 (8.5%)	12 (18.2%)
Hyperkinesia	2 (3.7%)	1 (1.5%)	1 (1.4%)	5 (7.6%)
Extrapyramidal disorder	1 (1.9%)	0	4 (5.6%)	4 (6.1%)
Dizziness	3 (5.6%)	4 (6.2%)	6 (8.5%)	3 (4.5%)
Psychiatric disorders	*21 (38.9%)*	*18 (27.7%)*	*17 (23.9%)*	*27 (40.9%)*
Agitation	6 (11.1%)	7 (10.8%)	4 (5.6%)	8 (12.1%)
Anxiety	4 (7.4%)	3 (4.6%)	1 (1.4%)	7 (10.6%)
Somnolence	1 (1.9%)	2 (3.1%)	2 (2.8%)	7 (10.6%)
Insomnia	4 (7.4%)	6 (9.2%)	4 (5.6%)	5 (7.6%)
Psychosis	8 (14.8%)	2 (3.1%)	3 (4.2%)	5 (7.6%)
Body as a whole - general disorders	*8 (14.8%)*	*9 (13.8%)*	*16 (22.5%)*	*11 (16.7%)*
Fatigue	0	2 (3.1%)	6 (8.5%)	3 (4.5%)
Gastro-intestinal system disorders	*4 (7.4%)*	*15 (23.1%)*	*14 (19.7%)*	*11 (16.7%)*
Nausea	2 (3.7%)	0	2 (2.8%)	4 (6.1%)
Diarrhoea	0	4 (6.2%)	1 (1.4%)	1 (1.5%)
Respiratory system disorders	*9 (16.7%)*	*15 (23.1%)*	*7 (9.9%)*	*8 (12.1%)*
Rhinitis	5 (9.3%)	8 (12.3%)	3 (4.2%)	3 (4.5%)
Heart rate and rhythm disorders	*7 (13.0%)*	*2 (3.1%)*	*4 (5.6%)*	*1 (1.5%)*
Tachycardia	5 (9.3%)	1 (1.5%)	3 (4.2%)	0

Source: Table AE.2 USA121
Patients may have had more than one adverse event.
Adverse events reported any time during treatment or within 49 days of end of treatment were included.
Incidence was based on the number of patients, not the number of events.

DEATHS, SERIOUS ADVERSE EVENTS, AND ADVERSE EVENTS LEADING TO DISCONTINUATION

The percent of patients with schizophrenia experiencing serious adverse events during double-blind was lower with risperidone depot [(13 (13.1%), 14 (13.6%), and 15 (15.0%)] than with placebo depot treatment (23 patients;23.5%). There was no difference among the three risperidone treatment groups for the overall incidence of serious adverse events (Table 38) during the double-blind period. There was also no difference among treatment groups in patients with schizophrenia for the incidence of treatment-emergent adverse events with discontinuation during the double-blind period (Table 38).

The safety profiles and clinical narratives for patients who died, had serious adverse events, or had adverse events leading to discontinuation have been reviewed and revealed no unusual pattern or events.

Table 38: Incidence of deaths, serious adverse events, and adverse events leading to discontinuation during the double-blind period: n (%) (patients with schizophrenia)

Event	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Deaths	1	0	0	0
Serious adverse events	23 (23.5%)	13 (13.1%)	14 (13.6%)	15 (15.0%)
Treatment-emergent adverse events leading to discontinuation	13 (13.3%)	10 (10.1%)	12 (11.7%)	12 (12.0%)

Source: Table AE.14A, 6B and Table SUB.7 USA121
Patients can be included in more than one category.

During the double-blind period, there was a higher incidence of any serious adverse event in patients with schizophrenia in the placebo depot group (23 patients, 23.5%), than with risperidone depot [13 (13.1%), 14 (13.6%), and 15 (15.0%) risperidone depot 25 mg, 50 mg, or 75 mg, respectively] (Table 39). The serious adverse events were in the psychiatric disorders, body as a whole, gastrointestinal disorders, and central and peripheral nervous systems disorders. The most frequently reported serious adverse events were psychosis, hallucination, agitation, suicide attempts, and anxiety. Except for psychosis in which the highest percentage of patients were in the placebo depot groups, there were no patterns in the reporting of the remaining serious adverse events.

Table 39: Incidence of serious treatment-emergent adverse events during the double-blind period: n (%) (patients with schizophrenia)

WHO system-organ class WHO-preferred term	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Any serious adverse event	23 (23.5%)	13 (13.1%)	14 (13.6%)	15 (15.0%)
Psychiatric disorders	*22 (22.4%)*	*13 (13.1%)*	*14 (13.6%)*	*14 (14.0%)*
Psychosis	17 (17.3%)	10 (10.1%)	8 (7.8%)	8 (8.0%)
Hallucination	2 (2.0%)	1 (1.0%)	4 (3.9%)	3 (3.0%)
Agitation	2 (2.0%)	2 (2.0%)	2 (1.9%)	2 (2.0%)
Suicide attempt[a]	2 (2.0%)	1 (1.0%)	4 (3.9%)	2 (2.0%)
Aggressive reaction	0	1 (1.0%)	0	1 (1.0%)
Delusion	0	0	1 (1.0%)	1 (1.0%)
Depression	0	0	0	1 (1.0%)
Anxiety	4 (4.1%)	0	1 (1.0%)	0
Apathy	1 (1.0%)	0	0	0
Insomnia	2 (2.0%)	1 (1.0%)	1 (1.0%)	0
Paranoid reaction	2 (2.0%)	0	2 (1.9%)	0
Body as a whole - general disorders	*1 (1.0%)*	*0*	*0*	*1 (1.0%)*
Injury	1 (1.0%)	0	0	1 (1.0%)
Gastro-intestinal system disorders	*0*	*0*	*0*	*1 (1.0%)*
Appendicitis	0	0	0	1 (1.0%)
Centr & periph nervous system disorders	*1 (1.0%)*	*0*	*1 (1.0%)*	*0*
Convulsions	1 (1.0%)	0	0	0
Dementia	0	0	1 (1.0%)	0

Source: Table AE.14A USA121

a: The adverse event of suicide attempt were thought or ideations and not actual attempts.

There were no between-group differences in the incidence of treatment-emergent adverse events that led to discontinuations during the double-blind period in patients with schizophrenia (Table 40). There were few adverse events leading to discontinuation in any organ class other than psychiatric disorders: 13 patients (13.3%), 10 (10.1%), 12 (11.7%), and 12 (12.0%) in the placebo depot, risperidone depot 25 mg, 50 mg, or 75 mg treatment groups, respectively. The most frequently reported adverse event was psychosis: 7 (7.1%), 5 (5.1%), 3 (2.9%), and 2 (2.0%) in the placebo depot, risperidone depot 25 mg, 50 mg, or 75 mg, respectively. All other adverse events were experienced by three or fewer patients in any group. Discontinuation due to psychosis was greater in the placebo and risperidone depot 25 mg groups than with 50 mg and 75 mg. Also, there was a higher incidence of discontinuations due to EPS-related adverse events with risperidone 50 mg and 75 mg than placebo and 25 mg.

Table 40: Incidence of treatment-emergent adverse events leading to discontinuations during the double-blind period: n (%) (patients with schizophrenia)

WHO system-organ class WHO-preferred term	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Any adverse event	13 (13.3%)	10 (10.1%)	12 (11.7%)	12 (12.0%)
Psychiatric disorders	*11 (11.2%)*	*9 (9.1%)*	*8 (7.8%)*	*8 (8.0%)*
Hallucination	1 (1.0%)	2 (2.0%)	2 (1.9%)	2 (2.0%)
Psychosis	7 (7.1%)	5 (5.1%)	3 (2.9%)	2 (2.0%)
Agitation	2 (2.0%)	2 (2.0%)	1 (1.0%)	1 (1.0%)
Anxiety	1 (1.0%)	0	2 (1.9%)	1 (1.0%)
Delusion	0	0	0	1 (1.0%)
Depression	1 (1.0%)	0	0	1 (1.0%)
Nervousness	1 (1.0%)	0	0	1 (1.0%)
Somnolence	0	0	0	1 (1.0%)
Suicide attempt	1 (1.0%)	0	3 (2.9%)	1 (1.0%)
Depression aggravated	0	0	1 (1.0%)	0
Thinking abnormal	0	0	1 (1.0%)	0
Centr & periph nervous system disorders	*1 (1.0%)*	*0*	*3 (2.9%)*	*5 (5.0%)*
Hyperkinesia	1 (1.0%)	0	2 (1.9%)	3 (3.0%)
Extrapyramidal disorder	0	0	1 (1.0%)	2 (2.0%)
Hypertonia	0	0	0	1 (1.0%)
Hypokinesia	0	0	0	1 (1.0%)
Dystonia	1 (1.0%)	0	0	0
Body as a whole - general disorders	*1 (1.0%)*	*0*	*1 (1.0%)*	*0*
Asthenia	0	0	1 (1.0%)	0
Injury	1 (1.0%)	0	0	0
Reproductive disorders, male	*0*	*1 (1.0%)*	*0*	*0*
Sexual function abnormal	0	1 (1.0%)	0	0
Respiratory system disorders	*1 (1.0%)*	*0*	*0*	*0*
Dyspnoea	1 (1.0%)	0	0	0
Secondary terms	*1 (1.0%)*	*0*	*0*	*0*
Inflicted injury	1 (1.0%)	0	0	0

Source: Table AE.6B USA121

Extrapyramidal symptom-related adverse events

In patients with schizophrenia, the overall incidence of EPS-related adverse events was higher in the risperidone depot 50 and 75 mg treatment groups compared with placebo depot treatment (13.3%, 10.1%, 24.3%, and 29.0% in the placebo depot, risperidone depot 25 mg, 50 mg, or 75 mg groups, respectively) (Table 41). Of the EPS-related adverse events, most patients experienced extrapyramidal disorder, hyperkinesia, and hypertonia with the highest incidence in the risperidone depot 75 mg group (Table 41). The EPS-related adverse events showed a similar pattern of incidence during both the supplementation period and after the supplementation was terminated. However,

the adverse event of hypertonia occurred in a higher percentage of patients in the risperidone depot 75 mg group than in any other treatment groups during the entire treatment period.

Table 41: Incidence of extrapyramidal symptom (EPS)-related adverse events: n (%) (patients with schizophrenia)

WHO-preferred term	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Any extrapyramidal symptom	13 (13.3%)	10 (10.1%)	25 (24.3%)	29 (29.0%)
Bradykinesia	0	0	1 (1.0%)	0
Dyskinesia tardive	0	0	0	1 (1.0%)
Dystonia	3 (3.1%)	0	0	2 (2.0%)
Extrapyramidal disorder	3 (3.1%)	4 (4.0%)	8 (7.8%)	10 (10.0%)
Gait abnormal	1 (1.0%)	0	1 (1.0%)	1 (1.0%)
Hyperkinesia	4 (4.1%)	2 (2.0%)	9 (8.7%)	10 (10.0%)
Hypertonia	5 (5.1%)	4 (4.0%)	5 (4.9%)	10 (10.0%)
Hypokinesia	0	0	1 (1.0%)	2 (2.0%)
Hyporeflexia	0	0	1 (1.0%)	0
Muscle contractions involuntary	0	1 (1.0%)	0	2 (2.0%)
Tetany	1 (1.0%)	0	0	1 (1.0%)
Tremor	0	0	3 (2.9%)	3 (3.0%)

Source: Table.AE.7 and AE.3 USA121
Patients may have had more than one event

Laboratory

I will present some overall laboratory conclusions with tables supporting the conclusions to follow.

Safety results from laboratory tests, ECG and vital sign findings revealed no clinically serious events. For the laboratory test findings, WBC counts that were elevated occurred without an apparent pattern across the treatment groups and were only transiently increased. Similarly, elevated liver enzyme values were also only transiently increased.

There were no prolonged QTcF values at endpoint. When there were large changes (> 60 msec) in QTcF values from baseline to endpoint, there were few cases of this magnitude (1, 2, 1, and 1 patient with placebo depot, risperidone depot 25 mg, 50 mg, or

75 mg) (Table 53), and the QTcF intervals for these patients were within normal limits throughout.

Vital sign changes, when they exceeded predefined limits, showed no pattern between treatment groups or were transient. Pulse rates were transiently high, but returned to normal levels; there was a similar pattern for low systolic or diastolic blood pressure. There were a few rare cases of orthostatic hypotension during double-blind treatment.

The magnitude of weight gain exhibited by patients receiving risperidone depot was in line with previous reports in patients treated with oral risperidone in a placebo-controlled trial (RIS-INT-6).

Table 44: Incidence in more than 2 patients in any group in changes outside of predefined limits in laboratory values: n (%) (patients with schizophrenia)

Laboratory parameter Criteria	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
ALT				
Abnormally high	4/74 (5.4%)	1/90 (1.1%)	5/78 (6.4%)	0
AST				
Abnormally high	4/77 (5.2%)	1/91 (1.1%)	0	0
Chloride				
Abnormally low	2/80 (2.5%)	1/90 (1.1%)	0	0
Abnormally high	1/80 (1.3%)	0	0	0
GGT				
Abnormally high	0	4/90 (4.4%)	0	0
Uric acid				
Abnormally high	4/78 (5.1%)	0	1/85 (1.2%)	1/84 (1.2%)
Hematocrit				
Abnormally low	0	1/89 (1.1%)	0	2/80 (2.5%)
Hemoglobin				
Abnormally low	0	1/88 (1.1%)	0	2/81 (2.5%)
Platelet count				
Abnormally low	0	1/90 (1.1%)	0	0
Abnormally high	2/75 (2.7%)	1/90 (1.1%)	0	0
WBC				
Abnormally high	5/75 (6.7%)	5/84 (6.0%)	3/80 (3.8%)	6/76 (7.9%)

Source: Table LAB.3 USA121

Table 45: Incidence of vital signs (supine) outside of predefined limits: number/total (%) in patients with schizophrenia at any time after baseline

Parameter Characteristic	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Pulse, beats/min				
Abnormally low	1/92 (1.1%)	1/94 (1.1%)	2/95 (2.1%)	1/84 (1.2%)
Abnormally high	11/92 (12.0%)	6/94 (6.4%)	8/95 (8.4%)	11/84 (13.1%)
Systolic BP, mmHg				
Abnormally low	2/94 (2.1%)	1/98 (1.0%)	1/100 (1.0%)	4/95 (4.2%)
Abnormally high	0	0	0	1/95 (1.1%)
Diastolic BP, mmHg				
Abnormally low	2/95 (2.1%)	0	0	1/95 (1.1%)
Abnormally high	1/95 (1.1%)	2/98 (2.0%)	1/98 (1.0%)	0

Source: Table VS.2 USA121

One patient may be in more than one category. Incidence was based on a post-baseline assessment that exceeded criteria values shown in Table 6.

Table 46: Incidence of vital signs (standing) outside of predefined limits: number/total (%)in patients with schizophrenia at any time after baseline

Parameter Characteristic	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Pulse, beats/min				
Abnormally low	0	0	1/81 (1.2%)	0
Abnormally high	14/80 (17.5%)	20/78 (25.6%)	21/81 (25.9%)	25/74 (33.8%)
Systolic BP, mmHg				
Abnormally low	2/93 (2.2%)	2/98 (2.0%)	5/99 (5.1%)	7/95 (7.4%)
Abnormally high	0	0	0	0
Diastolic BP, mmHg				
Abnormally low	2/95 (2.1%)	0	2/98 (2.0%)	1/95 (1.1%)
Abnormally high	4/95 (4.2%)	3/98 (3.1%)	1/98 (1.0%)	1/95 (1.1%)

Source: Table VS.3 USA121
One patient may be in more than one category. Incidence was based on a post-baseline assessment that exceeded criteria values shown in Table 6.

Table 47: Incidence of orthostatic hypotension at selected timepoints: n (%) (patients with schizophrenia)

Timepoint	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
Baseline	n=98	n=99	n=103	n=99
	1 (1.0%)	1 (1.0%)	0	0
Week 1	n=94	n=95	n=96	n=93
	0	0	0	0
Week 2	n=75	n=80	n=86	n=82
	0	0	1 (1.2%)	0
Week 3	n=66	n=75	n=81	n=74
	0	0	0	0
Week 12	n=29	n=39	n=43	n=44
	0	0	0	0
Endpoint	n=95	n=98	n=100	n=96
	0	0	1 (1.0%)	0

Source: Table VS.5 USA121

Table 49: Distribution of percent change from baseline at endpoint in body weight: n (%) (patients with schizophrenia)

	Placebo depot (N=98)		RIS depot 25 mg (N = 99)		RIS depot 50 mg (N = 103)		RIS depot 75 mg (N = 100)	
Weight change	n (%)	Mean Change SE	n (%)	Mean Change SE	n (%)	Mean Change SE	n (%)	Mean Change SE
Endpoint	N=83		N=90		N=87		N=83	
< -7%	9 (10.8%)	-9.2 (0.98)	6 (6.7%)	-9.0 (1.58)	2 (2.3%)	-7.3 (1.80)	0	
< 0% to -7%	49 (59.0%)	-2.2 (0.24)	35 (38.9%)	-2.0 (0.26)	29 (33.3%)	-1.7 (0.33)	32 (38.6%)	-1.0 (0.20)
> 0% to 7%	20 (24.1%)	1.9 (0.29)	40 (44.4%)	2.1 (0.23)	49 (56.3%)	2.1 (0.22)	40 (48.2%)	2.7 (0.27)
>7%	5 (6.0%)	6.7 (1.33)	9 (10.0%)	9.4 (1.82)	7 (8.0%)	9.4 (1.48)	11 (13.3%)	7.5 (0.82)

Source: Table VS.8 and 8A USA121

Table 50: ECG parameter-mean and mean change from baseline at endpoint (patients with schizophrenia)

Timepoint Analysis	Placebo depot (N = 98)			RIS depot 25 mg (N = 99)			RIS depot 50 mg (N = 103)			RIS depot 75 mg (N = 100)		
	N	Mean SE	Mean Change SE	N	Mean SE	Mean Change SE	N	Mean SE	Mean Change SE	N	Mean SE	Mean Change SE
Heart rate, bpm												
Baseline	93	73.8 (1.22)		98	75.1 (1.35)		100	74.2 (1.25)		98	75.1 (1.48)	
Endpoint	96	72.1 (1.35)	-2.2 (1.35)	97	72.5 (1.19)	-2.2 (1.33)	98	70.6 (1.20)	-3.4 (1.27)	95	73.3 (1.49)	-2.1 (1.49)
QT interval, msec												
Baseline	93	364.6 (3.06)		98	364.0 (3.24)		100	367.0 (3.03)		98	364.2 (3.22)	
Endpoint	96	367.8 (3.17)	4.5 (3.33)	96	369.2 (3.42)	4.7 (3.57)	98	375.4 (3.44)	8.1 (3.59)	95	370.2 (3.50)	6.7 (3.67)
QTc interval B, msec												
Baseline	93	401.3 (2.56)		98	403.0 (2.27)		100	404.5 (2.43)		98	402.9 (2.87)	
Endpoint	96	398.8 (2.69)	-2.1 (3.11)	96	402.3 (2.97)	0.5 (3.41)	98	403.7 (2.39)	-0.4 (2.97)	95	404.3 (2.76)	1.2 (3.41)
QTc interval F, msec												
Baseline	93	388.4 (2.32)		98	389.2 (2.10)		100	391.3 (2.15)		98	389.2 (2.38)	
Endpoint	96	387.8 (2.24)	0.1 (2.70)	96	390.6 (2.74)	2.0 (3.06)	98	393.7 (2.28)	2.6 (2.71)	92	392.2 (2.29)	3.2 (2.99)
QTc linear, msec												
Baseline	93	390.3 (2.19)		98	391.1 (1.89)		100	392.7 (2.10)		98	390.1 (2.33)	
Endpoint	94	388.8 (2.23)	-0.8 (2.61)	95	392.1 (2.61)	1.3 (2.86)	96	394.5 (2.17)	1.8 (2.60)	95	392.8 (2.30)	2.7 (2.90)
QT dispersion												
Baseline	77	30.6 (1.79)		78	30.7 (2.07)		82	32.9 (1.92)		72	32.1 (1.77)	
Endpoint	94	35.5 (1.52)	5.8 (2.18)	85	31.7 (1.92)	2.1 (2.90)	90	39.3 (1.93)	7.3 (3.17)	87	34.8 (1.82)	2.7 (2.57)
PR interval, msec												
Baseline	95	169.7 (1.96)		98	166.1 (1.95)		99	164.5 (1.86)		98	170.8 (2.15)	
Endpoint	96	166.0 (1.86)	-3.8 (1.86)	97	165.2 (1.92)	-1.4 (2.06)	98	165.3 (2.12)	1.6 (1.90)	95	167.0 (2.30)	-3.2 (1.92)
QRS interval, msec												
Baseline	93	93.7 (0.86)		98	93.5 (0.82)		100	95.6 (1.14)		98	92.1 (0.97)	
Endpoint	96	94.2 (0.92)	0.5 (1.06)	97	93.9 (0.87)	0.4 (1.11)	98	93.0 (0.92)	-2.8 (1.46)	95	93.2 (0.87)	1.2 (1.00)

Source: Table ECG.1 USA121

Table 51: ECG parameters beyond the predefined limits after baseline: n (%) (patients with schizophrenia)

Parameter Characteristic	Placebo depot (N = 98)	RIS depot 25 mg (N = 99)	RIS depot 50 mg (N = 103)	RIS depot 75 mg (N = 100)
QT interval (ms)				
Abnormally Low (<=200)	0	0	0	0
Abnormally High (>=500)	0	0	1/95 (1.1%)	0
Heart Rate (beats/min)				
Abnormally Low (<=50)	6/88 (6.8%)	3/88 (3.4%)	5/90 (5.6%)	4/83 (4.8%)
Abnormally High (>=100)	3/88 (3.4%)	6/88 (6.8%)	3/90 (3.3%)	5/83 (6.0%)
PR interval (ms)				
Abnormally High (>=210)	2/91 (2.2%)	5/94 (5.3%)	5/93 (5.4%)	3/86 (3.5%)
QRS interval (ms)				
Abnormally Low (<=50)	0	0	0	0
Abnormally High (>=120)	3/91 (3.3%)	2/96 (2.1%)	2/94 (2.1%)	1/90 (1.1%)

Source: Table ECG.8 USA121

Table 52: Classification of corrected QT intervals at endpoint (patients with schizophrenia)

	Placebo depot (N = 98)			RIS depot 25 mg (N = 99)			RIS depot 50 mg (N = 103)			RIS depot 75 mg (N = 100)		
	Classification at baseline			Classification at baseline			Classification at baseline			Classification at baseline		
Parameter Characteristic	Norm	Bord	Prolo	Norm	Bord	Prolo	Norm	Bord	Prolo	Norm	Bord	Prolo
QTcB class												
Normal	81	3	1	78	4	1	77	7	1	77	4	1
Borderline	4	0	0	7	4	0	8	1	0	8	2	0
Prolonged	3	1	0	1	0	0	1	0	0	1	0	0
QTcF class												
Normal	88	2	1	95	0	0	91	1	0	90	0	1
Borderline	1	1	0	0	0	0	2	1	0	2	0	0
Prolonged	0	0	0	0	0	0	0	0	0	0	0	0
QTcL class												
Normal	86	3	0	94	0	0	89	1	0	90	0	1
Borderline	2	1	0	0	0	0	3	0	0	2	0	0
Prolonged	0	0	0	0	0	0	0	0	0	0	0	0

Source: Table ECG.5 USA121

Normal (Norm) (M: ≤430 ms; F: ≤450); borderline (Bord) (M: ≥430ms to ≤450; F: ≥450 to ≤470); prolonged (Prolo) (M: >450; F:>470)

Table 53: Incidence of change for corrected QTc values at endpoint relative to baseline: n (%) (patients with schizophrenia)

QT correction Change criteria	Placebo depot	RIS depot 25 mg	RIS depot 50 mg	RIS depot 75 mg
QTcB	93	95	95	93
< 30 ms	83 (89.2%)	75 (78.9%)	80 (84.2%)	73 (78.5%)
30 – 60 ms	7 (7.5%)	18 (18.9%)	14 (14.7%)	19 (20.4%)
> 60 ms	3 (3.2%)	2 (2.1%)	1 (1.1%)	1 (1.1%)
QTcF	93	95	95	93
< 30 ms	82 (88.2%)	79 (83.2%)	81 (85.3%)	75 (80.6%)
30 – 60 ms	10 (10.8%)	14 (14.7%)	13 (13.7%)	17 (18.3%)
> 60 ms	1 (1.1%)	2 (2.1%)	1 (1.1%)	1 (1.1%)
QTcL	92	94	93	93
< 30 ms	83 (90.2%)	80 (85.1%)	81 (87.1%)	78 (83.9%)
30 – 60 ms	9 (9.8%)	13 (13.8%)	11 (11.8%)	15 (16.1%)
> 60 ms	0	1 (1.1%)	1 (1.1%)	0

Source: Table ECG. 4 USA121

RIS-INT-61

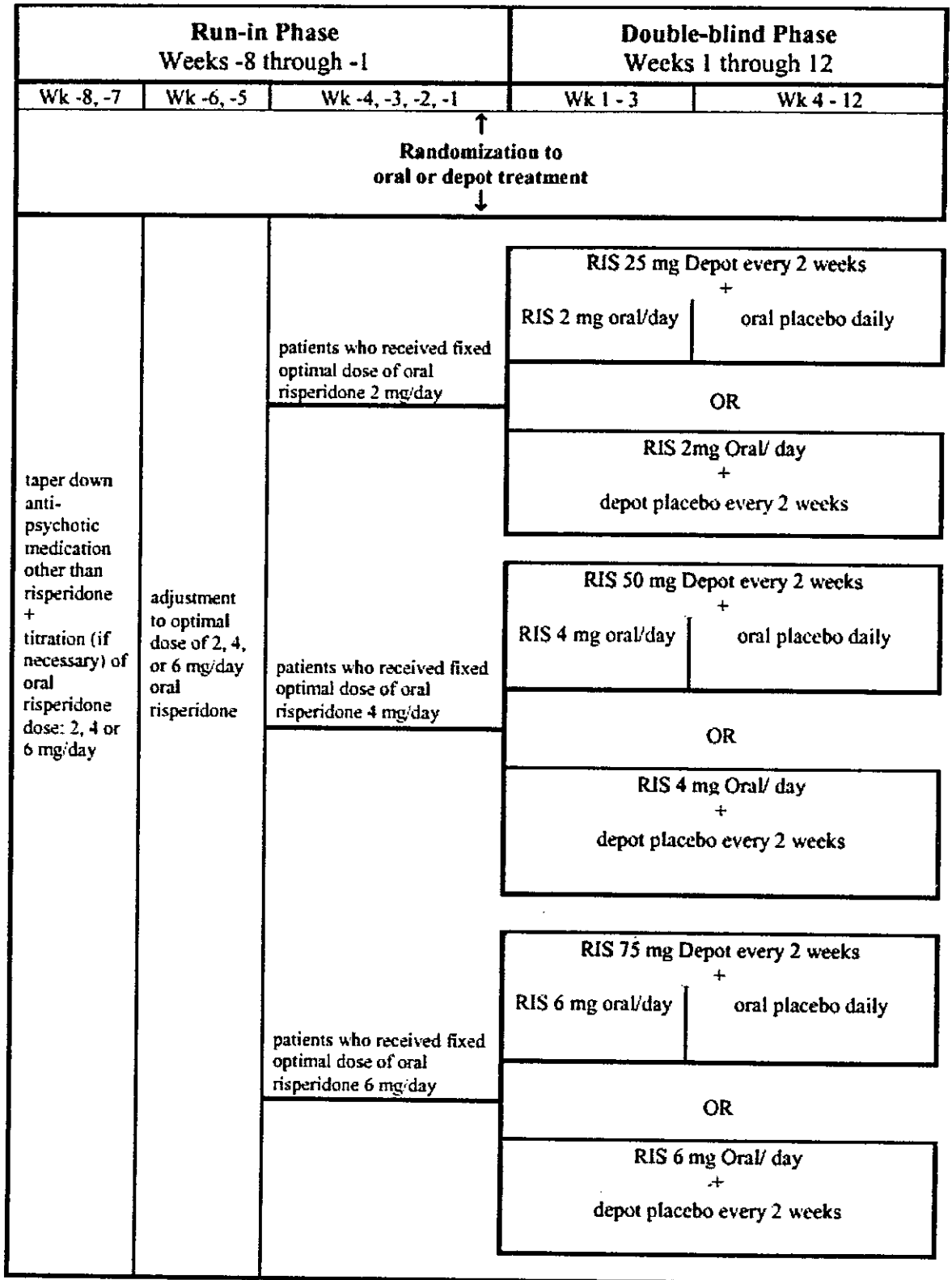
Principal Investigator

Pierre Chue, MBBCh, Clinical Associate Professor of Psychiatry, University of Alberta Hospital, Edmonton, Alberta, Canada

This was a double-blind, international multicenter trial in patients with schizophrenia. Risperidone depot injections (25, 50 or 75 mg) given every two weeks were compared with once daily intake of risperidone tablets (2, 4 or 6 mg). In total 670 subjects were to be included, 335 in each treatment group. Patients were either inpatients or outpatients. Patients completed an 8-week run-in period. During the first 2 weeks of the run-in period, pre-trial antipsychotic medication other than risperidone was tapered to discontinuation. It was replaced by oral risperidone at a once daily dose of 2, 4 or 6 mg. For the following two weeks the risperidone dose could be adjusted upwards or downwards to find an "optimal dose". The dose was then fixed for at least the last 4 weeks before randomization. The use of other antipsychotic medication was not allowed during the last 6 weeks of the run-in period. After the 8-week run-in period, patients were randomly allocated to one of

the two treatment groups using dynamic, central randomization. One group was treated with risperidone depot injections every two weeks and placebo tablets once daily. The other group received placebo injections every two weeks and risperidone tablets once daily. To ensure that adequate plasma levels of risperidone were maintained until sufficient release of risperidone from the microspheres had started, all active depot patients received oral supplementation with risperidone tablets during the first three weeks of the double-blind period; that is, from the first injection until one week after the second injection patients were to continue on the same dose of risperidone oral as during the last 4 weeks of the run-in period. That dose determined the dose level of depot (25, 50, 75 mg) to which the patient was assigned. Weekly visits occurred during the first four weeks of the run-in period, thereafter visits occurred _ every 2 weeks for the remainder of the run-in period and throughout the double-blind period. Efficacy assessments were performed at screening, at baseline (randomization), and at Weeks 8 and 12. Safety assessments were performed at screening, baseline (randomization), and Weeks 4 and 12. If a patient left the trial before 12 weeks, safety and efficacy assessments were performed as at Visit 7 (endpoint visit). The total trial duration was 20 weeks (an 8-week run-in period followed by a 12-week double-blind period). See Figure 1.

Figure 1: Trial design RIS-INT-61



Double-blind depot dose depends on optimal oral run-in dose: 2 mg → 25 mg; 4 mg → 50 mg; 6 mg → 75 mg.
RIS: risperidone

In total, 670 patients were to be randomized, 335 in each group. The aim was to have at least 100 patients in each of the three dose groups.

Patients who met all of the following criteria at screening were eligible for entry into the run-in period of this trial:

Aged 18 to 65, inclusive;
Diagnosis of schizophrenia according to the DSM IV criteria (295.10, 295.20, 295.30, 295.60, 295.90);
Total PANSS score of at least 50 at entry (screening/Visit A1);

During the 8-week run-in period, patients' other antipsychotic medication was discontinued and oral treatment with risperidone was started. After randomization to oral or depot active medication, patients received biweekly injections and daily oral tablets. Supplementation with oral risperidone was administered for the first 3 weeks of active depot treatment.

The sponsor states that the primary efficacy results of this non-inferiority trial demonstrated that risperidone depot treatment is as effective as risperidone oral treatment, when patients, stabilized on oral risperidone treatment, were transferred to depot treatment. The patients continued to improve after randomization to either oral or depot risperidone. This conclusion is based on total PANSS and positive and negative symptoms on the PANSS rating scale, and is also supported by the CGI evaluations. Active moiety plasma levels were comparable between risperidone oral and depot treatment for all dose levels (2, 4 and 6 mg versus 25, 50 and 75 mg) during the trial. The steady-state plasma concentrations increased dose-proportionally
for both treatments over the entire dose range.

The lack of a placebo control group makes interpretation of this trial problematic.

RIS-INT-57

RIS-INT-57, was a Phase 3, open-label, one-year, international multicenter trial to examine the long-term safety and tolerability of biweekly injections of risperidone depot microspheres in patients with stable schizophrenia or schizoaffective disorder.

At least 600 patients were to be included in the trial. In total, 50 elderly patients were to be recruited in this trial. Patients could be either in-patients or out-patients. If the patients were being treated with antipsychotics other than risperidone (oral or depot), they went through a 2-week run-in treatment with oral risperidone. All patients continued on oral risperidone for 2-3 weeks after the first injection. Safety and efficacy assessments were performed at baseline (i.e., at the time of first risperidone depot microspheres injection) and thereafter monthly, except for local tolerability (injection site evaluation) and adverse events which were evaluated every two weeks. The total trial duration was one year except for elderly patients recruited after January 1, 2000, for which the trial duration was 6 months. All patients should have had their endpoint visit at the latest on December 15, 2000.

A total of 786 patients were screened, 719 of whom received risperidone depot injection after completing the oral run-in period. A total of 725 patients were treated with risperidone depot injections. Six patients were already being treated with oral risperidone, and did not go through the oral run-in period. As per the protocol, it was possible to skip the oral run in for those patients currently treated with risperidone which explains the higher number of patients who received injection, compared to the number of patients in the oral run-in period. So, a total of 725 patients (615 with schizophrenia and 110 with schizoaffective disorder) were treated with risperidone depot injection, 474 of whom completed the trial. Thus a total of 251 patients discontinued the trial prematurely after they had received a depot injection: 215 of the 615 patients with schizophrenia and 36 of the 110 patients with schizoaffective disorder. In total, 65% of the patients in both diagnostic categories completed the trial. A total of 57 elderly ($\geq$ 65 patients) received depot injections; 27, 21, and 9 patients in the 25-mg, 50-mg, and 75-mg group, respectively.

The number of elderly patients who completed or discontinued trial RIS-INT-57 is summarized in Table 1. According to Protocol Amendment 2 of RIS-INT- 57 (dated November 24, 1999), elderly patients recruited as of January 1, 2000 only stayed in the trial for 6 months, after which they were eligible to enter the open extension trial RIS-INT-63. Of the 44 elderly patients who completed the trial, 19 completed at 6 months according to Amendment 2. The other 25 patients completed the trial at 1 year. The time of discontinuation for each of the 13 prematurely discontinued patients is provided in a listing shown in Table 2, along with the reason for discontinuation.

Table 1. Summary of the number (%) of elderly patients who completed/discontinued trial RIS-INT-57

RIS-INT-57	Risperidone Depot Microspheres			
Elderly Patient Disposition	25 mg	50 mg	75 mg	All
Patients with injection, n	27	21	9	57
Completed, n (%)	21 (78%)	16 (76%)	7 (78%)	44 (77%)
6 months, n	9	9	1	19
1 year, n	12	7	6	25
Discontinued, n (%)	6 (22%)	5 (24%)	2 (22%)	13 (23%)

Table 2. Listing of elderly patients who prematurely discontinued in trial RIS-INT-57

Risperidone depot Mode Dose	Day*	CRF ID	Age, years	Sex	Country Main Investigator	Termination Reason
25 mg	35	A31112	66	Male	Great Britain McDonald G.	Subject withdrew consent
	55	A30484	78	Female	Germany Huntemann R.	Other
	78	A31270	78	Male	Poland Chrzanowski W.	Death
	103	A31261	78	Female	Poland Chrzanowski W.	Adverse event
	128	A30430	66	Male	Poland Chrzanowski W.	Adverse event
	247	A31234	81	Female	Germany Huntemann R.	Subject withdrew consent
50 mg	42	A30100	65	Male	Sweden Varenius A.	Subject withdrew consent
	167	A30399	68	Male	Poland Chrzanowski W.	Subject withdrew consent
	172	A31250	78	Male	Germany Huntemann R.	Subject lost to follow-up
	222	A30509	66	Female	Germany Guenther W.	Subject withdrew consent
	340	A31082	80	Female	Great Britain Martin S.	Subject withdrew consent
75 mg	1	A30512	71	Male	Germany Guenther W.	Subject non-compliant
	5	A30983	65	Male	Netherlands Van Berkestijn J.	Subject ineligible to continue the trial

*Day patient discontinued the trial relative to the first injection.

Safety results from this trial are included in the safety section of this review.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety review reveals no new or unusual events and is similar in nature to the pattern seen in existing labeling for Risperdal. These trials included adult and elderly patients, in in- or out-patient populations with schizophrenia or schizoaffective disorder. The incidences and types of serious adverse events were lower and comparable between the 25-mg and 50-mg treatment groups, compared with the 75-mg group. Mean intensity of injection site pain was mild and diminished from first to last injection in all treatment groups. There were no clinically relevant mean changes from baseline to endpoint in laboratory values, vital signs, or ECG parameters for any patients treated with risperidone depot microspheres. In general, no clinically relevant differences in adverse event profiles were found for gender, race, or body mass index. Risperidone depot microspheres were safe and well tolerated in elderly patients (> 65 yrs). There were no clinically relevant differences in the safety profiles of non-elderly and elderly patients.

B. Description of Patient Exposure

This Integrated Summary of Safety presents data pertinent to the assessment of the safety and tolerability of risperidone depot microspheres in the treatment of schizophrenia and schizoaffective disorders in in-or out-patients. The summary contains the results from 13 Phase 1, Phase 2, and Phase 3, globally-conducted trials in patients diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. These trials included a total of 2101 patients: 1932 patients with schizophrenia, 163 patients with schizoaffective disorder, and 6 patients with schizophreniform disorder. Of these patients, 1927 participated in 6 repeated-dose trials: 1499 patients received risperidone depot microspheres injections of 25 mg (378 patients), 50 mg (558 patients), or 75 mg (563 patients) every 2 weeks; 107 patients received placebo depot injections; and 321 patients received oral risperidone tablets in daily doses of 2 mg (86 patients), 4 mg (126 patients), or 6 mg (109 patients). An additional 174 patients participated in 7

single-dose studies and received injections of risperidone depot microspheres in 25-mg, 37.5-mg, 50-mg, 62.5-mg, 75-mg, and 100-mg doses. See table below for repeat dose trial exposure totaling 542.89 PEY for the depot formulation.

The number of patients enrolled in RIS-INT-57, the open-label, 12-month safety trial (579 patients treated for approximately 6 months, and 361 patients treated for approximately 1 year), was supportive of long-term use of risperidone depot microspheres.

Table 11: Extent of exposure: pooled, repeated-dose trials n (%) (patients with schizophrenia)

Treatment duration (days)	Placebo depot (N=98)	RIS depot 25 mg (N=342)	RIS depot 50 mg (N=497)	RIS depot 75 mg (N=506)	RIS depot Total (N=1345)	RIS oral Total (N=321)
1-13	31 (31.6%)	30 (8.8%)	31 (6.2%)	32 (6.3%)	93 (6.9%)	9 (2.8%)
14-27	13 (13.3%)	28 (8.2%)	25 (5.0%)	21 (4.2%)	74 (5.5%)	8 (2.5%)
28-41	6 (6.1%)	11 (3.2%)	17 (3.4%)	22 (4.3%)	50 (3.7%)	7 (2.2%)
42-55	9 (9.2%)	11 (3.2%)	20 (4.0%)	23 (4.5%)	54 (4.0%)	14 (4.4%)
56-69	10 (10.2%)	52 (15.2%)	56 (11.3%)	50 (9.9%)	158 (11.7%)	53 (16.5%)
70-83	29 (29.6%)	105 (30.7%)	150 (30.2%)	129 (25.5%)	384 (28.6%)	230 (71.7%)
84-97	0	2 (0.6%)	3 (0.6%)	7 (1.4%)	12 (0.9%)	0
98-111	0	0	0	4 (0.8%)	4 (0.3%)	0
112-125	0	2 (0.6%)	1 (0.2%)	2 (0.4%)	5 (0.4%)	0
126-139	0	1 (0.3%)	3 (0.6%)	9 (1.8%)	13 (1.0%)	0
140-153	0	0	4 (0.8%)	3 (0.6%)	7 (0.5%)	0
154-167	0	15 (4.4%)	14 (2.8%)	8 (1.6%)	37 (2.8%)	0
168-181	0	0	2 (0.4%)	2 (0.4%)	4 (0.3%)	0
182-195	0	0	2 (0.4%)	5 (1.0%)	7 (0.5%)	0
196-209	0	1 (0.3%)	2 (0.4%)	5 (1.0%)	8 (0.6%)	0
210-299	0	5 (1.5%)	16 (3.2%)	32 (6.3%)	53 (3.9%)	0
≥300	0	79 (23.1%)	151 (30.4%)	152 (30.0%)	382 (28.4%)	0
Mean (SE)	35.8 (3.04)	125.7 (6.65)	151.9 (5.86)	157.5 (5.78)	147.3 (3.52)	65.1 (0.89)
Median	33.0	71.0	72.0	72.5	71.0	71.0
Range	1-77	1-353	1-351	1-368	1-368	1-81
Patient years of exposure	9.62	117.79	206.78	218.32	542.89	57.29

Source: Table SUB.6B ISS; Table SUB.6D ISS
Includes Trials RIS-USA-121, RIS-INT-57, RIS-INT-61, RIS-INT-31, RIS-SWE-17, RIS-INT-32.

C. Methods and Specific Findings of Safety Review

Data from the 13 completed clinical trials are included in the safety database. Data were analyzed in five separate groupings and were presented without integration:

1. Repeated-dose, 12-week, placebo-controlled trial (RIS-USA-121);

2. Six pooled, repeated-dose trials (RIS-USA-121, RIS-INT-57 (Months 1 to 3), RIS-INT-61, RIS-INT-31, RIS-SWE-17, RIS-INT-32);

3. Repeated-dose, open-label, long-term trial (RIS-INT-57);

4. Six pooled, single-dose trials (RIS-BEL-34, RIS-INT-25, RIS-INT-38, RIS-NED-13, RIS-USA-111, RIS-INT-54); and

5. Single-, intermediate-dose, pharmacokinetic trial (RIS-INT-72). This trial was completed in February 2001 and could not be included in the pooling for single-dose trials.

Within each grouping, further divisions were made according to indication (schizophrenia, schizoaffective disorder, other), treatment, and dosage. All randomized patients who received at least one injection of study medication are included in the safety analysis. Table 3 shows the number of patients in each ISS grouping according to treatment.

Table 3: Number of patients in each ISS grouping

ISS grouping	Number of patients[a] (Schizophrenic/schizoaffective/other)						
	Placebo depot[b]	RIS depot 25 mg	RIS depot 50 mg	RIS depot 75 mg	RIS depot 100 mg	RIS depot Total	RIS oral Total[c]
Repeated-dose, placebo-controlled (USA-121)	(98/9)	(99/6/0)	(103/14/0)	(100/10/0)	—	(302/30/0)	—
Pooled, repeated-dose (USA-121, INT-57, INT-61, INT-31, SWE-17, INT-32)	(98/9)	(342/35/1)	(497/59/2)	(506/54/3)	—	(1345/148/6)	(321/0/0)
Repeated-dose, long-term (INT-57)	—	(120/27/0)	(228/42/0)	(267/41/0)	—	(615/110/0)	—
Pooled, single-dose (BEL-34, INT-25, INT-38, NED-13, USA-111, INT-54)	—	(28/2/0)	(66/4/0)	(13/1/0)	(9/0/0)	(92/6/0)[d]	—
		RIS depot 37.5 mg	RIS depot 50 mg	RIS depot 62.5 mg			
Single, intermediate-dose (INT-72)	—	(24/0/0)	(26/0/0)	(26/0/0)	—	(76/0/0)	—

Source: Table SUB.3A ISS, Table SUB.3B ISS, Clinical Trial Report RIS-USA-121, Clinical Trial Report RIS-INT-57, Clinical Trial Report RIS-INT-72

a) Number of patients who received at least one dose of study medication.

b) Trial RIS-USA-121.

c) Trial RIS-INT-61.

d) Patients in crossover study RIS-INT-54 are counted only once for total number of patients.

Safety Methodology

Adverse events, laboratory data, vital sign values, electrocardiogram (ECG) parameters, Extrapyramidal Symptom Rating Scale (ESRS) scores, and extrapyramidal symptom (EPS)-, glucose-, and potentially prolactin-related adverse events were the assessment parameters examined to evaluate the safety of risperidone depot microspheres treatment. No integrated analyses of laboratory or electrocardiogram data were performed for the pooled, single-dose trials.

The first System Organ Class from the World Health Organization (WHO) dictionary was used to link preferred terms to body systems. The WHO Dictionary for Adverse Events (1st quarter of 2001) was used. Since the same adverse event verbatim could be coded differently across trials, a clinician examined these specific verbatim adverse events and recoded them consistently so adverse event system organ classes were the same across all trials.

A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose:
_ resulted in death,
_ was life-threatening,
_ required inpatient hospitalization or prolongation of existing hospitalization,
_ resulted in persistent or significant disability/incapacity,or
_ was a congenital anomaly/birth defect (ICH).

Serious adverse events, adverse events leading to discontinuation and deaths will be presented in the safety update section. Adverse events incidence is presented compared to placebo in the section for Study RIS-USA-121.

Clinical laboratory evaluations

MEANVALUES OVER TIME

There were no clinically relevant changes from baseline to the 3-month endpoint in mean laboratory values for any patients with schizophrenia or schizoaffective disorder treated with risperidone depot or risperidone oral medication. However, decreases in mean prolactin levels (measured only in RIS-INT-61) were found for all risperidone depot treatment groups, with the largest decrease seen in the 25-mg group. No comparable decrease in mean prolactin level was found in the risperidone oral treatment group. Overall, there were no clinically relevant changes from baseline to the 3-month endpoint in diastolic blood pressure, systolic blood pressure, or pulse rate in patients with schizophrenia or schizoaffective disorder.

CHANGES BEYOND PREDEFINED LIMITS

In patients with schizophrenia, there were few laboratory values that were beyond the predefined limits at anytime postbaseline. Across the three risperidone depot treatment groups, there were 36 patients (3.2%) with abnormally high ALT values, 26 patients (2.3%) with abnormally high GGT values, and 12 patients (1%) with abnormally high AST. No dose-related trends were found for these increased liver enzyme findings. For both AST and ALT, a higher percentage of patients in the placebo depot group (5.1% and 5.3%, respectively) had abnormally high values, compared with any of the active depot treatment groups. For the 25-mg, 50-mg, and 75-mg groups, there also were 61 patients with abnormally high white blood cell counts. Again, no

dose-related trend was found, although the highest incidence (7.4%) occurred in the 75-mg group. Seven percent (6.5%) of patients in the placebo depot group also had white blood cell counts above the predefined limit. Few patients in the risperidone oral treatment group had laboratory values outside of predefined limits. Most frequent abnormal laboratory values included 6 patients (2.1%) with high GGT levels, 4 patients (1.4%) with abnormally high white blood cell counts, and 3 patients (1.0%) with abnormally low hematocrit values. In this treatment group, 2 patients (0.7%) also had elevated ALT levels and 1 patient (0.3%) had an elevated AST level. None of these elevated levels led to clinically serious events.

Table 51: Incidence (≥2%) of changes outside of predefined limits in relevant laboratory values at anytime postbaseline: repeated-dose trials n (%) (patients with schizophrenia)

Laboratory parameter/ Criteria	Placebo depot	RIS depot 25 mg	RIS depot 50 mg	RIS depot 75 mg	RIS depot Total	RIS oral Total
Chloride						
Abnormally high	1/81 (1.2%)	2/300 (0.7%)	3/428 (0.7%)	0	5/1149 (0.4%)	0
Abnormally low	2/81 (2.5%)	1/300 (0.3%)	3/428 (0.7%)	2/421 (0.5%)	6/1149 (0.5%)	1/289 (0.3%)
Urea						
Abnormally high		4/214 (1.9%)	6/349 (1.7%)	3/340 (0.9%)	13/903 (1.4%)	2/290 (0.7%)
Abnormally low		3/214 (1.4%)	8/349 (2.3%)	3/340 (0.9%)	14/903 (1.6%)	2/290 (0.7%)
Uric acid						
Abnormally high	4/79 (5.1%)	0	6/432 (1.4%)	2/423 (0.5%)	8/1151 (0.7%)	1/290 (0.3%)
Abnormally low	0	0	0	1/423 (0.2%)	1/1151 (0.1%)	0
GGT						
Abnormally high	0	15/298 (5.0%)	0	11/411 (2.7%)	26/1138 (2.3%)	6/285 (2.1%)
Abnormally low	0	0	0	0	0	0
AST (SGOT)						
Abnormally high	4/78 (5.1%)	4/305 (1.3%)	3/432 (0.7%)	5/424 (1.2%)	12/1161 (1.0%)	1/287 (0.3%)
Abnormally low	0	0	0	0	0	0
ALT (SGPT)						
Abnormally high	4/76 (5.3%)	9/298 (3.0%)	16/412 (3.9%)	11/417 (2.6%)	36/1127 (3.2%)	2/280 (0.7%)
Abnormally low	0	0	0	0	0	0/280
Haematocrit						
Abnormally high	0	0	0	0	0	0
Abnormally low	0	6/302 (2.0%)	1/433 (0.2%)	6/417 (1.4%)	13/1152 (1.1%)	3/289 (1.0%)
WBC						
Abnormally high	5/77 (6.5%)	16/294 (5.4%)	16/404 (4.0%)	29/390 (7.4%)	61/1088 (5.6%)	4/276 (1.4%)
Abnormally low	0	1/294 (0.3%)	4/404 (1.0%)	1/390 (0.3%)	6/1088 (0.6%)	2/276 (0.7%)
Platelet count						
Abnormally high	2/76 (2.6%)	2/300 (0.7%)	0	2/414 (0.5%)	4/1136 (0.4%)	1/289 (0.3%)
Abnormally low	0	3/300 (1.0%)	10/422 (2.4%)	5/414 (1.2%)	18/1136 (1.6%)	2/289 (0.7%)

Source: Table LAB.3B ISS
Includes Trials RIS-USA-121, RIS-INT-57, RIS-INT-61, RIS-INT-31, RIS-SWE-17, RIS-INT-32.

ADVERSE EVENTS OF NOTE

Because of division interest in stroke while on risperidone 4 cases were found in the data base and are presented below.

- **RIS-USA-121:** Subject A30146 was diagnosed with lung cancer and multiple cerebrovascular accidents during the run-in when treated with oral risperidone 2-4 mg.

- **RIS-INT-61:** Subject A30015 was diagnosed with a temporary "right hand numbness" and "loss of right hand grip" that was unresolved at trial end. Patient was treated with 2 mg oral risperidone.

- **RIS-INT-57**: Subject A30050, treated with risperdone long acting 75 mg, was diagnosed with pulmonary embolism which led to an anoxic brain injury during transportation to the hospital.

- **RIS-INT-63:** Subject A30860, treated with risperidone long acting 75 mg, was diagnosed with a cerebral aneurysm based on MRI results.

SAFETY UPDATE

One additional toxicology study has been completed since the filing of NDA 21-346. The data are in the processing of being analyzed. The sponsor promises that a full report of findings will be forwarded to the FDA as soon as it is completed.

This 4-month safety update includes information from six ongoing studies (RIS-USA-196, RIS-INT-63, RIS-INT-62, RIS-JPN-16, RIS-USA-259, RIS-INT-85). As per agreement at the pre-NDA meeting of April 20, 2001, a summary of all safety findings (up to a cut-off date of May 15, 2001) is provided for RIS-USA-196 and RIS-INT-63, which are open-label, extension trials for the Phase 3 studies in the NDA submission (RIS-USA-121 and RIS-INT-61/RIS-INT-57, respectively). Also as per agreement with the FDA, deaths and serious adverse events were tabulated from the Pharmacovigilance database (up to a cut-off date of August 31, 2001) for the other four ongoing trials: RIS-INT-62 (Phase 3, open-label, comparative trial with olanzapine); RIS-JPN-16 (Phase 2, pharmacokinetic trial); RIS-USA-259 (Phase 3b, open-label trial exploring the switch from oral neuroleptics to risperidone depot microspheres); and RIS-INT-85 (Phase 3b, open-

label trial exploring the switch from typical depot neuroleptics to risperidone depot microspheres).

The two ongoing, open-label, extension trials (RIS-USA-196 and RIS-INT-63) included a total of 1050 patients. Of these, 966 were patients with a diagnosis of schizophrenia and 84 were patients with a diagnosis of schizoaffective disorder. Of the 1050 patients, 271 (25.8%) previously were enrolled in RIS-USA-121 and entered RIS-USA-196; 402 patients (38.3%) previously enrolled in RIS-INT-61 and 377 patients (35.9%) previously enrolled in RIS-INT-57 entered RIS-INT-63. Thirty-nine patients, currently enrolled in RIS-INT-63, were 65 years of age or older at trial entry. Thirty-seven of these patients previously were enrolled in RIS-INT-57, while the remaining two patients previously were enrolled in RIS-INT-61.

The overall conclusions of this 4-month safety update are based on analyses of pooled data from the two extension trials RIS-USA-196 and RIS-INT-63. Patients were grouped according to their "total" exposure to risperidone depot microspheres (0-6 months, 7-12 months, 13-18 months, or 19-24months). "Total" exposure was the sum of current exposure (during the extension trial) plus the patient's exposure in the previous trial, and was defined as the number of days from a patient's first risperidone depot microspheres injection (which may have occurred during the previous trial or at the beginning of the extension trial) to the last injection before the cut-off date of May 15, 2001.

The sponsor's conclusions are listed below in italics:

- *Risperidone depot microspheres, in mode doses of 25 mg, 50 mg, and 75 mg every 2 weeks, were safe and well tolerated in patients with schizophrenia or with schizoaffective disorder, receiving up to 24 months of treatment.*
- *Adverse events reported during the extension trials were similar to those reported during previous trials.*
- *Overall incidences of adverse events that occurred during the extension trials were comparable between patients in the 0-6 month "total" exposure group and patients treated for 3 months in the previous trials.*
- *When treatment-emergent adverse events occurring during the extension trials were examined by time of onset, there was an overall reduction in incidence across time.*
- *In general, no clinically relevant differences in adverse event profiles were found for gender or race.*

• The incidences of EPS-related adverse events tended to be higher for patients in the 0-6 and 7-12 month "total" exposure groups, and slightly lower for patients in the 13-18 and 19-24 month groups.
• The incidence of tardive dyskinesia during the extension trials was similar to the incidence reported in the ISS. The incidence of tardive dyskinesia does not seem to increase over time.
• Most adverse events were mild or moderate in severity and not related to trial mediation.
• There were no clinically relevant mean changes from previous or extension baselines to endpoint (last assessment prior to May 15, 2001) in laboratory values, vital signs, or ECG parameters for any patients treated with risperidone depot microspheres.
• The majority of patients gained weight from previous or extension baseline, but the average weight gain was small.
• Risperidone depot microspheres was well tolerated locally, as demonstrated by the low incidence of injection site-related adverse events.
• The incidence of treatment-emergent adverse events leading to discontinuation was highest in patients in the 0-6 month "total" exposure group and lowest in patients in the 13-18 month group.
• The incidence of serious adverse events increased with higher mode dose, and was highest in patients in the 0-6 month "total" exposure group. Most serious adverse events were psychiatric in nature and could be attributable to the underlying disease condition.
• The overall incidence of adverse events was lowest in the 25-mg mode dose group, and somewhat higher and comparable between the 50-mg and 75-mg mode dose groups.
• The incidence of treatment-emergent adverse events leading to discontinuation was lowest in the 50-mg mode dose group.
• Risperidone depot microspheres were safe and well tolerated in elderly patients (≥65 yrs). There were no clinically relevant differences in the safety profiles of non-elderly and elderly patients.

Please see safety data in trial RIS-USA-121 for placebo-study drug comparisons.

SUMMARY OF ALL DEATHS, SERIOUS ADVERSE EVENTS, AND ADVERSE EVENTS LEADING TO DISCONTINUATION FOR RISPERIDONE DEPOT MICROSPHERES TRIALS UP TO MAY 15, 2001.

Table 87 provides the total number of deaths, serious adverse events, and adverse events leading to discontinuation in all risperidone depot microspheres trials up to May 15, 2001. This table includes data from 13 trials reported in the original ISS for NDA 21-346, from the two ongoing, extension trials reported in this 4-month safety update, and from two of the other ongoing trials. Ongoing trials RIS-USA-259 and RIS-INT-85 did not begin until after the May 15, 2001 cut-off date and so are not included in this summary table.

Table 87 includes data from the following trials:

Seven completed, single dose, Phase I trials (reported in NDA 21-346): RIS-BEL-34, RIS-INT-25, RIS-INT-38, RIS-NED-13, RIS-USA-111, RIS-INT-54, RIS-INT-72.

Six completed, repeated-dose trials (reported in NDA 21-346): RIS-INT-31 (Phase 1), RIS-SWE-17 (Phase 1), RIS-INT-32 (Phase 2), RIS-USA-121 (Phase 3), RIS-INT-61 (Phase 3), RIS-INT-57 (Phase 3).

Two ongoing, repeated-dose, open-label, Phase 3, extension trials (reported in this 4-month safety update up to cut-off date of May 15, 2001): RIS-USA-196 and RIS-INT-62.

One ongoing, single-dose, Phase 2, pharmacokinetic trial (deaths, serious adverse events, and adverse events leading to discontinuation reported in this 4-month safety update): RIS-JPN-16.

One ongoing, repeated-dose, open-label, Phase 3, comparative trial with olanzapine (deaths, serious adverse events, and adverse events leading to discontinuation reported in this 4-month safety update): RIS-INT-62.

The largest source of data was the combination of the Integrated Summary of Safety (ISS) and the 4-month safety update databases. The combination of these two databases gave complete data for all completed Phase 1, 2, and 3 trials (excluding RIS-INT-72) and data up to May 15, 2001 for the two long-term, extension

trials (RIS-INT-63 and RIS-USA-196). Adding data from RIS-INT-72 gave the first row ('Closed Phase 1, 2, and 3 trials plus extension trials') under each type of event in this table. This combination also provided the group totals in the column headers.

For RIS-INT-63, the Janssen worldwide adverse event database (JIPSY) contained SAE reports prior to May 15, 2001 that had not been entered or indicated as serious in the RIS-INT-63 clinical database when the interim clinical database for the four-month safety update was finalized. By comparing the patients with these additional SAEs to those already accounted for, it was determined that 17 additional patients had their first SAE during RIS-INT-63 and also had no SAE in the RIS-INT-63 interim clinical database. These patients were added to the table in the second row under 'Patients with serious adverse events.'

The clinical trial database for RIS-INT-62 is not final and not all data have been reviewed.

The 'total' rows give the number of patients with each type of event across all risperidone depot microspheres trials as of May 15, 2001. Percentages were calculated only for the 'Closed Phase 1, 2, and 3 trials plus extension trials' rows since the denominators are accurate for those rows only.

Table 87: Incidence of deaths, serious adverse events, and adverse events leading to discontinuation during risperidone depot microspheres trials up to May 15, 2001

	Placebo depot (N=107)	RIS depot 25 mg (N=451)	RIS depot 50 mg (N=738)	RIS depot 75 mg (N=677)	RIS depot Total (N=1910)[a]	RIS oral Total (N=321)
Deaths[a]						
Closed Phase 1, 2, and 3 trials plus extension trials[b]	1 (1.0%)	4 (0.9%)	8 (1.1%)[b,e,g]	2 (0.3%)	14 (0.7%)	1 (0.3%)
RIS-INT-62, RIS-JPN-16[c]	–	0	0	0	0	–
Total	1	4	8	2	14	1
Patients with serious adverse events[a]						
Closed Phase 1, 2, and 3 trials plus extension trials[b]	25 (23.4%)	77 (16.7%)	143 (19.4%)	179 (26.4%)	401 (21%)	30 (9.3%)
Additional patients from RIS-INT-63[d]	–	5	5	7	17	–
RIS-INT-62[c]	–	2	4	5	11	–
RIS-JPN-16[c]	–	0	0	1	1	–
Total	25	84	152	192	430	30
Patients with adverse events leading to discontinuation[a]						
Closed Phase 1, 2, and 3 trials plus extension trials[b]	13 (12.1%)	43 (9.3%)[b]	53 (7.2%)[b]	54 (8.0%)	150 (7.8%)	13 (4.0%)
RIS-INT-62[c]	–	0	0	0	0	–
RIS-JPN-16[c]	–	0	0	0	0	–
Total	13	43	53	54	150	13

a) Refers to treatment-emergent adverse events that had outcome of death, were indicated as serious, or had action taken of permanent stop.

b) Combined data from ISS database, RIS-INT-72 database, and four month safety update database (RIS-INT-63 and RIS-USA-196 through May 15, 2001). Extension trial patients who were in the oral risperidone group (RIS-INT-61) or placebo depot group (RIS-USA-121) are included in both their original group and, as new patients, in the RIS depot group corresponding to their mode dose during the extension trial. All other patients are in the RIS depot group corresponding to their group in their original trial.

c) Based on JIPSY database.

d) Patients in RIS-INT-63 with SAEs prior to 15 May 2001 according to JIPSY database, but no SAE in RIS-INT-63 clinical cut-off database.

e) Based on clinical trial database as of November 11, 2001 and JIPSY database. Data has not been cleaned. One patient with unknown RIS dose was placed in the RIS depot 25 mg group. Nine olanzapine patients had serious adverse events by May 15, 2001. Two olanzapine patients (A30037 and A30513) discontinued due to adverse events by May 15, 2001. One olanzapine patient (A30559) committed suicide in RIS-INT-62.

f) Based on in-house monitoring data.

g) Does not include Patient A30068 who experienced an adverse event during the 15-week follow-up/washout period between Part 1 and Part 2 of Trial RIS-INT-54, but not within the 49-day therapeutic reach defined for the ISS.

Please see individual tables for these events below.

Table 1: Incidence of deaths during risperidone depot microspheres trials up to May 15, 2001

Patient CRFID	Trial	Sex	Age (yrs)	Total duration of depot treatment (days)[a]	Dose at onset	Days to onset[a]	Cause of death	Relationship to study medication according to the investigator
A30214	RIS-USA-121	M	33	57	Placebo depot	59	Death secondary to multiple traumatic injuries	None
A30731	RIS-INT-57	F	22	216	25 mg depot	219	Suicide	Doubtful
A31270	RIS-INT-57	M	78	71	25 mg depot	78	Cardiac failure/ pulmonary edema	Doubtful
A31212	RIS-INT-63	F	74	155	25 mg depot	163	Sudden death	None
A30183	RIS-USA-196	M	51	196	25 mg depot	200	Perforated bowel, secondary to colon cancer	None
A30055	RIS-INT-54	M	52	Single dose	50 mg depot (125-g production process)	32	Myocardial infarction/ cardiac arrhythmia	Doubtful
A30134	RIS-INT-72	M	48	Single dose	50 mg depot	37	Suicide	None
A30391	RIS-INT-57	F	28	30	25 mg depot (titrate dose= 50 mg depot)	30	Suicide	None
A30023	RIS-INT-57	M	40	295	50 mg depot	301	Suicide	None
A30895[b]	RIS-INT-57	F	64	28	50 mg depot	70	Breast cancer	None
A30548	RIS-INT-63	M	45	57	50 mg depot	70	Suicide	Possible
A30787	RIS-INT-63	M	25	268	50 mg depot	268	Suicide	None
A30847	RIS-INT-63	M	61	179	50 mg depot	179	Cardiac failure	Doubtful
A31287	RIS-INT-63	M	36	86	50 mg depot	86	Craniocerebral injury due to an automobile accident/ cerebral death	None
A30570	RIS-INT-57	F	33	212	75 mg depot	216	Suicide	None
A30235	RIS-INT-57	M	49	135	75 mg depot	149	Cardiac failure	None
A30701	RIS-INT-61	F	55	57	4 mg oral	63	Cardiac failure	None

Includes single-dose trials RIS-BEL-34, RIS-INT-25, RIS-INT-38, RIS-NED-13, RIS-USA-111, RIS-INT-54, RIS-INT-72; repeated-dose trials RIS-INT-31, RIS-SWE-17, RIS-INT-32, RIS-USA-121, RIS-INT-61, RIS-INT-57; and ongoing trials RIS-JPN-16, RIS-INT-62, RIS-INT-63, RIS-USA-196.

a) Days from depot treatment start.

b) The patient discontinued from the trial 13 days after her third depot injection because of adverse events (pruritus and ECG abnormal). The patient was diagnosed with breast cancer 42 days after her last depot injection and subsequently died from breast cancer.

Table 2: Treatment-emergent serious adverse events by body system and treatment: all closed Phase 1, 2, and 3 trials plus extension trials through May 15, 2001a) [n (%)]

WHO Organ System/ WHO Preferred Term	Placebo depot (N=107)	RIS depot 25 mg (N=461)	RIS depot 50 mg (N=738)	RIS depot 75 mg (N=677)	RIS depot Total (N=1910)[b]	RIS oral Total (N=321)
Any serious adverse event	25 (23.4%)	77 (16.7%)	143 (19.4%)	179 (26.4%)	401 (21.0%)	30 (9.3%)
Psychiatric disorders	24 (22.4%)	62 (13.4%)	121 (16.4%)	164 (24.2%)	348 (18.2%)	23 (7.2%)
Psychosis	19 (17.8%)	34 (7.4%)	60 (8.1%)	96 (14.2%)	190 (9.9%)	11 (3.4%)
Anxiety	4 (3.7%)	6 (1.3%)	33 (4.5%)	35 (5.2%)	75 (3.9%)	7 (2.2%)
Suicide attempt	2 (1.9%)	11 (2.4%)	24 (3.3%)	30 (4.4%)	65 (3.4%)	0
Hallucination	2 (1.9%)	9 (2.0%)	8 (1.1%)	21 (3.1%)	38 (2.0%)	2 (0.6%)
Depression	0	6 (1.3%)	14 (1.9%)	15 (2.2%)	35 (1.9%)	1 (0.3%)
Aggressive reaction	0	1 (0.2%)	7 (0.9%)	11 (1.6%)	19 (1.0%)	0
Insomnia	2 (1.9%)	4 (0.9%)	4 (0.5%)	11 (1.6%)	19 (1.0%)	3 (0.9%)
Paranoid reaction	2 (1.9%)	4 (0.9%)	4 (0.5%)	11 (1.6%)	19 (1.0%)	2 (0.6%)
Agitation	2 (1.9%)	3 (0.7%)	9 (1.2%)	9 (1.3%)	21 (1.1%)	4 (1.2%)
Drug abuse	0	5 (1.1%)	7 (0.9%)	9 (1.3%)	21 (1.1%)	0
Delusion	0	1 (0.2%)	6 (0.8%)	8 (1.2%)	15 (0.8%)	2 (0.6%)
Apathy	1 (0.9%)	1 (0.2%)	0	5 (0.7%)	6 (0.3%)	0
Depression aggravated	0	2 (0.4%)	2 (0.3%)	4 (0.6%)	8 (0.4%)	0
Nervousness	0	1 (0.2%)	3 (0.4%)	4 (0.6%)	8 (0.4%)	0
Manic reaction	0	1 (0.2%)	1 (0.1%)	3 (0.4%)	5 (0.3%)	0
Thinking abnormal	0	1 (0.2%)	1 (0.1%)	3 (0.4%)	5 (0.3%)	1 (0.3%)
Confusion	0	0	0	1 (0.1%)	1 (0.1%)	1 (0.3%)
Sleep disorder	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.3%)
Somnolence	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Anorexia	0	1 (0.2%)	0	0	1 (0.1%)	0
Concentration impaired	0	0	1 (0.1%)	0	1 (0.1%)	0
Delirium	0	0	1 (0.1%)	0	1 (0.1%)	0
Depression psychotic	0	0	1 (0.1%)	0	1 (0.1%)	0
Emotional lability	0	0	0	0	0	1 (0.3%)
Euphoria	0	0	2 (0.3%)	0	2 (0.1%)	0
Paranoia	0	0	0	0	0	1 (0.3%)
Personality disorder	0	1 (0.2%)	0	0	1 (0.1%)	2 (0.6%)
Body as a whole - general disorders	**1 (0.9%)**	**8 (1.7%)**	**13 (1.8%)**	**24 (3.5%)**	**45 (2.4%)**	**4 (1.2%)**
Injury	1 (0.9%)	5 (1.1%)	5 (0.7%)	19 (2.8%)	29 (1.5%)	2 (0.6%)
Asthenia	0	0	0	2 (0.3%)	2 (0.1%)	0
Back pain	0	0	0	1 (0.1%)	1 (0.1%)	1 (0.3%)
Leg pain	0	0	0	1 (0.1%)	1 (0.1%)	0
Oedema peripheral	0	1 (0.2%)	0	1 (0.1%)	2 (0.1%)	0
Therapeutic response increased	0	0	0	1 (0.1%)	1 (0.1%)	0
Blood alcohol excessive	0	0	1 (0.1%)	0	1 (0.1%)	1 (0.3%)
Chest pain	0	0	1 (0.1%)	0	1 (0.1%)	0
Death	0	1 (0.2%)	0	0	1 (0.1%)	0
Fever	0	1 (0.2%)	1 (0.1%)	0	2 (0.1%)	0
Malaise	0	0	1 (0.1%)	0	1 (0.1%)	0
Pain	0	0	1 (0.1%)	0	1 (0.1%)	0
Sudden death	0	1 (0.2%)	0	0	1 (0.1%)	0
Syncope	0	0	4 (0.5%)	0	4 (0.2%)	0

WHO Organ System/ WHO Preferred Term	Placebo depot (N=107)	RIS depot 25 mg (N=461)	RIS depot 50 mg (N=738)	RIS depot 75 mg (N=677)	RIS depot Total (N=1910)[b]	RIS oral Total (N=321)
Centr & periph nervous system disorders	**1 (0.9%)**	**2 (0.4%)**	**7 (0.9%)**	**6 (0.9%)**	**15 (0.8%)**	**3 (0.9%)**
Hyperkinesia	0	1 (0.2%)	0	2 (0.3%)	3 (0.2%)	1 (0.3%)
Convulsions	1 (0.9%)	0	2 (0.3%)	1 (0.1%)	3 (0.2%)	0
Dyskinesia	0	0	0	1 (0.1%)	1 (0.1%)	0
Dystonia	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Extrapyramidal disorder	0	0	0	1 (0.1%)	1 (0.1%)	0
Headache	0	1 (0.2%)	0	1 (0.1%)	2 (0.1%)	0
Apraxia	0	0	1 (0.1%)	0	1 (0.1%)	0
Dementia	0	0	1 (0.1%)	0	1 (0.1%)	0
Dizziness	0	0	1 (0.1%)	0	1 (0.1%)	0
Hypertonia	0	0	2 (0.3%)	0	2 (0.1%)	0
Hypoaesthesia	0	0	0	0	0	1 (0.3%)
Hypokinesia	0	0	0	0	0	1 (0.3%)
Neuroleptic malignant syndrome	0	0	1 (0.1%)	0	1 (0.1%)	0
Vertigo	0	1 (0.2%)	0	0	1 (0.1%)	0
Gastro-intestinal system disorder	**0**	**2 (0.4%)**	**6 (0.8%)**	**4 (0.6%)**	**12 (0.6%)**	**1 (0.3%)**
Gastro-intestinal disorder NOS	0	0	0	2 (0.3%)	2 (0.1%)	0
Abdominal pain	0	1 (0.2%)	0	1 (0.1%)	2 (0.1%)	0
Appendicitis	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Diarrhoea	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Nausea	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
GI haemorrhage	0	1 (0.2%)	0	0	1 (0.1%)	0
Haemorrhoids	0	0	0	0	0	1 (0.3%)
Intestinal perforation	0	0	1 (0.1%)	0	1 (0.1%)	0
Peritonitis	0	0	1 (0.1%)	0	1 (0.1%)	0
Saliva increased	0	0	1 (0.1%)	0	1 (0.1%)	0
Vomiting	0	0	3 (0.4%)	0	3 (0.2%)	0
Respiratory system disorders	**0**	**3 (0.7%)**	**2 (0.3%)**	**3 (0.4%)**	**8 (0.4%)**	**1 (0.3%)**
Bronchitis	0	1 (0.2%)	0	2 (0.3%)	3 (0.2%)	0
Pneumonia	0	1 (0.2%)	0	1 (0.1%)	2 (0.1%)	0
Pneumonia lobar	0	0	0	1 (0.1%)	1 (0.1%)	0
Asthma	0	0	0	0	0	1 (0.3%)
Chronic obstruct airways disease	0	0	1 (0.1%)	0	1 (0.1%)	0
Hyperventilation	0	0	1 (0.1%)	0	1 (0.1%)	0
Pulmonary oedema	0	1 (0.2%)	0	0	1 (0.1%)	0
Secondary terms	**0**	**4 (0.9%)**	**3 (0.4%)**	**3 (0.4%)**	**10 (0.5%)**	**3 (0.9%)**
Surgical intervention	0	1 (0.2%)	2 (0.3%)	3 (0.4%)	6 (0.3%)	0
Food poisoning	0	0	0	1 (0.1%)	1 (0.1%)	0
Lumbar disc lesion	0	0	0	1 (0.1%)	1 (0.1%)	0
Post-operative pain	0	0	0	1 (0.1%)	1 (0.1%)	0
Alcohol problem	0	3 (0.7%)	1 (0.1%)	0	4 (0.2%)	2 (0.6%)
Fall	0	0	1 (0.1%)	0	1 (0.1%)	0
Family stress	0	0	0	0	0	1 (0.3%)

WHO Organ System/ WHO Preferred Term	Placebo depot (N=107)	RIS depot 25 mg (N=461)	RIS depot 50 mg (N=738)	RIS depot 75 mg (N=677)	RIS depot Total (N=1910)[b]	RIS oral Total (N=321)
Vascular (extracardiac) disorder	0	2 (0.4%)	0	3 (0.4%)	5 (0.3%)	1 (0.3%)
Cerebrovascular disorder	0	0	0	2 (0.3%)	2 (0.1%)	1 (0.3%)
Phlebitis	0	1 (0.2%)	0	1 (0.1%)	2 (0.1%)	0
Vein varicose	0	1 (0.2%)	0	0	1 (0.1%)	0
Musculo-skeletal system disorder	0	1 (0.2%)	0	2 (0.3%)	3 (0.2%)	0
Arthralgia	0	0	0	1 (0.1%)	1 (0.1%)	0
Spondylitis ankylosing	0	0	0	1 (0.1%)	1 (0.1%)	0
Arthrosis	0	1 (0.2%)	0	0	1 (0.1%)	0
Synovitis	0	1 (0.2%)	0	0	1 (0.1%)	0
Platelet, bleeding & clotting disorders	0	0	0	2 (0.3%)	2 (0.1%)	0
Embolism pulmonary	0	0	0	1 (0.1%)	1 (0.1%)	0
Purpura	0	0	0	1 (0.1%)	1 (0.1%)	0
Cardiovascular disorders, general	0	2 (0.4%)	2 (0.3%)	1 (0.1%)	5 (0.3%)	2 (0.6%)
Cardiac failure	0	2 (0.4%)	1 (0.1%)	1 (0.1%)	4 (0.2%)	1 (0.3%)
Hypertension aggravated	0	0	0	0	0	1 (0.3%)
Pulse weak	0	0	1 (0.1%)	0	1 (0.1%)	0
Heart rate and rhythm disorders	0	1 (0.2%)	0	1 (0.1%)	2 (0.1%)	0
Bradycardia	0	0	0	1 (0.1%)	1 (0.1%)	0
Arrhythmia atrial	0	1 (0.2%)	0	0	1 (0.1%)	0
Liver and biliary system disorders	0	3 (0.7%)	2 (0.3%)	1 (0.1%)	6 (0.3%)	0
Hepatic enzymes increased	0	0	0	1 (0.1%)	1 (0.1%)	0
Cholecystitis	0	2 (0.4%)	1 (0.1%)	0	3 (0.2%)	0
Hepatocellular damage	0	0	1 (0.1%)	0	1 (0.1%)	0
Jaundice	0	1 (0.2%)	0	0	1 (0.1%)	0
Metabolic and nutritional disorders	0	0	4 (0.5%)	1 (0.1%)	5 (0.3%)	2 (0.6%)
LDH increased	0	0	0	1 (0.1%)	1 (0.1%)	0
Diabetes mellitus	0	0	0	0	0	1 (0.3%)
Glycosuria	0	0	1 (0.1%)	0	1 (0.1%)	0
Hyperglycaemia	0	0	0	0	0	1 (0.3%)
Hypervolaemia	0	0	1 (0.1%)	0	1 (0.1%)	0
Hypoglycaemia	0	0	1 (0.1%)	0	1 (0.1%)	0
Hypokalaemia	0	0	1 (0.1%)	0	1 (0.1%)	0
Hyponatraemia	0	0	1 (0.1%)	0	1 (0.1%)	0
Hypovitaminosis	0	0	1 (0.1%)	0	1 (0.1%)	0
Myo-, endo-, pericardial & valve disorders	0	2 (0.4%)	4 (0.5%)	1 (0.1%)	7 (0.4%)	0
Myocardial infarction	0	2 (0.4%)	3 (0.4%)	1 (0.1%)	6 (0.3%)	0
Angina pectoris	0	0	2 (0.3%)	0	2 (0.1%)	0

WHO Organ System/ WHO Preferred Term	Placebo depot (N=107)	RIS depot 25 mg (N=461)	RIS depot 50 mg (N=738)	RIS depot 75 mg (N=677)	RIS depot Total (N=1910)[b]	RIS oral Total (N=321)
Reproductive disorders, female disorders	**0**	**0**	**2 (0.3%)**	**1 (0.1%)**	**3 (0.2%)**	**0**
Intermenstrual bleeding	0	0	0	1 (0.1%)	1 (0.1%)	0
Uterovaginal prolapse	0	0	2 (0.3%)	0	2 (0.1%)	0
Resistance mechanism disorders	**0**	**0**	**0**	**1 (0.1%)**	**1 (0.1%)**	**0**
Abscess	0	0	0	1 (0.1%)	1 (0.1%)	0
White cell and res disorders	**0**	**0**	**0**	**1 (0.1%)**	**1 (0.1%)**	**0**
Leukocytosis	0	0	0	1 (0.1%)	1 (0.1%)	0
Lymphopenia	0	0	0	1 (0.1%)	1 (0.1%)	0
Neoplasm	**0**	**1 (0.2%)**	**3 (0.4%)**	**0**	**5 (0.3%)**	**0**
Breast neoplasm malignant female	0	0	1 (0.1%)	0	1 (0.1%)	0
Neoplasm NOS	0	1 (0.2%)	2 (0.3%)	0	4 (0.2%)	0
Red blood cell disorders	**0**	**0**	**0**	**0**	**0**	**1 (0.3%)**
Anaemia	0	0	0	0	0	1 (0.3%)
Reproductive disorders, male	**0**	**0**	**1 (0.1%)**	**0**	**1 (0.1%)**	**0**
Hernia inguinal	0	0	1 (0.1%)	0	1 (0.1%)	0
Skin and appendages disorders	**0**	**2 (0.4%)**	**0**	**0**	**2 (0.1%)**	**0**
Hyperkeratosis	0	1 (0.2%)	0	0	1 (0.1%)	0
Rash erythematous	0	1 (0.2%)	0	0	1 (0.1%)	0
Urinary system disorders	**0**	**0**	**2 (0.3%)**	**0**	**2 (0.1%)**	**0**
Urinary retention	0	0	1 (0.1%)	0	1 (0.1%)	0
Urinary tract infection	0	0	1 (0.1%)	0	1 (0.1%)	0
Vision disorders	**0**	**0**	**1 (0.1%)**	**0**	**1 (0.1%)**	**0**
Retinal disorder	0	0	1 (0.1%)	0	1 (0.1%)	0
Vision abnormal	0	0	1 (0.1%)	0	1 (0.1%)	0

Source: Table AE.6CX ISS.POOL; Listing AE.1 (RIS-INT-72)

a) Combined data from ISS database, RIS-INT-72 database, and four-month safety update database (RIS-INT-63 and RIS-USA-196 through May 15, 2001). Extension trial patients who were in the oral risperidone group (RIS-INT-61) or placebo depot group (RIS-USA-121) are included in both their original group and, as new patients, in the RIS depot group corresponding to their mode dose during the extension trial. All other patients are in the RIS depot group corresponding to their group in their original trial.

b) Patients in the cross-over trial, RIS-INT-54, are counted once. Patients taking RIS depot in both their previous and extension trial are counted once. Patients in RIS-INT-62 or RIS-JPN-16 are not included in this total. This total also includes 9 patients treated with RIS depot 100 mg (RIS-INT-38), 24 patients treated with RIS depot 37.5 mg (RIS-INT-72), and 26 patients treated with RIS depot 62.5 mg (RIS-INT-72). One 37.5-mg patient (neoplasm NOS) and one 62.5-mg patient (anxiety) experienced a treatment-emergent AE that was serious.

NOTE: A review of the sponsor's drug safety surveillance database (JIPSY) resulted in 29 additional patients with serious adverse events by May 15, 2001. These events have not undergone clinical data review and are not included in this table. See Section 13 of the Four Month Safety Update for more details.

Table 3: Treatment-emergent adverse events leading to discontinuation by body system and treatment: all closed Phase 1, 2, and 3 trials plus extension trials through May 15, 2001[a] [n (%%)]

WHO Organ System/ WHO Preferred Term	Placebo depot (N=107)	RIS depot 25 mg (N=861)	RIS depot 50 mg (N=738)	RIS depot 75 mg (N=677)	RIS depot Total (N=1910)[b]	RIS oral Total (N=321)
Any discontinuation due to adverse event	13 (12.1%)	43[c] (9.3%)	53 (7.2%)	54 (8.0%)	150 (7.8%)	13 (4.0%)
Psychiatric disorders	11 (10.3%)	28 (6.1%)	32 (4.3%)	40 (5.9%)	100 (5.2%)	7 (2.2%)
Psychosis	7 (6.5%)	13 (2.8%)	13 (1.8%)	11 (1.6%)	37 (1.9%)	2 (0.6%)
Hallucination	1 (0.9%)	3 (0.7%)	3 (0.4%)	7 (1.0%)	13 (0.7%)	1 (0.3%)
Anxiety	1 (0.9%)	1 (0.2%)	4 (0.5%)	4 (0.6%)	9 (0.5%)	2 (0.6%)
Delusion	0	1 (0.2%)	1 (0.1%)	4 (0.6%)	6 (0.3%)	1 (0.3%)
Depression	1 (0.9%)	3 (0.7%)	2 (0.3%)	4 (0.6%)	9 (0.5%)	0
Suicide attempt	1 (0.9%)	3 (0.7%)	8 (1.1%)	4 (0.6%)	15 (0.8%)	0
Agitation	2 (1.9%)	6 (1.3%)	4 (0.5%)	3 (0.4%)	13 (0.7%)	1 (0.3%)
Paranoid reaction	0	1 (0.2%)	1 (0.1%)	3 (0.4%)	5 (0.3%)	1 (0.3%)
Somnolence	0	0	2 (0.3%)	3 (0.4%)	5 (0.3%)	1 (0.3%)
Apathy	0	0	0	2 (0.3%)	2 (0.1%)	0
Drug abuse	0	0	0	2 (0.3%)	2 (0.1%)	0
Insomnia	0	2 (0.4%)	2 (0.3%)	2 (0.3%)	6 (0.3%)	1 (0.3%)
Libido decreased	0	0	0	1 (0.1%)	1 (0.1%)	0
Nervousness	1 (0.9%)	0	0	1 (0.1%)	1 (0.1%)	0
Thinking abnormal	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Aggressive reaction	0	0	3 (0.4%)	0	3 (0.2%)	0
Concentration impaired	0	0	1 (0.1%)	0	1 (0.1%)	0
Depression aggravated	0	1 (0.2%)	1 (0.1%)	0	2 (0.1%)	0
Impotence	0	2 (0.4%)	0	0	2 (0.1%)	0
Centr & periph nervous system disorders	1 (0.9%)	7 (1.5%)	9 (1.2%)	8 (1.2%)	24 (1.3%)	1 (0.3%)
Extrapyramidal disorder	0	2 (0.4%)	2 (0.3%)	3 (0.4%)	7 (0.4%)	0
Hyperkinesia	1 (0.9%)	2 (0.4%)	2 (0.3%)	3 (0.4%)	7 (0.4%)	1 (0.3%)
Dyskinesia	0	0	0	1 (0.1%)	1 (0.1%)	0
Dystonia	1 (0.9%)	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Hypertonia	0	2 (0.4%)	2 (0.3%)	1 (0.1%)	5 (0.3%)	0
Hypokinesia	0	0	0	1 (0.1%)	1 (0.1%)	0
Convulsions	0	0	2 (0.3%)	0	2 (0.1%)	0
Dizziness	0	1 (0.2%)	0	0	1 (0.1%)	0
Tremor	0	0	1 (0.1%)	0	1 (0.1%)	0
Vertigo	0	1 (0.2%)	0	0	1 (0.1%)	0
Body as a whole - general disorders	1 (0.9%)	2 (0.4%)	1 (0.1%)	2 (0.3%)	5 (0.3%)	0
Asthenia	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	0
Injury	1 (0.9%)	1 (0.2%)	0	1 (0.1%)	2 (0.1%)	0
Death	0	1 (0.2%)	0	0	1 (0.1%)	0
Malaise	0	1 (0.2%)	0	0	1 (0.1%)	0
Cardiovascular disorders, general	0	1 (0.2%)	2 (0.3%)	2 (0.3%)	5 (0.3%)	0
Cardiac failure	0	0	0	1 (0.1%)	1 (0.1%)	0
ECG abnormal	0	1 (0.2%)	2 (0.3%)	1 (0.1%)	4 (0.2%)	0

WHO Organ System/ WHO Preferred Term	Placebo depot (N=107)	RIS depot 25 mg (N=461)	RIS depot 50 mg (N=738)	RIS depot 75 mg (N=677)	RIS depot Total (N=1910)[a]	RIS oral Total (N=321)
Metabolic and nutritional disorders	0	2 (0.4%)	2 (0.3%)	2 (0.3%)	6 (0.3%)	0
Weight increase	0	1 (0.2%)	1 (0.1%)	2 (0.3%)	4 (0.2%)	0
Cachexia	0	1 (0.2%)	0	0	1 (0.1%)	0
Hyponatraemia	0	0	1 (0.1%)	0	1 (0.1%)	0
Vascular (extracardiac) disorders	0	0	1 (0.1%)	2 (0.3%)	3 (0.2%)	0
Cerebrovascular disorder	0	0	0	2 (0.3%)	2 (0.1%)	0
Thrombophlebitis	0	0	1 (0.1%)	0	1 (0.1%)	0
Heart rate and rhythm disorders	0	0	0	1 (0.1%)	1 (0.1%)	1 (0.3%)
Bundle branch block	0	0	0	1 (0.1%)	1 (0.1%)	1 (0.3%)
Platelet, bleeding & clotting disorders	0	0	0	1 (0.1%)	1 (0.1%)	0
Embolism pulmonary	0	0	0	1 (0.1%)	1 (0.1%)	0
Reproductive disorders, female	0	1 (0.2%)	1 (0.1%)	1 (0.1%)	3 (0.2%)	1 (0.3%)
Amenorrhoea	0	0	1 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.3%)
Lactation nonpuerperal	0	1 (0.2%)	1 (0.1%)	0	2 (0.1%)	0
Reproductive disorders, male	0	1 (0.2%)	0	1 (0.1%)	2 (0.1%)	1 (0.3%)
Breast discharge	0	0	0	1 (0.1%)	1 (0.1%)	0
Sexual function abnormal	0	1 (0.2%)	0	0	1 (0.1%)	1 (0.3%)
Application site disorders	0	0	1 (0.1%)	0	1 (0.1%)	1 (0.3%)
Injection site pain	0	0	1 (0.1%)	0	1 (0.1%)	1 (0.3%)
Endocrine disorders	0	0	1 (0.1%)	0	1 (0.1%)	2 (0.6%)
Hyperprolactinaemia	0	0	1 (0.1%)	0	1 (0.1%)	2 (0.6%)
Gastrointestinal system disorders	0	0	3 (0.4%)	0	3 (0.2%)	0
Intestinal perforation	0	0	1 (0.1%)	0	1 (0.1%)	0
Peritonitis	0	0	1 (0.1%)	0	1 (0.1%)	0
Saliva increased	0	0	1 (0.1%)	0	1 (0.1%)	0
Vomiting	0	0	1 (0.1%)	0	1 (0.1%)	0
Liver and biliary system disorders	0	2 (0.4%)	1 (0.1%)	0	3 (0.2%)	0
Cholecystitis	0	1 (0.2%)	0	0	1 (0.1%)	0
Gamma-GT increased	0	0	1 (0.1%)	0	1 (0.1%)	0
Jaundice	0	1 (0.2%)	0	0	1 (0.1%)	0
SGOT increased	0	0	1 (0.1%)	0	1 (0.1%)	0
SGPT increased	0	0	1 (0.1%)	0	1 (0.1%)	0
Myo-, endo-, pericardial & valve disorders	0	0	1 (0.1%)	0	1 (0.1%)	0
Myocardial infarction	0	0	1 (0.1%)	0	1 (0.1%)	0

WHO Organ System/ WHO Preferred Term	Placebo depot (N=107)	RIS depot 25 mg (N=461)	RIS depot 50 mg (N=738)	RIS depot 75 mg (N=677)	RIS depot Total (N=1910)[b]	RIS oral Total (N=321)
Respiratory system disorders	1 (0.9%)	0	0	0	0	1 (0.3%)
Asthma	0	0	0	0	0	1 (0.3%)
Dyspnoea	1 (0.9%)	0	0	0	0	0
Secondary terms	1 (0.9%)	1 (0.2%)	0	0	1 (0.1%)	0
Alcohol problem	0	1 (0.2%)	0	0	1 (0.1%)	0
Inflicted injury	1 (0.9%)	0	0	0	0	0
Skin and appendages disorders	0	1 (0.2%)	1 (0.1%)	0	2 (0.1%)	0
Rash	0	0	1 (0.1%)	0	1 (0.1%)	0
Rash erythematous	0	1 (0.2%)	0	0	1 (0.1%)	0
Urinary system disorders	0	0	2 (0.3%)	0	2 (0.1%)	0
Urinary incontinence	0	0	1 (0.1%)	0	1 (0.1%)	0
Urinary retention	0	0	1 (0.1%)	0	1 (0.1%)	0
White cell and rex disorders	0	0	0	0	0	1 (0.3%)
Leucopenia	0	0	0	0	0	1 (0.3%)

Source: Table AE.5BX ISS.POOL

a) Combined data from ISS database, RIS-INT-72 database, and four-month safety update database (RIS-INT-63 and RIS-USA-196 through May 15, 2001). Extension trial patients who were in the oral risperidone group (RIS-INT-61) or placebo depot group (RIS-USA-121) are included in both their original group and, as new patients, in the RIS depot group corresponding to their mode dose during the extension trial. All other patients are in the RIS depot group corresponding to their group in their original trial.

b) Patients in the cross-over trial, RIS-INT-54, are counted once. Patients taking RIS depot in both their previous and extension trial are counted once. Patients in RIS-INT-62 or RIS-JPN-16 are not included in this total. This total also includes 9 patients treated with RIS depot 100 mg (RIS-INT-38), 24 patients treated with RIS depot 37.5 mg (RIS-INT-72), and 26 patients treated with RIS depot 62.5 mg (RIS-INT-72). None of these patients died or had an adverse event leading to discontinuation.

c) Does not include Patient A30068 who experienced an adverse event during the 15-week follow-up/washout period between Part 1 and Part 2 of RIS-INT-54, but not within the 49-day therapeutic reach defined for the ISS.

Eight patients, all with schizophrenia, died in the repeated-dose studies in the original submission. Four patients committed suicide (RIS-INT-57), one patient died of multiple injuries that were not self-inflicted (RIS-USA-121), and three died from cardiac failure (RIS-INT-57 and RIS-INT-61). In addition, one patient with schizophrenia in RIS-INT-57, was diagnosed with breast cancer 42 days after her last injection and died approximately 3 months after discontinuing from the trial. In the single-dose trials, two patients died from myocardial infarctions (RIS-INT-54, one patient beyond the 49-day therapeutic window for the ISS) and one patient died from suicide (RIS-INT-72). The patients who died of myocardial infarction or cardiac failure, all had predisposing factors. In the trial population of 1345 patients with schizophrenia who received risperidone depot microspheres in the repeated-dose trials, four patients (0.3%) died of suicide.

A total of six patients, one from RIS-USA-196 and five from RIS-INT-63, died during the extension trials. All six entered the trials with a diagnosis of schizophrenia. Causes of death were: perforated bowel secondary to colon cancer, suicide (two patients), cardiac failure, craniocerebral injury due to an automobile accident, and sudden death. Only one patient (sudden death) was more than 65 years of age.

D. Adequacy of Safety Testing

Adverse events, laboratory data, vital sign values, electrocardiogram (ECG) parameters, Extrapyramidal Symptom Rating Scale (ESRS) scores, and extrapyramidal symptom (EPS)-, glucose-, and potentially prolactin-related adverse events were the assessment parameters examined to evaluate the safety of risperidone depot microspheres treatment.

Safety data were derived from a total of 2101 patients (1932 patients with schizophrenia, 163 patients with schizoaffective disorder, and 6 patients with schizophreniform disorder). Of these patients, 1499 patients received risperidone depot microspheres in repeated-dose trials, corresponding to approximately 543 patient-years of exposure.

The Division agreed that the number of patients enrolled in RIS-INT-57, the open-label, 12-month safety trial (579 patients treated for approximately 6 months, and 361 patients treated for approximately 1 year),

DRUG-DRUG AND DRUG-DISEASE INTERACTION

No specific drug-drug or drug-disease interaction trials were performed with risperidone depot microspheres.

WITHDRAWAL EFFECTS

No examination of withdrawal effects of risperidone depot microspheres administration was performed.

OVERDOSE AND ABUSE POTENTIAL

No cases of overdose were reported in premarketing studies with RISPERDAL Long-Acting Microspheres. There has been no systematic examination of RISPERDAL Long-Acting Microspheres in animals or humans for its tolerance, physical dependence or abuse potential. Risperidone is not considered a controlled substance.

VIII. Dosing, Regimen, and Administration Issues

The sponsor's dosing recommendations which seem reasonable are reproduced below in italics.

1 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The subgroup analyses were performed for total PANSS, positive and negative symptoms subscales, and CGI. Analyses were performed for subgroups of patients defined by the following demographic variables:

_ Sex (male, female)
_ Age group (<65 years, _65 years)
_ Race (black, white and other)

In RIS-USA-121 and RIS-INT-61 patients were divided into two groups based on the median baseline total PANSS score in the trial:

	RIS-USA-121	RIS-INT-61
High severity group	>81	>67
Low severity group	_81	_67

No specific drug-drug or drug-disease interaction trials were performed with risperidone depot microspheres.

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

Subgroup analysis by sex, race, and body mass index (BMI) did not show differences for treatment-emergent adverse events.

SEX:

Overall a higher percentage of females than males reported adverse events in the combined risperidone depot groups. A dose-related increase in adverse events was found in females, 66.9%, 71.0%, and 73.8% for the 25-mg, 50-mg, and 75-mg groups, respectively. In males, incidences of adverse events were

comparable between the 25-mg (67.0%) and 50-mg (66.9%) groups, and somewhat higher in the 75-mg group (72.0%). The adverse event profile looks similar across genders.

In the first 3 months of treatment, weight increase was more frequently reported in females (3.4%) in the combined depot group, versus 2% in males. However, from 3 months onward, more males (5.4%) reported weight gain compared with females (2.4%) (Table AE.1F ISS). No other relevant differences were observed between genders. Table 43 presents treatment-emergent adverse events during the first 3 months of treatment for male and female patients with schizophrenia.

Table 43: Treatment emergent adverse events occurring in ≥5% and more than two patients in any treatment group during the first 3 months of treatment by gender: repeated dose trials n (%) (patients with schizophrenia)

WHO Organ System WHO Preferred Term	Male					Female				
	Placebo depot	RIS depot 25 mg	RIS depot 50 mg	RIS depot 75 mg	RIS depot Total	Placebo depot	RIS depot 25 mg	RIS depot 50 mg	RIS depot 75 mg	RIS depot Total
	(N=301)	(N=215)	(N=159)	(N=357)	(N=731)	(N=109)	(N=127)	(N=139)	(N=240)	(N=414)
Any adverse event	67 (83.8%)	144 (67.0%)	240 (66.3%)	256 (71.8%)	641 (68.9%)	84 (77.8%)	86 (66.9%)	98 (71.0%)	170 (70.8%)	295 (71.3%)
Psychiatric disorders	49 (61.3%)	79 (36.7%)	113 (32.6%)	171 (47.9%)	367 (39.4%)	60 (55.6%)	38 (29.6%)	51 (37.0%)	71 (47.7%)	160 (38.6%)
Anxiety	12 (15.0%)	19 (8.8%)	29 (8.2%)	50 (14.0%)	98 (10.5%)	5 (16.7%)	7 (5.5%)	15 (10.8%)	25 (10.4%)	47 (11.4%)
Insomnia	21 (26.3%)	23 (10.7%)	38 (10.6%)	59 (16.5%)	120 (12.9%)	5 (16.7%)	12 (9.4%)	18 (13.0%)	19 (12.5%)	49 (11.8%)
Psychosis	17 (21.3%)	13 (7.9%)	20 (5.6%)	47 (13.2%)	84 (9.0%)	6 (33.3%)	7 (5.5%)	6 (4.3%)	25 (10.4%)	38 (9.2%)
Agitation	24 (30.0%)	14 (6.5%)	21 (5.9%)	30 (8.4%)	65 (7.0%)	0	10 (7.9%)	9 (6.5%)	15 (10.1%)	34 (8.2%)
Depression	3 (3.8%)	11 (5.1%)	11 (3.1%)	24 (6.7%)	46 (4.9%)	0	7 (5.5%)	7 (5.0%)	9 (6.0%)	23 (5.6%)
Hallucination	5 (6.3%)	5 (2.3%)	9 (2.5%)	15 (4.2%)	29 (3.1%)	0	4 (3.1%)	3 (2.2%)	6 (4.0%)	13 (3.1%)
Paranoid reaction	4 (5.0%)	1 (0.5%)	4 (1.1%)	9 (2.5%)	14 (1.5%)	0	0	0	1 (0.7%)	1 (0.2%)
Nervousness	4 (5.0%)	2 (0.9%)	5 (1.4%)	7 (2.0%)	13 (1.4%)	2 (5.6%)	2 (1.6%)	1 (0.7%)	4 (2.7%)	7 (1.7%)
Central & peripheral nervous system disorders	**25 (31.3%)**	**48 (22.3%)**	**100 (27.9%)**	**103 (28.8%)**	**251 (27.0%)**	**3 (16.7%)**	**31 (24.4%)**	**58 (37.5%)**	**66 (30.9%)**	**115 (27.8%)**
Headache	10 (12.5%)	24 (11.2%)	41 (11.4%)	41 (11.5%)	106 (11.4%)	2 (11.1%)	15 (11.8%)	12 (8.7%)	17 (11.4%)	44 (10.6%)
Extrapyramidal disorder	3 (3.8%)	5 (2.3%)	13 (3.6%)	19 (5.3%)	37 (4.0%)	0	5 (3.9%)	6 (4.3%)	9 (6.0%)	20 (4.8%)
Dizziness	5 (6.3%)	7 (3.3%)	14 (3.9%)	15 (4.2%)	36 (3.9%)	0	4 (3.1%)	9 (6.5%)	10 (6.7%)	23 (5.6%)
Hypertonia	2 (2.5%)	11 (5.1%)	18 (5.0%)	14 (3.9%)	43 (4.6%)	2 (11.1%)	4 (3.1%)	4 (2.9%)	12 (8.1%)	20 (4.8%)
Hypotonia	5 (6.3%)	3 (1.4%)	13 (3.6%)	12 (3.4%)	28 (3.0%)	0	2 (1.6%)	2 (1.4%)	8 (5.4%)	12 (2.9%)
Tremor	0	3 (1.4%)	2 (0.6%)	12 (3.4%)	17 (1.8%)	0	2 (1.6%)	9 (6.5%)	4 (2.7%)	15 (3.6%)
Body as a whole – general disorders	**13 (16.3%)**	**30 (14.0%)**	**52 (14.5%)**	**59 (16.5%)**	**141 (15.1%)**	**6 (33.3%)**	**24 (18.9%)**	**27 (19.4%)**	**22 (14.8%)**	**73 (17.6%)**
Asthenia	0	4 (1.9%)	13 (3.6%)	18 (5.0%)	35 (3.8%)	0	6 (4.7%)	10 (7.2%)	5 (3.4%)	21 (5.1%)
Pain	2 (2.5%)	7 (3.3%)	11 (3.0%)	7 (2.0%)	17 (1.8%)	1 (5.6%)	3 (2.4%)	5 (3.6%)	2 (1.3%)	10 (2.4%)
Injury	5 (6.3%)	2 (0.9%)	5 (1.4%)	14 (3.9%)	21 (2.2%)	1 (5.6%)	1 (0.8%)	2 (1.4%)	1 (0.7%)	4 (1.0%)
Respiratory system disorders	**11 (13.8%)**	**29 (13.5%)**	**39 (11.1%)**	**47 (13.2%)**	**116 (12.5%)**	**3 (16.7%)**	**22 (17.3%)**	**10 (7.2%)**	**21 (14.1%)**	**53 (12.8%)**
Rhinitis	5 (6.3%)	14 (6.5%)	21 (5.8%)	25 (6.4%)	59 (6.2%)	3 (16.7%)	10 (7.9%)	7 (5.1%)	6 (4.0%)	23 (5.6%)
Bronchitis	0	4 (1.9%)	4 (1.1%)	5 (1.4%)	13 (1.4%)	0	3 (2.4%)	1 (0.7%)	4 (2.7%)	8 (1.9%)

WHO Organ System WHO Preferred Term	Male					Female				
	Placebo depot	RLS depot 25 mg	RLS depot 50 mg	RLS depot 75 mg	RLS depot Total	Placebo depot	RLS depot 25 mg	RLS depot 50 mg	RLS depot 75 mg	RLS depot Total
	(N=903)	(N=2153)	(N=1591)	(N=1357)	(N=5101)	(N=133)	(N=1279)	(N=1301)	(N=1199)	(N=4114)
Heart rate and rhythm disorders	11 (13.6%)	5 (2.3%)	10 (2.8%)	11 (3.1%)	26 (2.8%)	1 (5.6%)	6 (4.7%)	9 (6.5%)	7 (4.7%)	22 (5.3%)
Tachycardia	5 (7.5%)	1 (0.5%)	5 (1.4%)	5 (1.4%)	11 (1.2%)	0	1 (0.8%)	6 (4.3%)	2 (1.3%)	9 (2.2%)
Gastrointestinal system disorders	8 (10.0%)	33 (15.3%)	56 (15.6%)	58 (16.2%)	147 (15.8%)	4 (33.3%)	21 (16.5%)	26 (18.8%)	28 (18.8%)	75 (18.1%)
Vomiting	3 (3.8%)	4 (1.9%)	4 (1.1%)	7 (2.0%)	15 (1.6%)	1 (16.7%)	2 (1.6%)	4 (2.9%)	3 (2.0%)	9 (2.2%)
Metabolic and nutritional disorders	4 (5.0%)	8 (3.7%)	13 (3.6%)	8 (2.2%)	29 (3.1%)	1 (5.6%)	6 (4.7%)	7 (5.1%)	7 (4.7%)	20 (4.8%)
Weight increase	1 (1.3%)	5 (2.3%)	8 (2.2%)	5 (1.4%)	18 (1.9%)	0 (0.0%)	2 (1.6%)	3 (2.2%)	3 (2.0%)	8 (1.9%)

Source: Table 4.2.1.7.1.3.3

Includes Trials RIS-INT-3A-121, RIS-INT-37, RIS-INT-61, RIS-INT-31, RIS-SWE-17, RIS-INT-32.

RACE:

Overall, more black patients reported adverse events compared with white patients (77.2% versus 67.4%) in the combined depot group. Regardless of race, the highest number of adverse events was reported in the 75-mg group for depot-treated patients. Psychiatric disorders were the most frequently reported adverse events in both racial groups. In this category, somnolence was reported more frequently by black patients (11.4%) than white patients (2.6%). Smaller differences were seen in the overall reporting of agitation (10.8% in black patients versus 5.6% in white patients), depression (1.2% in black patients versus 6.1% in white patients), and anxiety (12.2% in white patients versus 5.4% in black patients). Headache was more frequently reported in black patients (16.8% versus 10.1% in white patients). While there were no dose-related increases in headache observed in white patients in the depot treatment groups, such increases were clearly observed in black patients, 8.7%, 16.4%, and 22.7%, in the 25-mg, 50-mg, and 75-mg groups, respectively. Gastrointestinal disorders also were more frequently reported by black patients (25.1%) compared with white patients (15%). A higher percentage of black patients reported skin problems, primarily in the 75-mg group (15.2% in blacks versus 5% in whites). This was due to a difference in reporting of rash in this dose group, 7.6% in blacks compared with 1% in whites.

Very few black patients were treated beyond 3 months; most black patients were enrolled in RIS-USA-121, which only treated patients up to 12 weeks. Therefore, no attempt was made to compare the adverse events between racial groups after the first 3 months of treatment. Table 44 presents treatment-emergent adverse events during the first 3 months of treatment by race for patients with schizophrenia.

Table 44: Treatment emergent adverse events occurring in ≥5% of patients in any treatment group during the first 3 months of treatment by race: repeated dose trials n (%) (patients with schizophrenia)

WHO Organ System WHO Preferred term	White					Black				
	Placebo dosed	RIS dosed 25 mg	RIS dosed 50 mg	RIS dosed 75 mg	RIS dosed Total	Placebo dosed	RIS dosed 25 mg	RIS dosed 50 mg	RIS dosed 75 mg	RIS dosed Total
	(N=451)	(N=263)	(N=402)	(N=402)	(N=1067)	(N=137)	(N=86)	(N=155)	(N=66)	(N=167)
Any Adverse Event	37 (82.2%)	169 (64.3%)	268 (66.7%)	282 (70.1%)	719 (67.4%)	93 (67.9%)	56 (65.1%)	89 (57.4%)	55 (83.3%)	129 (77.2%)
Psychiatric disorders	25 (55.6%)	83 (31.6%)	153 (38.1%)	159 (39.5%)	419 (39.4%)	24 (64.9%)	20 (43.5%)	14 (25.5%)	34 (51.5%)	68 (40.7%)
Insomnia	5 (11.1%)	22 (8.4%)	46 (11.4%)	63 (15.7%)	131 (12.3%)	7 (18.9%)	10 (21.7%)	3 (5.5%)	11 (16.7%)	24 (14.4%)
Anxiety	8 (17.8%)	22 (8.4%)	39 (9.7%)	69 (17.2%)	130 (12.2%)	5 (13.5%)	4 (8.7%)	1 (1.8%)	7 (10.6%)	9 (5.4%)
Psychosis	10 (22.2%)	14 (5.3%)	20 (5.0%)	57 (14.2%)	91 (8.5%)	9 (24.3%)	5 (10.9%)	3 (5.5%)	9 (13.6%)	17 (10.2%)
Depression	2 (4.4%)	16 (6.1%)	28 (6.9%)	33 (8.2%)	77 (7.2%)	1 (2.7%)	1 (2.2%)	0	1 (1.5%)	2 (1.2%)
Amnesia	10 (22.2%)	14 (5.3%)	21 (5.2%)	25 (6.2%)	60 (5.6%)	8 (21.6%)	4 (8.7%)	3 (5.5%)	11 (16.7%)	18 (10.8%)
Hallucination	1 (2.2%)	7 (2.7%)	10 (2.5%)	18 (4.5%)	35 (3.3%)	4 (10.8%)	0	1 (1.8%)	2 (3.0%)	3 (1.8%)
Somnolence	1 (2.2%)	3 (1.1%)	12 (3.0%)	13 (3.2%)	28 (2.6%)	2 (5.4%)	6 (13.0%)	5 (9.1%)	8 (12.1%)	19 (11.4%)
Suicide attempt	0	2 (0.8%)	10 (2.5%)	16 (4.0%)	28 (2.6%)	3 (8.1%)	0	0	0	0
Nervousness	1 (2.2%)	2 (0.8%)	6 (1.5%)	9 (2.2%)	17 (1.6%)	4 (10.8%)	0	0	2 (3.0%)	2 (1.2%)
Amnesia	0	2 (0.8%)	2 (0.5%)	1 (0.2%)	5 (0.5%)	2 (5.4%)	0	0	0	0
Central & peripheral nervous system disorders	15 (33.3%)	59 (22.4%)	101 (24.9%)	101 (26.6%)	266 (24.9%)	11 (29.7%)	7 (15.2%)	22 (40.0%)	29 (43.9%)	58 (34.7%)
Headache	8 (17.8%)	26 (10.2%)	41 (10.2%)	39 (9.7%)	106 (10.2%)	2 (5.4%)	4 (8.7%)	9 (16.4%)	15 (22.7%)	28 (16.8%)
Dizziness	1 (2.2%)	12 (4.6%)	15 (3.7%)	17 (4.2%)	44 (4.1%)	3 (8.1%)	0	4 (7.3%)	3 (4.5%)	7 (4.2%)
Extrapyramidal disorder	0	7 (2.7%)	15 (3.7%)	21 (5.2%)	43 (4.0%)	3 (8.1%)	0	2 (3.6%)	5 (7.6%)	7 (4.2%)
Dystonia	2 (4.4%)	4 (1.5%)	14 (3.5%)	23 (5.6%)	41 (3.8%)	3 (8.1%)	2 (4.3%)	4 (7.3%)	3 (4.5%)	10 (6.0%)
Hypertonia	2 (4.4%)	3 (1.1%)	10 (2.5%)	14 (3.5%)	27 (2.5%)	3 (8.1%)	0	3 (5.5%)	5 (7.6%)	8 (4.8%)
Dystonia	3 (6.7%)	1 (0.4%)	1 (0.2%)	4 (1.0%)	6 (0.6%)	0	0	0	2 (3.0%)	2 (1.2%)
Tremor	0	5 (1.9%)	8 (2.0%)	11 (2.7%)	24 (2.2%)	0	0	3 (5.5%)	3 (4.5%)	6 (3.6%)
Gastrointestinal system disorders	8 (17.8%)	31 (11.8%)	66 (16.4%)	63 (15.7%)	160 (15.0%)	6 (16.2%)	15 (32.6%)	12 (21.8%)	15 (22.7%)	42 (25.1%)
Constipation	0	7 (2.7%)	10 (2.5%)	12 (3.0%)	29 (2.7%)	1 (2.7%)	3 (6.5%)	1 (1.8%)	4 (6.1%)	8 (4.8%)
Dyspepsia	2 (4.4%)	3 (1.1%)	14 (3.5%)	10 (2.5%)	27 (2.5%)	0	4 (8.7%)	3 (5.5%)	3 (4.5%)	8 (4.8%)
Nausea	3 (6.7%)	2 (0.8%)	12 (3.0%)	12 (3.0%)	26 (2.4%)	2 (5.4%)	1 (2.2%)	1 (1.8%)	4 (6.1%)	6 (3.6%)
Vomiting	4 (8.9%)	4 (1.5%)	6 (1.5%)	8 (2.0%)	18 (1.7%)	2 (5.4%)	1 (2.2%)	2 (3.6%)	2 (3.0%)	5 (3.0%)
Salivation increased	0	4 (1.5%)	3 (0.7%)	4 (1.0%)	11 (1.0%)	1 (2.7%)	4 (8.7%)	2 (3.6%)	1 (1.5%)	6 (3.6%)
Abdominal pain	1 (2.2%)	4 (1.5%)	7 (1.7%)	3 (0.7%)	14 (1.3%)	2 (5.4%)	1 (2.2%)	1 (1.8%)	3 (4.5%)	4 (2.4%)

WHO Organ System WHO Preferred term	White					Black				
	Placebo dose	RIS dose 25 mg	RIS dose 50 mg	RIS dose 75 mg	RIS dose Total	Placebo dose	RIS dose 25 mg	RIS dose 50 mg	RIS dose 75 mg	RIS dose Total
	(N=451)	(N=263)	(N=202)	(N=402)	(N=1067)	(N=37)	(N=46)	(N=55)	(N=66)	(N=167)
Body as a whole - general disorders	10 (2.2%)	42 (16.0%)	65 (16.2%)	60 (14.9%)	167 (15.7%)	8 (21.6%)	7 (15.2%)	7 (12.7%)	10 (15.2%)	24 (14.4%)
Fatigue	0	8 (3.0%)	18 (4.5%)	18 (4.5%)	44 (4.1%)	0	0	3 (5.5%)	2 (3.0%)	5 (3.0%)
Injury	4 (0.9%)	3 (1.1%)	6 (1.5%)	11 (2.7%)	20 (1.9%)	2 (5.4%)	0	0	2 (3.0%)	2 (1.2%)
Back pain	0	4 (1.5%)	7 (1.7%)	8 (2.0%)	19 (1.8%)	3 (8.1%)	2 (4.3%)	0	0	2 (1.2%)
Chest pain	1 (0.2%)	1 (0.4%)	6 (1.5%)	6 (1.5%)	13 (1.2%)	2 (5.4%)	0	0	1 (1.5%)	1 (0.6%)
Respiratory system disorders	5 (11.1%)	36 (13.7%)	44 (10.9%)	50 (12.4%)	130 (12.2%)	8 (21.6%)	11 (23.9%)	4 (7.3%)	10 (15.2%)	25 (15.0%)
Rhinitis	2 (0.4%)	15 (5.7%)	24 (6.0%)	23 (5.7%)	62 (5.8%)	6 (16.2%)	6 (13.0%)	3 (5.5%)	4 (6.1%)	13 (7.8%)
Pharyngitis	1 (0.2%)	4 (1.5%)	3 (0.7%)	8 (2.0%)	15 (1.4%)	2 (5.4%)	0	0	2 (3.0%)	2 (1.2%)
Coughing	1 (0.2%)	3 (1.1%)	6 (1.5%)	5 (1.2%)	14 (1.3%)	3 (8.1%)	3 (6.5%)	3 (1.8%)	3 (4.5%)	7 (4.2%)
Skin and appendages disorders	4 (8.9%)	12 (4.6%)	17 (4.2%)	20 (5.0%)	49 (4.6%)	2 (5.4%)	1 (2.2%)	3 (5.5%)	10 (15.2%)	14 (8.4%)
Rash	1 (0.2%)	5 (1.9%)	4 (1.0%)	4 (1.0%)	13 (1.2%)	2 (5.4%)	0	0	5 (7.6%)	5 (3.0%)
Heart rate and rhythm disorders	7 (1.6%)	10 (3.8%)	16 (4.0%)	16 (4.0%)	42 (3.9%)	2 (5.4%)	0	2 (3.6%)	2 (3.0%)	4 (2.4%)
Tachycardia	5 (1.1%)	1 (0.4%)	9 (2.2%)	7 (1.7%)	17 (1.6%)	0	0	1 (1.8%)	0	1 (0.6%)
Metabolic and nutritional disorders	3 (0.7%)	7 (2.7%)	13 (3.2%)	11 (2.7%)	33 (3.1%)	1 (2.7%)	6 (13.0%)	2 (3.6%)	4 (6.1%)	12 (7.2%)
Weight increase	1 (0.2%)	4 (1.5%)	11 (2.7%)	8 (2.0%)	23 (2.2%)	1 (2.7%)	3 (6.5%)	2 (3.6%)	2 (3.0%)	7 (4.2%)
Cardiovascular disorders, general	3 (0.7%)	12 (4.6%)	9 (2.2%)	5 (1.2%)	26 (2.4%)	2 (5.4%)	2 (4.3%)	4 (7.3%)	3 (4.5%)	9 (5.4%)
ECG abnormal	3 (0.7%)	5 (1.9%)	4 (1.0%)	2 (0.5%)	11 (1.0%)	0	0	3 (5.5%)	2 (3.0%)	5 (3.0%)
Hypertension	0	2 (0.8%)	3 (0.7%)	1 (0.2%)	6 (0.6%)	2 (5.4%)	2 (4.3%)	2 (3.6%)	0	4 (2.4%)

Source: Table 14.1.1.1/53

Includes Trials RIS-USA-121, RIS-INT-57, RIS-INT-61, RIS-INT-31, RIS-SWE-17, RIS-INT-32.

The majority of patients were white (1393 white patients with schizophrenia in the pooled, repeated-dose trials). There was a total of 222 black patients with schizophrenia in the repeated-dose trials. The adverse event pattern does not show differences of major clinical relevance between the racial groups.

BMI:

Overall, more adverse events were reported with increasing BMI category :64.9%, 71.7% and 73.2%, respectively, for the low (BMI _ 20 to <25), median (BMI _ 25 to <30) and high (BMI _ 30) BMI categories. Adverse events related to psychiatric disorders were most frequently reported: 35.1% (BMI _ 20 to <25), 38.9% (BMI _ 25 to <30) and 44.7% (BMI _ 30). Commonly reported adverse events in this body system included insomnia, psychosis, and anxiety. Central and peripheral nervous system disorder-related adverse events were comparable across BMI categories. A slightly higher incidence of respiratory system disorders occurred in the highest BMI category : 15.4% (BMI _ 30) versus 11.7% (BMI _ 25 to <30) and 11.8% (BMI _ 20 to <25). No other differences of clinical relevance were observed. Table 45 presents treatment-emergent adverse events during the first 3 months of treatment by BMI category for patients with schizophrenia.

Table 45: **Treatment emergent adverse events occurring in ≥5% and more than two patients in any treatment group during the first 3 months of treatment by BMI category: repeated dose trials n (%) (patients with schizophrenia)**

WHO Organ System WHO Preferred Term	<20		≥20 to <25		≥25 to <30		≥30	
	Placebo depot (N=2)	RIS depot Total (N=6)	Placebo depot (N=104)	RIS depot Total (N=423)	Placebo depot (N=28)	RIS depot Total (N=453)	Placebo depot (N=27)	RIS depot Total (N=306)
Any adverse event	1 (50.0%)	40 (64.5%)	54 (89.5%)	275 (64.9%)	23 (82.1%)	325 (71.7%)	20 (74.1%)	290 (33.3%)
Psychiatric disorders	0	21 (33.9%)	23 (56.3%)	149 (35.1%)	13 (46.4%)	176 (38.9%)	17 (63.0%)	117 (44.1%)
Agitation	0	6 (9.7%)	8 (21.1%)	24 (5.7%)	3 (12.1%)	54 (12.5%)	3 (25.0%)	14 (5.5%)
Insomnia	0	9 (14.5%)	4 (10.5%)	44 (10.4%)	5 (17.9%)	54 (11.9%)	4 (14.8%)	39 (14.9%)
Anxiety	0	5 (8.1%)	5 (13.2%)	39 (9.2%)	6 (21.4%)	52 (11.5%)	4 (14.8%)	32 (13.1%)
Depression	0	3 (4.8%)	1 (2.6%)	21 (5.0%)	0	12 (2.6%)	1 (3.7%)	13 (5.3%)
Hallucination	0	6 (9.7%)	3 (7.9%)	13 (3.1%)	2 (7.1%)	5 (1.1%)	1 (3.7%)	25 (6.1%)
Tremor	0	1 (1.6%)	6 (15.8%)	9 (2.1%)	3 (10.7%)	5 (1.1%)	3 (11.1%)	45 (10.9%)
Suicide attempt	0	3 (4.8%)	0	9 (2.1%)	2 (7.1%)	7 (1.5%)	0	10 (2.5%)
Somnolence	0	1 (1.6%)	2 (5.3%)	15 (3.5%)	0	22 (4.9%)	0	11 (2.8%)
Central & peripheral nervous system disorders	**0**	**15 (24.2%)**	**15 (39.5%)**	**114 (26.9%)**	**7 (25.0%)**	**134 (29.6%)**	**5 (18.5%)**	**103 (26.4%)**
Headache	0	8 (12.9%)	5 (13.2%)	38 (9.0%)	4 (14.3%)	61 (13.5%)	3 (11.1%)	45 (11.5%)
Extrapyramidal disorder	0	2 (3.2%)	3 (7.9%)	18 (4.2%)	0	24 (5.3%)	0	13 (3.3%)
dyspraxia	0	2 (3.2%)	2 (5.3%)	19 (4.5%)	1 (3.6%)	25 (5.5%)	1 (3.7%)	20 (5.1%)
dizziness	0	1 (1.6%)	5 (13.2%)	22 (5.2%)	0	16 (3.5%)	1 (3.7%)	21 (5.4%)
dyskinesia	0	1 (1.6%)	4 (10.5%)	12 (2.8%)	1 (3.6%)	15 (3.3%)	0	12 (3.1%)
Body as a whole – general disorders	**0**	**11 (17.7%)**	**7 (18.4%)**	**62 (14.6%)**	**6 (21.4%)**	**66 (14.6%)**	**5 (18.5%)**	**73 (18.8%)**
Fatigue	0	3 (4.8%)	0	15 (3.5%)	0	23 (5.1%)	0	14 (3.6%)
Injury	0	1 (1.6%)	2 (5.3%)	10 (2.4%)	3 (10.7%)	6 (1.3%)	0	7 (1.8%)
Pain	0	2 (3.2%)	1 (2.6%)	6 (1.4%)	0	7 (1.5%)	1 (3.7%)	26 (6.7%)
Gastrointestinal system disorders	**1 (50.0%)**	**12 (19.4%)**	**4 (10.5%)**	**64 (15.1%)**	**0**	**74 (16.3%)**	**4 (14.8%)**	**71 (17.9%)**
Constipation	0	3 (4.8%)	1 (2.6%)	17 (4.0%)	0	13 (2.9%)	0	10 (2.5%)
Vomiting	1 (50.0%)	2 (3.2%)	1 (2.6%)	6 (1.4%)	0	8 (1.8%)	3 (11.1%)	8 (2.0%)
Respiratory system disorders	**0**	**5 (8.1%)**	**4 (10.5%)**	**50 (11.8%)**	**4 (14.3%)**	**53 (11.7%)**	**5 (18.5%)**	**61 (15.4%)**
Rhinitis	0	2 (3.2%)	2 (5.3%)	21 (5.0%)	2 (7.1%)	31 (6.9%)	4 (14.8%)	29 (7.3%)

Source: Table A8.1.1.1SS
Includes Trials RIS-USA-121, RIS-INT-53, RIS-INT-61, RIS-INT-51, RIS-SWE-17, RIS-INT-32.

AGE:

The safety of risperidone depot microspheres in the elderly population (> 65 years) was compared to the safety profile in the non-elderly population (<65 years).

PULSE RATE

Overall, baseline supine pulse rate was slightly higher in the elderly group, when compared with the non-elderly age group. There was a decrease in mean supine pulse rate toward endpoint for the _ 65 age group that was higher than for the <65 age group (-1.1. and +0.2 bpm at endpoint, respectively).

WEIGHT

Mean weight and body mass index were lower in the elderly age group compared with the non-elderly group (68.8 kg and 82.2 kg, respectively). Whereas there was an increase in weight for the non-elderly patients (+2.4 kg at endpoint), this effect was less pronounced in the elderly population (+0.3 kg at endpoint.

QTc

Regardless of the correction factor used, the mean values in the elderly age group were slightly higher compared with the non-elderly group. At endpoint, the same observations were made and, in general, only slight changes in QTc values were noted over time in both age groups.

LABORATORY RESULTS

The incidence of abnormally low or high values for any laboratory examination was very low or none for most parameters. Overall, the laboratory results were similar in the elderly and non-elderly.

RESULTS

No unusual or unexpected adverse events occurred with risperidone depot in this population.

The incidence of adverse events in elderly patients was similar to the general population.

The incidence of EPS-related adverse events was similar in elderly and non-elderly patients.

Mean weight gain tended to be less in elderly patients compared with non-elderly patients.

No clinically relevant differences were found in laboratory results, vital signs, or ECG parameters between elderly and non-elderly patients.

SAFETY CONCLUSIONS:

The safety review reveals no new or unusual events and is similar to the pattern seen in existing labeling for Risperdal. These trials included adult and elderly patients, in in- or out-patient populations with schizophrenia or schizoaffective disorder. The incidences and types of serious adverse events were lower and comparable between the 25-mg and 50-mg treatment groups, compared with the 75-mg group. Mean intensity of injection site pain was mild and diminished from first to last injection in all treatment groups. There were no clinically relevant mean changes from baseline to endpoint in laboratory values, vital signs, or ECG parameters for any patients treated with risperidone depot microspheres. In general, no clinically relevant differences in adverse event profiles were found for gender, race, or body mass index. Risperidone depot microspheres were safe and well tolerated in elderly patients ($\geq$ 65 yrs). There were no clinically relevant differences in the safety profiles of non-elderly and elderly patients.

C. Evaluation of Pediatric Program

There has been no pediatric program to date.

D. Comments on Data Available or Needed in Other Populations

Outside of a pediatric program I have no comments for this section.

X. Conclusions and Recommendations

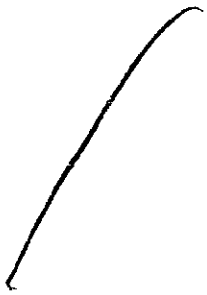
A. Conclusions

Risperidone depot microspheres appear to be effective in the treatment of patients with schizophrenia over a dose range of 25, 50 and 75 mg when administered every 2 weeks as IM

injections. Efficacy was demonstrated by the significantly improved total PANSS score for all risperidone dose groups when compared to placebo depot treatment. The statistical review done by Sharon Yan, Ph.D. also shows study RIS-USA-121 to be positive. There are no safety issues which would prevent approval.

B. Recommendations

I have several recommendations for labeling. —



Throughout the label the sponsor's tables and statistics appear to be accurate and based on data in the submission.

Earl D. Hearst, M.D.
Medical Reviewer
HFD-120

cc:file\tlaughren\ehearst\shardeman

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

/s/

Earl Hearst
5/13/02 09:20:41 AM
MEDICAL OFFICER

Thomas Laughren
5/21/02 01:50:22 PM
MEDICAL OFFICER
I agree that this NDA is approvable, from a clinical/statistical standpoint; see memo to file for more detailed comments.--TPL