CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

NDA:	21-346
DRUG NAME:	Risperdal Consta® (Risperidone) Depot Microspheres Injection
INDICATION:	Schizophrenia
SPONSOR:	Janssen Research Foundation
STATISTICAL REVIEWER:	Sharon Yan, Ph.D.
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DISTRIBUTION

HFD-120 Dr. Katz, Director
Dr. Laugren, Team Leader
Dr. Hearst
Mr. Hardeman, Project Manager

HFD-710 Dr. Chi, Director
Dr. Jin, Team Leader

HFD-700 Dr. Anello, Deputy Director

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1 Introduction

Risperdal Consta is an extended release form of risperidone, microencapsulated in biological polymers, to be administered every 2 weeks by intramuscular injection for the treatment of schizophrenia.

This application consists of three phase III studies. The efficacy of Risperdal Consta is based on a placebo-controlled trial RIS-USA-121. In addition to trial RIS-USA-121, the sponsor Janssen submitted two other phase III studies: a non-inferiority trial RIS-INT-61 and a long term open label trial RIS-INT-57. In these trials patients received biweekly injections of 25 mg, 50 mg, or 75 mg Risperdal Consta for as long as 12 weeks (RIS-USA-121, RIS-INT-61) or 12 months (RIS-INT-57).

In this review, only the placebo controlled efficacy study RIS-USA-121 is discussed.

2 Study RIS-USA-121

2.1 Objective

The primary objective of the trial was to compare the efficacy of risperidone depot microspheres 25 mg, 50 mg, or 75 mg with placebo on the symptoms of schizophrenia over a 12-week period. The study was powered to demonstrate a statistically significant difference from placebo for at least one dose of risperidone depot microspheres on change from baseline at the endpoint in total PANSS.

2.2 Study Design

This was a multicenter, randomized, double-blind, parallel group trial. The duration of the trial was 14 weeks, consisting of a 1-week screening period, a 1-week run-in period, and a 12-week double-blind period.

Titration was done prior to randomization in the run-in period, during which patients were discontinued from other neuroleptics and started on oral risperidone of up to 4 mg/day. Only those subjects who remained in the trial through the 1-week run-in period were randomized.

During the double-blind treatment period patients received an injection of placebo, 25 mg, 50 mg 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. The dose of the oral treatment was dependent on the dose of the depot formulation to which the patient was randomized (i.e., placebo tablet with placebo depot, 2 mg tablet with 25 mg depot, 4 mg tablet with 50 mg depot, and 6 mg tablet with 75 depot).

A total of 416 patients with schizophrenia were to be included, 104 in each treatment group. Subjects were either inpatients or outpatients. Randomization was centralized and stratified according to whether the subject was inpatient or outpatient and the subject's PANSS total scores (> or <= 80) at the time of randomization. Efficacy and safety assessment was performed at baseline and thereafter every 2 weeks.

Patients who had either completed RIS-USA-121 in its entirety or fulfilled withdrawal criteria after having been randomized in the trial were offered the possibility of enrolling in the open label extension trial RIS-USA-196.

The trial was started on October 21, 1999 and ended on December 15, 2000. The final version of Statistical Analysis Plan was dated January 2, 2002. The trial was conducted in 47 centers in the United States.

2.3 Inclusion and Exclusion Criteria

Main Inclusion Criteria

- Male or female age 18 to 55 years, inclusive;
- Diagnosis of schizophrenia according to the DSM IV criteria;
- Baseline Positive and Negative Syndrome Scale (PANSS) score between 60 and 120, inclusive (1-7 scoring);
- Patient was otherwise healthy on the basis of a pre-trial physical examination.

Main Exclusion Criteria

- Patients who had received depot antipsychotic 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 screening visit was exclusionary, but nicotine and caffeine dependencies were not exclusionary;
- Tardive dyskinesia associated with more than mild symptomatology in the opinion of the investigator;
- History of neuroleptic mallignant syndrome;
- Documented organic disease of central nervous system;
- Current seizure disorder requiring medication;
- A clinical significant ECG abnormality in the opinion of the investigator.

2.4 Efficacy Measures and Statistical Methods

Patients were interviewed at screening (Visit 1), at randomization (Visit 3), and at Weeks 2, 4, 6,

8, 10 and 12 (Visits 5, 7, 10, 12, 15, and 17/endpoint) using the Structured Clinical Interview - Positive and Negative Syndrome Scale (SCI-PANSS).

2.4.1 Primary Efficacy Parameter - Positive and Negative Syndrome Scale (PANSS)

The primary efficacy parameter was the change in the total PANSS score from baseline (Visit 3) to endpoint. This parameter consisted of the sum of all 30 PANSS items.

2.4.2 Analysis of Primary Efficacy Endpoint

The primary statistical objective of the trial was to determine if the change in total PANSS score from Visit 3 to endpoint of at least one dose group of patients receiving risperidone depot microspheres was statistically significant different from the patients receiving placebo depot. An analysis of covariance model with factors of investigator site and baseline PANSS was to be used. Dunnett's procedure was used to control for type I error of 5%.

If a PANSS item is missing, it was imputed with the closest integer to the average of the remaining items within the sub-scale (positive, negative, and general psychopathology) at the time point. If more than 15% of the items were missing, i.e., if 5 or more items were missing, no imputation was performed and the total score and the score of the involved sub-scales were left missing.

An analysis similar to the primary analysis on total PANSS was also to be done for percentage change in total PANSS and the positive symptom subscale.

2.4.3 Secondary Efficacy Parameters and Analyses

PANSS Subscales

The following subscales of PANSS were to be calculated:
1. Positive symptoms factors;
2. Negative symptoms factors;
3. Disorganized thoughts factors;
4. Uncontrolled hostility/excitement factors;
5. Anxiety/depression factors

An analysis similar to the primary analysis on total PANSS was to be done for each of the above subscales.

PANSS Clinical Improvement

Any subject whose total PANSS score improved (decreased) by 20% or more from Visit 3 was to

be considered as clinically improved. The time to this level of improvement or censoring time was also to be calculated.

The number of subjects who experienced a clinical improvement was to be tabulated at each assessment point. The treatment groups were to be compared via a Cochran-Mantel-Haenzel test controlling for investigator and baseline PANSS strata.

The time to clinical improvement for each treatment group was to be estimated by Kaplan-Meier method. Treatment groups were to be compared using a generalized Wilcoxon test stratified for investigator and controlling for baseline PANSS strata.

Clinical Global Impression (CGI/CGI-C)

The CGI was also used as an efficacy measure. Patients were rated for overall severity of illness at randomization, Week 2, and weekly thereafter using CGI Severity Scale. From Week 2 through Week 12, the CGI-Change score was also rated.

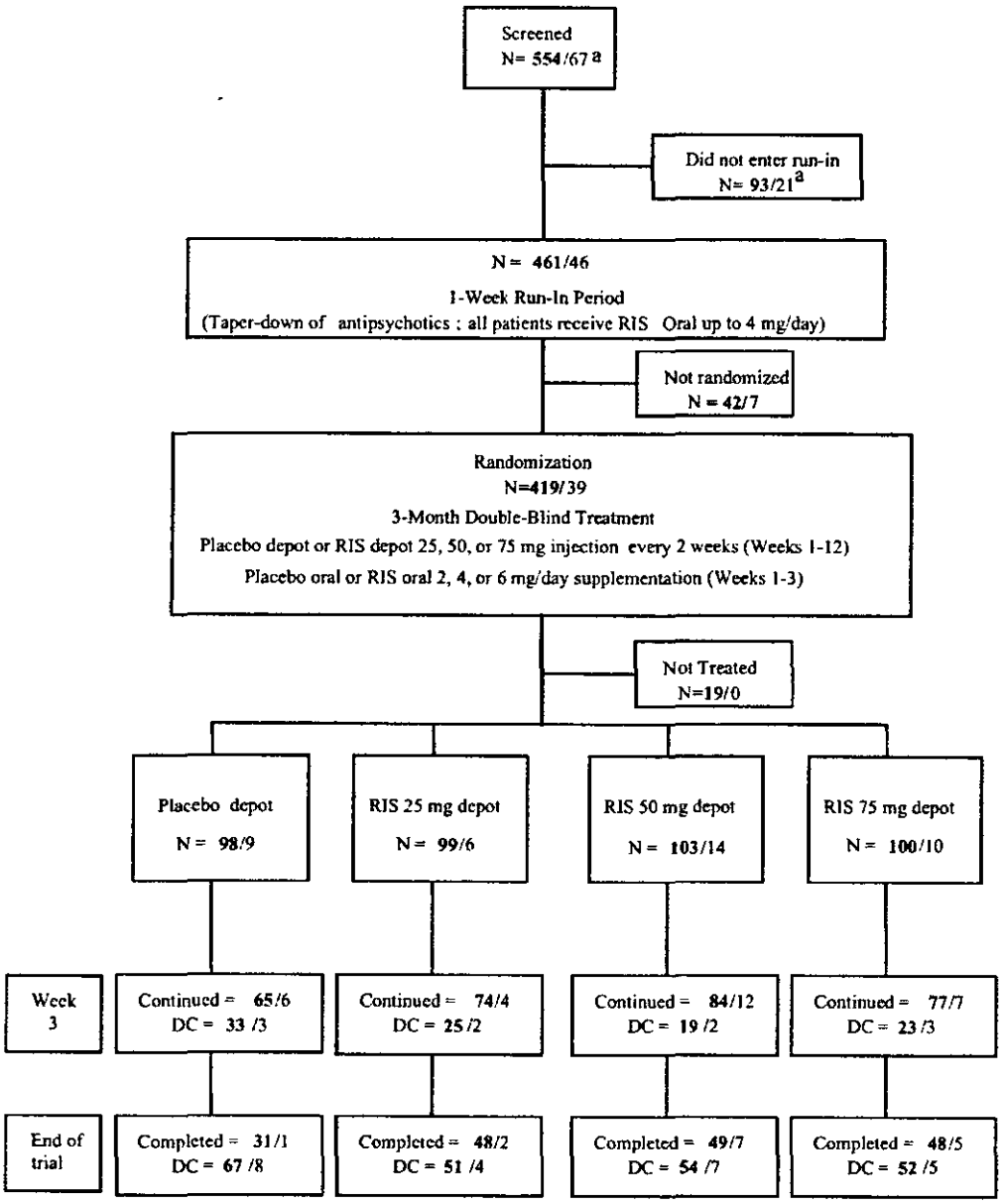
Differences between treatment groups in frequency counts of CGI and CGI-C were to be assessed via the Van-Elteren test controlling for investigator and baseline PANSS strata. In addition, the change from baseline in CGI was to be analyzed using the same method as for total PANSS.

2.5 Results - Sponsor's Analysis

2.5.1 Subject Disposition

A total of 621 subjects were screened, 554 with schizophrenia and 67 with schizoaffective disorder or with no diagnosis recorded on the CRF page. One hundred fourteen subjects failed screening and the remaining 507 subjects (461 with schizophrenia and 46 with schizoaffective disorder or missing diagnosis) entered run-in period. Sixty-eight subjects discontinued during the run-in period due to various reasons and 439 subjects (400 with schizophrenia and 39 with schizoaffective disorder or missing diagnosis) were randomized and entered double-blind treatment period. A complete summary of patient disposition is displayed in the following chart.

As the result of Amendment 2, inclusion criteria were changed to stop recruiting patients with diagnosis of schizoaffective disorder, as requested by the agency. Therefore, patients with schizoaffective disorder are excluded from the efficacy analyses.



Source: Table SUB.6 and SUB 7 USA121
a: Included patients with schizoaffective disorder and patients with missing diagnosis.
N or DC = total number or number of discontinued patients with schizophrenia / total number or number of discontinued schizoaffective disorder

The sponsor reported that there were no major differences in the incidence between treatment groups in reasons for discontinuation of treatment in patients with schizophrenia during the double-blind period with the exception of insufficient response. More patients discontinued in the placebo depot group than in the risperidone depot groups, and most of those discontinuations were due to insufficient response. Compared to the two highest risperidone depot dose groups, more patients in the 25 mg group discontinued due to insufficient response. Reasons for discontinuations during double-blind treatment for schizophrenia patients are summarized in Table 1.

Table 1. 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.

2.5.2 Demographic and Baseline Characteristics

The sponsor reported that 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. Most patients were racially black or white. There was a higher percentage of women in the risperidone depot 25 mg and 75 mg groups than in the placebo depot or risperidone 50 mg depot group (p=0.025 for overall treatment group comparison).

Table 2. 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

The sponsor reported that in patients with schizophrenia, the baseline disease characteristics for schizophrenia type, mean age at onset, mean age at first hospitalization and number of previous hospitalizations were balanced among the treatment groups. At least 93% of the patients in each group had a diagnosis of either paranoid schizophrenia or undifferentiated schizophrenia (Table 3).

Table 3. Baseline disease characteristics (patients with schiziphrenia)

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)

2.5.3 Sponsor's Efficacy Evaluation

2.5.3.1 Data Set Analyzed

Thirty-five subjects with schizoaffective disorder entered the trial prior to the protocol amendment to exclude them, and had at least one depot injection and at least one post-baseline PANSS. There were 9 in placebo group, 4 in risperidone 25 mg group, 12 in risperidone 50 mg group, and 10 in risperidone 75 mg group. These subjects are not included in the efficacy analyses.

The primary analysis set was the patients with schizophrenia who had at least one post-baseline PANSS assessment ("ITT schizophrenia"). For efficacy analyses, data from one site was excluded because of noncompliance with GCP requirements. The primary analysis set included 370 subjects: 92 in placebo group, 93 in risperidone 25 mg group, 98 in risperidone 50 mg group, and 87 in risperidone 75 mg group. LOCF was used in the tables presented by the sponsor.

2.5.3.2 Primary Efficacy Variable - Total PANSS Score

The primary efficacy parameter was the change from baseline in total PANSS score at endpoint. The results are summarized in Table 4.

Table 4. Total PANSS score - mean and mean change from baseline to endpoint - LOCF analysis (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	92	2.5 (1.73)	93	-6.1 (2.08)	98	-8.7 (1.55)	87	-5.6 (1.88)
Least squares mean		2.6		-6.2		-8.5		-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.

The sponsor reported that change in each risperidone depot group was significantly better than the one in 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 depot 25 mg group and depot 75 mg group. Estimated least square means, which adjust the raw means for effects of site and baseline value in the statistical model, were also best in the depot 50 mg group, followed by depot 75 mg group and depot 25 mg group.

Analysis by Timepoint

PANSS assessments were scheduled for every two weeks. Total PANSS by treatment group over time is plotted in Figure 1. Change from baseline over time is plotted in Figure 2. Both observed data and results from last-observation-carry-forward approach were plotted.

Figure 1. Total PANSS score over time - mean (+-SE) (patients with schizophrenia)

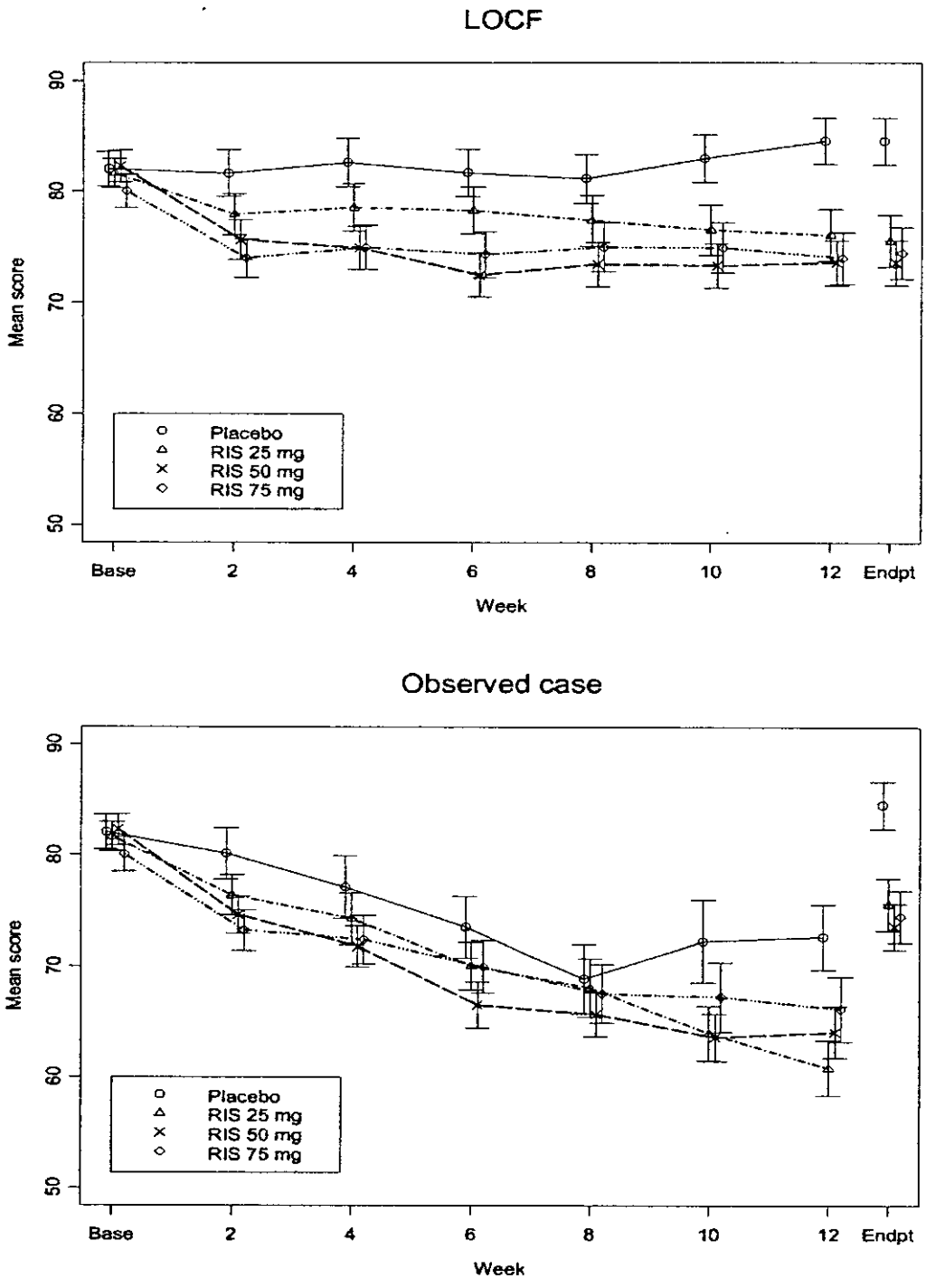
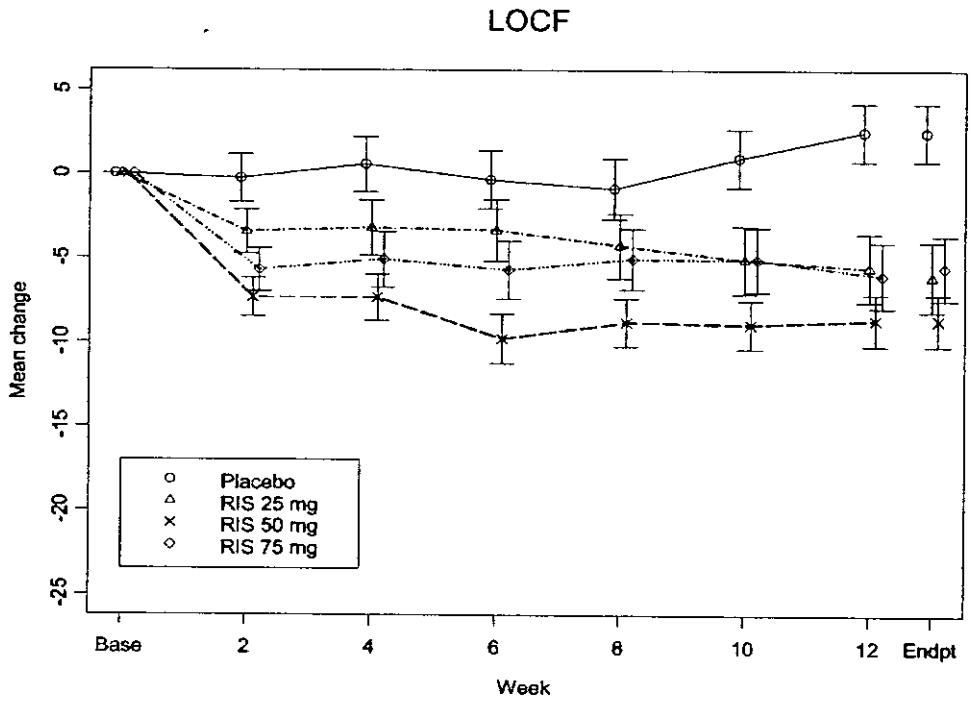
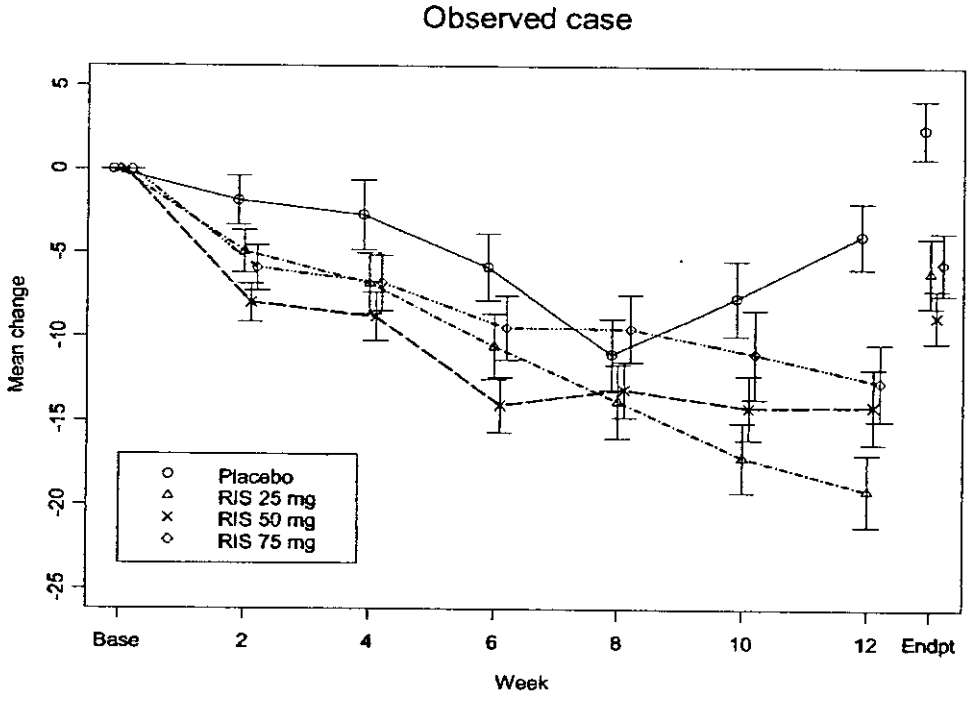


Figure 2. Total PANSS score over time - mean change (+_SE) (patients with schizophrenia)





2.5.3.3 Secondary Efficacy Variables

Positive and Negative Symptoms PANSS Subscales

Change from baseline in the positive and negative subscales at the endpoint is summarized in Table 5. The sponsor reported that the change in each risperidone depot group was significantly greater than in the placebo group for both subscales (p<=0.046).

Table 5. PANSS Positive and Negative Symptoms subscales - mean and mean change from baseline to endpoint - LOCF analysis (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.

Other PANSS Subscales

Other subscales of PANSS were: disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression. Change from baseline to endpoint for these subscales is summarized in Table 6.

Table 6. Other PANSS subscales - mean and mean change from baseline to endpoint - LOCF analysis (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)
Disorganized thoughts								
Baseline	92	19.1 (0.53)	93	18.9 (0.48)	98	18.5 (0.50)	87	18.7 (0.50)
Endpoint	92	19.9 (0.64)	93	17.7 (0.65)	98	17.1 (0.61)	87	17.4 (0.60)
Change from baseline to endpoint: Mean Least squares mean	92	0.8 (0.49) 0.9	93	-1.1 (0.59) -1.2	98	-1.3 (0.48) -1.5	87	-1.3 (0.53) -1.8
Betw-group diff on LS means (RIS - Placebo) and 95% CI				-2.1 (-3.9, -0.4)		-2.4 (-4.1, -0.7)		-2.7 (-4.4, -0.9)
p-value[a] (comparison with placebo on change)				0.012		0.003		0.001
Uncontrolled hostility/excitement								
Baseline	92	7.8 (0.36)	93	7.1 (0.27)	98	8.1 (0.35)	87	7.2 (0.29)
Endpoint	92	8.9 (0.46)	93	8.1 (0.45)	98	7.2 (0.38)	87	7.6 (0.38)
Change from baseline to endpoint: Mean Least squares mean	92	1.1 (0.42) 1.2	93	1.0 (0.45) 0.8	98	-0.8 (0.28) -0.6	87	0.3 (0.31) -0.1
Betw-group diff on LS means (RIS - Placebo) and 95% CI				-0.4 (-1.6, 0.8)		-1.8 (-3.0, -0.6)		-1.3 (-2.6, -0.1)
p-value[a] (comparison with placebo on change)				0.801		0.002		0.033
Anxiety/depression								
Baseline	92	10.6 (0.37)	93	10.4 (0.33)	98	10.8 (0.31)	87	10.6 (0.38)
Endpoint	92	10.5 (0.40)	93	9.4 (0.37)	98	9.1 (0.35)	87	9.1 (0.40)
Change from baseline to endpoint: Mean Least squares mean	92	-0.1 (0.39) 0.0	93	-1.0 (0.34) -1.0	98	-1.6 (0.29) -1.5	87	-1.6 (0.36) -1.6
Betw-group diff on LS means (RIS - Placebo) and 95% CI				-1.0 (-2.1, 0.04)		-1.6 (-2.6, -0.5)		-1.7 (-2.8, -0.6)
p-value[a] (comparison with placebo on change)				0.064		0.001		0.001

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.

Clinical Global Impression

Clinical Global Impression (CGI) of each patient was recorded at baseline and weekly. Clinical Global Impression of change (CGI-C) was also recorded since baseline. The distribution of CGI ratings at baseline and endpoint is summarized in Figure 3 and Table 7.

Figure 3 Percent of patients with Clinical Global Impression at baseline and endpoint (patients with schizophrenia)

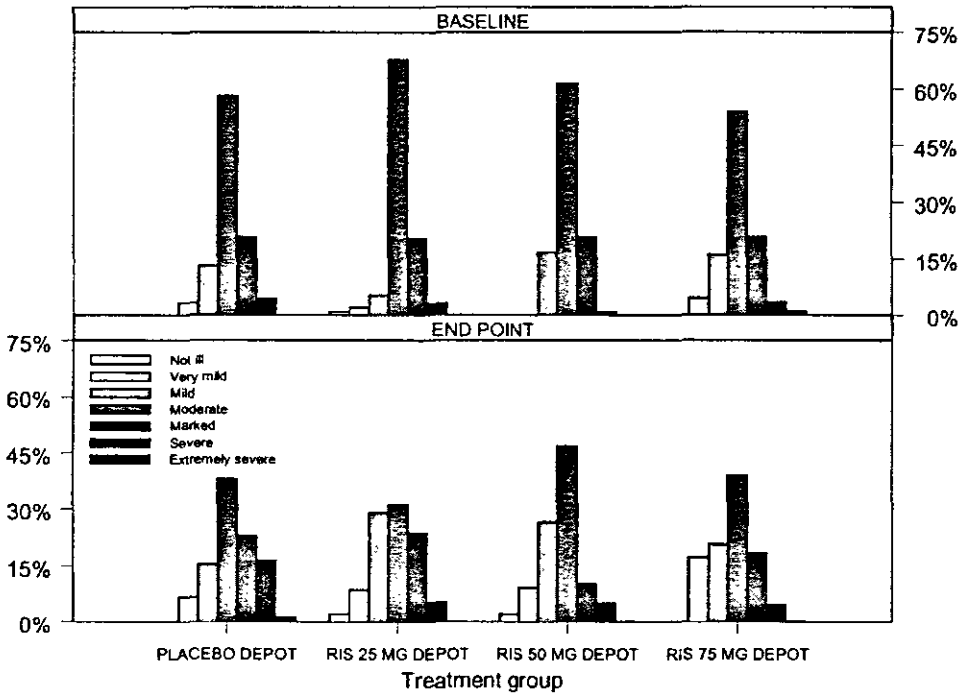


Table 7. Clinical Global Impression (CGI - mean and mean change from baseline at endpoint - LOCF analysis (patients with schizophrenia)

	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.

2.6 Efficacy Results - Reviewer's Analysis

2.6.1 Analysis of the Primary Endpoint - Total PANSS Score

This reviewer has replicated the sponsor's analyses and results from this reviewer's analyses agree with the ones obtained by the sponsor.

For the efficacy analysis of the primary endpoint, change in PANSS total score, the treatment effect carries a p-value of 0.0001 from the ANOVA model. The model was adjusted by baseline PANSS score and investigator. Both baseline PANSS score and investigator had a significant effect on the treatment result (baseline p=0.0388, investigator p=0.0167). The treatment effect remained significant when investigator effect was removed from the model.

The comparison between each of the three dose groups and placebo was tested simultaneously from the analysis model by using the Dunnett's adjustment. The difference between each of the dose group in the change of total PANSS scores from Dunnett's adjustment was statistically significant in favor of risperidone depot (p-values < 0.01), with the largest reduction in the total PANSS score shown in the 50 mg depot (p <= 0.0001).

The model assumption of normality of the data was examined, and a p-value of 0.0217 was obtained, pointing to a violation of the normal assumption. Rank transformation of the data didn't help to normalize the data, and non-parametric Kruskal-Wallis test was applied. A p-value of 0.0001 was obtained from the Kruskal-Wallis test, indicating that a significant difference between the treatment groups in the change from baseline of the total PANSS score exists. Pairwise comparisons between each of the dose group and placebo group were conducted. It was found that subjects in each of the three dose groups had a larger reduction in the total PANSS score than the subjects in the placebo group (p-values < 0.001). Note that the baseline and center were not adjusted in the Kruskal-Wallis test and p-values from the pairwise comparisons were not adjusted for multiple dose groups.

Mean, mean change, and details of the results are reported in Section 2.5 of Sponsor's Analysis.

Observed Case Analysis of Total PANSS Score

Due to the large percentage of patients discontinued from the trial, the analysis of total PANSS score from observed cases was performed. The results are presented in the following table.

Table 8. Total PANSS score - mean and mean change from baseline to endpoint (observed case)

	Placeb depot N=29	RIS depot 25 mg N=38	RIS depot 50 mg N=43	RIS depot 75 mg N=42
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline	76.6 (15.4)	79.9 (14.1)	78.2 (11.9)	78.8 (14.1)
Endpoint	72.7 (15.8)	60.8 (15.3)	64.1 (15.4)	66.2 (19.0)
Change from baseline	-3.9 (10.5)	-19.1 (13.0)	-14.1 (14.7)	-12.7 (14.7)
p-value[a]		0.0001	0.0116	0.0538

a. p-values are from primary ANOVA model with Dunnett's adjustement

Similar to the results from LOCF analysis, the normal assumption was violated (p=0.0296). The non-parametric Kruskal-Wallis test was applied, and the p-values of the treatment difference between each of the risperidone depot dose groups as compared to placebo depot are 0.0001, 0.0022, and 0.0090 respectively for risperidone depot 25 mg group, 50 mg group, and 75 mg.

Total PANSS Score by Demographic Characteristics

Descriptive statistics of the change from baseline in the total PANSS score by demographic characteristics are presented in the following table.

Table 9. Total PANSS - mean (SD) by demographic characteristics - LOCF analysis

Characteristic	Placebo N=92	25 mg n=93	50 mg n=98	75 mg n=87	Nominal p-value
Age (year)[1]					
< 39 (n=181)	-1.55 (16.96)	-2.75 (20.73)	-10.09 (15.75)	-7.35 (20.15)	0.2647
>= 39 (n=189)	6.19 (15.52)	-8.60 (19.37)	-6.73 (14.70)	-4.02 (15.10)	0.0001
Sex					
Female (n=94)	4.53 (10.39)	-3.79 (18.09)	-5.83 (11.31)	-1.30 (19.90)	0.3839
Male (n=276)	2.03 (17.73)	-7.13 (20.96)	-9.33 (16.09)	-7.79 (15.95)	0.0003
Race					
Black (n=155)	0.94 (15.27)	-10.36 (18.58)	-10.16 (14.53)	-6.07 (18.92)	0.0013
Caucasian (n=158)	1.43 (15.57)	-1.14 (21.89)	-6.41 (15.75)	-2.83 (15.71)	0.1350
Hispanic (n=39)	3.36 (16.76)	-5.58 (20.29)	-7.80 (15.22)	-14.67 (16.55)	0.3403
Oriental (n=8)		-13.25 (18.01)	-10.50 (21.30)		0.2582
Other (n=10)	32.33 (25.81)	-0.67 (12.01)	-24.33 (4.16)	-23.00 (N.A)[2]	not tested

1. The median age of 39 is used as a cut-point. 2.There was only one subject in this group.

It appears that the treatment had a larger effect in the older age group than in the younger age group, and the reduction in PANSS score is larger in the males than in the females.

2.6.2 Analyses of Secondary Efficacy Parameters

Secondary efficacy parameters, including subscales PANSS scores, were analyzed using the same method as for the primary parameter. The results obtained by this reviewer agree with the ones from the sponsor's analyses.

For subscales of the PANSS scores, treatment effect was significant for Positive Symptoms, Negative Symptoms, and Disorganozed Thoughts. Subscales of Anxiety/Depression and Uncontrolled Hostility/Excitement were not significant for the 25 mg depot group, but were significant for the other two dose groups.

CGI is a 7-point scale and patients were measured as not ill, very mild, mild, moderate, marked,

severe, or extremely severe. CGI-C is also a 7-point scale which measures a patient's improvement after the treatment with ratings of very much improved, much improved, minimally improved, unchanged, minimally worse, much worse, or very much worse. The data submitted by the sponsor does not include parameter CGI-C. Only CGI was included in data set. Although it was found that treatment effect was statistically significant in favor of risperidone depot in the change from baseline of CGI, this reviewer believes that CGI-C would be more meaningful than the calculated change in CGI.

Details of the results are presented in Section 2.5 of sponsor's analyses. Note that although p-values from analyses of secondary efficacy parameters were adjusted by Dunnett's method for multiple dose comparisons, they need to be further adjusted for multiple endpoints.

3 Reviewer's Conclusion

Study RIS-USA-121 has provided sufficient evidence that Risperdal Consta is efficacious with respect to reduction in total PANSS score. The reduction in the three risperidone depot groups were 6.1 points in the 25 mg risperidone depot group, 8.7 points in the 50 mg group, and 5.6 points in the 75 mg group, and the placebo group showed an average increase of 2.6 points. Each of the three risperidone depot dose groups showed a significant difference in the reduction of total PANSS score as compared to placebo group.

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Sharon Yan
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George Chi
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Statistical Review and Evaluation

Review of Carcinogenicity Study

NDA#:	**21-346**
APPLICANT:	**Janssen Research Foundation**
NAME OF DRUG:	**Risperdal (risperidone) Depot Microspheres Injection**
INDICATION:	**Schizophrenia**
STUDIES REVIEWED:	**EDMS-BEBE-2644186, Carcinogenicity Study in Wistar Rats, Report Date, June 27, 2001**

PHARMACOLOGY REVIEWER: Lois Freed, Ph.D. (HFD-120)

STATISTICAL REVIEWER: Roswitha Kelly, M.S. (HFD-710)

Roswitha Kelly, M.S.
Mathematical Statistician

Kun Jin, Ph.D.
Team Leader

George Chi, Ph.D.
Director, Division of Biometrics 1

Distribution: NDA 21-346 (Risperdal Consta)
HFD-120/Steve Hardeman
HFD-120/Barry Rossloff Ph.D.
HFD-120/Lois Freed, Ph.D.
HFD-710/Kun Jin, Ph.D.
HFD-710/George Chi, Ph.D.
HFD-710/Roswitha Kelly, M.S.
HDS-700/Charles Anello, Sc.D.
File Directory: c:\Data\My Documents\Risperidol_C_2.doc

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1.0 Note on Levels of Statistical Significance

Trends in tumor incidence rates are tested for statistical significance at α=0.025 and 0.005 for rare and common tumors, respectively. These levels of significance ensure despite the multiplicity of testing an overall false positive rate of about 10 percent in the two-year, two-species, two-gender bioassay. This submission, however, reports on only one two-year study for the i.m. depot formulation. Therefore, both trends and pair-wise comparisons are being tested at α=0.05 and 0.01 for rare and common tumors, respectively. Additional carcinogenicity studies using the oral formulation are available. However, the different dosage form and route of administration may result in different tumor patterns and therefore, from a statistical point of view this study is considered the only primary one for risperidone i.m. depot.

2.0 Rat Study (Experiment Number 4729)

2.1 Introduction

Riperidone was administered every two weeks intramuscularly to SPF Wistar rats in a depot formulation (microspheres) at dosages of 5 and 40 mg/kg. One control group was injected with NaCl 0.9% and a vehicle control group was injected with placebo microspheres. Rats were housed individually and had free and continuous access to fresh tap water and feed. The 200 animals per gender were randomized into groups of 50 animals receiving the saline solution, the placebo microspheres, the low dose Risperdal, or the high dose Risperdal. Animals remaining after two years of administration were sacrificed. All tissues were microscopically examined for all animals, with the exception of the cervix, where a transverse section of the uterine cervix was prepared for some animals.

2.2 Sponsor's Results

Mortality was assessed by a two-sided Fisher's Exact test and Peto's one-tailed trend analysis. Neoplastic changes were assessed with a one-way age-adjusted Peto trend analysis. The death-rate method was applied to fatal tumors and the prevalence method to incidental tumor types. Peto's ad-hoc runs were used to define the time intervals. Equidistant dose levels of 0, 1, and 2 were used for control, low, and high dose groups, respectively. If tumors occurred in both contexts, their statistics were combined. For tumor totals of 8 or less, the exact age-adjusted Cochran-Armitage trend was computed giving the 'exact' p-value. A one-tailed Fisher's Exact test was used to compare group incidences.

Mortality was significantly increased for males in the high dose group during the last three months of study. The trend test with the saline control group was statistically significant (p=0.018). The trend test with the vehicle was not statistically significant

(p=0.136). For the females, the reverse was observed: the trend test with the saline group was not statistically significant (p=0.144), but reached statistical significance with the vehicle group (p=0.026). The sponsor considered the latter finding not relevant since there was no statistical significance with the saline control group. The sponsor concluded that no test article-related increase in mortality was seen in males treated with 5 mg/kg of the risperdal consta formulation and in females treated with up to 40 mg/kg of the compound. Among males dosed at 40 mg/kg, a slight increase in mortality was observed towards the end of the 24-month study. Mortality was comparable between the control and vehicle groups.

Tables 1 and 2 were extracted from the sponsor's Tables T157 - T164, showing the statistically significant increases in tumors against either control group by either trend test or pair-wise comparison:.

Table 1: Sponsor's Significant Tumor Findings among Female Rats

Tissue	Tumor	C vs. Low	C vs. High	Veh vs. Low	Veh vs. High	Trend with C	Trend with Veh
Adrenal Gland	Pheochromocytoma Benign	NS	NS	NS	NS	0.0464	NS
Mammary Gland	Neoplasia	< 0.01	< 0.01	< 0.001	< 0.001	0.0011	0.0000
Mammary Gland	Adenocarcinoma	< 0.01	< 0.01	< 0.01	< 0.01	0.0034	0.0003
Pancreas	Islet Cell Adenoma	NS	< 0.01	NS	< 0.01	0.0009	0.0012
Thyroid	Follicular Tumor	NS	NS	NS	NS	NS	0.0278
Thyroid	Follicular Adenoma	NS	NS	NS	NS	0.0323	0.0278

C=Saline Control; Veh=Placebo Microspheres; Low=5 mg/kg risperidol; High=40mg/kg risperidol.

Table 2: Sponsor's Significant Tumor Findings among Male Rats

Tissue	Tumor	C vs. Low	C vs. High	Veh vs. Low	Veh vs. High	Trend with C	Trend with Veh
Adrenal Gland	Pheochromocytoma (b and m)	NS	< 0.01	NS	< 0.05	0.0006	0.0029
Adrenal Gland	Pheochromocytoma (benign)	NS	< 0.01	NS	< 0.01	0.0013	0.0017
Kidney	Renal Tubular Tumors	NS	< 0.05	NS	< 0.05	0.0020	0.0024
Kidney	Tubular Adenoma	NS	NS	NS	NS	0.0073	0.0084
Mammary Gland	Neoplasia	NS	NS	NS	NS	0.0258	NS
Pancreas	Islet Cell Tumor	NS	< 0.05	NS	< 0.05	0.0071	0.0107
Pancreas	Islet Cell Adenoma	NS	<0.05	NS	NS	0.0069	0.0311
Pituitary	Adenoma	NS	< 0.05	NS	< 0.05	0.0048	0.0159
Thyroid	Follicular Tumor	NS	NS	< 0.01	< 0.01	NS	0.0038
Thyroid	Follicular Adenoma	NS	NS	< 0.05	< 0.01	NS	0.0070

C=Saline Control; Veh=Placebo Microspheres; Low=5 mg/kg risperidol; High=40mg/kg risperidol.

2.3 Reviewer's Results

The findings will be discussed in the following order:

2.3.1 Mortality and Tumor Findings for Female Rats with Saline Control
2.3.2 Mortality and Tumor Findings for Male Rats with Saline Control
2.3.3 Mortality and Tumor Findings for Female Rats with Vehicle Control
2.3.4 Mortality and Tumor Findings for Male Rats with Vehicle Control
2.3.5 Differences between the Control Groups

The sponsor's and this reviewer's survival analyses were apparently performed by the same program (NCI program by D.B. Thomas et al (1977)), but the resulting p-values were different. This reviewer could reproduce the sponsor's results by using ordinal scaling and a one-sided trend test in mortality. However, her methods are those routinely applied to carcinogenicity studies by the Office of Biostatistics. In particular, mortality trend tests are assessed two-sided and all trends are weighed by the actual doses, unless there are overriding pharmacological concerns (e.g. saturation of absorption).

Furthermore, exact permutation trend tests (one-sided with increasing dose) were used for incidence rates of incidental or fatal tumors, or of tumors occurring in both contexts but not during the same time interval, regardless of the number of tumor-bearing animals involved. When tumors occurred in both contexts and during the same time interval, a normal approximation was used. Again, actual dose values were used as weights in the trend tests and fixed time intervals (NTP partitions) were used by this reviewer, whereas the sponsor chose ad-hoc runs. All analyses were run against each control separately. No further multiplicity adjustment of the levels of significance were employed. This reviewer did not perform any pair-wise comparisons other than for comparing the two control groups.

In the reviewer's tables, the low dose is labeled 'medium', whereas the sponsor had called it 'low'. This difference is only in labeling and has no effect on the results; the weight of 5 mg/kg was used in all analyses involving this group.

Significant tumor trend tests are highlighted in the detailed tables. Summary tables of significant tumor findings are given in Tables 3 and 4 in the Summary section.

2.3.1 Mortality and Tumor Findings for Female Rats with Saline Control

Table 5 shows the number of females dying during the pre-specified time intervals. More than half of the animals survived till terminal sacrifice. At study end, survival was somewhat better among the control animals, but this difference did not approach statistical significance (Table 6, Figure 1).

Table 7 lists the p-values for trend in tumor incidences. Significant trends were observed for islet cell adenoma of the pancreas and benign pheochromocytoma of the adrenal glands. Adenocarcinoma of the mammary gland and follicular adenoma of the thyroid are considered common tumors and do not reach statistical significance. The findings are consistent with the sponsor's. The trend tests of certain groupings of tumors as suggested by the reviewing pharmacologist did not reach statistical significance (Table 8).

2.3.2 Mortality and Tumor Findings for Male Rats with Saline Control

Table 9 shows that the males also experienced excellent survival, which was best among the controls. The difference between saline controls and treated did not reach statistical significance (Table 10 and Figure 2).

Table 11 lists the p-values for trend in tumor incidences. Significant trends were observed for adenoma of the pituitary, benign pheochromocytoma of the adrenal gland, islet cell adenoma of the pancreas, and tubular adenoma of the kidney. Table 12 shows certain groupings of tumors. Of these, benign and malignant pheochromocytomas of the adrenal gland, islet cell adenomas or carcinomas of the pancreas, adenomas, adenocarcinomas, or fibroadenomas of the mammary gland, and tubular adenomas or carcinomas of the kidney reached statistical significance. These findings are consistent with the sponsor's.

2.3.3 Mortality and Tumor Findings for Female Rats with Vehicle Control

Table 13 shows that the female vehicle control also experienced better survival than the two treated groups, again not to a statistically significant degree (Table 14, Figure 3).

Table 15 lists the p-values for trend in tumor incidences. Significant trends were observed for adenocarcinoma of the mammary gland and islet cell adenoma of the pancreas. Other tumor findings were not considered statistically significant when the tumor was judged common based on the concurrent controls. Of the grouped tumors, only adenocarcinomas (acinar, papillary, etc.) of the mammary gland reached statistical significance, when the rarity of the tumors are taken into account (Table 16).

2.3.4 Mortality and Tumor Findings for Male Rats with Vehicle Control

Table 17 shows that male vehicle controls also experienced better survival than the two treated groups, again not to a statistically significant degree (Table 18, Figure 4).

Table 19 lists the p-values for trend in tumor incidences. Significant trends were observed for benign pheochromocytoma of the adrenal glands, follicular adenoma of the thyroid glands, and tubular adenoma of the kidneys. In addition, adenoma of the pituitary and islet cell adenoma of the pancreas approached statistical significance for common tumors ($p=0.0151$ vs. $\alpha=0.010$). Of the grouped tumors (Table 20), benign and malignant

pheochromocytoma of the adrenal gland, tubular adenomas or carcinomas of the kidney, islet cell adenomas or carcinomas of the pancreas, and adenomas or adenocarcinomas of the thyroid also reached statistical significance. Again, these findings are consistent with the sponsor's.

2.3.5 Difference between the Two Control Groups

Among the female rats there was no statistical difference between the survival curves of the saline control group and the vehicle control group with placebo microspheres ($p=0.4067$). None of the differences in the two background rates in tumors approached statistical significance. Among the male rats, similarly, there was no statistical difference in survival between the two control groups ($p=0.5334$). There were 7 animals in the saline control group, which had follicular adenoma of the thyroid, whereas none of the vehicle control animals had this tumor. A two-sided comparison was statistically significant ($p=0.0123$ vs. $\alpha=0.01$). As noted above, the trend with the saline control group was not statistically significant, whereas the trend with the vehicle control group reached statistical significance, if the tumor can be considered rare (based on the vehicle control experience).

3.0 Summary

This was a two-year study in SPF Wistar rats, where 50 animals per gender received either NACl 0.9%, the vehicle with placebo microspheres, or risperdal consta at 5 or 40 mg/kg intramuscularly every two weeks.

The sponsor's statistical methods were appropriate, but they differed slightly from those consistently applied to carcinogenicity studies by the Office of Biostatistics. Differences in weights for trend, one-sided versus two-sided testing, and determination of time intervals contributed to numeric differences, but in general, conclusions were similar. This reviewer did not perform pair-wise comparisons between control groups and treated groups.

The sponsor concluded that mortality was significantly affecting the high dose males when compared to the saline control group. This reviewer concluded that survival of either gender was not significantly affected using two-sided trend tests with either the saline control or the vehicle control groups.

The reviewer's statistically significant tumor findings (trends with increasing dose, rarity of tumor determined by control group employed) are summarized below.

Table 3: Reviewer's Significant Tumor Findings among Female Rats

Tissue	Tumor	Trend with Saline Control	Trend with Vehicle Microspheres
Adrenal Gland	Pheochromocytoma, Benign	0.0464	0.1140
Mammary Gland	Adenocarcinoma	0.0176	0.0049
Mammary Gland	Adenocarcinoma, combined acinar, papillary, etc.	0.0394	0.0107
Pancreas	Islet Cell Adenoma	0.0007	0.0006

Table 4: Reviewer's Significant Tumor Findings among Male Rats

Tissue	Tumor	Trend with Saline Control	Trend with Vehicle Microspheres
Adrenal Gland	Pheochromocytoma (benign)	0.0006	0.0008
Adrenal Gland	Combined benign and malignant Pheochromocytoma	0.0004	0.0014
Kidney	Tubular Adenoma	0.0073	0.0081
Kidney	Combined tubular adenoma and adenocarcinoma	0.0020	0.0023
Mammary Gland	Adenocarcinoma and Fibroadenoma, predominant	0.0258	0.0874
Pancreas	Islet Cell Adenoma	0.0037	0.0150
Pancreas	Combined islet cell adenoma and carcinoma	0.0033	0.0055
Pituitary	Adenoma	0.0063	0.0151
Thyroid	Follicular Adenoma	0.4756	0.0347
Thyroid	Combined Follicular Adenoma and Adenocarcinoma	0.5202	0.0270

The sponsor reported some additional statistically significant tumor findings due to groupings or due to using the less stringent α-level of 0.05, irrespective of the rarity of the tumors.

In summary, this reviewer concluded that survival was not significantly negatively affected by treatment with the compound. Both genders experienced statistically significant increases in several tumors, with findings in the adrenal gland, mammary gland, and pancreas occurring in both genders. With the exception of follicular adenoma of the thyroid for male rats, it mattered little which control group was used in the trend tests.

Table 5: Number of Deaths per Time Interval, Female Rats with Saline Control

Number of Animals
Species: Rat
Sex: Female

	Treatment Group			
	CTRL1	MED	HIGH	Total
	N	N	N	N
Week				
0-52	4	3	1	8
53-78	2	6	6	14
79-91	1	5	5	11
92-105	9	7	9	25
106-107	34	29	29	92
Total	50	50	50	150

Table 6: Mortality Trend for Female Rats, Saline Control

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.53	0.4648
	Depart from Trend	0.96	0.3262
	Homogeneity	1.50	0.4729
Kruskal-Wallis	Dose-Mortality Trend	0.50	0.4793
	Depart from Trend	1.01	0.3150
	Homogeneity	1.51	0.4700

Figure 1: Kaplan-Meier Curves for Female Rats with Saline Control

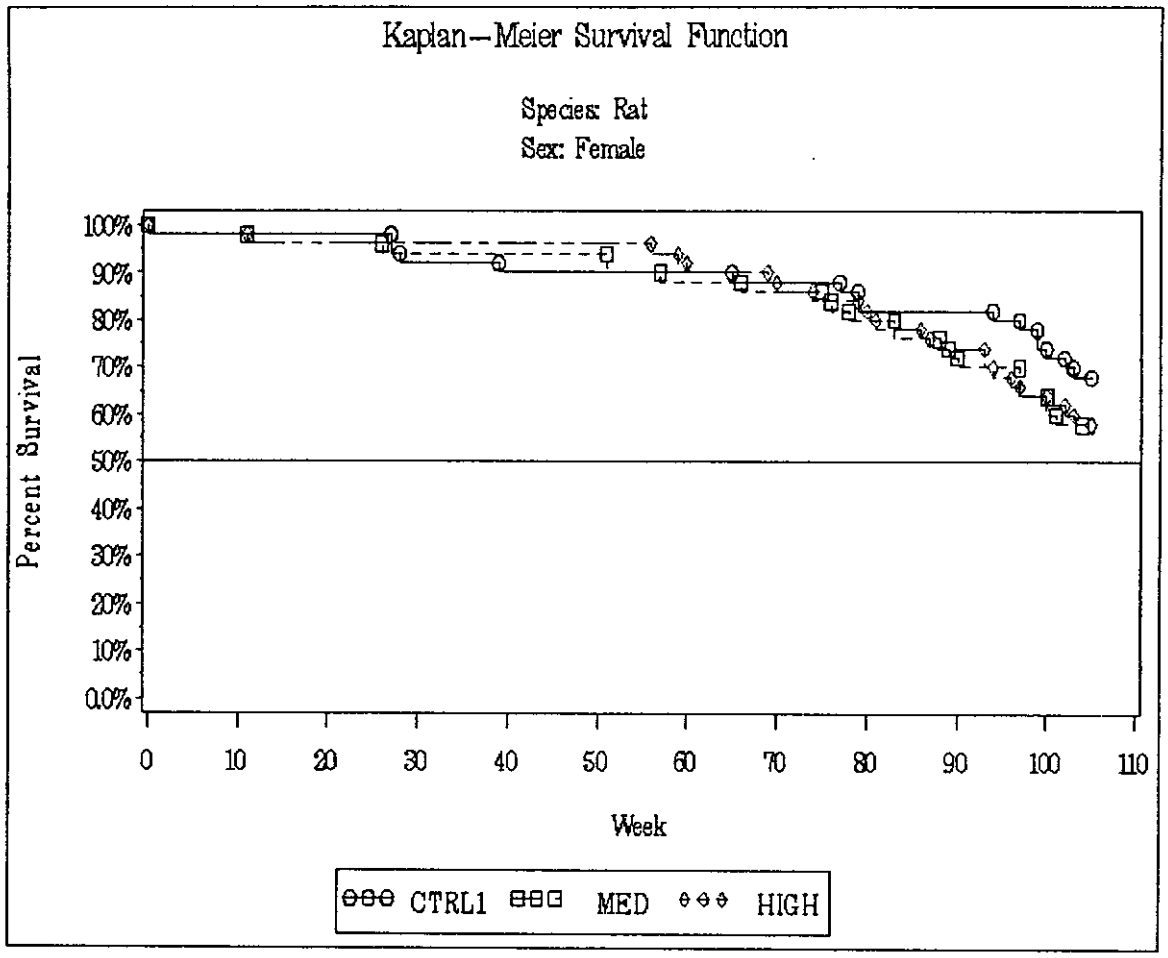

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Table 7: Tumor Trend among Female Rats, Saline Control

Test for Dose-Tumor Positive Linear Trend

Source: Female Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
Abdominal mesothelium	D7	Mesothelioma, malignant	MM2	2%	1	0	0	FA	1.0000	0.7997
Pituitary gland	E1	Adenoma	4	64%	32	28	32	MX	0.2895	0.2841
Pituitary gland	E1	Craniopharyngioma	Z82	.0%	0	1	0	FA	0.6641	0.7196
Adrenal glands	E3	Adenoma, cortical	462	2%	1	1	2	IN	0.2931	0.2117
Adrenal glands	E3	Phaeochromocytoma, benign	Z91	.0%	0	1	3	IN	0.0464	0.0254
Adrenal glands	E3	Phaeochromocytoma, malign	Z92	.0%	0	1	0	IN	0.6304	0.7086
Thyroid glands	E4	Adenoma, follicular	451	2%	1	3	5	IN	0.0508	0.0483
Thyroid glands	E4	Adenocarcinoma, follicula	632	2%	1	0	0	IN	1.0000	0.7975
Thyroid glands	E4	C-cell adenoma	E4	6%	3	1	3	IN	0.3952	0.3168
Thyroid glands	E4	C-cell carcinoma	E8	2%	1	1	0	IN	0.8670	0.8423
Ovaries	G31	Adenoma, tubulostromal	452	.0%	0	1	0	IN	0.6304	0.7086
Ovaries	G31	Granulosa-theca cell tumo	G44	6%	3	0	0	IN	1.0000	0.9230
Ovaries	G31	Sex cord stromal tumour,	G45	4%	2	0	0	IN	1.0000	0.8851
Ovaries	G31	Fibroma	M21	.0%	0	1	0	IN	0.6304	0.7086
Uterus	G33	Polyp	422	18%	9	3	1	IN	0.9948	0.9864
Uterus	G33	Carcinoma	8	4%	2	0	0	FA	1.0000	0.8740
Cervix	G34	Polyp	422	4%	2	0	1	IN	0.6887	0.5463
Spleen	H1	Hemangioma	MV8	2%	1	0	0	IN	1.0000	0.7975
Lymph node(s), mesenteric	H39	Hemangioma	MV8	.0%	0	4	0	IN	0.8806	0.9191
Lymph node(s), mesenteric	H39	Hemangiosarcoma	MV9	4%	2	0	0	MX	1.0000	0.8836
Hematopoietic system	H4	Thymoma, predominantly ly	H152	10%	5	3	0	IN	0.9953	0.9840
Hematopoietic system	H4	Thymoma, predominantly ly	H154	2%	1	2	0	IN	0.8228	0.8631
Mammary gland	I2	(Fibro)adenoma	44	.0%	0	0	1	IN	0.4286	0.1309
Mammary gland	I2	Fibroadenoma.	441	6%	3	6	5	IN	0.3518	0.3777

		predominant								
Mammary gland	I2	Fibroadenoma, predominant	442	4%	2	3	1	MX	0.7614	0.7871
Mammary gland	I2	Adenocarcinoma	6	8%	4	12	14	MX	0.0208	0.0176
Mammary gland	I2	Adenocarcinoma, acinar	621	.0%	0	1	0	FA	0.6356	0.7127
Mammary gland	I2	Adenocarcinoma, papillary	625	.0%	0	1	0	IN	0.6304	0.7086
Liver	L1	Hepatocellular adenoma	L1	4%	2	3	3	IN	0.3306	0.3305
Soft tissue	M8	Fibrohistiocytic sarcoma	M241	.0%	0	1	1	MX	0.3219	0.2773
Soft tissue	M8	Hemangioma	MV8	.0%	0	1	0	IN	0.6304	0.7086
Brain	N1	Granular cell tumor, beni	Z41	2%	1	0	0	IN	1.0000	0.7975
Pancreas	P	Adenoma, islet cell	493	.0%	0	1	7	IN	0.0007	0.0002
Urinary bladder	U3	Leiomyoma	M71	4%	2	0	0	IN	1.0000	0.8943

Table 8: Combined Tumors for Female Rats with Saline Control

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL1	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
Adrenal glands	111	Phaeochromocytoma,benign and malignant	222	.0%	0	2	3	IN	0.0630	0.0644
Adrenal glands	111	Adenoma and Adenocarcinoma,cortical	333	2%	1	1	2	IN	0.2931	0.2117
Thyroid glands	333	C-cell adenoma and carcinoma	444	8%	4	2	3	IN	0.5791	0.5232
Thyroid glands	333	Adenoma and Adenocarcinoma,follicular	555	4%	2	3	5	IN	0.1058	0.0930
Mammary gland	555	(Fibro)adenoma , Fibroadenoma, predominant	666	10%	5	8	7	MX	0.3830	0.3982
Mammary gland	555	Adenocarcinoma, acinar, papillar, etc.	777	8%	4	14	14	MX	0.0394	0.0328
Any organ	999	Hemangioma and Hemangiosarcoma	999	6%	3	5	0	MX	0.9849	0.9803

Table 9: Number of Deaths per Time Interval, Male Rats with Saline Control

Number of Animals
Species: Rat
Sex: Male

	Treatment Group			
	DOSE1	DOSE2	DOSE3	Total
	N	N	N	N
Week				
0-52	.	1	2	3
53-78	1	5	1	7
79-91	1	3	5	9
92-104	4	4	7	15
105-106	44	37	35	116
Total	50	50	50	150

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Table 10: Mortality Trend for Male Rats, Saline Control

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	2.72	0.0994
	Depart from Trend	2.29	0.1299
	Homogeneity	5.01	0.0817
Kruskal-Wallis	Dose-Mortality Trend	2.56	0.1098
	Depart from Trend	2.56	0.1095
	Homogeneity	5.12	0.0774

Figure 2: Kaplan-Meier Curves for Male Rats with Saline Control

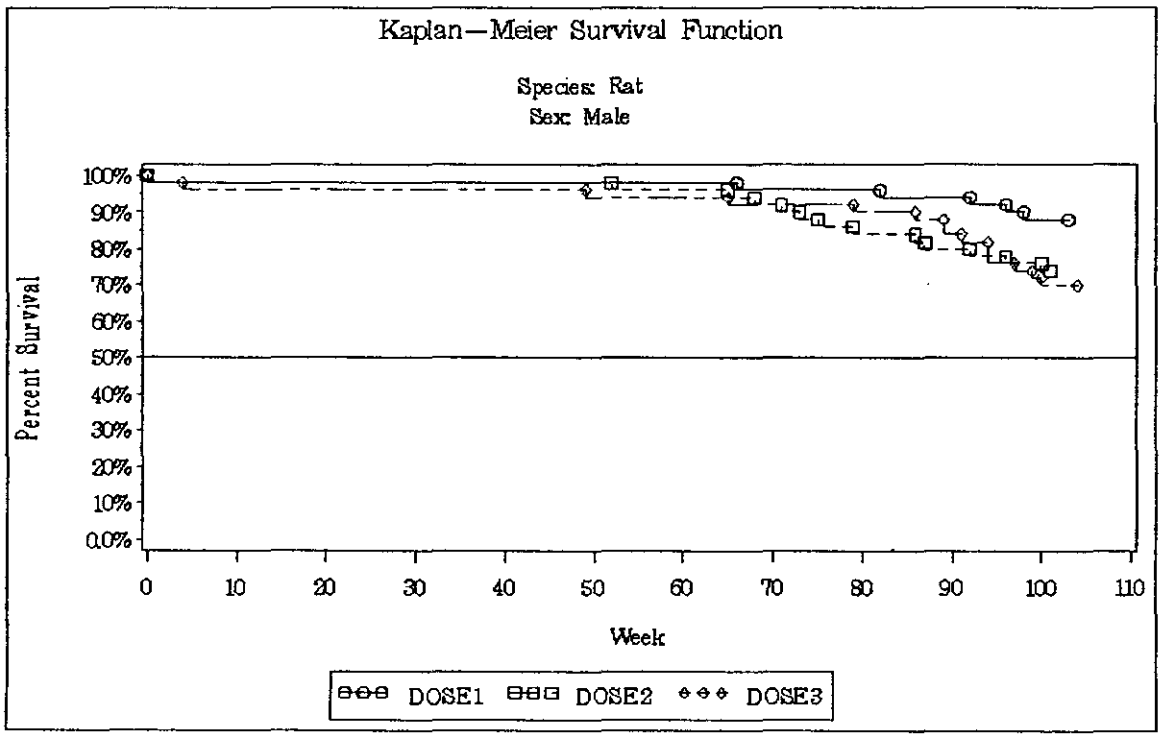

Table 11: Tumor Trend among Male Rats, Saline Control

Test for Dose-Tumor Positive Linear Trend

Source: Male Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL1	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
Jaw	D12	Carcinoma, squamous cell	871	.0%	0	1	0	IN	0.8571	0.6473
Stomach	D3	Sarcoma	M61	2%	1	0	0	FA	1.0000	0.7948
Stomach, forestomach	D31	Papilloma	21	2%	1	0	0	IN	1.0000	0.8623
Small intestine	D4	Leiomyoma	M71	2%	1	0	0	IN	1.0000	0.7917
Abdominal mesothelium	D7	Mesothelioma, malignant	MM2	2%	1	1	1	IN	0.5327	0.4534
Pituitary gland	E1	Adenoma	4	22%	11	14	23	MX	0.0073	0.0063
Adrenal glands	E3	Adenoma, cortical	462	4%	2	1	4	IN	0.1363	0.0862
Adrenal glands	E3	Adenocarcinoma, cortical	662	2%	1	0	0	IN	1.0000	0.7917
Adrenal glands	E3	Phaeochromocytoma, benign	Z91	4%	2	2	11	IN	0.0006	0.0003
Adrenal glands	E3	Phaeochromocytoma, malign	Z92	2%	1	1	1	IN	0.5327	0.4534
Thyroid glands	E4	Adenoma, follicular	451	14%	7	6	7	IN	0.4756	0.4565
Thyroid glands	E4	Adenocarcinoma, follicula	632	6%	3	1	1	IN	0.8106	0.7330
Thyroid glands	E4	C-cell adenoma	E4	10%	5	2	2	IN	0.8340	0.7892
Parathyroid gland(s)	E5	Adenoma	4	2%	1	0	0	IN	1.0000	0.7906
Testes	G11	Leydig cell tumor, benign	ML1	.0%	0	2	0	IN	0.6141	0.7661
Spleen	H1	Hemangio(endothelio)ma	MV1	.0%	0	1	0	IN	0.6207	0.7004
Lymph node(s), mesenteric	H39	Hemangioma	MV8	.0%	0	1	1	IN	0.3042	0.1586
Hematopoietic system	H4	Malignant lymphoma	H11	2%	1	2	0	FA	0.8324	0.8665
Hematopoietic system	H4	Myeloid leukemia	H21	.0%	0	1	0	FA	0.6281	0.7035
Hematopoietic system	H4	Histiocytic sarcoma	H62	2%	1	0	0	FA	1.0000	0.8036
Skin	I1	Papilloma	21	2%	1	0	0	IN	1.0000	0.7917
Skin	I1	Kerato-acanthoma	32	2%	1	0	0	IN	1.0000	0.7917
Mammary gland	I2	Fibroadenoma, predominant	441	.0%	0	0	1	IN	0.3017	0.0692
Mammary gland	I2	Adenocarcinoma	6	.0%	0	0	2	IN	0.0892	0.0168

Liver	L1	Hepatocellular adenoma	L1	8%	4	4	4	IN	0.4911	0.4806
Liver	L1	Hepatocarcinoma	L2	4%	2	0	0	IN	1.0000	0.8715
Bone	M1	Osteoma	M91	.0%	0	1	0	IN	0.6207	0.7004
Bone, stifle joint	M15	Sarcoma	M61	.0%	0	1	0	IN	0.6207	0.7004
Skeletal muscle, psoas mu	M611	Hemangiosarcoma	MV9	.0%	0	0	1	IN	0.2957	0.0664
Soft tissue	M8	Lipoma	M11	.0%	0	0	1	IN	0.3017	0.0692
Soft tissue	M8	Fibrosarcoma	M240	.0%	0	0	1	FA	0.3308	0.0830
Soft tissue	M8	Fibrohistiocytic sarcoma	M241	.0%	0	0	1	FA	0.3358	0.0854
Soft tissue	M8	Hemangioma	MV8	2%	1	0	0	IN	1.0000	0.7917
Soft tissue	M8	Hemangiosarcoma	MV9	2%	1	0	0	IN	1.0000	0.7917
Brain	N1	Granular cell tumor, mali	Z42	.0%	0	0	1	IN	0.3017	0.0692
Brain	N1	Meningioma	Z811	2%	1	0	0	IN	1.0000	0.7917
Brain	N1	Meningeal sarcoma	Z812	2%	1	0	0	FA	1.0000	0.7926
Eyelid	O122	Papilloma, sebaceous squa	27	2%	1	0	0	IN	1.0000	0.7917
Pancreas	P	Adenoma, islet cell	493	4%	2	1	8	IN	0.0037	0.0014
Pancreas	P	Adenoma, mixed islet cell	494	.0%	0	1	0	IN	0.6207	0.7004
Pancreas	P	Carcinoma, islet cell	663	2%	1	0	2	IN	0.2876	0.1491
Kidneys	U1	Adenoma, tubular	418	.0%	0	0	4	IN	0.0073	0.0012
Kidneys	U1	Adenocarcinoma, tubular	626	.0%	0	0	1	IN	0.3017	0.0692

Table 12: Combined Tumors for Male Rats with Saline Control

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL1	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
Adrenal glands	111	Phaeochromocytoma,benign and malignant	222	4%	2	3	12	IN	0.0004	0.0002
Thyroid glands	333	C-cell adenoma and carcinoma	444	10%	5	2	2	IN	0.8259	0.7809
Thyroid glands	333	Adenoma and Adenocarcinoma,follicular	555	18%	9	7	8	IN	0.5202	0.5011
Pancreas	666	Adenoma and carcinoma ,islet cell , mixed islet cell	777	6%	3	2	10	IN	0.0033	0.0015
Mammary Gland	M999	Adenocarcinoma and Fibroadenoma, predominant	M999	.0%	0	0	3	IN	0.0258	0.0044
Kidneys	888	Adenoma and Adenocarcinoma,tubular	999	.0%	0	0	5	IN	0.0020	0.0003

Table 13: Number of Deaths per Time Interval, Female Rats with Vehicle Control

Number of Animals
Species: Rat
Sex: Female

	Treatment Group			
	CTRL2	MED	HIGH	Total
	N	N	N	N
Week				
0-52	3	3	1	7
53-78	3	6	6	15
79-91	1	5	5	11
92-105	4	7	9	20
106-107	39	29	29	97
Total	50	50	50	150

Table 14: Mortality Trend for Female Rats, Vehicle Control

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.83	0.1758
	Depart from Trend	3.26	0.0711
	Homogeneity	5.09	0.0785
Kruskal-Wallis	Dose-Mortality Trend	1.50	0.2200
	Depart from Trend	2.94	0.0867
	Homogeneity	4.44	0.1086

Figure 3: Kaplan-Meier Curves for Female Rats with Vehicle Control

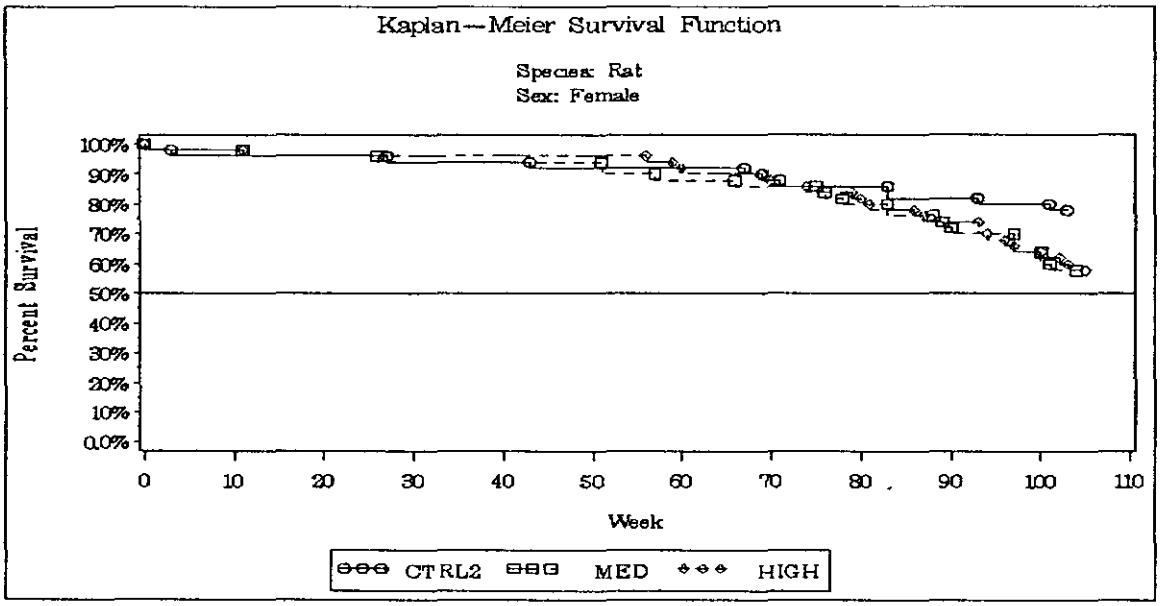

Table 15: Tumor Trend for Female Rats, Vehicle Control

Test for Dose-Tumor Positive Linear Trend

Source: Female Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL2	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
Small intestine, duodenum	D41	Leiomyoma	M71	2%	1	0	0	IN	1.0000	0.7879
Pituitary gland	E1	Adenoma	4	54%	27	28	32	MX	0.0853	0.0822
Pituitary gland	E1	Craniopharyngioma	Z82	.0%	0	1	0	FA	0.6641	0.7196
Adrenal glands	E3	Adenoma, cortical	462	4%	2	1	2	IN	0.4142	0.3260
Adrenal glands	E3	Phaeochromocytoma, benign	Z91	2%	1	1	3	IN	0.1140	0.0671
Adrenal glands	E3	Phaeochromocytoma, malign	Z92	.0%	0	1	0	IN	0.5979	0.6960
Thyroid glands	E4	Adenoma, follicular	451	2%	1	3	5	IN	0.0453	0.0437
Thyroid glands	E4	C-cell adenoma	E4	12%	6	1	3	IN	0.6852	0.6503
Thyroid glands	E4	C-cell carcinoma	E8	.0%	0	1	0	IN	0.8000	0.7963
Ovaries	G31	Adenoma, tubulostromal	452	.0%	0	1	0	IN	0.5979	0.6960
Ovaries	G31	Sertoli cell tumor, benig	G21	2%	1	0	0	IN	1.0000	0.7879
Ovaries	G31	Granulosa-theca cell tumo	G44	2%	1	0	0	IN	1.0000	0.7879
Ovaries	G31	Fibroma	M21	.0%	0	1	0	IN	0.5979	0.6960
Uterus	G33	Polyp	422	12%	6	3	1	IN	0.9759	0.9572
Uterus	G33	Adenocarcinoma	6	2%	1	0	0	IN	1.0000	0.7879
Uterus	G33	Carcinoma	8	2%	1	0	0	IN	1.0000	0.7879
Uterus	G33	Sarcoma	M61	2%	1	0	0	IN	1.0000	0.7879
Cervix	G34	Polyp	422	.0%	0	0	1	IN	0.2990	0.0679
Cervix	G34	Leiomyoma	M71	2%	1	0	0	IN	1.0000	0.7879
Spleen	H1	Hemangioma	MV8	2%	1	0	0	IN	1.0000	0.7879
Lymph node(s), mesenteric	H39	Hemangioma	MV8	2%	1	4	0	IN	0.9400	0.9502
Hematopoietic system	H4	Thymoma, predominantly ly	H152	4%	2	3	0	IN	0.8965	0.9163
Hematopoietic system	H4	Thymoma.	H153	2%	1	0	0	IN	1.0000	0.7879

		predominantly ep								
Hematopoietic system	H4	Thymoma, predominantly ly	H154	2%	1	2	0	IN	0.7923	0.8488
Skin	I1	Kerato-acanthoma	32	2%	1	0	0	IN	1.0000	0.7879
Mammary gland	I2	Adenoma, acinar	411	2%	1	0	0	IN	1.0000	0.7879
Mammary gland	I2	(Fibro)adenoma	44	.0%	0	0	1	IN	0.4000	0.1169
Mammary gland	I2	Fibroadenoma, predominant	441	4%	2	6	5	IN	0.2553	0.2831
Mammary gland	I2	Fibroadenoma, predominant	442	2%	1	3	1	MX	0.6329	0.6966
Mammary gland	I2	Adenocarcinoma	6	4%	2	12	14	MX	0.0070	0.0049
Mammary gland	I2	Adenocarcinoma, acinar	621	.0%	0	1	0	FA	0.6356	0.7127
Mammary gland	I2	Adenocarcinoma, papillary	625	.0%	0	1	0	IN	0.5979	0.6960
Liver	L1	Hepatocellular adenoma	L1	2%	1	3	3	IN	0.1636	0.1836
Soft tissue	M8	Fibrohistiocytic sarcoma	M241	.0%	0	1	1	MX	0.3032	0.2652
Soft tissue	M8	Hemangioma	MV8	.0%	0	1	0	IN	0.5979	0.6960
Pancreas	P	Adenoma, islet cell	493	.0%	0	1	7	IN	0.0006	0.0002
Kidneys	U1	Papilloma, transitional c	23	2%	1	0	0	IN	1.0000	0.7879

Table 16: Combined Tumors for Female Rats with Vehicle Control

Organ Code	Organ Name	Tumor Code	Tumor Name	CTRL 2	MED	HIGH	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
111	Adrenal glands	222	Phaeochromocytoma,benign and malignant	1	2	3	0.1355	0.1207	1	2%	IN
111	Adrenal glands	333	Adenoma and Adenocarcinoma,cortical	2	1	2	0.4142	0.3260	2	4%	IN
333	Thyroid glands	444	C-cell adenoma and carcinoma	6	2	3	0.7730	0.7347	6	12%	IN
333	Thyroid glands	555	Adenoma and Adenocarcinoma,follicula	1	3	5	0.0453	0.0437	1	2%	IN
555	Mammary gland	666	(Fibro)adenoma and Fibroadenoma, predominant	3	8	7	0.2101	0.2240	3	6%	MX
555	Mammary gland	777	Adenocarcinoma, acinar, papillary, etc.	2	14	14	0.0145	0.0107	2	4%	MX
999	Any organ	999	Hemangioma and hemangiosarcoma	2	5	0	0.9704	0.9700	2	4%	IN

Table 17: Number of Deaths per Time Interval, Male Rats with Vehicle Control

Number of Animals
Species: Rat
Sex: Male

	Treatment Group			
	CTRL2	MED	HIGH	Total
	N	N	N	N
Week				
0-52	.	1	2	3
53-78	2	5	1	8
79-91	3	3	5	11
92-104	4	4	7	15
105-106	41	37	35	113
Total	50	50	50	150

Table 18: Mortality Trend for Male Rats, Vehicle Control

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.15	0.2845
	Depart from Trend	0.70	0.4041
	Homogeneity	1.84	0.3982
Kruskal-Wallis	Dose-Mortality Trend	0.97	0.3236
	Depart from Trend	0.79	0.3734
	Homogeneity	1.77	0.4134

Figure 4: Kaplan-Meier Curves for Male Rats with Vehicle Control

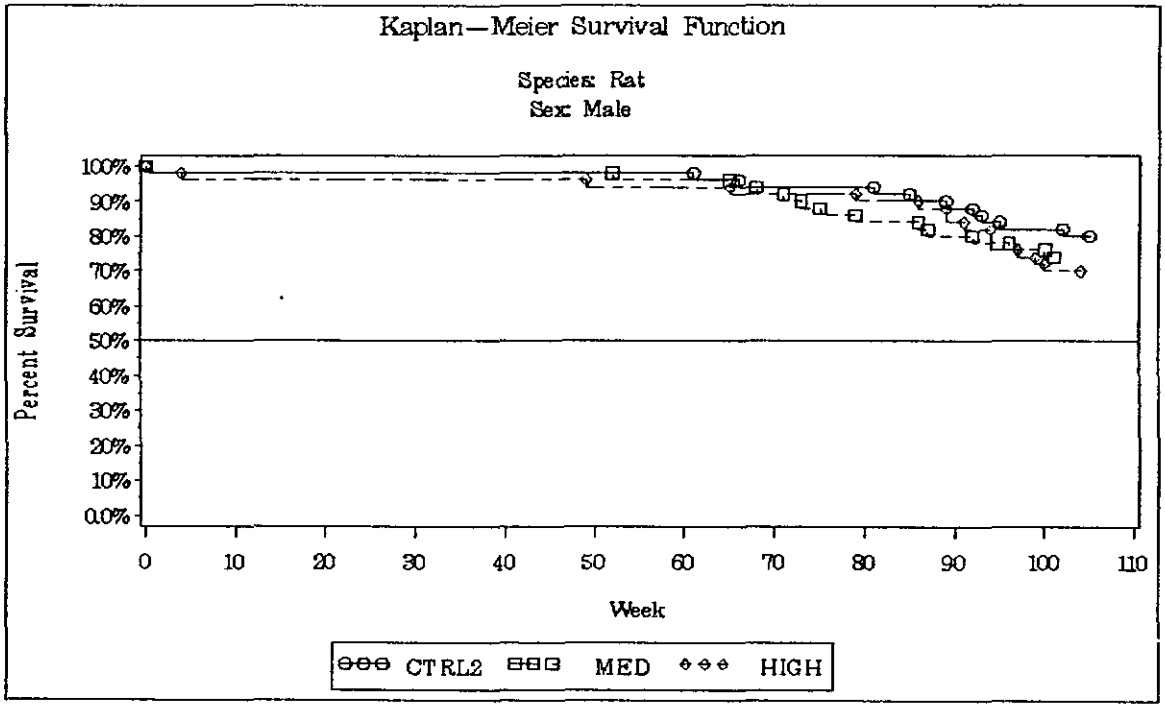

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Table 19: Tumor Trend for Male Rats, Vehicle Control

Test for Dose-Tumor Positive Linear Trend

Source: Male Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL2	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
Jaw	D12	Carcinoma, squamous cell	871	.0%	0	1	0	IN	0.7500	0.6165
Abdominal mesothelium	D7	Mesothelioma, malignant	MM2	.0%	0	1	1	IN	0.2987	0.2525
Pituitary gland	E1	Adenoma	4	24%	12	14	23	MX	0.0171	0.0151
Adrenal glands	E3	Adenoma, cortical	462	2%	1	1	4	IN	0.0559	0.0277
Adrenal glands	E3	Ganglioneuroma	Z61	2%	1	0	0	IN	1.0000	0.7965
Adrenal glands	E3	Phaeochromocytoma, benign	Z91	4%	2	2	11	IN	0.0008	0.0003
Adrenal glands	E3	Phaeochromocytoma, malign	Z92	2%	1	1	1	IN	0.5525	0.4679
Thyroid glands	E4	Adenoma, follicular	451	.0%	0	6	7	IN	0.0347	0.0372
Thyroid glands	E4	Adenocarcinoma, follicula	632	.0%	0	1	1	IN	0.2987	0.2525
Thyroid glands	E4	C-cell adenoma	E4	2%	1	2	2	IN	0.3761	0.3668
Thyroid glands	E4	C-cell carcinoma	E8	2%	1	0	0	IN	1.0000	0.7965
Testes	G11	Leydig cell tumor, benign	ML1	.0%	0	2	0	IN	0.6307	0.7740
Spleen	H1	Hemangio(endothelio)ma	MV1	2%	1	1	0	IN	0.8704	0.8302
Lymph node(s), mesenteric	H39	Hemangioma	MV8	2%	1	1	1	IN	0.5119	0.3812
Lymph node(s), mesenteric	H39	Hemangiosarcoma	MV9	2%	1	0	0	IN	1.0000	0.7965
Hematopoietic system	H4	Malignant lymphoma	H11	.0%	0	2	0	FA	0.6542	0.7862
Hematopoietic system	H4	Myeloid leukemia	H21	.0%	0	1	0	FA	0.6441	0.7095
Skin	I1	Carcinoma, basal cell	854	2%	1	0	0	FA	1.0000	0.8069
Mammary gland	I2	Fibroadenoma, predominant	441	.0%	0	0	1	IN	0.3097	0.0730
Mammary gland	I2	Adenocarcinoma	6	2%	1	0	2	IN	0.2262	0.1067
Liver	L1	Hepatocellular adenoma	L1	12%	6	4	4	IN	0.6732	0.6425
Bone	M1	Osteoma	M91	.0%	0	1	0	IN	0.6372	0.7067
Bone. stifle	M15	Sarcoma	M61	.0%	0	1	0	IN	0.6372	0.7067

joint										
Skeletal muscle, psoas mu	M611	Hemangiosarcoma	MV9	.0%	0	0	1	IN	0.3036	0.0701
Soft tissue	M8	Lipoma	M11	2%	1	0	1	IN	0.5254	0.3213
Soft tissue	M8	Liposarcoma	M12	2%	1	0	0	FA	1.0000	0.8050
Soft tissue	M8	Fibrosarcoma	M240	.0%	0	0	1	FA	0.3385	0.0867
Soft tissue	M8	Fibrohistiocytic sarcoma	M241	.0%	0	0	1	FA	0.3407	0.0878
Brain	N1	Tumor of glia, malignant	Z36	2%	1	0	0	FA	1.0000	0.8049
Brain	N1	Granular cell tumor, mali	Z42	.0%	0	0	1	IN	0.3097	0.0730
Eyelid	O122	Schwannoma, benign	Z511	2%	1	0	0	IN	1.0000	0.7965
Pancreas	P	Adenoma, islet cell	493	6%	3	1	8	IN	0.0150	0.0080
Pancreas	P	Adenoma, mixed islet cell	494	.0%	0	1	0	IN	0.6372	0.7067
Pancreas	P	Carcinoma, islet cell	663	.0%	0	0	2	IN	0.1445	0.0384
Kidneys	U1	Adenoma, tubular	418	.0%	0	0	4	IN	0.0081	0.0014
Kidneys	U1	Adenocarcinoma, tubular	626	.0%	0	0	1	IN	0.3097	0.0730
Kidneys	U1	Lipoma	M11	2%	1	0	0	IN	1.0000	0.7965

Table 20: Combined Tumors for Male Rats with Vehicle Control

Organ Code	Organ Name	Tumor Code	Tumor Name	CTRL 2	MED	HIGH	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
111	Adrenal glands	222	Phaeochromocytoma,benign and malignant	3	3	12	0.0014	0.0007	3	6%	IN
333	Thyroid glands	444	C-cell adenoma and carcinoma	2	2	2	0.5438	0.5059	2	4%	IN
333	Thyroid glands	555	Adenoma and Adenocarcinoma,follicular	0	7	8	0.0270	0.0264	0	.0%	IN
666	Pancreas	777	Adenoma and carcinoma,islet cell, mixed islet cell	3	2	10	0.0055	0.0029	3	6%	IN
M999	Mammary Gland	M999	Adenocarcinoma and Fibroadenoma, predominant	1	0	3	0.0874	0.0333	1	2%	IN
888	Kidneys	999	Adenoma and Adenocarcinoma,tubular	0	0	5	0.0023	0.0004	0	.0%	IN

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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

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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:

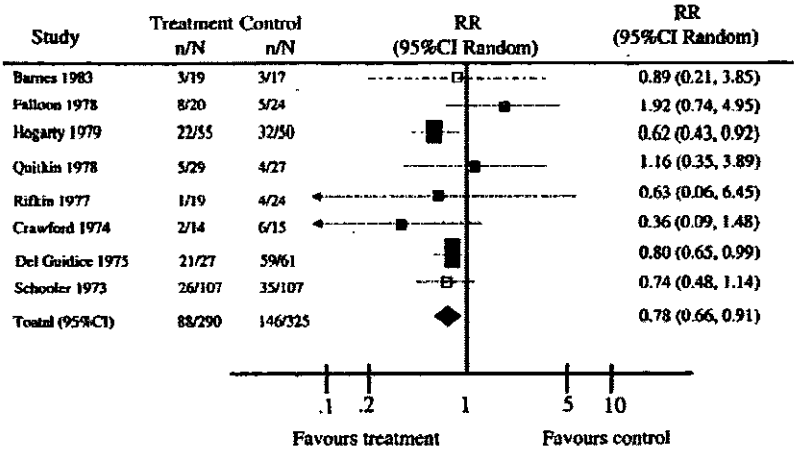
We have previously acknowledged a clinical need for a long acting injectable form of risperidone. We asked the sponsor to summarize and provide documentation to support this belief. The sponsor supplies 64 research papers supporting their position. There are reference links to refer the reader to the 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 1989	Randomised, double-blind, 1 year.	Schizophrenia (PSE), N=36, mean age 40yrs, sex: 12M, 18F.	1. Fluphenazine decanoate 25mg/IM biweekly. 2. Pimozide: dose 6mg/day
Farkas 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 62 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-naive 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 CONSTA during 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[a] 365[b]
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 (haloperidone, 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 minimum 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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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

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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 (≥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-INT-23	RIS depot 50 mg	Single injection + 10-week follow-up	Open-label, multicenter
RIS-INT-34	RIS depot 100 mg	Single injection + 10-week follow-up	Open-label, single-center
RIS-NED-13	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 to 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

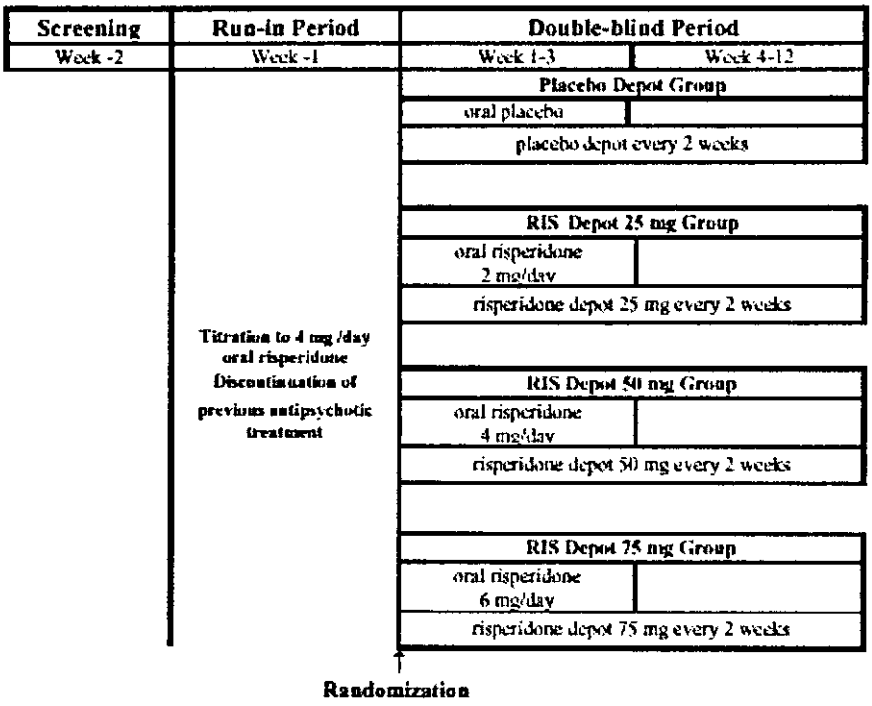
RIS-USA-121

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);

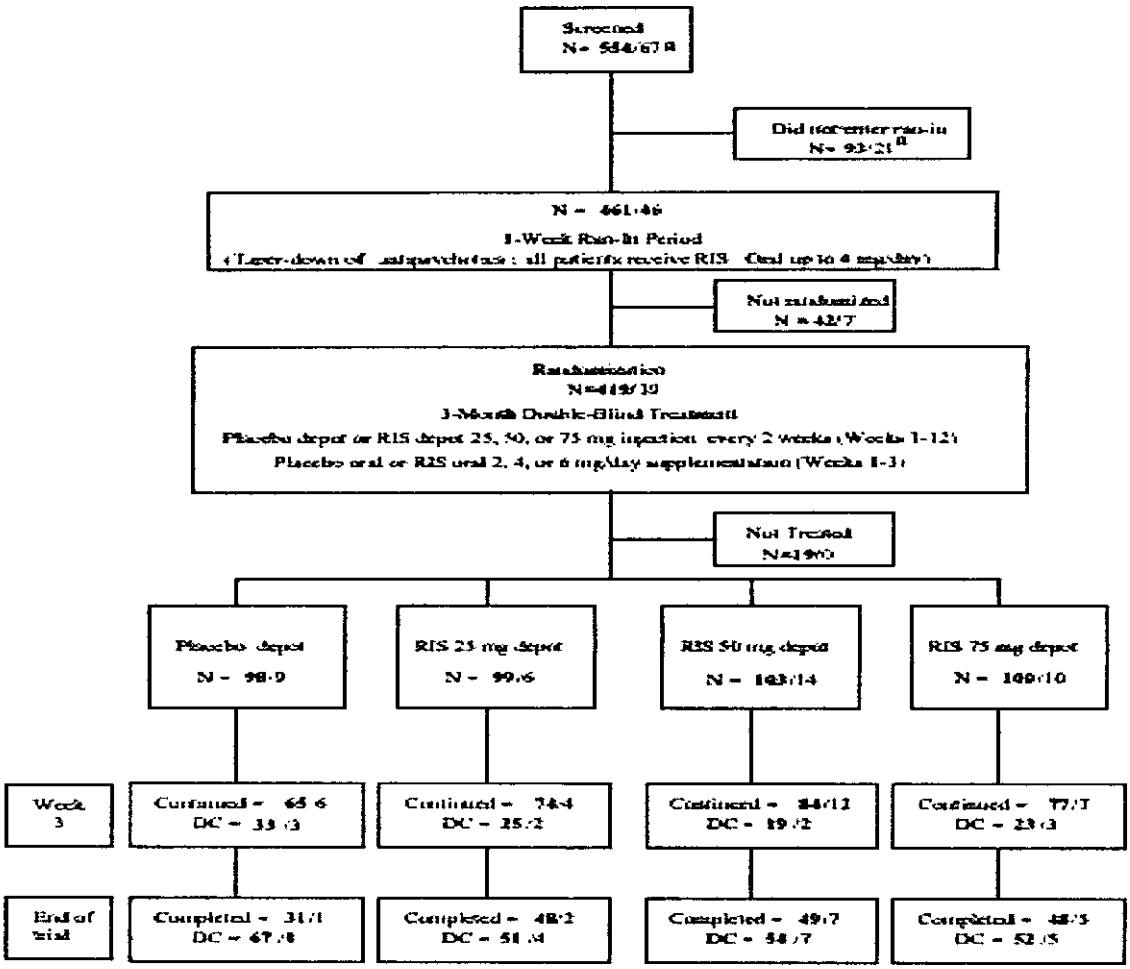
_ Patient and, when appointed, patient's guardian or legal representative, had signed the informed consent form;
_ Patient was otherwise healthy on the basis of a pre-trial physical examination, medical history, electrocardiogram and the results of blood biochemistry, hematology tests and a urinalysis 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.



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.ule.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'n 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

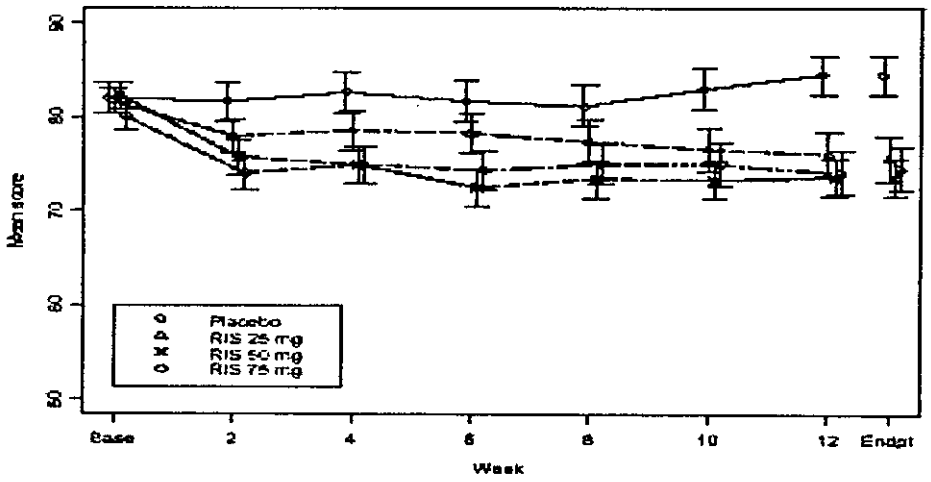
Source: Table PANSS.1 and PANSS.4 USA121

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

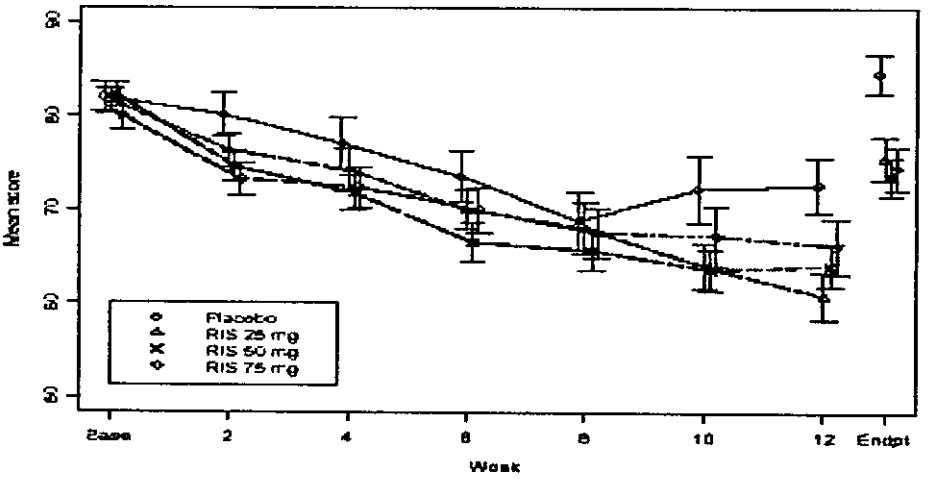


Table 26: Clinical Global Impression (CGI)-mean and mean change from baseline at endpoint (patients with schizophrenia)

	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 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.

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	73.1 (1.48)	
Endpoint	96	72.1 (1.33)	-2.2 (1.33)	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)	4.3 (3.33)	96	369.2 (3.42)	4.7 (3.57)	98	375.4 (3.44)	8.1 (3.59)	95	370.2 (3.30)	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)	95	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 (1.62)	2.7 (2.37)
PR interval, msec												
Baseline	93	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	168.3 (2.12)	1.6 (1.90)	95	167.0 (2.30)	-3.2 (1.95)
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.3 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

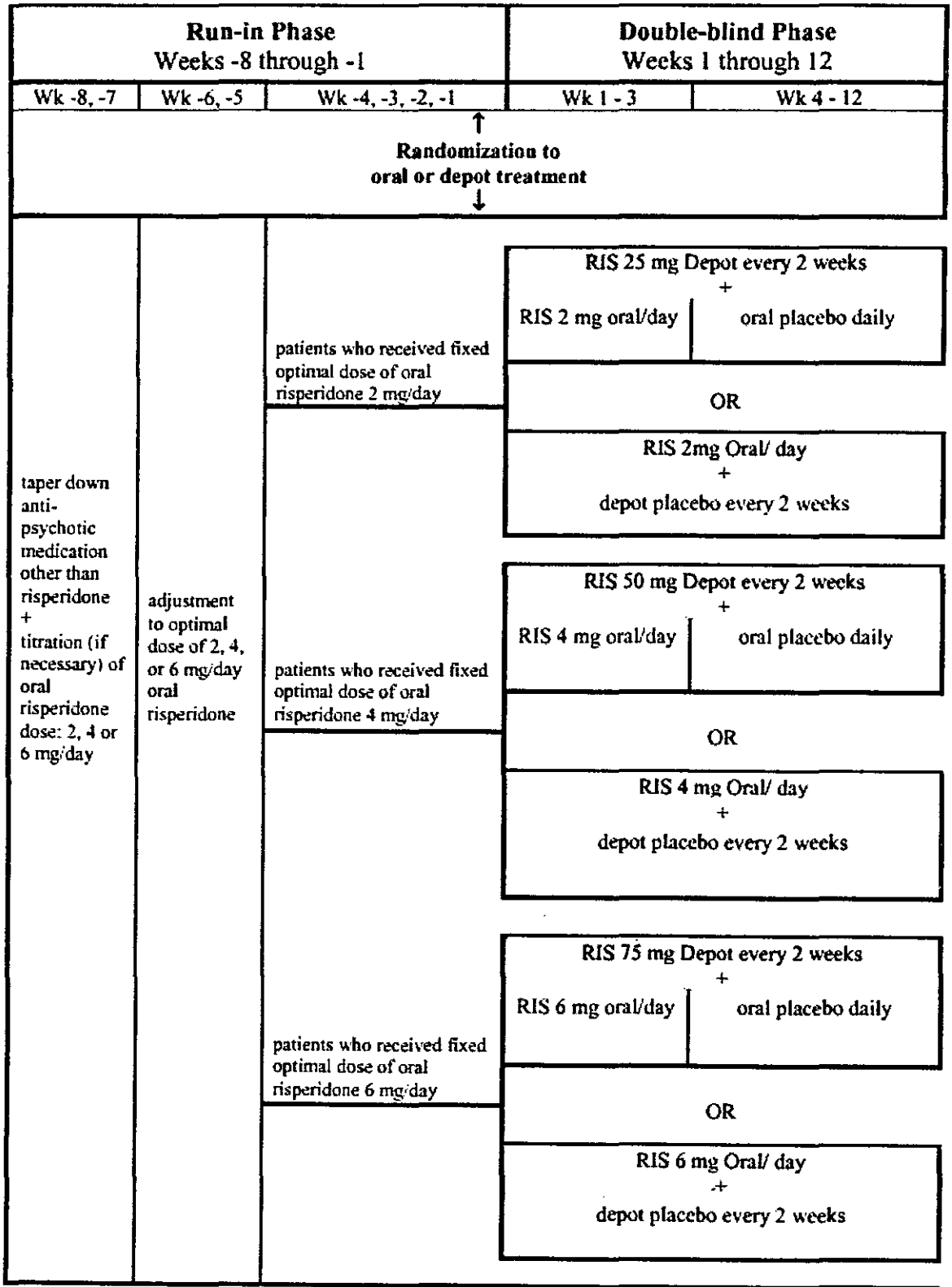
Principal Investigator

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 Varenus 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 I.	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=461)	RIS depot 50 mg (N=738)	RIS depot 75 mg (N=677)	RIS depot Total (N=1910)[f]	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]	2 (0.3%)	14 (0.7%)	1 (0.3%)
RIS-INT-62, RIS-JPN-16[d]	–	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[c]	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[e]	–	2	4	5	11	–
RIS-JPN-16[d]	–	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[c]	13 (12.1%)	43 (9.3%)[g]	53 (7.2%)[g]	54 (8.0%)	150 (7.8%)	13 (4.0%)
RIS-INT-62[e]	–	0	0	0	0	–
RIS-JPN-16[d]	–	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 (made 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 (JPSY) 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=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 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)[24]	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%)
Gastro-intestinal 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 (N=301)	RLS depot 25 mg (N=215)	RLS depot 50 mg (N=159)	RLS depot 75 mg (N=357)	RLS depot Total (N=911)	Placebo depot (N=198)	RLS depot 25 mg (N=127)	RLS depot 50 mg (N=139)	RLS depot 75 mg (N=249)	RLS depot Total (N=414)
Any adverse event	63 (83.8%)	144 (67.0%)	240 (66.5%)	263 (73.8%)	641 (68.9%)	144 (72.8%)	86 (66.9%)	98 (71.0%)	110 (79.9%)	295 (74.8%)
Psychiatric disorders	49 (65.3%)	79 (36.7%)	117 (32.6%)	171 (47.9%)	367 (39.4%)	110 (55.6%)	38 (29.6%)	51 (37.0%)	71 (47.7%)	160 (38.8%)
Anxiety	12 (16.0%)	19 (8.8%)	29 (8.1%)	50 (14.0%)	98 (10.5%)	21 (10.6%)	7 (5.5%)	15 (10.9%)	20 (13.4%)	42 (10.1%)
Insomnia	21 (28.0%)	23 (10.7%)	38 (10.6%)	59 (16.5%)	120 (12.9%)	33 (16.7%)	12 (9.4%)	18 (13.0%)	19 (12.8%)	49 (11.8%)
Psychosis	27 (36.0%)	13 (6.0%)	20 (5.6%)	47 (13.2%)	80 (8.6%)	66 (33.3%)	7 (5.5%)	6 (4.3%)	25 (16.8%)	38 (9.2%)
Agitation	24 (32.0%)	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 (4.0%)	11 (5.1%)	11 (3.1%)	24 (6.7%)	46 (5.0%)	0	7 (5.5%)	7 (5.0%)	9 (6.0%)	23 (5.6%)
Hallucination	5 (6.7%)	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 (5.3%)	1 (0.5%)	4 (1.1%)	9 (2.5%)	14 (1.5%)	0	0	0	1 (0.7%)	1 (0.2%)
Nervousness	4 (5.3%)	2 (0.9%)	5 (1.4%)	7 (2.0%)	13 (1.4%)	11 (5.6%)	2 (1.6%)	1 (0.7%)	4 (2.7%)	7 (1.7%)
Central & peripheral nervous system disorders	**25 (33.3%)**	**48 (22.3%)**	**100 (27.9%)**	**103 (28.8%)**	**251 (27.5%)**	**33 (16.7%)**	**31 (24.4%)**	**38 (27.5%)**	**46 (30.9%)**	**115 (27.8%)**
Headache	13 (17.3%)	24 (11.2%)	41 (11.5%)	41 (11.5%)	106 (11.6%)	21 (10.6%)	15 (11.8%)	12 (8.6%)	17 (11.4%)	44 (10.6%)
Extrapyramidal disorder	3 (4.0%)	5 (2.3%)	13 (3.6%)	19 (5.3%)	37 (4.1%)	0	5 (3.9%)	6 (4.3%)	9 (6.0%)	20 (4.8%)
Dizziness	5 (6.7%)	7 (3.3%)	14 (3.9%)	15 (4.2%)	36 (3.9%)	0	4 (3.1%)	9 (6.5%)	16 (10.7%)	29 (7.0%)
Hypertonia	2 (2.7%)	11 (5.1%)	18 (5.0%)	14 (3.9%)	43 (4.6%)	2 (1.1%)	4 (3.1%)	4 (2.9%)	12 (8.1%)	20 (4.8%)
Hypotonia	5 (6.7%)	3 (1.4%)	13 (3.6%)	12 (3.4%)	28 (3.1%)	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%)	6 (4.2%)	17 (4.1%)
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%)**	**23 (19.0%)**	**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 (2.7%)	7 (3.3%)	3 (0.8%)	7 (2.0%)	17 (1.8%)	11 (5.6%)	3 (2.4%)	5 (3.6%)	2 (1.3%)	10 (2.4%)
Injury	5 (6.7%)	2 (0.9%)	5 (1.4%)	14 (3.9%)	21 (2.3%)	11 (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%)**	**5 (16.7%)**	**22 (17.3%)**	**10 (7.2%)**	**21 (14.1%)**	**53 (12.8%)**
Rhinitis	5 (6.7%)	14 (6.5%)	21 (5.9%)	25 (6.4%)	58 (6.2%)	3 (16.7%)	10 (7.9%)	7 (5.0%)	8 (5.4%)	25 (6.0%)
Bronchitis	0	4 (1.9%)	4 (1.1%)	5 (1.4%)	13 (1.4%)	0	3 (2.4%)	1 (0.7%)	8 (5.4%)	12 (2.9%)

	Male					Female				
WHO Organ System WHO Preferred Term	Placebo depot (N=[illegible])	RLS depot 25 mg (N=215)	RLS depot 50 mg (N=159)	RLS depot 75 mg (N=357)	RLS depot Total (N=731)	Placebo depot (N=[illegible])	RLS depot 25 mg (N=127)	RLS depot 50 mg (N=138)	RLS depot 75 mg (N=[illegible])	RLS depot Total (N=414)
Heart rate and rhythm disorders	11 (13.6%)	5 (2.3%)	10 (2.8%)	11 (3.1%)	26 (2.8%)	3 (5.6%)	6 (4.7%)	9 (6.5%)	7 (4.7%)	22 (5.3%)
Tachycardia	6 (7.4%)	1 (0.5%)	5 (1.4%)	5 (1.4%)	11 (1.2%)	0	1 (0.8%)	6 (4.3%)	2 (1.4%)	9 (2.2%)
Gastrointestinal system disorders	8 (10.0%)	33 (15.3%)	56 (15.6%)	58 (16.2%)	147 (15.8%)	6 (11.3%)	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%)	3 (5.6%)	6 (4.7%)	8 (5.8%)	7 (4.7%)	20 (4.8%)
Weight increase	1 (1.3%)	5 (2.3%)	10 (2.8%)	5 (1.4%)	19 (2.0%)	3 (5.6%)	2 (1.6%)	3 (2.2%)	5 (3.4%)	10 (2.4%)

Source: Table 11.17.1.3.3

Includes Trials RLS-4/USA-121, RLS-INT-57, RLS-INT-61, RLS-SWE-17, RLS-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 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=145)	(N=263)	(N=402)	(N=402)	(N=1067)	(N=37)	(N=86)	(N=65)	(N=68)	(N=169)
Any Adverse Event	87 (82.2%)	169 (64.3%)	268 (66.7%)	282 (70.1%)	719 (67.4%)	31 (83.8%)	55 (63.9%)	39 (74.9%)	56 (82.3%)	129 (76.3%)
Psychiatric disorders	75 (55.6%)	83 (31.6%)	153 (34.1%)	159 (43.3%)	419 (39.4%)	24 (64.9%)	20 (43.5%)	14 (25.5%)	34 (51.5%)	68 (48.3%)
Insomnia	5 (11.1%)	22 (8.4%)	46 (11.4%)	63 (15.7%)	131 (12.3%)	7 (18.9%)	19 (21.7%)	3 (5.5%)	11 (16.7%)	24 (14.4%)
Anxiety	8 (17.9%)	22 (8.4%)	39 (9.7%)	69 (17.2%)	130 (12.2%)	5 (13.5%)	14 (2.3%)	1 (1.8%)	7 (10.6%)	21 (5.8%)
Psychosis	30 (22.2%)	14 (5.3%)	20 (5.0%)	57 (14.2%)	91 (8.5%)	9 (24.3%)	5 (10.0%)	3 (5.5%)	9 (13.6%)	17 (10.2%)
Depression	21 (6.4%)	16 (6.1%)	28 (4.5%)	35 (8.7%)	55 (6.1%)	1 (2.7%)	1 (1.2%)	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 (4.7%)	3 (5.5%)	11 (16.2%)	18 (10.6%)
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 (9.2%)	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%)	107 (26.6%)	266 (24.9%)	11 (29.7%)	13 (15.2%)	22 (40.0%)	29 (43.9%)	56 (34.7%)
Headache	8 (17.8%)	26 (10.2%)	41 (10.2%)	39 (9.7%)	106 (10.2%)	2 (5.4%)	4 (4.7%)	9 (16.4%)	15 (22.7%)	28 (16.9%)
Hyperkinesia	1 (2.2%)	12 (4.6%)	15 (3.7%)	19 (4.7%)	46 (4.3%)	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%)
Dizziness	2 (4.4%)	4 (1.5%)	14 (3.5%)	23 (5.6%)	41 (3.8%)	3 (8.1%)	2 (2.3%)	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 (17.4%)	12 (21.8%)	15 (22.7%)	42 (25.1%)
Constipation	0	5 (1.9%)	10 (2.5%)	12 (3.0%)	27 (2.5%)	1 (2.7%)	3 (3.5%)	2 (3.6%)	4 (6.1%)	9 (5.3%)
Dyspepsia	2 (4.4%)	3 (1.1%)	14 (3.5%)	10 (2.5%)	27 (2.5%)	0	4 (4.7%)	1 (1.8%)	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 (1.2%)	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 (1.2%)	2 (3.6%)	2 (3.0%)	5 (3.0%)
Stomach increased	0	4 (1.5%)	7 (1.7%)	4 (1.0%)	15 (1.4%)	1 (2.7%)	4 (4.7%)	1 (1.8%)	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%)	2 (2.3%)	1 (1.8%)	3 (4.5%)	6 (3.6%)

WHO Organ System WHO Preferred term	White					Black				
	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=451)	(N=263)	(N=252)	(N=402)	(N=1067)	(N=137)	(N=66)	(N=55)	(N=46)	(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%)	10 (15.2%)	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 (11.0%)	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%)	1 (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 (6.7%)	7 (2.7%)	15 (3.7%)	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 (6.7%)	12 (4.6%)	9 (2.2%)	3 (0.7%)	24 (2.6%)	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: Tabs AE.1 to ISS

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)**

	<20		≥20 to <25		≥25 to <30		≥30	
WHO Organ System WHO Preferred Term	Placebo depot (N=21)	RIS depot Total (N=62)	Placebo depot (N=104)	RIS depot Total (N=424)	Placebo depot (N=28)	RIS depot Total (N=453)	Placebo depot (N=27)	RIS depot Total (N=306)
Any adverse event	8 (50.0%)	40 (64.5%)	54 (69.5%)	276 (65.0%)	23 (82.1%)	325 (71.7%)	20 (74.1%)	290 (33.2%)
Psychiatric disorders	4	21 (33.9%)	28 (26.9%)	149 (35.1%)	13 (46.4%)	176 (38.9%)	17 (63.0%)	117 (44.1%)
Agitation	0	6 (9.7%)	8 (7.7%)	24 (5.7%)	7 (25.0%)	54 (11.9%)	7 (25.9%)	34 (11.1%)
Insomnia	0	9 (14.5%)	4 (3.8%)	44 (10.4%)	5 (17.9%)	54 (11.9%)	4 (14.8%)	59 (14.9%)
Anxiety	0	5 (8.1%)	5 (4.8%)	39 (9.2%)	6 (21.4%)	52 (11.5%)	4 (14.8%)	52 (13.1%)
Depression	0	3 (4.8%)	1 (1.0%)	21 (5.0%)	0	12 (2.6%)	1 (3.7%)	23 (5.8%)
Hallucination	0	6 (9.7%)	3 (2.9%)	13 (3.1%)	2 (7.1%)	9 (2.0%)	1 (3.7%)	25 (6.3%)
Tiredness	0	1 (1.6%)	6 (5.8%)	40 (9.4%)	3 (10.7%)	37 (8.2%)	3 (11.1%)	45 (11.4%)
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 (1.9%)	15 (3.5%)	0	22 (4.9%)	0	11 (2.8%)
Central & peripheral nervous system disorders	**4**	**15 (24.2%)**	**15 (14.4%)**	**114 (26.9%)**	**7 (25.0%)**	**134 (29.6%)**	**5 (18.5%)**	**103 (26.4%)**
Headache	0	8 (12.9%)	5 (4.8%)	38 (9.0%)	4 (14.3%)	61 (13.5%)	3 (11.1%)	45 (11.5%)
Extrapyramidal disorder	0	2 (3.2%)	3 (2.9%)	18 (4.2%)	0	24 (5.3%)	0	13 (3.3%)
dyspraxinesia	0	2 (3.2%)	2 (1.9%)	19 (4.5%)	1 (3.6%)	25 (5.5%)	1 (3.7%)	20 (5.1%)
dizziness	0	1 (1.6%)	5 (4.8%)	23 (5.4%)	0	16 (3.5%)	1 (3.7%)	21 (5.4%)
dyskinesia	0	1 (1.6%)	4 (3.8%)	12 (2.8%)	1 (3.6%)	15 (3.3%)	0	12 (3.1%)
Body as a whole – general disorders	**4**	**11 (17.7%)**	**7 (6.7%)**	**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 (1.9%)	10 (2.4%)	3 (10.7%)	6 (1.3%)	0	7 (1.8%)
Pain	0	2 (3.2%)	1 (1.0%)	6 (1.4%)	0	7 (1.5%)	1 (3.7%)	26 (6.7%)
Gastrointestinal system disorders	**1 (50.0%)**	**12 (19.4%)**	**8 (10.5%)**	**64 (15.1%)**	**0**	**74 (16.3%)**	**4 (14.8%)**	**71 (17.9%)**
Constipation	0	3 (4.8%)	1 (1.0%)	17 (4.0%)	0	13 (2.9%)	0	10 (2.5%)
Vomiting	1 (50.0%)	2 (3.2%)	1 (1.0%)	6 (1.4%)	0	14 (3.1%)	3 (11.1%)	10 (2.5%)
Respiratory system disorders	**4**	**5 (8.1%)**	**8 (10.5%)**	**50 (11.8%)**	**4 (14.3%)**	**53 (11.7%)**	**5 (18.5%)**	**61 (15.4%)**
Rhinitis	0	2 (3.2%)	2 (1.9%)	21 (5.0%)	2 (7.1%)	31 (6.8%)	4 (14.8%)	29 (7.3%)

Source: Table AE.11.ISS
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

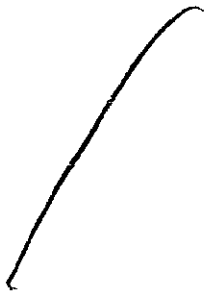
A. Conclusions

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-346

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA 21-346

Trade Name: **Risperdal Consta**
Generic Name: **risperidone long acting injection**
Applicant Name: **Johnson & Johnson**
HFD-120
Approval Date: **10/29/03**

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? **YES**

b) Is it an effectiveness supplement? **NO**
If yes, what type(SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES

If your answer is " no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity? **YES**

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? **FIVE**

e) Has pediatric exclusivity been granted for this Active Moiety? **NO**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such). **NO**

If yes, NDA # Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade? NO

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE- YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either # 1 or # 2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer " yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e. g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non- covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer " no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #20-272	**Risperdal Tablet**
NDA #20-588	**Risperdal Oral Solution**
NDA #21-444	**Risperdal M-Tab**

2 Combination product.

If the product contains more than one active moiety (as defined in Part II, # 1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never- before- approved active moiety and one previously approved active moiety, answer " yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE- YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i. e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? **NO**

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation # 1, Study # **RIS-USA-121**

Investigation # 2, Study # **RIS-INT-101**

Investigation # 3, Study # **RIS-INT-57**

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets " new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i. e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation # 1 **NO**

Investigation # 2 **NO**

Investigation # 3 **NO**

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # Study #
NDA # Study #
NDA # Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation # 1 **NO**

Investigation # 2 **NO**

Investigation # 3 **NO**

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # Study #

NDA # Study #

NDA # Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in # 2(c), less any that are not "new"):

Investigation #1, Study # RIS-USA-121

Investigation #2, Study # RIS-INT-61

Investigation #3, Study # RIS-INT-57

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was " conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation # 1 **IND #52,982** **YES**

Investigation # 2 **IND #52,982** **YES**

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.) **NO**

If yes, explain: **N/A**

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

/s/

Steve Hardeman
10/30/03 08:40:49 AM

For AP Action

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA: 21-346	Efficacy Supplement Type SE-	Supplement Number
Drug: Risperdal Consta (risperidone) Long Acting Injection	Applicant: Janssen Research Foundation	
RPM: Steven D. Hardeman, R.Ph.	HFD-120	Phone # 301-594-5525
Application Type: (*) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(✓) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	10/29/03 6 mos
❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✓) Paid
• User Fee waiver N/A	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception N/A	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No
• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(✓) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted N/A	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified N/A

Exclusivity (approvals only)	
• Exclusivity summary	✓ In Package.
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
General Information	
❖ Actions	
• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	~~N/A~~ Not Approvable 6/28/02
• Status of advertising (approvals only)	(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(✓) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release (✓) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	✓
• Most recent applicant-proposed labeling	✓
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	✓
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A First
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	✓
• Reviews	See CMC review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	✓
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	✓
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	✓
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Statistical review(s) *(indicate date for each review)*	
❖ Biopharmaceutical review(s) *(indicate date for each review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
CMC review(s) *(indicate date for each review)*	✓
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (✓) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	✓
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

For N/A Action

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA: 21-346	Efficacy Supplement Type SE-	Supplement Number	
Drug: Risperdal Consta (risperidone) Long Acting Injection		Applicant: Janssen Research Foundation	
RPM: Steven D. Hardeman, R.Ph.		HFD-120	Phone # 301-594-5525
Application Type: (*) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	(✓) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	6-30-02 10 months
❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(✓) Paid
• User Fee waiver N/A	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception N/A	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No
• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(✓) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted N/A	21 CFR 314.50(i)(1)(i)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified N/A

Exclusivity (approvals only)	
• Exclusivity summary	N/A
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	11/f
General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA ( ) AE (✓) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (✓) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	✓
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	✓
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	✓
• Reviews	See CMC review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	

Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	✓
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	✓
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Statistical review(s) *(indicate date for each review)*	
❖ Biopharmaceutical review(s) *(indicate date for each review)*	
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
CMC review(s) *(indicate date for each review)*	
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	✓
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
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❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

MEMORANDUM

DATE: October 29, 2003

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-346

SUBJECT: Action Memo for NDA 21-346, for the use of Risperdal (risperidone) Consta

NDA 21-346, for the use of Risperdal (risperidone) Consta, an intramuscular depot formulation of the currently available atypical anti-psychotic drug risperidone, was submitted by Janssen Research Foundation on 8/31/01. The application contained the results of a single randomized trial, pharmacokinetic and safety data, and pre-clinical data. While the review team had determined that the clinical data established the effectiveness of the treatment for patients who were acutely psychotic, and there were no clinical adverse events that would preclude approval, several pre-clinical findings were worrisome. In particular, adrenal and renal tumors, and osteodystrophy were seen in the rat carcinogenicity study. These findings raised serious questions about the safety of this product, and, because of these findings, a Not Approvable letter was issued on 6/28/02. In that letter, we noted several points:

1) the sponsor had not submitted a compelling argument that there was a mechanism that explained the appearance of these tumors, and did not present an adequate argument that the tumors were known to be irrelevant for humans,
2) no reproductive toxicology studies had been performed with the depot, and the pre-clinical data suggested that there could be significant differences in the reproductive effects of the depot compared to the oral product,
3) several impurities in the depot formulation were not present in the oral formulation, and had not been qualified.

As a result of these findings, we had concluded that the NDA was Not Approvable. To support approval, the sponsor was given the option of documenting that the depot formulation offered a clinical benefit over the oral formulation or presenting data that the animal findings were not relevant for humans. Further, we asked the sponsor to qualify the new impurities, and perform an embryofetal development study.

In addition to these critical deficiencies, we had a number of CMC questions, and several Clinical Pharmacology questions (including a request for a Phase 4 commitment for the sponsor to submit in vitro dissolution data from on-going stability tests on validation lots of all proposed dosage strengths).

We met with the sponsor on 2/25/03 to discuss these issues. At that meeting, the sponsor proposed to address the primary deficiencies by providing evidence that depot formulations (generically, and not specifically risperidone) prevent more relapses than oral formulations in long-term treatment (presumably due to increased compliance), and to complete the embryofetal study in Phase 4. The Division agreed that the sponsor could attempt to resolve the deficiencies in this manner, although we gave no commitment that this approach would be successful.

The sponsor responded to the Not Approvable letter with a submission dated 4/28/03. The submission consisted of a number of articles from the literature that were intended to address the clinical issues, additional data and arguments intended to further address the relevance of the animal findings (including their previously announced intention to perform the embryofetal study in Phase 4), and responses to the CMC and clinical pharmacology requests. This submission has been reviewed by Dr. Earl Hearst, medical reviewer (review dated 10/24/03), Dr. Lois Freed, pharmacologist (review dated 10/29/03), Dr. Gurpreet Gill-Sangha, chemist (review dated 10/22/03), Dr. Sally Yasuda, Office of Clinical Pharmacology and Biopharmaceutics, (review dated 8/15/03), and Dr. Tom Laughren, Psychiatric Drugs Team Leader (memo dated 10/28/03). The clinical team recommends that the application be approved, while Dr. Freed recommends that the sponsor be required to perform the embryofetal study prior to approval.

In brief, although the sponsor has provided numerous articles from the medical literature that ostensibly address the question of the utility of depot formulations (as compared to oral preparations of drugs to treat schizophrenia), they have submitted only a single non-published, brief attempt to marshal the available evidence on the question of whether or not depot formulations provide an advantage over oral treatments.

Specifically, the sponsor provides a brief document, prepared by Drs. Claudia Mentschel, Stefan Leucht, and John Kane of the Zucker Hillside Hospital in New York, that purports to be a meta-analysis of all available studies in which patients were randomized to depot or oral treatments, and in which relapses were compared. This analysis includes eight (8) studies previously published in the medical literature, and represents a sub-set of the studies included in a meta-analysis of all such studies, performed and published by Adams, et al, in 1999. In this latter publication, the authors concluded that depot formulations did not prevent relapses "more effectively" than oral preparations. However, Mentschel et al have found fault with this analysis for several reasons: 1) Adams included studies that were only 4-8 weeks in duration, too short to adequately assess relapses, 2) Adams included in-patient studies, which by their nature are likely inadequate to assess compliance, and 3) Adams counted patients who discontinued early from these studies for whom the exact reason for discontinuation was unknown as having relapsed. In the Mentschel analysis,

then, only out-patient studies of at least 10 months duration were included, and patients who discontinued for unknown reasons were not counted as having relapsed. The sponsor provided neither the raw data for the studies they included nor the articles that served as the basis for their analysis. Mentschel et al did state that they used the same analytic methodology as Adams (a random effects model with relative risks as effect sizes).

In the sponsor's analysis, a total of 8 studies were included; the most recent was published in 1983; the range of dates for the other 7 studies was from 1974-1980. Study sizes ranged from 36 to 290. All studies were randomized, parallel groups studies in which patients were randomized to either fluphenazine depot or oral medication; in 4 of the studies, the oral preparation was fluphenazine, in 2 studies the oral preparation was pimozide, and in one each the oral drug was penfluridol and trifluoperazine. We have no details about these studies.

According to the sponsor's analysis, the estimate of the relative risk of relapses in 2/8 studies numerically favored the oral drug (in one the oral drug was pimozide, in one it was penfluridol), but in each case the 95% confidence intervals (CI) included 1. In the remaining 6/8 studies, the estimate of the relative risk numerically favored depot, and in 2/6, the 95% confidence intervals excluded 1 (in both cases, the oral drug was fluphenazine; in one case, the upper bound of the CI was 0.99; in the other, the upper bound of the CI was 0.92). In the overall model, the estimate of the relative risk was 0.78, with a 95% CI of (0.66, 0.91). The p-value for the overall effect was 0.002. When, as did Adams, et al, the authors counted patients for whom the reason for discontinuation was unknown as having relapsed, the p-value for the overall effect was 0.14 (the authors state that there was no significant difference in drop-out rates).

As noted above, the sponsor also attempted to address the animal tumor findings, and these data and arguments have been reviewed in detail by Dr. Freed.

Briefly, the sponsor attempted a number of approaches to address these issues:

1) They enlisted Dr. Gordon Hard, an expert whose published work had suggested that renal tumors were associated with severe chronic renal disease (this work had served as the basis for the Division's view, expressed in the Not Approvable letter, that, in this case, the tumors could not be explained by this mechanism, since there was no correlation between chronic renal disease and tumors in the sponsor's study), to examine the renal tissue in the CA study.
2) They performed studies to assess cellular proliferation and apoptosis in renal tissues from the CA study.
3) They performed a re-analysis of renal tissue from control animals in 4 previous CA studies (2 in Wiga rats, 2 in Hannover rats; the latter were the sub-strain used in the CA study).

4) They performed an 8 week mechanistic study in Wiga and Hannover rats.

The sponsor notes that Dr. Hard concluded that the renal injury seen in the CA study was insufficient to explain the tumor occurrence (this had been the division's conclusion at the end of the initial review). However, Dr. Hard did conclude that there was no evidence that the tumors were drug related, based on the fact that risperidone is non-genotoxic, and that there was no evidence of increased renal distal tubule hyperplasia or microscopic findings consistent with direct cytotoxicity, although he did recommend additional studies to rule out this latter possibility.

As Dr. Freed notes, none of the other studies submitted support the sponsor's conclusion that the renal tumors seen in rats are either species (there is no mouse study) or sub-strain (Wiga vs Hannover) specific, or that the tumors have no relevance for humans. Indeed, the cellular proliferation study demonstrated that there was an increase in cellular proliferation (a mechanism widely believed to be relevant for tumor formation) in the high dose male rats with tumors, and not in control or high dose male rats without tumors. Based on these findings, the sponsor admits that Dr. Hard's conclusion that there is no evidence that the tumors were drug-related "...becomes questionable.".

Regarding the adrenomedullary tumors, the sponsor suggested that, in fact, these tumors were seen in the oral risperidone CA studies, and that, therefore, there were no real differences (in this regard) between oral and IM depot administration. Dr. Freed notes that this conclusion is not well supported, given that the occurrence of the tumor in the IM study was clearly dose related, and this was not the case in the oral study.

Regarding the impurities issue, the sponsor has lowered the specification for the ——— to '—— (from ——), which is below the level of quantification; this resolves the issue for these impurities.

Regarding the ——— impurity, the sponsor has reduced the specification to —— (also from ——); the limit of quantification for this impurity, however, is —— (the sponsor argues that toxicity studies done using the oral route exposed animals to drug containing '—— of this impurity, and that on a dose basis, assuming 100% bioavailability of the impurity, these studies cover the exposure to this impurity that would result from the depot formulation). They provide no evidence that the bioavailability of this impurity is 100%. Nonetheless, the small difference between the limit of quantification and the proposed specification does not warrant repeating toxicity studies.

However, as Dr. Freed points out, the genotoxic potential of this impurity has not been evaluated. Therefore, she recommends that the sponsor be required to perform an appropriate study in Phase 4.

COMMENTS

The application for Risperdal Consta was initially not approved because pre-clinical data suggested that the IM depot was associated both with tumors and osteodystrophy in rats, findings that were not seen with studies of the oral product. While it was not obvious why these different routes of administration should give rise to such different findings, the markedly increased incidence of osteodystrophy (along with the somewhat less impressive incidence of tumors) strongly suggested that the findings were not artifactual. The division found the sponsor's attempts to identify a mechanism of tumor formation wanting.

At a meeting with the sponsor on 2/25/03, the division agreed that the sponsor could attempt to make the argument that depot formulations offer a benefit over oral preparations, based on improved compliance with treatment, and that this benefit could justify approving the product. The division requested that the sponsor submit evidence to support this conclusion. We agreed that if this argument was made successfully, we would consider not only approving the application, but we would also consider doing so prior to the completion of the embryofetal study.

In response, the sponsor has submitted numerous articles from the literature that they believe support their view that depot formulations are valuable and offer a benefit over oral formulations, and that atypical anti-psychotics are superior to typical anti-psychotic drugs in treating symptoms of schizophrenia. In addition, they have attempted to further address the tumor findings in the rat.

Regarding the clinical issue, much of what the sponsor has submitted addresses the question of the importance of patient compliance with prescribed anti-psychotic medication. We agree that this is, quite obviously, critical to the effective use of these products. However, this obvious conclusion does not address our primary concern.

That primary concern, as expressed in our meeting with the sponsor, is that there should be a demonstrable benefit of this particular proposed treatment over currently available treatments in order to justify the marketing of this product in the face of the existing animal data.

The sole potentially relevant data that the sponsor has submitted to address this point is the analysis by Mentschel et al, which purports to describe a meta-analysis of 8 controlled trials comparing fluphenazine depot to various oral anti-psychotic medications, and that ostensibly demonstrates a statistically significant improvement in relapse rate on depot compared to oral treatment.

There is much that is unknown about this analysis, including the details of the individual studies included (especially the conduct of these studies, whether the doses used produced a fair comparison between oral and depot treatments, the

nature of the discontinuations and whether this produced an important bias, the details of the statistical analyses, etc.). Dr. Laughren has examined the Adams article; while the individual studies included in the sponsor's analysis presumably are a subset of the studies described in this article, we cannot reliably determine if there are other studies included in that (Adams) article that might also have been included in the sponsor's meta-analysis. For example, the sponsor's criteria for including a study in its analysis was that the study enroll outpatients, and be of at least 10 months duration; we are not clear why 10 months was chosen as the minimum duration of a study that should have been included. Did, for example, Adams describe any studies that were of reasonable duration (say, 6 months) that the sponsor excluded from their analysis? Indeed, given the differences in study design across the studies, it is not even clear that such a meta-analysis is appropriate.

Although the review team concludes that this meta-analysis supports the conclusion that depot formulations result, in practice, in fewer relapses compared to oral products, I believe that the analysis is presented in insufficient detail to provide very useful data on this question. (For example, I believe it is not unreasonable to consider patients whose reason for discontinuation is unknown as having relapsed; such analyses are often performed as "worst case" analyses, and although they are not usually primary analyses, it is worth noting that because the meta-analysis is a post hoc analysis, it too is not a primary analysis in a real sense). Even if the analysis could be considered acceptable, it obviously does not address the question of whether or not Risperdal Consta provides a benefit compared to oral risperidone.

For these reasons, then, I consider this effort not to provide particularly compelling evidence that Risperdal Consta confers a benefit beyond that provided by oral risperidone. I do acknowledge, as described by Dr. Laughren, that the sponsor has submitted a few additional articles that purport to demonstrate the superiority of atypical anti-psychotic drugs compared to typical anti-psychotic medications, both in terms of symptom control, side effect profile, and degree of compliance, but these data are not presented in sufficient detail to permit an independent review. In addition, while these studies are intended to address an important issue (the value of having atypical anti-psychotics available [currently only typical antipsychotics are available as depots]) they do not address the primary question posed in this application; namely, does risperidone IM depot provide a benefit compared to risperidone oral?

However, I am convinced, based upon conversations with the review team and other experts, that the availability of a depot formulation of an atypical anti-schizophrenia treatment can provide an important contribution to the armamentarium in this field. While the data submitted do not provide very strong evidence in favor of this conclusion (neither, of course, does it refute this conclusion), nevertheless, there is a prima facie case to be made that the use of a depot formulation will, at least in some patients, increase compliance compared

to the oral formulation (while it is true that there may be patients who would prefer to take the oral medication over the depot, this does not undermine the conclusion that other patients would benefit from the availability of the depot). Further, as noted above, there are currently only two depot formulations of anti-psychotic medications available; fluphenazine and haloperidol. There is general agreement in the expert community that the availability of a depot formulation of an atypical anti-psychotic medication would be very worthwhile. For these reasons, then, it seems reasonable to approve the depot, assuming that it can be used safely.

Obviously, we had concluded earlier, at the time of the Not Approvable action, that, absent evidence that the depot provided a benefit over the oral product, it could not be marketed safely.

While I must acknowledge that, in my view, the sponsor has provided no new compelling evidence **establishing** such a benefit of the depot, as noted above, I am now convinced that the availability of the depot can be considered to provide such a benefit, at least for some patients. Is this (unquantifiable) benefit sufficient to overcome the risk posed by the animal findings?

I believe now that it is. While, as I have just noted, the benefit of the depot cannot, in any real sense, be quantified, neither can the risk to humans of the findings seen in the animals.

The sponsor has submitted no new data that minimizes these signals, either of tumor formation or of the osteodystrophy. In my view, these signals still stand, and their meaning for patients is unknown (in particular, I do not believe that the sponsor has submitted any information that supports the view that these findings are irrelevant for people). Nonetheless, given my current view of the utility of the depot formulation, I now believe that the potential (unknowable) risks posed to humans related to the animal findings are acceptable, given that the animal data are described clearly, and relatively prominently, in product labeling. I believe this latter end can be achieved by including a description of the tumor and osteodystrophy findings prominently in the Precautions section of labeling with a statement that these findings have not been seen in animal studies of oral risperidone. In this way, the prescriber can be made aware that an alternative product, oral risperidone, is not associated with these findings, and can make a more reasonable choice between these products.

I also agree with Dr. Laughren that the embryofetal study may be completed in Phase 4 (I understand that a dose-finding study is on-going).

Finally, there continue to be no clinical adverse events that would preclude approval.

The sponsor has responded to the other requests included in the Not Approvable letter, and has agreed to the completion of additional studies in Phase 4: the embryofetal study; a study to further characterize the osteodystrophy; a study to examine the genotoxicity of the process impurity, ———, and in vitro release data from on-going stability tests on validation lots of all strengths.

For the reasons given above, then, I will issue an Approval letter with appended final labeling to which the sponsor and we have agreed.

Russell Katz, M.D.

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

/s/

Russell Katz
10/29/03 02:10:36 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

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

DATE: October 28, 2003

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for
Risperdal Consta (risperidone long-acting injection) for the treatment of schizophrenia

TO: File NDA 21-346
[**Note:** This overview should be filed with the 4-28-03 response to our 6-28-02 nonapprovable letter.

1.0 BACKGROUND

I refer to my memo of 6-21-02 for a more detailed accounting of the issues leading up to the nonapproval action for this application.

In summary, there were several preclinical issues that were the basis for our nonapproval action:
-The tumor profile in the 2-year IM depot carcinogenicity study in the rat was different than observed in the 2-year oral studies in mouse and rat. Mechanistic studies and explanations were inadequate to dismiss the findings, and there was no exposure margin to argue that it was a threshold effect that could be dismissed.
-We found that reliance on the oral risperidone reproductive toxicology studies was problematic, since the chronic tox studies suggested different toxicity profiles for the oral and IM forms.
-There were insufficient data to support 1 impurity found in the IM but not the oral formulation.

In addition, in our 6-28-02 letter, we asked for responses on several other matters in our letter, as follows:
-Several CMC deficiencies
-Several comments regarding biopharmaceutics issues:
  -We asked for a commitment to submit in vitro release data from ongoing stability studies within 4 months of approval, along with revised in vitro release specifications.
  -We proposed slightly revised interim in vitro release specifications.
  -We asked for revised data sets for population pharmacokinetic analyses.

We also made requests for additional data apart from the nonapproval letter:
-In a 2-25-03 meeting, we asked the sponsor to submit a comprehensive package of published papers to support their argument that Risperdal Consta, as the first depot form of an atypical antipsychotic, would provide a clinical benefit that would outweigh our concerns about preclinical data.
-In a 3-18-03 request, we asked for a safety update as part of the complete response.

On 4-28-03, the sponsor submitted a complete response.

2.0 CHEMISTRY

It is my understanding that all remaining CMC issues have been resolved.

3.0 PHARMACOLOGY

3.1 Tumor Profile in the 2-year IM Depot Carcinogenicity Study in the Rat

The pharmacology review of the 4-28-03 response was not complete and available to me at the time of my completion of this memo, however, it is my impression that there remains a signal for 2 different tumor types with the depot form of risperidone not seen for the oral form. In addition, there was revealed a finding of osteodystropy that was not seen in the oral studies. Nevertheless, I am persuaded that the potential clinical benefit of this new formulation for risperidone outweighs the concern raised by these signals, and it is my view that this concern can be adequately addressed by describing these findings in labeling.

3.2 Reproductive Toxicology Studies

As noted, we found that reliance on the oral risperidone reproductive toxicology studies was problematic, since the chronic tox studies suggested different toxicity profiles for the oral and IM forms. There was continued discussion of when a complete report on a repeat IM depot embryofetal developmental toxicity study would need to be submitted. In our 2-25-03 meeting we indicated that ordinarily this would be needed prior to our taking a final approval action, however, at that meeting, we agreed to consider the strength of the case that could be made for clinical benefit in deciding exactly when the final report would be needed. As was the case for the tumor and toxicity findings, I am persuaded that the potential clinical benefit of this new formulation for risperidone outweighs the concern raised by the absence of reproductive toxicology data specific to this depot formulation, at least with regard to the timing for completion of the needed study. While the pharmacology team continues to feel that the results of this study should be available prior to taking a final action, it is my view that this requirement can be satisfied postapproval.

3.3 Qualification of Impurity

It is my understanding that the pharmacology group has reached the conclusion that sufficient data regarding this impurity have been submitted to justify permitting the requirement for an in vitro gentoxicity assay to be conducted postapproval, and I agree.

4.0 BIOPHARMACEUTICS

All the biopharmaceutical concerns delineated in the nonapproval letter have been addressed by the sponsor, and it is the view of OCPB that, once there is agreement on labeling, this application can be approved. I agree.

5.0 CLINICAL DATA

5.1 Rationale for Clinical Benefit

As noted, in a 2-25-03 meeting with the sponsor, we reached agreement that we may well accept an argument that the potential clinical benefit of having a depot form of risperidone available would outweigh the preclinical concerns that were the basis for the nonapproval action. A key issue was the availability of data from controlled trials demonstrating an advantage in lower relapse rates in patients randomized to depot forms of typical antipsychotic drugs compared to those randomized to oral forms. We indicated the possibility of our willingness to rely on such findings in our consideration of making Risperdal Consta available as the first atypical antipsychotic in depot form. We indicated our willingness to consider such a move in part due to the generally accepted better tolerability of atypical drugs like risperidone compared to typical antipsychotic drugs. However, we had asked the sponsor to pull together a comprehensive package of published papers to support their argument, and they have submitted this package as part of their response.

The sponsor provided a response, including 64 references, and, in particular, including the following findings pertinent to this question of potential advantage in making Risperdal Consta available:
-An as yet unpublished manuscript by Mentschel, et al, provides data from a meta-analysis involving RCTs of at least 10 months duration comparing long-acting vs oral typical antipsychotics in outpatients. This effort was prompted by a Cochrane review by Adams, et al, of a larger set of studies, including many that were often only 4-8 weeks in length, and some that were inpatient. The Adams, et al, review, did not find any advantage for the depot typical antipsychotics over oral typical antipsychotics, however, Mentschel, et al, argue that it was not appropriate to include short-term studies, or inpatient studies, since a benefit would not be readily demostrated in either circumstance. Their analysis focusing on 8 longer-term outpatient studies revealed overall relapse rates of 45% for oral medication compared to 30% with depot, yielding an absolute risk reduction of 14% and a relative risk reduction of 32% ($p = 0.002$). These data were submitted to provide support for the view that, in general, depot antipsychotics provide an advantage over oral medications with regard to relapse.

-Several issues need to be addressed for the Mentschel, et al, analysis.

-One question is whether or not the comparisons were fair from the standpoint of dosing. For the studies for which we have information on the dosing of depot and oral medications, it is my view that the oral dose is an adequate match for the depot dose. This is obviously a judgement, since there is no precise guidance for dose equivalencies for these different formulations.

-Another issue is the fact that the Cochrane analysis used a very conservative approach to assessing dropouts for whom no specific cause was listed, i.e., they were all considered relapses. The Mentschel, el al, analysis did not make this assumption, and alternatively, relied on patients meeting protocol specified definitions of relapse to be considered relapses. The analysis favored depot over oral formulations only when the latter approach was taken. I agree with the approach taken by Mentschel, et al, and in fact, this is our usual approach taken when analyzing relapse data. Thus, I am not particularly troubled by lack of significance taking the more idiosyncratic approach proposed by the Cochrane group.

-A third potential concern is the choice of studies for the Mentschel analysis. As noted, they focused on outpatient studies of at least 10 months duration. Unfortunately, it is not clear from either the Mentschel, et al, manuscript or the Adams, et al, paper describing the Cochrane analysis precisely which studies were left out of the Mentschel, et al, analysis. Nevertheless, I agree in principle with the criteria proposed by Mentschel, et al, for their choice of studies.

-A soon to be published manuscript by Leucht, et al, provides data from a meta-analysis involving RCTs comparing oral typical and atypical antipsychotics with regard to relapse, and revealed overall relapse rates of 23% for typical antipsychotics compared to 15% for atypical antipsychotics ($p = 0.0001$). It was not clear from these data that the advantage could be explained on the basis of improved compliance. These data were submitted to provide support for the view that, in general, atypical antipsychotics provide an advantage over typical antipsychotics with regard to relapse.

-In another soon to be published study looking at the occurrence of new cases of TD in patients treated with either a typical antipsychotic, haloperidol, or various atypical antipsychotics, in trials of a year or more in duration revealed annual risks of TD of 0.91% for the atypical drugs compared to 5.3% for haloperidol. These data were submitted to provide support for the view that, in general, atypical antipsychotics provide an advantage over typical antipsychotics with regard to TD.

-There aren't any systematic data comparing compliance rates for oral and depot antipsychotics, at least not from direct comparisons. It is very difficult to define and measure compliance, and this, in part, explains the lack of systematic data on this issue. However, the sponsor has provided data from separate studies, suggesting overall nonadherence rates of 26% for depot antipsychotics compared with 40-50% for oral antipsychotics. It's not clear to me exactly where these numbers are derived from, and my impression is that we simply do not have any good data pertinent to this issue.

Comment: While this is not a completely settled issue, I think the sponsor has made a reasonable case that there would be a sufficient advantage in having a depot form of risperidone available to outweigh our concerns about the preclinical data. Relapse is clearly not a good outcome in schizophrenia, and I think there are sufficient data available to suggest an advantage for depot drugs compared to oral drugs in delaying time to relapse. The key piece of evidence, in my view, is the Mentschel, et al, manuscript. Admittedly, this is not a well-documented review, and it is not an analysis that we have independently replicated. My view that it is sufficient evidence is in part based on my judgment that the advantages of a depot form over an oral form are self-evident (namely, that lack of compliance for

the depot form would be immediately obvious, and, therefore, alert the treatment team that a patient may need special attention), and that little supportive data are needed to buttress this view. While, ideally, one would have data on better compliance as well, this is almost impossible to study, and I am persuaded that relapse is the outcome of real clinical concern in any case. There are also data suggestive of inherent advantages for atypicals over typicals, both with regard to effectiveness in preventing relapse, and regarding safety, in particular a likely lower risk of TD. These data are not directly germane to the question of depot vs oral forms, however, they do support the general view that a depot form of these newer, possible more effective and better tolerated agents, would be desirable. Thus, even though there are no data directly showing an advantage for depot risperidone over oral risperidone with regard to relapse, I think one can get there with reasonable ease by extrapolation.

5.2 Safety Update

We informed the sponsor on 3-18-03 that a complete response to the NA letter would need to include a safety update, and the response included safety data covering a period from 3-15-01 to 3-18-03. Safety data were included from completed and ongoing J&J studies, non-IND studies, postmarketing experience (the depot formulation is available in 22 countries worldwide), and worldwide literature.

There were 3 completed and 4 ongoing J&J studies (all open label, however, study 62 involved a 1-year comparison with olanzapine) contributing safety data from n=1664 Risperdal Consta patients (total exposure time for these patients = 2053 person-years). There was an estimated 358 person-years of Risperdal Consta exposure in non-IND studies.
-Completed Studies: There were 2 deaths in patients taking Risperdal Consta, neither reasonably considered drug-related, and 77 other SAEs, mostly psychiatric, and no unusual pattern of other SAEs.

-Ongoing Studies: There were 14 deaths in patients taking Risperdal Consta, with no unusual causes or patterns, and 677 other SAEs, mostly psychiatric, and no unusual pattern of other SAEs.
-Non-IND Studies: There were 12 deaths in patients taking Risperdal Consta, again with no unusual causes or patterns, and 242 other SAEs, mostly psychiatric, and no unusual pattern of other SAEs.
For postmarketing reports, the sponsor estimated person-years of exposure based on sales, and this yielded an estimate of approximately 3000 person-years. There were 12 reports of death in patients taking Risperdal Consta, with a fairly typical distribution of causes, except for 1 case of liver failure. No information was available on this case. There were 47 patients taking Risperdal Consta for whom nonfatal SAEs were reported, the most common being psychiatric, and no unusual pattern for the other SAEs. There was 1 case of SJS.

The sponsor's literature review included 61 published papers. The sponsor provided only a listing of the titles of these papers, along with a warrant that "all adverse events observed in the literature were qualitatively similar to those reported in the Investigator's Brochure." Dr. Hearst reviewed the titles, and indicated that he found nothing to indicate any new safety concerns.

Dr. Hearst reviewed the safety data for certain events of particular interest, i.e., hyperglycemia, diabetes, and stroke. There were several instances of each of these events, however, there were no

comparison groups (with the exception of 1 study), and thus, these reports are difficult to evaluate. The numbers of cases did not seem unusual, given the high background rate for all of these events. Conclusion Regarding Safety: There were no new safety findings that would impact on an approval decision or on labeling.

6.0 WORLD LITERATURE

As noted, a literature review was included in this response, and revealed no important new safety information.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, risperidone LA is now approved for the treatment of schizophrenia in 22 countries worldwide.

8.0 LABELING

We have not yet reached agreement with J&J on final labeling as of the time of completion of this memo.

9.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Janssen has submitted sufficient data to support the conclusion that risperidone LA is effective and acceptably safe in the treatment of schizophrenia. As noted, I feel the animal toxicity and carcinogenicity findings can be adequately addressed by describing them in labeling. Thus, I recommend that we issue the attached approval letter once we have reached agreement with J&J on final labeling.

cc:
Orig NDA 21-346
HFD-120
HFD-120/TLaughren/RKatz/AMosholder/EHearst/SHardeman

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/s/

Thomas Laughren
10/28/03 01:23:02 PM
MEDICAL OFFICER

MEMORANDUM OF MEETING MINUTES

MEETING DATE: 2/25/03
LOCATION: WOCH - Conf. Room E
APPLICATION: NDA 21-346 Risperdal Consta (risperidone) Long-Acting Injection
TYPE OF MEETING: Complete Response
MEETING CHAIR: Russell Katz, M.D.
MEETING RECORDER: Steve Hardeman, R.Ph.

FDA ATTENDEES

Robert Temple, M.D., Director, ODEI
Russell Katz, M.D., Director, DNDP
Tom Laughren, M.D., Psychopharm Team Leader
Robert Levin, M.D., Medical Reviewer
Teresa Podruchny, M.D., Medical Reviewer
Barry Rosloff, Ph.D., Pharm/Tox Team Leader
Lois Freed, Ph.D., Pharm/Tox Team Leader
Steve Hardeman, R.Ph, Senior Regulatory Project Manager

SPONSOR ATTENDEES

Johnson and Johnson
Garry Neil, M.D., Senior V.P. Research and Development
Jack Grebb, M.D., Senior V.P. CNS/Pain Research and Development
Graham Burton, M.D., Senior V.P. Regulatory Affairs and Quality Assurance
William Powers, Ph.D., V.P. Preclinical Development
Alex Gorsky, President, Janssen Pharmaceutica, U.S.
Fred Grossman, D.O., Psychiatry Franchise Leader
Todd McIntyre, Ph.D., Regulatory Affairs
Claude McGowan, Ph.D., Regulatory Affairs
Tricia Desantis, Regulatory Affairs

Johnson and Johnson Consultant

Alkermes, Inc.
Don Burstyn, Ph.D., V.P. Regulatory Affairs

BACKGROUND

As a follow-up to the Not Approvable letter of 6/28/02 and to the meeting of 7/26/02, the sponsor requested a meeting to discuss their plans for providing a complete response.

DISCUSSION POINTS

- The sponsor outlined the potential clinical benefit of depot risperidone.
  - The Division agreed that there is a potential clinical benefit of having a depot atypical antipsychotic. The complete response should contain a detailed review of the existing data to include depot vs. oral studies data. A compelling argument should be made that depot antipsychotics improve compliance and decrease relapse.
- The sponsor reviewed their proposed response to the toxicology concerns.
  - The Division agreed to consider approving the i.m. depot formulation without a complete resolution of the carcinogenicity findings in rat if the sponsor provides data demonstrating that the i.m. depot formulation provides a clinical benefit. In addition to the nonclinical studies listed by the sponsor as being available at the time of resubmission, the Division requested summary and individual data for incidences of adrenomedullary findings (including adrenal pheochromocytoma) from the oral carcinogenicity study in rat. The Division noted that if the sponsor proposes strain or substrain differences as an explanation for the differences in tumor profile between the oral and i.m. depot studies, it would be important to provide data by which to compare the relevance of each strain or substrain for assessing human risk.
  - It is the Division's position that the full study report for the i.m. depot embryofetal development study should be submitted to the NDA prior to approval. The Division noted that, in contrast to the carcinogenicity issue for which data are available for basing a risk/benefit assessment, no reproduction studies have been conducted using the i.m. depot formulation. The Division also noted that potential reproductive toxicity (e.g., teratogenicity) is more of a concern with an i.m. depot formulation due to the inability to rapidly terminate exposure. The Division will, however, consider the potential for a clinical benefit when making a decision as to the need for the embryofetal development study prior to approval. (The sponsor noted that the Division did not ask for an embryofetal development study at the pre-NDA meeting. The Division responded that the study request was based on data reviewed subsequent to that meeting [i.e., during review of the NDA].)
  - The Division recommended that an oral dose group be included in the i.m. depot embryofetal development study in order to provide a direct comparison between the two routes and to help bridge to the oral embryofetal development study. The sponsor noted that oral and i.m. depot dosing would result in different patterns of exposure. The Division did not consider this a problem, but agreed to further discuss this issue with the sponsor.
  - The sponsor stated that the impurities issue raised by the Division has been resolved and would be adequately addressed in the resubmission.
  - The sponsor requested a copy of the Executive CAC minutes. The sponsor was informed that the ExeCAC had agreed with the Division on the tumor findings in the i.m. depot study and that the minutes would provide no additional information to help the sponsor prepare a complete response.

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/s/

Russell Katz
4/1/03 01:21:39 PM

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Meeting Date:	**5/10/01**
Location:	**WOCII - Rm 4028**
IND:	**52,982**
Drug:	**Risperidone Long Acting Injectable**
Sponsor:	**Janssen**
Type of Meeting:	**CMC Pre-NDA**
Meeting Chair:	**Robert Seevers, Ph.D.**
Meeting Recorder:	**Steven D. Hardeman, R.Ph.**

Participants: see attached.

Meeting Objective: Discussion of Janssen's CMC plans to submit a new drug application for a long acting injectable version of risperidone

Discussion Points (bullets):

Attached sponsor minutes (emailed 5-25-01) appear accurate and will be archived as official minutes of this meeting.

Risperdal® Long Acting Injectable
Minutes of May 10, 2001 FDA/Janssen CMC Pre-NDA Meeting

A CMC pre-NDA meeting was held on May 10, 2001 with the Division of Neuropharmacological Drug Products to discuss Janssen's plans for submission of an NDA in August, 2001. The following attendees were present at the meeting:

Janssen

Jorge Cruz: Post Approval Regulatory Affairs
Peter D'Hoore: Team Leader
Greg Dennis, PhD: Microbiology
Lisa Lumia: CMC Global Regulatory Affairs

Alkermes

Bob Adkins: Manufacturing
Don Burstyn, PhD: Regulatory Affairs
Lionel Murray, PhD: Quality Control
Jim Wright, PhD: Development

FDA

David Hussong, PhD: Microbiologist
Steve Hardemann, R.Ph: Regulatory Project Leader
Robert Seevers, PhD: Chemistry Team Leader
Maria Sunzel, PhD: Biopharmaceutics Reviewer
Ramana Uppoor, PhD: Biopharmaceutics Team Leader

The discussions were based on the list of questions that were submitted in the pre-NDA briefing document (April 25, 2001, Serial No. 032). The questions and major points that were discussed are presented below. FDA responses are highlighted in bold and italics.

Prior to the discussion of the questions a brief overview of the depot project was given by Janssen. Janssen also noted that for purposes of the pre-NDA presentation, the NDA is being referred to as Risperdal® Long Acting Injectable. Janssen acknowledges that the name is pending acceptance by OPDRA.

Drug Substance: Based upon the revised strategy discussed in the Drug Substance section of this pre-NDA package, does FDA agree that risperidone extended release microspheres for injection may be manufactured with risperidone drug substance produced at Cork, Ireland with the new synthetic process?

FDA did not object to the manufacture of risperidone extended release microspheres with the optimized risperidone drug substance. FDA acknowledged that this statement is based upon the assumption that the risperidone drug substance comparability (current synthesis vs optimized synthesis) will be demonstrated and submitted in conjunction with the current commercial product.

Janssen acknowledged that the risperidone DMF (DMF ———) will be updated with the appropriate comparability data and a Prior Approval Supplement will be submitted to the Risperdal® tablets NDA 20-272 in May,2001.

FDA further commented that this strategy should present no problems assuming that all data are acceptable. Depending upon the nature of the questions and issues that could arise with the NDA Supplement, there could be implications for the Risperdal Long Acting Injectable NDA. FDA noted that if this situation does occur, Janssen would be made aware of the situation as expeditiously as possible.

Drug Product – Specifications

Does FDA agree with the proposed regulatory tests and specifications for risperidone extended release microspheres for injection and diluent?

FDA noted that there was nothing objectionable with regard to the proposed specifications for the microspheres and diluent. However, the Agency can not really agree to the proposed specifications until all data and justifications are reviewed during the NDA process.

The following specific items were discussed by FDA with regard to the microspheres:

- ***For ——— , if the specification is not the same or tighter than the specification for the current commercial product, a justification will need to be provided in the NDA. The Agency pointed out that a wider specification is not an issue as long as appropriate justification (ie: data) for the specification is included in the submission.***

- ***——— specifications should reflect the manufacturing capability of the process, not simply the ICH limits. The limits proposed in ICH are considered safety limits, but limits for this product should take into consideration the capability of the process, as well.***

- ***For Sterility testing, Dr. Hussong noted that a ——— is acceptable. Additionally, he requested that Janssen demonstrate that ———***

- ***Dr. Hussong further requested that the calculation/computation used to determine the ——— needs to be included in the NDA.***

The following specific item was discussed by FDA with regard to the diluent:

- ***FDA noted that the diluent testing references the EP methodology. FDA stated that Janssen should be performing the corresponding USP testing for these methods, including ——— or stating why the method***

is not performed. Comparability for the two methods can be demonstrated or in cases where the methods are harmonized, simply state USP.

Does FDA agree with Janssen's proposal for a combination (37° C water bath and accelerated 45° C water bath) *in vitro* release test for risperidone extended release microspheres for injection, based upon the correlation and supporting information provided in the Drug Product Specifications/Methods section of this pre-NDA package?

The Agency agreed in principle that the combination method for in vitro release testing was acceptable. The Biopharmaceutics Division has requested that a teleconference be set up to further discuss the specifics of the method, specifications, etc. A briefing package will be prepared by Janssen for this teleconference which will include the proposed methodology and specifications, rational/justification for the combination method and a discussion of the discriminating ability of the 45 °C water bath method.

The Biopharmaceutics Division requested that all dissolution data, methods, etc. included in the CMC section of the NDA also be included in Item 6 of the NDA. Janssen agreed with this request.

Container Closure: Does FDA agree that Janssen may implement the safety needle design recognizing that [redacted] for the risperidone extended microspheres for injection vials and diluent syringes will need to be adjusted, in addition to the current [redacted] As discussed in the Container Closure section of this pre-NDA package, the [redacted] will be determined once the commercial safety needle is available.

FDA recognized Janssen's intention to comply with the current requirements for safety needles. Dr. Seevers agreed with the outlined approach to justify the [redacted] 2. He further noted that all data and rational used for the justification should be included in the NDA.

Drug Product – Stability: Does FDA agree that the stability data package planned for submission in the NDA is acceptable? Specifically, we would like FDA's concurrence on the proposed protocols for the commitment and marketed stability batches for both the risperidone extended release microspheres for injection and the diluent.

Dr. Seevers requested clarification on whether or not the planned storage for the product in the kit is under refrigeration. Janssen confirmed that the instructions for the kit will be to store under refrigerated conditions.

Dr. Seevers further questioned whether or not the NDA will be filed with all stability data necessary for assessment of expiration dating at the time of submission. He further explained that submission of a large volume of data during the end phase of the review process may constitute a major amendment

and as such re-start the review time clock. Janssen confirmed that the NDA will be filed with 12 months of stability data for both the microspheres and diluent.

Dr. Seevers questioned the availability of in-use reconstituted stability data since these data are necessary to include in the labeling for hospital use of the product. Janssen confirmed that these studies have been conducted and these data will be part of the NDA.

Dr. Seevers noted that the protocols for the commitment batches (microspheres and diluent) seemed appropriate. Janssen clarified that it is our intention to use the diluent and microspheres validation batches as the commitment batches. FDA acknowledged and agreed with this approach.

Dr. Seevers deferred the acceptance/agreement of the marketed stability protocols until the NDA review process. He suggested that if it is our intention to study [redacted] ***time intervals) as noted in the protocols contained in the briefing package, then these time points should be studied with the commitment batches (ie: validation batches). Janssen clarified that it is our intention to study the microspheres and diluent separately on marketed stability. It is not our intention to test the same lot of diluent included in the kit with the microspheres. Again the Agency acknowledged and accepted this approach.***

Planned Post Approval Activities – Monovial Adapter:

With regard to the proposal outlined for the post approval change associated with the monovial adapter, does FDA agree with the following:

Modifications may be made to the current Alkermes facility, as proposed and explained in this package, even though the new [redacted] will not be included at the time of the original NDA.

Dr. Seevers noted that he could not comment on the planned facility modifications and that Janssen should contact the District Field Office to coordinate the facility changes and their impact on the planned PAI inspection for the NDA.

The [redacted] may be submitted as a Changes Being Effected – 30 Day Supplement, based on the information proposed in this package, including the information outlined to demonstrate product comparability and [redacted] stability data for [redacted] of risperidone extended release microspheres for injection in the new container-closure system.

FDA did not agree that the change for the [redacted] ***could be submitted as a CBE. This change in the container closure system is a Prior Approval***

Supplement, as noted in the current guidance.

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/s/

Robert H. Seevers
7/25/01 10:26:59 AM

Minutes of the Pre-NDA Meeting for RISPERDAL (risperidone) Depot Microspheres April 20, 2001

SUMMARY OF DISCUSSIONS AT MEETING

A pre-NDA meeting was held on April 20, 2001 with the Division of Neuropharmacological Drug Products to discuss JRF's plans for submitting an NDA for risperidone long-acting injectable in August, 2001. Attendees at the meeting were as follows:

JRF	FDA
Marielle Eerdekens, MD: Clin. Development	Russell Katz, MD: Division Director
Erik Mannaert, PhD: Pharmacokinetics	Thomas Laughren, MD: Team Leader
Claude McGowan, PhD: Reg. Affairs Liaison	Andrew Mosholder, MD: Clinical Reviewer
Patrick Sterkens, IR: Nonclinical	Maria Sunzel, PhD: Biopharm Reviewer
Keith Karcher, MS: Biostatistics	Barry Rosloff, PhD: Pharm/Tox Team Leader
Todd McIntyre, PhD: Global Reg. Affairs	Lois Freed, PhD: Pharm/Tox Reviewer
Grant Ko, MD: Clinical Development	Kun Jin, PhD: Statistical Team Leader
	Kallappa Koti, PhD: Statistician
	Steve Hardeman, RPh: Reg. Project Manager

The discussions were based on the list of questions that were submitted in the briefing document. Therefore, the questions and the major points that were discussed are listed below (FDA responses are italicised and bolded).

CLINICAL/BIOSTATISTICS/AND CLINICAL PHARMACOKINETICS

1. At our End-of-Phase (EOP) 2 meeting on April 13, 1999, the Division stated that a single study with assay sensitivity would be required to support the submission of a fileable NDA for the risperidone long-acting injectable formulation. The Division also stated that if the results from the placebo-controlled trial, RIS-USA-121, are positive, no other clinical data would be required for a fileable NDA.

   The NDA for the risperidone long-acting injectable formulation will include the following Phase 3 trials:

   Placebo-controlled trial

   RIS-USA-121 To demonstrate the efficacy and safety of risperidone long-acting injectable formulation.

   Supportive trials

   RIS-INT-61 Comparative, 'noninferiority' trial with oral risperidone

   RIS-INT-57 Open-label, long-term safety trial

- Does the Division agree that the efficacy and safety data from these trials (see Section 4.5.3) are adequate for the filing and review of the NDA?

  Dr. Katz responded that yes, there appears to be adequate information for the filing and review of the NDA.

- Given the efficacy and safety results of RIS-USA-121 (see Section 4.5.3), do the data from RIS-USA-121 appear to demonstrate sufficient evidence of the efficacy and safety of risperidone long-acting injectable for the Division to approve the NDA?

  Although this was considered a review issue, RIS-USA-121 seems sufficient for approval. Efficacy data from RIS-INT-61 can be included in the NDA, but the FDA has no interest in this trial and it will not be used in the label. Dr. Laughren reiterated what had been said at the EOP-2 meeting: oral supplementation would need to be included in the dosing section of the label because the effectiveness of the entire treatment regimen was tested. The proposed paragraph in the labeling section of the briefing document probably does not reflect sufficient information about oral supplementation.

  As a follow-up question, JRF asked for confirmation that, based on what was provided in the briefing package, FDA had not identified any refusal-to-file (RTF) issues. Dr. Katz stated that, with one exception, no other RTF issues had been identified (for more details, see pp 8-9 for the discussion regarding Question 2 of the nonclinical section).

2. Based on recommendations from the FDA (correspondence dated January 21, 2000), JRF submitted an amendment to RIS-USA-121 (Serial No. 016, February 29, 2000), which limited the patient population to those patients with schizophrenia. As shown in the following table, 39 patients with schizoaffective disorder had entered the trial before this amendment was made. Similarly, 615 patients in RIS-INT-57 had a diagnosis of schizophrenia, although 110 patients had schizoaffective disorder. To comply with recommendations from the FDA, the primary efficacy and safety analyses will be based on data from patients with schizophrenia. Additional analyses of patients with schizoaffective disorder and all patients were conducted. (JRF acknowledges the ongoing discussions with the FDA regarding the indication for RISPERDAL.)

Trial	Number of Patients		
	Schizophrenia	Schizoaffective	Total
RIS-USA-121	400	39	439
RIS-INT-57	615	110	725

- Is this approach acceptable to the Division?

Yes, the approach appears acceptable, providing the primary analysis of patients with schizophrenia is positive.

3. As discussed during the EOP-2 meeting, an open-label, 12-month safety trial (RIS-INT-57) was conducted to support the long-term safety of the risperidone long-acting injectable formulation. As shown in the following table, a total of 725 treated patients participated in the trial, including 615 patients with schizophrenia and 110 patients with schizoaffective disorder. A total of 579 patients (489 patients with schizophrenia) have been treated for approximately 6 months (≥155 days), and 361 patients (301 patients with schizophrenia) have been treated for approximately 1 year (≥337 days).

Study	Number of Patients		
	Schizophrenia	Schizoaffective	Total
RIS-INT-57	615	110	725
Treated for 6 mos	489	90	579
Treated for 1 yr	301	60	361

- Does the Division concur that there are a sufficient number of patients in this trial to support a statement in the label about the safety of the long-term use of risperidone long-acting injectable?

Yes, the number of patients was considered sufficient for this decision, although FDA was noncommittal regarding a statement about long-term use in the label and indicated that it would ultimately be a review issue. JRF should only describe findings.

On a related point, JRF noted that there seemed to be a difference in language regarding long-term use of antipsychotics in several labels, citing as examples those for olanzapine and ziprasidone. FDA responded that they had labeled what the companies had studied, did not intend to create confusion, and would investigate possible inconsistencies.

The design of a long-term maintenance/relapse prevention trial was also discussed. Dr. Laughren stated that the design of such a trial would preferably include a stable

baseline period of 12 weeks and for responders, a subsequent randomized treatment period (placebo versus active) of a minimum of 6 months duration.

4. The FDA requested that JRF demonstrate, from a pharmacokinetic perspective, bioequivalence between risperidone oral and long-acting injectable formulations. Bioequivalence has been established in a Phase 2, pharmacokinetic trial (RIS-INT-32), and through limited pharmacokinetic blood sampling in a Phase 3, non-inferiority trial (RIS-INT-61).

   The FDA also requested that JRF compare the Phase 3 (to-be-marketed) formulation with formulations used in Phase 1 and Phase 2 trials. Data from a single-dose, pharmacokinetic study, RIS-INT-54, demonstrated that Phase 2 and Phase 3 formulations were equivalent with respect to extent of absorption (AUC), but not for C_{max}.

   The long-acting injectable formulation used in Phase 3 clinical trials (N=~1500 patients treated with risperidone long-acting injectable) is the same as the to-be-marketed formulation. Therefore, no formal bioequivalence trial was performed with the to-be-marketed formulation.

- Does the Division concur that JRF has fulfilled the requests for the biopharmaceutical approach?

  The Division agreed.

APPEARS THIS WAY
ON ORIGINAL

5. At the EOP-2 meeting, JRF described a phenomenon of high fluctuations in plasma levels observed in a few patients (9 of 145 patients) treated with risperidone long-acting injectable formulations during Phase 1 and Phase 2 trials, although these peak plasma concentrations did not exceed values observed with an oral dose of 8 mg risperidone. In line with the Division's agreement at the EOP-2 meeting on the proposed sampling scheme (1st, 4th, and 7th day after the injection) for the Phase 3 clinical trials with the optimized injectable formulation, JRF plans to use these data to describe the variability in plasma exposure in the pharmacokinetic section of the label.

- Is this approach still considered acceptable to the Division?

JRF's approach seems reasonable, but the Division will need to see the results. Dr. Katz acknowledged that the briefing document indicated that peak plasma concentrations for all patients observed to date were below those observed with the 8 mg oral formulation, information presumably intended to assure the FDA that there was no safety issue. However, Dr. Katz stated that the Division was more concerned about whether this was a potential product performance issue: with early release, plasma levels may fall below therapeutic levels before the end of the treatment cycle. With the aid of back-up slides, JRF illustrated that early release was considered to be a Phase 1 formulation issue. JRF further stated that two datasets will be available to allay these concerns:

- ***Data from two pharmacokinetic studies (RIS-INT-54 and RIS-INT-72) in which the to-be-marketed formulation was used and frequent plasma samples were collected.***
- ***Pharmacokinetic data from plasma samples collected on Days 1, 4, and 7 after injection from more than 1000 patients who participated in the Phase 3 trials.***

FDA agreed that these data would help JRF address this issue in the NDA and would facilitate their review.

6. In the placebo-controlled trial, RIS-USA-121, and in pharmacokinetic trials, JRF has provided pharmacokinetic evidence of dose proportionality of 25, 50, and 75 mg of the risperidone long-acting injectable formulation (see Section 4.4.4.1). Single-dose, pharmacokinetic data have also been obtained with the intermediate doses of 37.5 and 62.5 mg in trial, RIS-INT-72.

- Based on the pharmacokinetic evidence of dose proportionality, does the Division agree that data from RIS-INT-72 will be sufficient to support the recommended use of the intermediate dose of 37.5 mg in the product label (see Section 4.1.1)?

If the Division agrees with JRF that the 25 mg – 75 mg data demonstrate dose proportionality, then the 37.5 mg dose should be acceptable. Of course, text in the label depends on the outcome of the review.

7. The pooled analysis for the ISS will include all completed Phase 1, 2, and 3 trials, except for RIS-INT-72 (see Section 4.4.1, Table 6). This single-dose, pharmacokinetic trial was designed to assess the intermediate doses of 37.5 mg and 62.5 mg of risperidone long-acting injectable. The trial will not be completed in time for incorporation into the pooled database and, for this reason, safety data from RIS-INT-72 will be presented separately in the ISS.

- Is this approach acceptable to the Division?

Yes

- The ISS pooled datasets, excluding RIS-INT-72, will be provided electronically. Is this approach acceptable to the Division?

Yes

8. Pharmacokinetic, efficacy, and safety data from 49 elderly patients (≥65 years old) have been collected during the long-term safety trial, RIS-INT-57. During the EOP-2 meeting, the Division agreed that JRF did not need to conduct a separate efficacy trial in elderly patients, as long as some data (preferably pharmacokinetic and safety data) were provided for these patients.

- Does the Division agree that JRF has provided information from a sufficient number of elderly patients to support a recommended dose of 25 mg IM every 2 weeks in elderly patients [i.e. identical to the recommended dose for nonelderly patients (Section 4.1.1)]?

Dr. Laughren asked whether JRF had collected pharmacokinetic data in elderly patients. He noted that in the label for oral risperidone, a lower starting dose for the

elderly (0.5 mg b.i.d) is recommended. However, for the new formulation, JRF is proposing the same starting dose in elderly and nonelderly patients. Dr. Laughren said that dosing recommendations for the elderly will be determined during the review and will depend on the similarity of the pharmacokinetic profiles for the elderly and nonelderly. If the pharmacokinetic profile of the elderly is markedly different from that of the nonelderly with the new formulation, JRF may need to provide a lower starting dose for elderly patients – to which Dr. Katz added, "if you have a lower dose". If pharmacokinetic profiles of the elderly and nonelderly are substantially different, FDA may request that JRF conduct a pharmacokinetic trial. This will be determined during the review.

Dr. Katz confirmed that no separate efficacy trial in the elderly would be required.

9. On May 5, 2000, JRF submitted a proposal to the Division for conducting 2 trials with RISPERDAL Oral Solution in children and adolescent patients with schizophrenia (see Section 4.5.10). The proposal included protocol outlines for a pharmacokinetic trial (RIS-USA-160) and a placebo-controlled trial in children and adolescent patients with schizophrenia (RIS-USA-231). We will address requirements for the risperidone long-acting injectable formulation in children and adolescents when discussions concerning the proposed studies have concluded.

The Division noted that they have been remiss in responding to JRF, that they still owe JRF a response, and hope to provide one soon. It was further noted that the Division has yet to respond to other sponsors with antipsychotics.

10. Based on the statistical analysis plan for the Phase 3 studies (RIS-USA-121, RIS-INT-61, and RIS-INT-57), the ISE, and ISS (see Sections 4.5.5 to 4.5.7), does the Division agree that the clinical data will be analysed and presented in a manner suitable for the Agency to file and review the NDA?

FDA asked if JRF's imputation scheme for missing items in the PANSS subscales was specified in the protocol. JRF responded that although the imputation scheme was not in the protocol, it was included in the statistical analysis plan (SAP), which was finalised and approved prior to breaking the blind.

FDA also asked if the pooling strategy for small sites that JRF used for exploring treatment-by-investigator interactions was specified in the protocol. JRF responded that this also was specified in the SAP. While acceptable, FDA suggested that the two documents should be consistent.

There was some discussion about the planned ANCOVA analysis of change from baseline in total PANSS score. Due to disagreement between the biostatistics reviewer and the statistical team leader about the importance of treating the baseline PANSS score as a random effect, it was decided that a separate teleconference would be held to discuss the issue further. [Postmeeting note: Claude McGowan contacted Steve Hardeman on Friday, 27 April 2001, about the need for a teleconference to discuss this issue. Steve responded to Claude on Monday, 30 April 2001, and related that Dr. Jin, the statistical team leader, indicated this would not be an issue and that no further discussion would be required. Steve further added that the SAP for the Phase 3 studies is adequate for the filing and review of the NDA.]

11. Individual trial datasets will be provided for the three Phase 3 trials, RIS-USA-121, RIS-INT-61, and RIS-INT-57.

- Is this approach acceptable to the Division?

Yes

12. Patient exposure (duration of treatment) to risperidone long-acting injectable will be calculated as the number of days from the date of the first injection to the date of the last injection. This definition includes the 3 weeks of oral supplementation following the first injection.

- Is this approach acceptable to the Division?

Yes

13. Treatment-emergent adverse events will be defined as those adverse events with an onset between the first injection with risperidone long-acting injectable and up to 49 days after the last injection. This definition includes the 3 weeks of oral supplementation following the first injection and, for the majority of patients, the main release phase of risperidone (see Section 4.4.4.1) following the last injection.

- Is this definition of treatment-emergent adverse events acceptable to the Division?

Yes

14. ECGs were centrally read by ——— Cardiac Alert in RIS-USA-121, RIS-INT-61, and RIS-INT-57. Three correction factors will be applied to the analysis of QT data, using Bazett's formula, Fridericia's formula, and the linear formula according to Sagie et al. (see Section 4.5.5.1.3.5). Based upon discussions with a number of academic cardiologists, JRF

believes that Fridericia's formula is a more reliable correction factor for risperidone, which causes an increase in heart rate. For this reason, the focus of the clinical research reports and integrated summary documents will be on analysis results using Fridericia's formula. However, reference will be made to results based on all 3 correction factors.

- Is this approach acceptable to the Division?

While the FDA agreed that Bazett's formula overcorrects for increased heart rate, they also believe that Fridericia's formula undercorrects and, therefore, may also be misleading. The Division offered to share with JRF an internal guidance document, which describes two correction factors that the Division prefers to either the Bazett's or Fridericia's correction factors. Steve Hardeman will provide a copy to Claude McGowan. [Postmeeting note: The guidance on QT analysis has been received by JRF.] JRF noted that the clinical research reports are almost finalized and requested that the proposed analysis be included only in the ISS. FDA agreed that the results of the QT analysis proposed by the Division need only be included in the ISS.

15. The NDA will include data up to April 30, 2001 (inclusive); the incidence of deaths and serious adverse events reported in the 4 ongoing trials (RIS-INT-63, RIS-USA-196, RIS-JPN-16, RIS-INT-62) would be summarized in the ISS up to this data cut-off date. The 4-month safety update will include all safety data from the 2 ongoing, open-label extension trials, RIS-INT-63 and RIS-USA-196 (see Section 4.5.4), up to and including the data cutoff date of May 15, 2001. For the two remaining ongoing trials, RIS-JPN-16 (single-dose, pharmacokinetic trial) and RIS-INT-62 (comparative, non-inferiority trial with olanzapine tablet), interim safety data will not be available at the time of the 4-month safety update. However, the incidence of deaths and serious adverse events in these trials will be updated as of August 31, 2001.

- Is this approach acceptable to the Division?

Yes

NONCLINICAL

1. At the Carcinogenicity Assessment Committee (CAC) meeting of April 13, 1999, the design and dose selection of the rat carcinogenicity study were discussed. Based on this meeting, the FDA made recommendations to JRF. The written reply to these recommendations is included in Attachment 2 of this briefing document.

- Does the FDA concur with the responses to these recommendations?

Yes

- Has JRF adequately addressed all issues related to the local site carcinogenic potential of risperidone long-acting injectable?

Yes, although it will depend on review of the data.

2. JRF has conducted several toxicology studies with the risperidone long-acting injectable formulation (Section 4.3.4.1, Table 5), including tolerance studies in several species, primary irritation studies in the rabbit, and repeated-dose toxicity studies in the rat and dog. Although no reproductive or mutagenicity studies were conducted with the risperidone long-acting injectable formulation, these studies are available for oral risperidone (RISPERDAL Tablet NDA, 20-272). In addition, acute and chronic toxicology studies of the microspheres vehicle have been conducted by Alkermes (DMF).

- Does the FDA concur that reproductive and mutagenicity studies conducted with orally administered risperidone are sufficient for the filing and review of the NDA for the risperidone long-acting injectable formulation?

When JRF inquired about potential RTF issues (see Question 1 in the clinical/ biostatistics/and clinical pharmacokinetic section), FDA noted that there was one potential issue. There was some concern about the lack of reproductive data with the copolymer, which could become a RTF issue if not adequately addressed. JRF asked whether FDA's concern was specific or was based on a general lack of information about the copolymer. FDA confirmed that the concern was based on a general lack of knowledge about the copolymer, although there are several products on the market that use the microsphere technology. JRF explained that the copolymer is broken down into two endogenous compounds, lactic acid and glycolic acid (hydroxyacetic acid). After some discussion, FDA agreed that if JRF addressed the metabolic disposition of the copolymer, a RTF would be avoided. JRF responded that this data would be included in the NDA. FDA noted that addressing the issue proactively would probably avoid a RTF, but added that if the data were not compelling, Segment 2 and Segment 3 reproductive studies could be requested.

Dr. Sunzel asked if JRF had evaluated the effect of temperature increase (fever) on the microspheres. JRF responded that in vitro release data as a function of temperature are available.

With respect to the Division's request for in vitro genotoxicity data, FDA asked whether JRF intended to cite another company's data. If so, Dr. Katz noted the NDA might have to be filed as a 505 b (2) application, which is used when the sponsor relies

on data in the label of another product. After the business relationship between JRF and Alkermes was explained, it was considered not to be relevant to the toxicity data provided by Alkermes in their DMF. However, if JRF were to cite data from a mutagenicity study conducted by a third party, it might still be relevant. JRF indicated that it would probably be easier to conduct the study.

GENERAL

1. In Section 3.1.2 of this briefing document, we have provided a summary of issues raised by the Division during the EOP-2 meeting (Table 2). Resolution of these issues, as well as others raised since the submission of the IND, are summarized in Table 1 (see Section 3.1.1).

- Does the Division agree that these issues have been adequately addressed (Table 1)?

Yes

- Does the Division agree that no additional issues have been identified?

Yes

2. The proposed label changes have been outlined in Section 4.1.

- Does the Division concur that the proposed changes to the label would be acceptable, providing that the Division's review of the data substantiate and agree with JRF's conclusions?

The proposed changes to the label are probably acceptable, but this is a review issue. FDA asked whether JRF was planning to use a separate label for the new formulation. JRF replied that it was still considering options vis-à-vis ease of use by prescribers once launched. FDA noted that they preferred one label for the oral and new formulations for ease of tracking.

3. The nomenclature, risperidone depot microspheres, has been used in clinical and nonclinical research reports that will be submitted in the NDA. However, JRF is contemplating using nomenclature such as 'risperidone long-acting injectable' for the RISPERDAL label.

- Is the proposed nomenclature for the label consistent with that used for this type of formulation?

The Division will consult with OPDRA on this issue, but encouraged JRF to submit a proposal under the IND, which would be forwarded to OPDRA. JRF noted that the

term, 'long-acting', was being explored as an alternative to 'depot' because of the negative connotations of the latter term for some patients. For this reason, JRF is considering use of the term 'long-acting' both in the trademark and, more generally, as a descriptive term in publications and promotional material. FDA indicated that they could not guarantee its acceptability, but OPDRA would make the determination of whether the terminology was confusing or was a potential safety issue.

Before leaving, JRF reminded FDA that while clinical data for all doses would be submitted, JRF does not intend to market doses above 50 mg.

Dr. Katz indicated that they were flexible, but that the decision would depend on their review of the data.

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/s/

Thomas Laughren
5/17/01 08:59:31 AM

MEMORANDUM

DATE: June 28, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-346

SUBJECT: Action Memo for NDA 21-346, for the use of Risperdal Consta in patients with schizophrenia

NDA 21-346, for the use of Risperdal Consta, an intramuscular injection of risperidone to be administered every 2 weeks in patients with schizophrenia, was submitted by Janssen Research Foundation on 8/31/01. Risperidone is already marketed for the same indication in several oral formulations. The application includes reports of numerous studies, including a single adequate and well-controlled trial (Study 121) that purports to demonstrate the effectiveness of the treatment in patients with schizophrenia.

The application has been reviewed by Dr. Gurpreet Gill-Sangha, chemist (review dated 6/24/02), Dr. Vinayak Pawar, microbiologist (review dated 4/29/02), Dr. Maria Sunzel, Office of Clinical Pharmacology and Biopharmaceutics (review dated 6/21/02), Dr. Lois Freed, pharmacologist (review dated 6/25/02), Dr. Sharon Yan, statistician (review dated 5/2/02), Dr. Earl Hearst, medical reviewer (review dated 5/13/02), and Dr. Tom Laughren, team leader, psychiatric drugs (memo dated 6/21/02). The review team has concluded that the treatment is effective, and that the clinical safety data support approval, and I agree.

However, Dr. Freed has identified several findings that are of concern. Specifically, she has noted the occurrence of adrenal and kidney tumors in males, as well as osteodystrophy in both sexes, in a rat carcinogenicity study of the injectable product, findings that were not seen with the oral product. In addition, she has identified —impurities in the final product that would require qualification, for which the sponsor has not provided appropriate data.

In particular, the frequency of the tumors (benign and malignant combined), in male rats is:

	Saline Control	Vehicle Control	Low Dose	High Dose
Pheochromocytoma	3/50	3/50	3/50	12/50
Renal Tubular tumors	0/50	0/50	0/50	5/50

The frequency of osteodystrophy (sternum) is as follows:

	Saline Control	Vehicle Control	Low Dose	High Dose
Males	0/50	1/50	1/50	33/50
Females	7/50	4/50	8/50	21/50

(This study also revealed increases in other tumor types, including mammary gland, pituitary, and pancreas; these are tumors often seen with anti-psychotic drugs, as well as with oral risperidone, and are considered to be related to elevated prolactin and of no relevance for humans.) The sponsor has addressed the unique tumor data, suggesting that these tumors are also the result of elevated prolactin (prolactin is increased with injectable risperidone).

In particular, the sponsor proposes that the elevated prolactin resulted in an exacerbation of chronic renal disease, which, through a complex sequence of metabolic events (including derangements of calcium homeostasis), resulted in osteodystrophy and kidney tumors. Dr. Freed has performed an extensive review of this proposed mechanism through a detailed literature review, and concludes that this explanation is not persuasive.

I agree. Briefly, as Dr. Freed points out, although the literature describes associations between chronic renal disease and kidney tumors and osteodystrophy in the rat, and there are multiple histologic findings in the kidney in this study, these findings are not consistent with the typical description of chronic renal disease. Further, the literature suggests that tumors/osteodystrophy are only seen in the context of severe renal disease, which is not seen in this study (indeed, the sponsor has concluded that chronic renal disease was not increased in the male rats, in which tumors occurred, while it was increased in females, in which tumors did not occur). Dr. Freed also contemplates the possibility that increased prolactin might directly cause osteodystrophy, but support for this mechanism in the literature is not compelling.

Regarding the occurrence of pheochromocytoma, the sponsor again proposes increased prolactin as the cause, with or without a contribution of chronic renal disease. Again, while the literature discusses a possible association between elevated prolactin and these tumors, it is not definitive on this point. In addition, and critically, the sponsor has performed a study to examine the potential mechanism(s) responsible for the differences seen between the oral and injectable product, and has determined that, in fact, the AUC for prolactin after oral administration is greater than that seen after intramuscular administration. If elevated prolactin were a critical step in the genesis of these pathologies, we would expect to see them in studies of the oral product; we, of course, do not (the sponsor's claim that the difference in the pattern of the prolactin increase with the oral as compared to the injectable is responsible for the different findings is entirely conjecture and also not at all persuasive).

It is also important to note that these findings occur at a dose that results in AUCs of risperidone (and its active metabolite) that are ***lower*** than those seen with the recommended maximum human dose. Therefore, there is no threshold for the tumor findings (the sponsor has documented that the drug is not genotoxic).

I believe that these findings, as well as the absence of other studies now necessary as a result of these findings (see below), support a Not Approvable action.

Although there is a statistically significant increase in the occurrence of adrenal and renal tumors in male rats at the high dose, one could argue that these findings are not numerically large, and could be considered a chance finding. That is, it might be argued that this finding is not unique to intramuscular risperidone, and that had another study been performed with the oral drug, such a finding might have emerged.

I believe, however, that this finding is a "real" finding, and, at least in the context of this single study, not likely to be a chance finding. I believe that the pharmacology team (Drs. Freed and Rosloff) agrees with this. Whether or not such a finding would have emerged had additional studies been performed with the oral drug is, of course, unknown (even if it had, our actions as a result of it would likely have been different-see below).

The appearance of these new tumors (and the magnitude of their occurrence) as a result of a simple change in route of administration may raise questions about the validity or meaning of these results; after all, such a finding is unexpected (we had asked the sponsor to perform this study because we were concerned about local, not systemic, tumor production). However, the occurrence and strikingly high incidence of osteodystrophy in this study (in both sexes), cannot be subject to the claim that this is a chance finding. This finding, coupled with the absence of this finding with oral risperidone, makes it clear, beyond doubt, that a change in route can give rise to important, new toxicities. Of course, the mechanism of this finding is unknown (it is worth noting that this product represents not just a simple change in route of administration, but also, of course, a change in the formulation, which, in addition to the presence of new components [with potential toxicities], could have effects on the distribution of the drug itself, with unknown consequences), but this does not negate the finding, of course.

Therefore, the tumor findings must, in my view, be given credence. That is, we have seen that a change in route can give rise to a clear, unambiguous, new finding (osteodystrophy). We have also seen that the tumor findings are statistically significant in this study, establishing that, while not representing an overwhelming numerical increase, they are likely not a chance finding. Further, as discussed earlier, the sponsor's attempts to dismiss the findings on the basis

of a proposed mechanism are not, in my view, persuasive (indeed, even if one accepted their proposed mechanism(s), this would not establish the findings as irrelevant for humans, as Dr. Freed has pointed out). Taken together, these factors lead me to conclude that IM risperidone, in this formulation, should be considered carcinogenic in animals, at this time.

Despite this conclusion, one could argue that the application should be approved, with appropriate language in labeling. I do not agree.

I can see little justification for making this product available while the question of its potential carcinogenicity is open. This product is not a therapeutic advance of the sort that might justify its marketing with this finding. While the product was designed, ostensibly, to increase compliance in schizophrenic patients (an important goal), the sponsor has not demonstrated that this would result. One could imagine that patients might, in fact, be less compliant with this product than with the oral product (for example, they might not return to the clinic to receive the injection, they might not tolerate an injection in the long term, etc.). In any event, this product represents, at best, a potential advantage that has not been demonstrated. Of course, the sponsor might be able to either justify the marketing of this product in the face of these findings (perhaps by performing a study that documents increased compliance), or document that these findings are not relevant to humans. However, at this time, they have done neither.

It is possible that these findings might be considered relevant for oral risperidone as well. However, even if these findings had been seen with oral risperidone when that application was under review, we might have still approved it with appropriate language in labeling; such an action might have been justified because a new treatment for schizophrenia is considered an important advance. As I have noted above, however, these considerations do not obtain at this point for the injectable. Beyond this, of course, the signal exists only for the injectable, and, as explained above, there is sufficient reason to believe, at this time, that this finding is real, and that such a difference in findings between the two products is believable. For this reason, I believe that no action is indicated at the moment with regard to the oral product. If subsequent events support the conclusion that these findings are relevant for the oral product, we will need to take appropriate action.

In addition, as Dr. Freed points out, the tumor and osteodystrophy findings necessitate additional embryofetal studies. Although we had told the sponsor at early meetings that no such studies would be required with this product, this was with the understanding that no important findings would emerge in the other animal studies; unfortunately, other findings were seen that make the new studies necessary prior to approval. The lack of such studies, by itself, would support a Not Approval action.

As Dr. Freed has also noted, the sponsor has not provided evidence that ~of the —— impurities that require qualification have been qualified.

Finally, Drs. Sunzel and Gill-Sangha have additional comments to be sent to the sponsor. These are not reasons for a Not Approvable action. Importantly, as Dr. Gill-Sangha notes, the ultimate approval of the application is dependent upon a satisfactory inspection of the API facility in Italy.

For the reasons stated above, then, I have concluded that the application is Not Approvable, and I will issue the attached letter.

Russell Katz, M.D.

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/s/

Russell Katz
6/28/02 10:12:14 AM
MEDICAL OFFICER

6/25/02

NDA 21-346 – MEMO TO FILE

I concur with the recommendations made in Dr. Freed's review of 6/25/02. Differences in the chronic toxicity and to a lesser extent carcinogenicity findings suggest a meaningful difference in the preclinical safety profiles of the p.o. and i.m. formulations of risperidone. An embryofetal development study of the i.m. formulation would help determine if this difference extends to the area of reproduction. It is recommended that such a study use a group dosed orally for comparison.

Barry Rosloff
Supervisory Pharmacologist

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/s/

Barry Rosloff
6/25/02 05:33:58 PM
PHARMACOLOGIST

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 21, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Risperdal Consta (risperidone long-acting injection) for the treatment of schizophrenia

TO: File NDA 21-346
[**Note:** This overview should be filed with the 8-31-01 original submission.]

1.0 BACKGROUND

Risperidone is a 5HT2/D2 receptor antagonist that is currently marketed in an immediate release tablet and a solution (Risperdal) for the treatment of schizophrenia. This formulation consists of extended release microspheres that are to be suspended in a diluent provided with the microsphere powder just prior to deep, IM gluteal injection every two weeks. The sponsor wishes to market 3 dosage strengths: 25, 37.5, and 50 mg. The proposed dose range for risperidone long-acting injection (risperidone LA) is 25 to 50 mg every 2 weeks.

The rationale for this depot formulation is improved compliance, a problem with schizophrenic patients. There are currently two other depot antipsychotic formulations available, i.e., fluphenazine and haloperidol decanoate.

We held three meetings with the sponsor during the development of this product:

The first meeting **(6-19-97)** was held shortly after the submission of the IND (IND 52,982; submitted 3-18-97). The purpose of this meeting was to generally discuss what would be needed in a development program for this product:
-While we noted that a clinical trial showing a difference would be necessary, we agreed that a single positive trial would suffice. Since this formulation is generally used for maintenance treatment, we

strongly recommended a randomized withdrawal trial. However, even at this early point, they did not seem inclined toward a maintenance study.
-There was some preliminary discussion of what would be needed regarding carcinogenicity. We requested additional documentation from a 6-month IM dog study and a proposal for a study to document that there are no local injection site changes. Alternatively, they were invited to try to make a case that further testing was not needed.

An **EOP2 meeting** was held on **4-13-99**:
-The sponsor submitted protocols for study 121 (a 12-wk, placebo-controlled fixed dose acute study), study 61 (a noninferiority trial for European registration), and study 57 (a 12-month safety study).
-We again strongly encouraged a randomized withdrawal trial, but indicated that, in principle, study 121 would suffice, if positive.
-Since the plan for study 121 included oral supplementation during the early weeks of depot treatment, to prevent dropouts, we indicated that the drug would be recommended for use with early supplementation.
-We suggested that priority review would be unlikely.
-The required PK program was discussed in detail.
-A plan was discussed for further evaluation of excessive fluctuation of plasma levels that had been observed in a few patients.
-There was extensive discussion of the carcinogenicity requirements for this formulation. It was noted that the CAC had discussed the sponsor's proposed 24-month rat study, and that, due to concern regarding local changes observed in several species, they were not inclined to accept the plan for submission of the NDA with only 12-month interim sacrifice data. We also asked for documentation for their dose selection.

A **preNDA meeting** was held on **4-20-01**:
-We again discussed study 121, and indicated that, in principle, this was sufficient to show efficacy.
-The plan to analyze patients with schizophrenia and schizoaffective disorder separately was endorsed.
-We generally endorsed the adequacy of the expected exposure data for this formulation.
-It was again confirmed that the PK program, as described, appeared to be adequate.
-There was additional discussion of the concern about excessive fluctuation in plasma level observed in a few phase 1 subjects. The sponsor described a plan to fully explore this issue for the NDA, and this appeared to be adequate.
-There was discussion of what would be needed to support dosing recommendations for the elderly, namely, actual PK data.

This NDA required reviews by the CMC, pharmacology/toxicology, biopharmaceutics, and clinical groups. The CMC review was conducted by Gurpreet Gill-Sangha, Ph.D. The pharmacology/toxicology review was conducted by Lois Freed, Ph.D. The biopharmaceutics review was conducted by Maria Sunzel, Ph.D., with additional consultation by Vanitha Sekar, Ph.D. The primary review of the efficacy and safety data was done by Earl Hearst, M.D., from the clinical group. Sharnon Yan, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

As noted, the studies supporting this supplement were conducted under IND 52,982, which was originally submitted 3-18-97. The original NDA was submitted 8-31-01.

We decided not to take this NDA to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

I am not aware of any CMC concerns that would preclude an approvable action on this NDA.

3.0 PHARMACOLOGY

As noted, the sponsor was asked to conduct a 2-year carcinogenicity study in rats to further explore local changes observed in earlier studies. The rat study was conducted, and revealed several findings of concern (see review by Lois Freed, Ph.D., for details). Significant, dose-related effects were observed for 2 new tumor types in male rats, i.e., benign pheochromocytoma and renal adenoma. Neither tumor was observed to be dose-related in the oral studies with risperidone. In addtion, there was a substantial, dose-related occurrence of osteodystropy with risperidone LA, again a finding not observed with oral risperidone. This latter finding gives some credibility of this alternative route of administration being associated with a different profile of toxicity. It is further significant that the exposure levels in the rats at which these effects were observed are only slightly in excess of levels seen in humans at the recommended doses, and the exposures at the next lower dose at which the effects were not observed are well below human exposures. While the sponsor has made an effort to explain the findings as prolactin related, Dr. Freed has argued that a careful look at the actual prolactin data and the animals experiencing these effects does not support the sponsor's argument.

At the time of completing this memo, this issue is not finally resolved and the primary and supervisory pharmacology reviews have not been finalized. However, it is my impression, based on data and arguments that I have heard thus far, that this is a significant problem for this drug. In a sense, this is a convenience form of this drug, and it is associated with a signal of risk in rats that is not observed with oral risperidone. Thus, I think it would not be unreasonable to not approve this NDA, pending a response from the sponsor to present a better argument, if possible, regarding why this signal may not be relevant for humans.

4.0 BIOPHARMACEUTICS

This depot formulation provides a small initial release of drug, followed by a lag time of about 3 weeks, and then continues for 4 to 6 weeks. With q 2weeks dosing, steady state is reached in 2 months. Oral supplementation is needed during the first 3 weeks to cover patients during the lag

phase. While there was some concern about excessive early release in an initial formulation, this was not seen with the TBM formulation in the phase 3 trial.

The pharmacokinetics of risperidone LA have been adequately characterized and I am not aware of any biopharmaceutics concerns that would preclude an approvable action on this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of study 121, a 12-week, acute study of 3 fixed doses of risperidone LA and placebo in patients with schizophrenia. The sponsor also submitted results of study 61, a noninferiority trial comparing risperidone LA and risperidone tablets, conducted for purposes of European registration. Since we have not accepted this approach to efficacy in this condition, this study was not reviewed with regard to efficacy. Efficacy data were also collected for a third study, i.e., 57, a 12 month, open safety study. Since the efficacy data from this trial are not interpretable from our standpoint, these data were also not reviewed.

5.1.2 Summary of Study RIS-USA-121

This was a randomized, double-blind, parallel group, 12-week, fixed-dose study comparing risperidone LA (25, 50, or 75 mg, q2wks, IM) and placebo in adult inpatients or outpatients meeting DSM-IV criteria for schizophrenia or schizoaffective disorder. Patients selected for this study were discontinued from their current antipsychotic medications and switched to oral risperidone 4 mg/day during a 1-week run-in period. Only patients who successfully completed this open run-in were randomized. Randomization was stratified based on inpatient/outpatient status and on baseline PANSS total score ($> \text{or} \leq 80$). Patients randomized to risperidone LA were given supplemental oral risperidone during the first 3 weeks of the trial (with dose depending on risperidone LA dose, i.e., 2 mg/day for 25 mg group, 4 mg/day for 50 mg group, and 6 mg/day for 75 mg group). During the trial, a decision was made to stop recruiting patients with schizoaffective disorder, and thus, the patients were roughly 90% schizophrenic. The analysis will focus only on patients with schizophrenia. There were roughly 90 patients per each of the 4 groups in the sample analyzed (n=370). There were substantial dropouts before reaching the 12 week endpoint, with the % completing to 12 weeks ranging from 32 (for placebo) to 48% (for all 3 drug groups). [Note: The dropout rate of 52% for drug patients is quite high, but not too surprising, given that this was a 12-week trial, with a placebo arm, so that clinicians may have been more inclined to drop patients who were not optimally controlled. This high dropout rate is also balanced by the fact that the OC analyses were also significantly in favor of drug.] The patients were about 3/4 male, mostly black or Caucasian, and the mean age was about 38 years.

Assessments included the PANSS and CGI, at baseline and q2 weeks. The primary outcome was change from baseline to endpoint in PANSS total score, and I will focus on that outcome. As is usually the case, the ITT data set included all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup PANSS assessment. The LOCF analysis was considered primary, but OC was also done. ANCOVA was the statistical model employed, with baseline score as the covariate. If the overall analysis was significant, pairwise comparisons of active drug groups with placebo were made. The overall analysis for PANSS was highly significant ($p<0.0001$), as were all the pairwise comparisons of active drug vs placebo (in both LOCF and OC analyses):

Efficacy Results on PANSS Total Score for RIS-USA-121 (LOCF)

	Baseline PANSS	Δbaseline PANSS	[P-value(vs pbo)]
Ris LA 25 mg (n=93)	**81.7**	**-6.1**	**p<0.002**
Ris LA 50mg (n=98)	**82.3**	**-8.7**	**p<0.002**
Ris LA 75 mg (n=87)	**80.1**	**-5.6**	**p<0.002**
Placebo (n=92)	**82.0**	**+2.6**	

While not described here, results on the 5 subscales of the PANSS (including positive and negative symptoms), the CGI, and OC analyses, generally favored all 3 risperidone groups over placebo. Subgroup analyses based on age, gender, and race suggested some possible differences, however, overall, the effect appeared to be preserved regardless of demographic subgroup, at least numerically.

Comment: Both Drs. Hearst and Yan considered this a positive study, and I agree.

5.1.3 Comment on Other Important Clinical Issues Regarding Risperidone LA Schizophrenia

Evidence Bearing on the Question of Dose/Response for Efficacy

All 3 dose groups beat placebo, and the 50 mg group was numerically the best. Labeling should reflect this finding of no clear evidence of an advantage of the higher dose groups over the 25 mg group, and this should be the target dose.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender, age, and race. While there were some differences suggested in responsiveness in different subgroups, I do not feel the data are sufficient to be the basis for any labeling statements suggestive of differences.

Size of Treatment Effect

-CVA: Given recent interest in looking at the occurrence of cerebrovascular accidents (CVAs) in patients with vascular dementia taking atypical antipsychotics, it was noteworthy that there were 4 reports of "CVA" among patients receiving risperidone in this program. Two of these involved oral risperidone and two were taking risperidone LA.

-A30860 (RIS-INT-63): 38 y/o male; taking risperidone LA 75 mg IM q2wks for approximately 8 months; experienced increase in psychotic symptoms and also "concentration problems, was easily irritated, had a sleep disorder, and could not find the right words." He was discontinued from risperidone LA and hospitalized. An MRI revealed a "probable cerebral aneurysm." Folowup information was not available.

-A30050 (RIS-INT-57): 54 y/o male; taking risperidone LA 75 mg IM q2wks for approximately 10 weeks; he was hospitalized with a pulmonary embolism, and was also noted to have "anoxic brain injury," that was judged to have occurred during transport to the hospital; few details are avaiblable; apparently discharged to a nursing home.

-A30146 (RIS-USA-121): 44 y/o male; taking oral risperidone LA 2-4 mg/day for approximately 9 days; at that time he was hospitalized and diagnosed with metastatic lung cancer, but also noted on MRI to have "multiple CVAs that were felt to be embolic and not due to metastases." He had expressive aphasia, dysarthria, and right handed weakness.

-A30015 (RIS-INT-61): 44 y/o female; taking oral risperidone LA 2 mg/day for approximately 6 months; experienced right handed numbness and some loss of strength in her right hand; she was diagnosed with "possible stroke."

These cases all seem very different, with clear alternative explanations for the CVAs in 3 of the cases; the fourth case is unclear as to diagnosis or cause. Thus, I don't view this as a signal of risk for risperidone, but rather, as events most likely unrelated to taking risperidone in either form.

5.2.2 Conclusions Regarding Safety of Risperidone LA in Schizophrenia

There were no new safety findings to suggest a substantially different safety profile for risperidone LA compared to that observed for oral risperidone, and no basis for substantially different labeling for risperidone LA compared to that for oral risperidone.

5.3 Clinical Sections of Labeling

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

There was no literature to review in this application.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, risperidone LA is not approved for the treatment of schizophrenia anywhere at this time. We will ask for an update on the regulatory status of risperidone LA for the treatment of schizophrenia in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

Three sites were inspected and found to be satisfactory.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's draft dated 8-31-01.

10.2 Foreign Labeling

Risperidone LA is not approved for the treatment of schizophrenia anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a literature update and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Janssen has submitted sufficient data to support the conclusion that risperidone LA is effective and acceptably safe in the treatment of schizophrenia, with the exception of the rat carcinogenicity data. This concern regarding a signal for carcinogenicity is discussed under 3.0 (Pharmacology). The sponsor needs to make a stronger case that this signal is not of sufficient relevance to humans before we could consider the final approval of this product. [redacted] However, I would also not object to

a nonapproval action, based on these findings.

cc:
Orig NDA 21-346
HFD-120
HFD-120/TLaughren/RKatz/AMosholder/EHearst/SHardeman

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/s/

Thomas Laughren
6/21/02 09:50:16 AM
MEDICAL OFFICER

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(ODS; HFD-400)

DATE RECEIVED: 09/18/01	DUE DATE: 05/20/02	ODS CONSULT #: 01-0207

TO:
Russel Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH:
Steven D. Hardeman, R.Ph
Project Manager, Division of Neuropharmacological Drug Products
HFD-120

PRODUCT NAME:	**NDA SPONSOR:** Janssen Pharmaceutical
Risperdal Consta™ (Risperidone for Injection) 25 mg, 37.5 mg and 50 mg **NDA:** 21-346	

SAFETY EVALUATOR: David Diwa, Pharm.D.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) has performed a review of the proposed proprietary name *Risperdal Consta™* to determine the potential for confusion with approved proprietary and established names as well as pending drug names.

DMETS RECOMMENDATION: DMETS has no objections to use of the proposed proprietary name *Risperdal Consta™*. In addition, we recommend revising the labels and labeling as outlined in section III of this review in order to minimize potential errors with the use of this product.

DMETS' decision is considered tentative. The firm should be notified that this name, and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names, and established names from the signature date of this document.

Carol Holquist, R.Ph
Deputy Director
Division of Medication Errors & Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 480-8173

Jerry Phillips, R.Ph
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Consulted use of "Long Acting" to Dan Boring of LNC to get comment on the correct nomenclature of the established name. No response to date.

Steve Hardeman, RPL /HFD-120

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
HFD-400; ROOM 15B32
CENTER FOR DRUG EVALUATION AND RESEARCH

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 05/3/02

NDA: 21-346

NAME OF DRUG: Risperdal Consta™ (Risperidone for Injection) 25 mg, 37.5 mg and 50 mg

NDA HOLDER: Janssen Pharmaceutical

I. INTRODUCTION

This consult was written in response to a September 18, 2001, request from the Division of Neuropharmacological Drug Products (HFD-120) for an assessment of the proposed proprietary drug name, *Risperdal Consta™*, regarding potential name confusion with other proprietary and established drug names. In addition, the container label, carton labeling and insert labeling were also submitted for review and comment.

The sponsor, Janssen Pharmaceutical, currently markets Risperdal (risperidone) as a 1 mg/mL oral solution as well as 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg oral tablets.

PRODUCT INFORMATION

Risperdal Consta (Risperidone for Injection) is a combination of extended release microspheres for injection and a diluent for parenteral use. The product is an antipsychotic agent indicated for the treatment of schizophrenia. The extended release microspheres formulation is a white to off-white powder, which will be available in strengths of 25 mg, 37.5 mg and 50 mg risperidone per vial. The diluent for parenteral use is a clear, colorless solution in which the microspheres will be suspended prior to injection. The recommended dose of Risperdal Consta is 25 mg every two weeks by deep intramuscular (IM) gluteal injection. The maximum dose should not exceed 50 mg every two weeks. Oral Risperdal should be given with the first injection and continued for 3 weeks to ensure that adequate plasma concentrations are maintained prior to the release phase of risperidone from the injection site. Injections should be alternated between the two buttocks. Two different dosing strengths of Risperdal Consta should not be combined in a single administration. The product should be stored in the refrigerator at temperatures between 2°C to 8°C (36°F-46°F). If refrigeration is unavailable, the product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration.

Risperdal Consta will be provided in — The Alaris system will contain a vial of microspheres, a pre-filled syringe of 2 mL diluent, one SmartSite Needle-Free Vial Access Device, and one NeedlePro 20 gauge safety needle

II. RISK ASSESSMENT

The DMETS medication error staff conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] and SAEGIS™ Pharma-In-Use database[v] for existing drug names which sound-alike or look-alike to *Risperdal Consta* to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[vi]. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

Information was gathered from the DMETS Expert Panel regarding their professional opinions on the safety of the proprietary name *Risperdal Consta*. This included potential concerns regarding drug marketing and promotion relating to the proposed name. The group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical experience, other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel was concerned about the potential risk of sound-alike/look-alike name confusion between the proposed name and the proprietary names *Concerta, Constilac* and *Constulose*. These products are listed in Table 1 below, along with the dosage forms available and usual dosage.

DDMAC did not have any concerns with the name *Risperdal Consta* in regard to promotional claims.

TABLE 1

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Risperdal Consta	Risperidone for Injection 25 mg, 37.5 mg, 50 mg	25 mg IM every 2 weeks	
Concerta	Methylphenidate Extended Release Tablets 8 mg, 36 mg	Children (≥6 yrs): 5 mg twice daily . Adults: 20 mg to 30 mg daily in 2 to 3 divided doses	SA/LA
Constilac	Lactulose Syrup 8 oz and 16 oz bottles, and 30 mL unit dose.	15 to 30 mL or 10 g to 20 g of lactulose daily	SA/LA
Constulose	Lactulose Oral Solution; 237 mL, 946 mL		

*Frequently used, not all-inclusive. **LA: look-alike, SA-sound-alike.

[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iii] Drug Information Handbook 1999-2000, Lacy CF, Armstrong LL, Goldman MP, Lance LL (eds) Lexi-Comp Inc, Hudson

[iv] New Drug Approvals 98-01, and the electronic online version of the FDA Orange Book.

[v] Data provided by T&T's SAEGIS ™ online service available at www.thomson-thomson.com

[vi] WWW location http://www.uspto.gov/tmdb/index.html.

B. AERS DATABASE SEARCH

DMETS searched the FDA Adverse Event Reporting System (AERS) database for all postmarketing safety reports of medication errors associated with the name Risperdal. The MedDRA Preferred Term (PT) "Medication Error," the drug names "Risperdal%," and "risperidone%", were used to perform the search.

A total of 95 reports from the AERS search were retrieved and reviewed. Of the 95 reports, 6 accounts involved the misinterpretation of Risperdal. All 6 events pertained to *actual* occurrence of medication errors. Results are listed in attachment A on page 10.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. 3-Needle and Alaris System

2. Diluent (——————Alaris System)

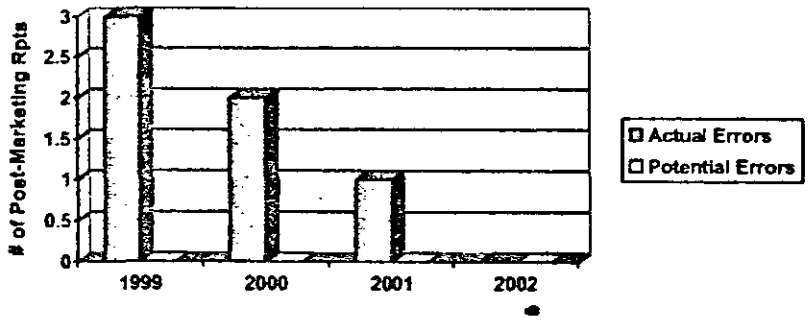
DMETS has concerns with the proposed packaging configuration for the diluent. By providing a —— ——————— there is potential risk that the diluent may be injected in error instead of the active ingredient. Post-marketing experience has demonstrated errors occurring with the inadvertent administration of diluent as a result of the diluent being provided in a ——————— Therefore, we recommend supplying the diluent in a vial ———————

3. AERS Database results

DMETS identified six (6) post-marketing reports of medication error relating to the use of Risperdal. Two reports involved medication errors between Risperdal and Requip (ropinirole). Four other medication error reports involved confusion between Risperdal and Relafen, Remeron, Rocaltrol, and carbergoline. Although Risperdal products have been available since December 1993, we identified six (6) medication error reports between Risperdal and various drug products, which were randomly received by the Agency. The number and year in which the post-marketing reports were received by the agency is shown in figure 1 on page 5. These reports did not show any specific pattern of name and packaging similarity with the drugs dispensed in error (see attachment A). Therefore, there is insufficient evidence at this time to conclude that the proprietary name, Risperdal, has significant potential for name confusion. DMETS will continue to monitor post-marketing medication errors in association with Risperdal.

Figure 1

Medication Error Reports Related to Risperdal



4. Established name

The term "Long Acting" in the established name of this product is not an officially recognized dosage form. We recommend that the Division consult Don Boring of the CDER Labeling and Nomenclature Committee (LNC) for comment on the correct nomenclature of the established name.

5. Look-alike and sound-alike names

In reviewing the name, "*Risperdal Consta*," the proprietary drug names *Concerta, Constulose, and Constilac* were identified as having the most potential for name confusion with the proposed modifier "*Consta*".

Concerta (methylphenidate extended release tablets) is a CNS stimulant and schedule II controlled substance used in the management of attention deficit hyperactivity disorder. It is available as 18 mg extended release oral tablets. The recommended starting dose is 18 mg once daily. The dose may be individually adjusted in 18 mg increments up to a maximum of 54 mg a day. Certain aspects of the proposed name raise some concern. *Concerta* and the proposed modifier *Consta* sound somewhat similar. They also look similar, both sharing the prefix "*Con*" and the suffix "*ta*". However, *Risperdal Consta* is an injectable product that will be administered once every two weeks as compared with *Concerta,* which is administered by mouth every day. In addition, the proposed modifier will be used in conjunction with the proprietary name Risperdal. The risk of selecting a wrong product from storage shelves is minimal since Risperdal *Consta* will be refrigerated and *Concerta* is stored at room temperature. Moreover, *Concerta* is a schedule II controlled substance with more prescribing and dispensing restrictions that will further decrease the risk of confusion with Risperdal *Consta.* Therefore, based on information currently available, the risk of name confusion between *Concerta* and Risperdal *Consta* is minimal.

Constulose is a hyperosmotic laxative used in the treatment of constipation. It is Alpharma's proprietary name for lactulose oral solution and is available in a concentration of 10 g lactulose per 15 mL. The product is packaged in 237 mL and 946 mL containers. Although *Constulose* and the proposed modifier *Consta*, share the prefix "*Const*", *Constulose* contains 10 letters while *Consta* contains only six. The suffix "*lose*" in *Constalose* is distinguishable from *Consta* in script and sound. In addition, the proposed modifier "*Consta*" will be used in conjunction with the proprietary name Risperdal. These

products are also different because *Constulose* is orally administered whereas Risperdal *Consta* will be administered intramuscularly. While *Constulose* is usually dosed 15 to 30 mL daily, the recommended dose of Risperdal *Consta* is 25 mg every 2 weeks. Moreover, the risk of selecting a wrong product from pharmacy storage shelves is minimal since *Risperdal Consta* will be refrigerated and *Constulose* is stored at room temperature. Therefore, the potential risk of name confusion between *Constulose* and Risperdal *Consta* appears to be minimal.

Constilac, a product manufactured by Alra Laboratories, is another proprietary name for lactulose syrup. It is used in the treatment of constipation and is available in a concentration of 10 g of lactulose per 15 mL. The product is packaged in 8 oz and 16 oz bottles, and unit dose packages of 30 mL. Although *Constilac* and the proposed modifier *Consta* share the prefix "*Const*", *Constilac* contains 9 letters while *Consta* contains only 6 letters. The suffix "*lac*" in *Constilac* is distinguishable from the modifier *Consta* in script and sound. Moreover, a prescription for Risperdal *Consta* will contain both the proprietary name and the modifier *Consta*. *Constilac* is orally administered whereas Risperdal *Consta* will be administered intramuscularly. In addition, *Constilac* is usually dosed 15 to 30 mL daily, while the recommended dose of *Risperdal Consta* is 25 mg administered every 2 weeks. Furthermore, the risk of selecting a wrong product from pharmacy storage shelves is minimal since *Risperdal Consta* will be refrigerated and *Consilac* is stored at room temperature. Based on information currently available, the potential risk of name confusion between *Constilac* and *Consta* appears to be minimal.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In reviewing the container label, carton labeling and the package insert labeling for *Risperdal Consta*, DMETS has focused on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user errors.

A. 2 mL DILUENT (Pre-filled Syringe: [redacted]

1. We note that recent revisions to the container labels and carton labeling dated March 29, 2002, did not include the diluent label. The following comments refer to the old pre-filled syringe label. The statement identifying the diluent content should be listed first so that it is more prominent. In addition, a statement should be provided identifying the pre-filled syringe contents as a diluent for *Risperdal Consta.*

2. DMETS recommends providing the diluent in a vial rather than a pre-filled syringe in order to prevent the inadvertent administration of diluent without active ingredient.

B. THE ALARIS SMARTSITE ACCESS DEVICE DOSE-PACK

1. CONTAINER LABEL

   a. Provide a statement indicating that the vial of microspheres is for single use only.

   b. Provide a statement indicating that the product is for glutteal intramuscular injection only.

   c. Express the strength as milligrams per vial for all strengths. For example, the label should read "25 mg/vial."

d. We notice that information relating to the NDC number, active ingredients and storage has been repeated on two separate panels. Delete the duplicate information.

e. Provide information indicating that the product should be reconstituted prior to use.

f. Provide space between the strength and "mg". In addition, increase the prominence of the expression "mg".

2. CARTON LABELING

a. Provide a statement indicating the strength of the reconstituted product. For example: once reconstituted each mL contains XX mg of risperidone.

b. Relocate information about the dose pack contents from the side panel (Panel 3) to the principal display panel (Panel 1).

c. See comment B1f.

d.

3. PACKAGE INSERT LABELING

Dosage and Administration

a. The statement "Do not administer intravenously" found in the second paragraph of the Dosage and Administration section should be emphasized in the Instructions for Use section.

c. The statement ' should be revised to include the meaning of the For example the above statement should read

C. THE 3-NEEDLE SYSTEM

1. CONTAINER LABELS

See statements B1a through B1e.

2. CARTON LABELING

a. See comments under B1a, B2a, and B3c.

b. The content list, storage temperature directions and the cautionary statement "keep out of the reach of children" printed in white appear illegible against the green background. Increase the font size and/or use contrasting colors to increase the prominence.

c.

d.

f. Provide a statement indicating the strength of the reconstituted product. For example: once reconstituted each mL contains XX mg of risperidone.

g. Provide space between the strength and "mg".

h. Increase the prominence of the statement "for gluteal intramuscular injection only" on panel 3.

i.

3. PACKAGE INSERT LABELING

a. The statement "Do not administer intravenously" found in the second paragraph of the dosage and Administration section should be emphasized in the Instructions for Use section.

b. See comment B3c.

IV. RECOMMENDATIONS:

1. DMETS has no objection to the use of the proposed proprietary drug name *Risperdal Consta.*

2. We recommend implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3 In addition, we recommend that the Division consult Don Boring of the CDER Labeling and Nomenclature Committee (LNC) for comment on the correct nomenclature of the established name.

We would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact the project manager, Sammie Beam, R.Ph. at 301-827-3242.

David Diwa, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety

APPEARS THIS WAY
ON ORIGINAL

ATTATCHMENT A

Table of Pertinent Medication Errors from the AERS Database

	AERS/DQRS /USP #	DATE OF EVENT/ REPORT	INTENDED PRODUCT	DISPENSED PRODUCT	ABBREVIATED NARRETIVE/OUTCOME
1	3274299-1		Relafen 500 mg	Risperdal 1 mg	A pharmacy technician filled Risperdal 1 mg instead of Relafen 500 mg for a long-term-care (LTC) patient. According the reporter, the error occurred, because the two products are located next to each other and are similar in appearance. A LTC nurse discovered the error before administration.
2	3450738-8		Remeron 30 mg	Risperdal 3 mg	A retail chain pharmacist misread the prescription for Remeron 30 mg, and filled it with Risperdal 0.3 mg instead. A physician discovered the error on after reviewing the patient's prescription vial. The patient ingested the incorrect medication and this "did not contribute to patient's mental health."
3	3508601-X		Rocaltrol 0.25 mcg	Risperdal 0.25 mg	A hospital pharmacist misinterpreted the written prescription for Rocaltrol 0.25 mcg and filled it with Risperdal 0.25 mg. A nurse discovered the error prior to administration.
4	3513894-9		Dostinex 2 mg (Carbergoline)	Risperdal 2 mg	A 68 year-old male patient with Parkinson's disease received Risperdal 2 mg instead of carbergoline 2 mg. He took Risperdal 2 mg daily from 12/27/99 to 01/01/00. He reported "feeling out of it", loss of appetite, bouts of sobbing, sweating, panic attacks, and restlessness.
5	3626379-6		Requip	Risperdal	A patient was admitted to the hospital for "altered mental status." The patient's supply of "Requip" was determined to be "Risperdal." The incorrect prescription was filled at a community pharmacy 8 days ago. The patient recovered without complication 12 to 14 hours after the admission.
6	3237479-7		Requip 0.5 mg (ropinirole)	Risperdal 0.5 mg	A 79 year-old patient received Risperdal 0.5 mg instead of ropinirole (Requip) 0.5 mg. Apparently, a doctor misspelled "ropinirole." The patient became lethargic and confused temporarily after ingesting Risperdal.

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/s/

David Diwa
5/17/02 10:57:27 AM
PHARMACIST

Alina Mahmud
5/17/02 11:00:19 AM
PHARMACIST

Carol Holquist
5/17/02 11:07:53 AM
PHARMACIST

Jerry Phillips
5/17/02 11:29:54 AM
DIRECTOR

Executive CAC
Date of Meeting: 4/23/02
Rat Carcinogenicity Study

Committee: Joseph Contrera, Ph.D., HFD-900, Acting Chair
Jeri El Hage, Ph.D., HFD-510, Alternate Member
Robin Huff, Ph.D. HFD-570, Alternate Member
Barry N. Rosloff, Ph.D., HFD-120, Supervisory Pharmacologist
Lois M. Freed, Ph.D., HFD-120, Presenting Reviewer

Author of Draft: Lois M. Freed, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #**21-346**
Drug Name: risperidone i.m. depot
Sponsor: Janssen Pharmaceutica

Rat Carcinogenicity Study: a 2-yr carcinogenicity study was conducted in Wistar rats at doses of 0, 5, and 40 mg/kg. The study included both saline and vehicle controls. The following tumors were identified by the sponsor as significant drug-related findings: (a) increase in mammary adenocarcinomas in LDF, (b) increase in pancreatic islet cell tumors (particularly adenomas) in HDM and HDF, (c) increase in pituitary adenomas and adrenomedullary pheochromocytomas in HDM, (d) increase in mammary gland tumors (particularly adenocarcinomas) in HDF, (e) decrease in ovarian polyps and absence of ovarian tumors in females, (f) "marginal" increase in solid renal corticotubular tumors in HDM, (g) a significant trend in mammary gland tumors in males (compared to SC), (h) a significant trend in adrenal pheochromocytoma in females (compared to SC). No vehicle- or drug-related findings were detected at the injection site.

Executive CAC Recommendations and Conclusions: the ExeCAC concurred with the following tumor findings: (a) mammary gland adenocarcinomas in LDF and HDF, (b) pancreatic islet cell tumors [adenoma, combined adenoma/carcinoma] in HDM and pancreatic islet cell adenomas in HDF. (c) adrenal pheochromocytomas [benign, combined benign/malignant] in HDM, (d) renal tubular tumors [adenoma, combined adenoma/adenocarcinoma] in HDM, (e) pituitary adenomas in HDM. The Committee noted that the HD may have exceeded the MTD in males, based on body weight/clinical signs data.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling