

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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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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TABLE OF CONTENTS

1 Introduction 3

2 Study RIS-USA-121 3

2.1 Objective..... 3

2.2 Study Design..... 3

2.3 Inclusion and Exclusion Criteria..... 4

2.4 Efficacy Measures and Statistical Methods..... 4

 2.4.1 Primary Efficacy Parameter - Positive and Negative Syndrome Scale (PANSS).....5

 2.4.2 Analysis of Primary Efficacy Endpoint5

 2.4.3 Secondary Efficacy Parameters and Analyses5

2.5 Results - Sponsor's Analysis..... 6

 2.5.1 Subject Disposition6

 2.5.2 Demographic and Baseline Characteristics8

 2.5.3 Sponsor's Efficacy Evaluation10

 2.5.3.1 Data Set Analyzed10

 2.5.3.2 Primary Efficacy Variable - Total PANSS Score10

 2.5.3.3 Secondary Efficacy Variables.....14

2.6 Efficacy Results - Reviewer's Analysis 16

 2.6.1 Analysis of the Primary Endpoint - Total PANSS Score.....16

 2.6.2 Analyses of Secondary Efficacy Parameters18

3 Reviewer's Conclusion 19

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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 mg 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 \leq 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 malignant 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.

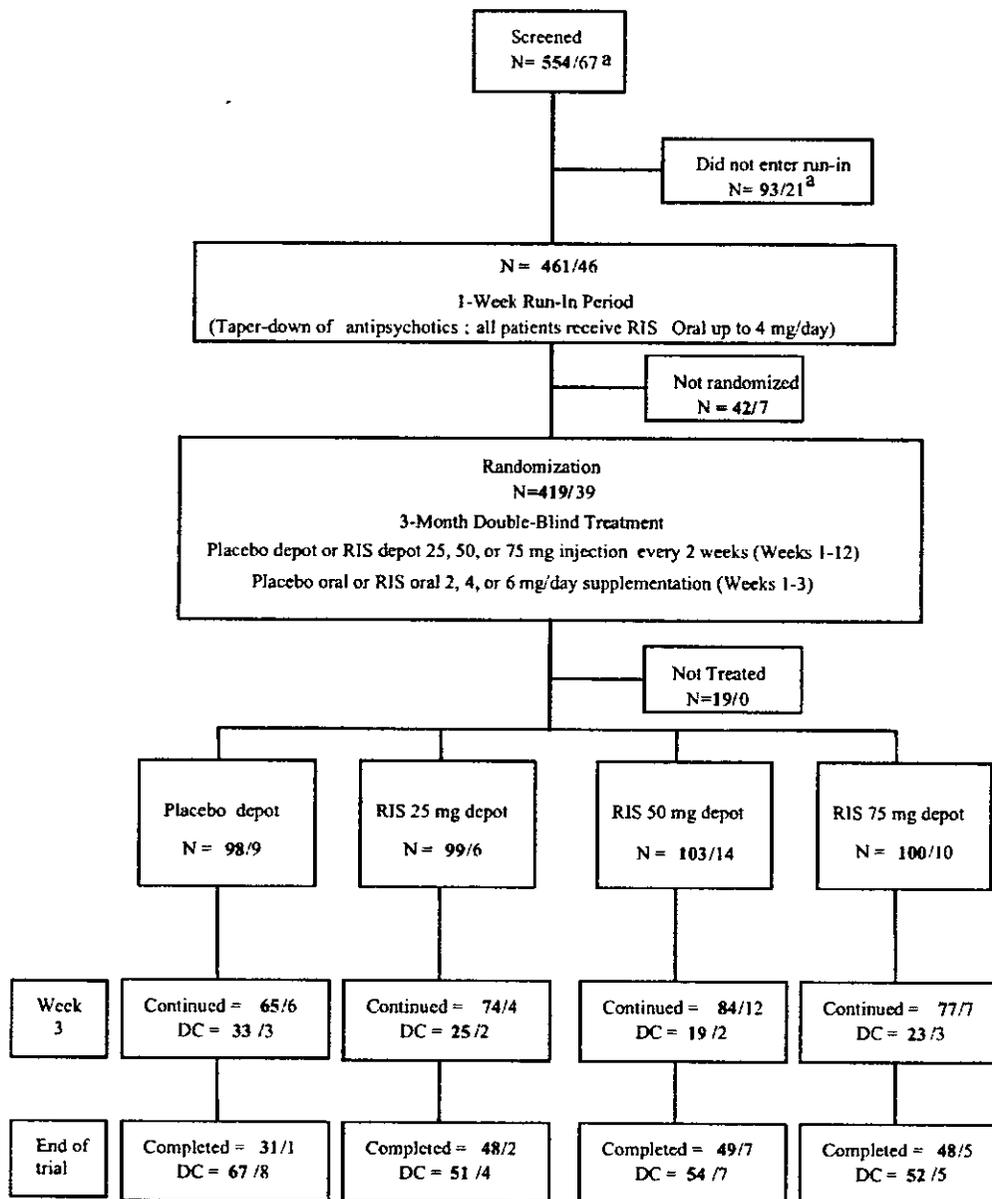
Differences between treatment groups in frequency counts of CGI and CGI-C were to be assessed via the Van-Elteren test controlling for investigator and baseline PANSS strata. In addition, the change from baseline in CGI was to be analyzed using the same method as for total PANSS.

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).

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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).

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Table 3. 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, Mean (SE); Range	n=91 22.0 (0.66) (9-42)	n=97 22.8 (0.76) (8-44)	n=100 21.4 (0.7) (7-42)	n=97 20.3 (0.63) (9-43)
Age at first hospitalization, Mean (SE); Range	n=89 24.4 (0.8) (14-47)	n=91 25.1 (0.93) (0-47)	n=94 23.3 (0.79) (8-45)	n=94 23.2 (0.91) (0-50)
Number of previous hospitalizations Median (range)	n=89 4 (0-28)	n=96 3.5 (0-99)	n=101 4 (0-50)	n=94 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 ($p \leq 0.002$).

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.

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

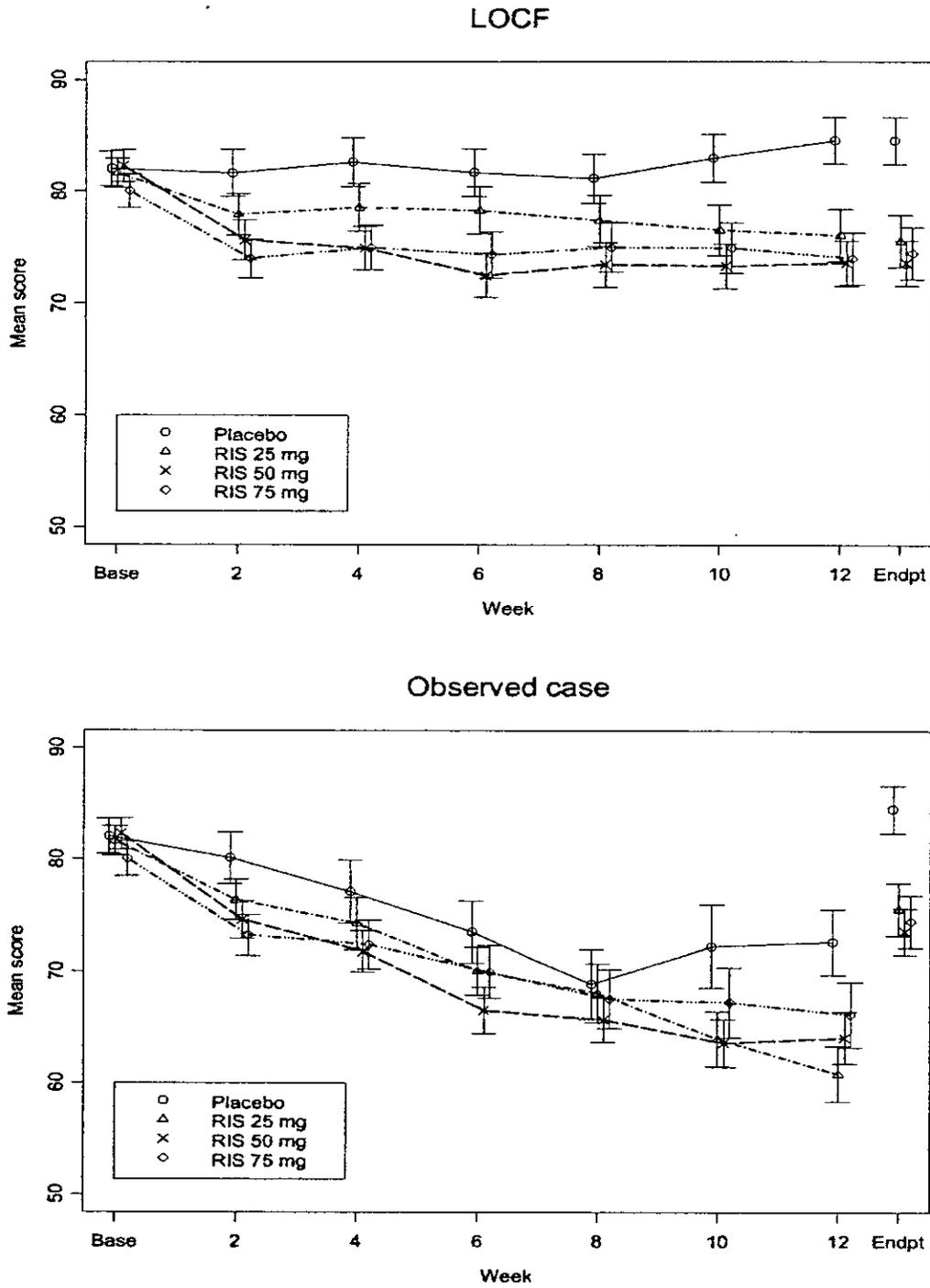
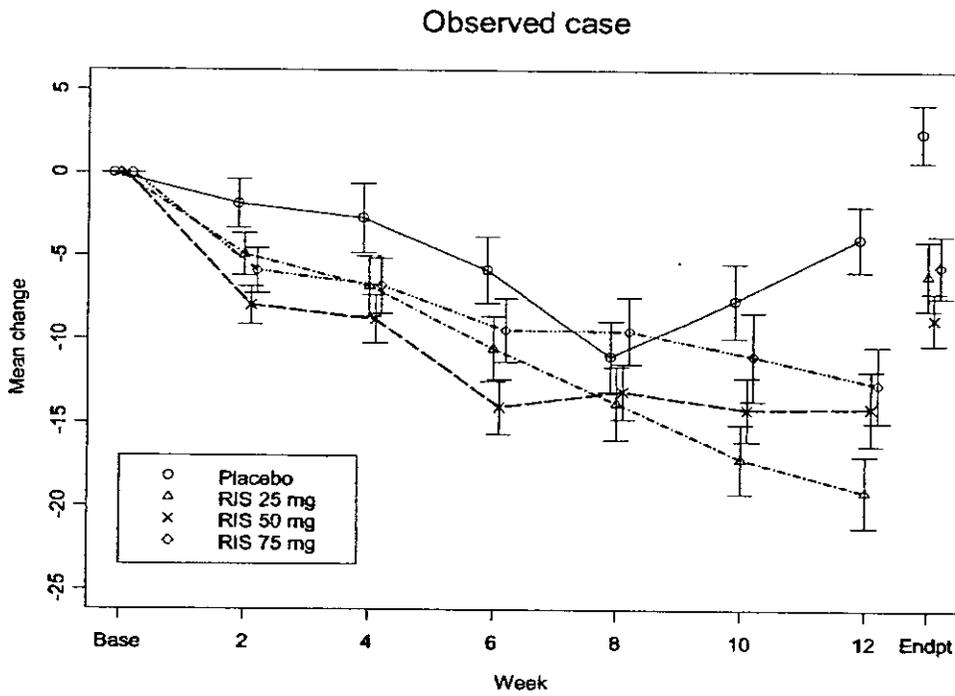
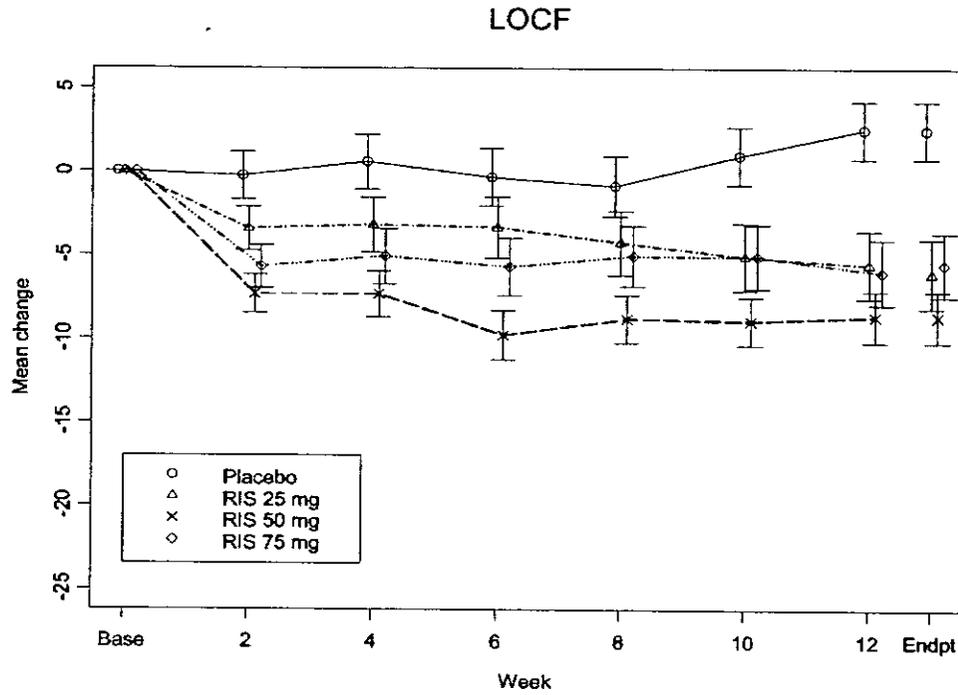


Figure 2. Total PANSS score over time - mean change (+_SE) (patients with schizophrenia)



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 ($p \leq 0.046$).

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	92	0.3 (0.65)	93	-2.2 (0.67)	98	-3.4 (0.51)	87	-2.0 (0.67)
Least squares mean		-0.2		-2.3		-3.5		-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	92	0.4 (0.44)	93	-2.8 (0.62)	98	-1.5 (0.56)	87	-1.1 (0.60)
Least squares mean		0.9		-2.4		-1.2		-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	92	0.8 (0.49)	93	-1.1 (0.59)	98	-1.3 (0.48)	87	-1.3 (0.53)
Least squares mean		0.9		-1.2		-1.5		-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	92	1.1 (0.42)	93	1.0 (0.45)	98	-0.8 (0.28)	87	0.3 (0.31)
Least squares mean		1.2		0.8		-0.6		-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	92	-0.1 (0.39)	93	-1.0 (0.34)	98	-1.6 (0.29)	87	-1.6 (0.36)
Least squares mean		0.0		-1.0		-1.5		-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)

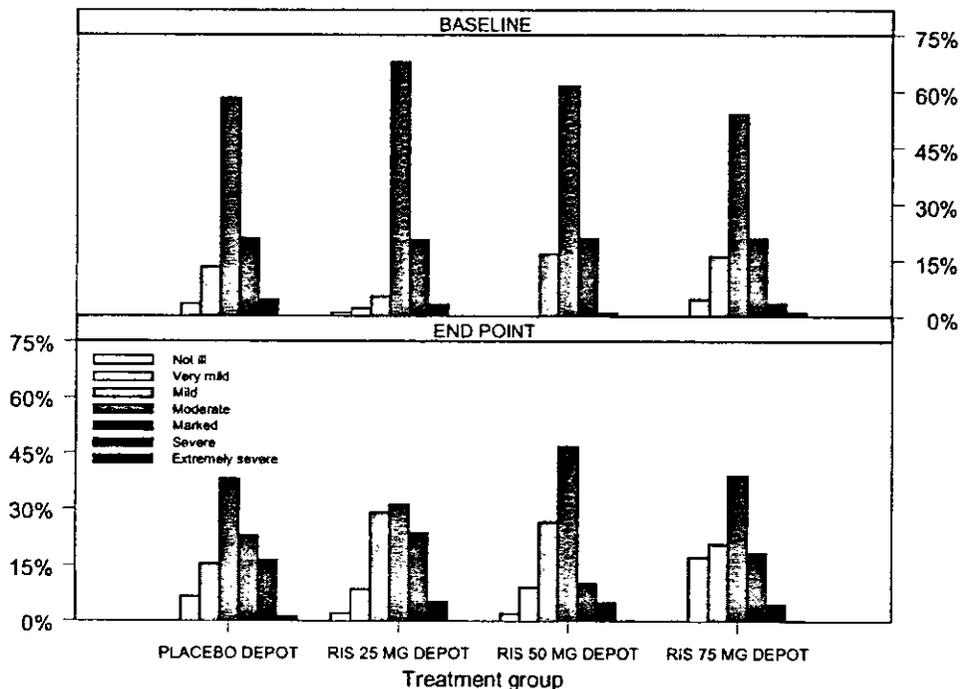


Table 7. Clinical Global Impression (CGI - mean and mean change from baseline at endpoint - LOCF analysis (patients with schizophrenia))

	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.

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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 ($p \leq 0.0001$).

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 adjustment

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 Disorganized 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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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

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Table of Contents

NDA#: 21-346	1
1.0 Note on Levels of Statistical Significance	3
2.0 Rat Study (Experiment Number 4729)	3
2.1 Introduction.....	3
2.2 Sponsor's Results.....	3
2.3 Reviewer's Results.....	5
2.3.1 Mortality and Tumor Findings for Female Rats with Saline Control.....	5
2.3.2 Mortality and Tumor Findings for Male Rats with Saline Control	6
2.3.3 Mortality and Tumor Findings for Female Rats with Vehicle Control	6
2.3.4 Mortality and Tumor Findings for Male Rats with Vehicle Control.....	6
2.3.5 Difference between the Two Control Groups	7
3.0 Summary	7

Table of Tables

Table 1: Sponsor's Significant Tumor Findings among Female Rats	4
Table 2: Sponsor's Significant Tumor Findings among Male Rats.....	4
Table 3: Reviewer's Significant Tumor Findings among Female Rats	8
Table 4: Reviewer's Significant Tumor Findings among Male Rats.....	8
Table 5: Number of Deaths per Time Interval, Female Rats with Saline Control	9
Table 6: Mortality Trend for Female Rats, Saline Control	10
Table 7: Tumor Trend among Female Rats, Saline Control	12
Table 8: Combined Tumors for Female Rats with Saline Control.....	13
Table 9: Number of Deaths per Time Interval, Male Rats with Saline Control.....	14
Table 10: Mortality Trend for Male Rats, Saline Control.....	15
Table 11: Tumor Trend among Male Rats, Saline Control.....	16
Table 12: Combined Tumors for Male Rats with Saline Control	17
Table 13: Number of Deaths per Time Interval, Female Rats with Vehicle Control.....	18
Table 14: Mortality Trend for Female Rats, Vehicle Control.....	19
Table 15: Tumor Trend for Female Rats, Vehicle Control.....	20
Table 16: Combined Tumors for Female Rats with Vehicle Control	22
Table 17: Number of Deaths per Time Interval, Male Rats with Vehicle Control	23
Table 18: Mortality Trend for Male Rats, Vehicle Control	23
Table 19: Tumor Trend for Male Rats, Vehicle Control.....	25
Table 20: Combined Tumors for Male Rats with Vehicle Control.....	26

Table of Figures

Figure 1: Kaplan-Meier Curves for Female Rats with Saline Control.....	11
Figure 2: Kaplan-Meier Curves for Male Rats with Saline Control	15
Figure 3: Kaplan-Meier Curves for Female Rats with Vehicle Control	19
Figure 4: Kaplan-Meier Curves for Male Rats with Vehicle Control.....	24

1.0 Note on Levels of Statistical Significance

Trends in tumor incidence rates are tested for statistical significance at $\alpha=0.025$ 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 $\alpha=0.05$ 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

Risperidone 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 NACI 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

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Table 6: Mortality Trend for Female Rats, Saline Control

Dose-Mortality Trend Tests

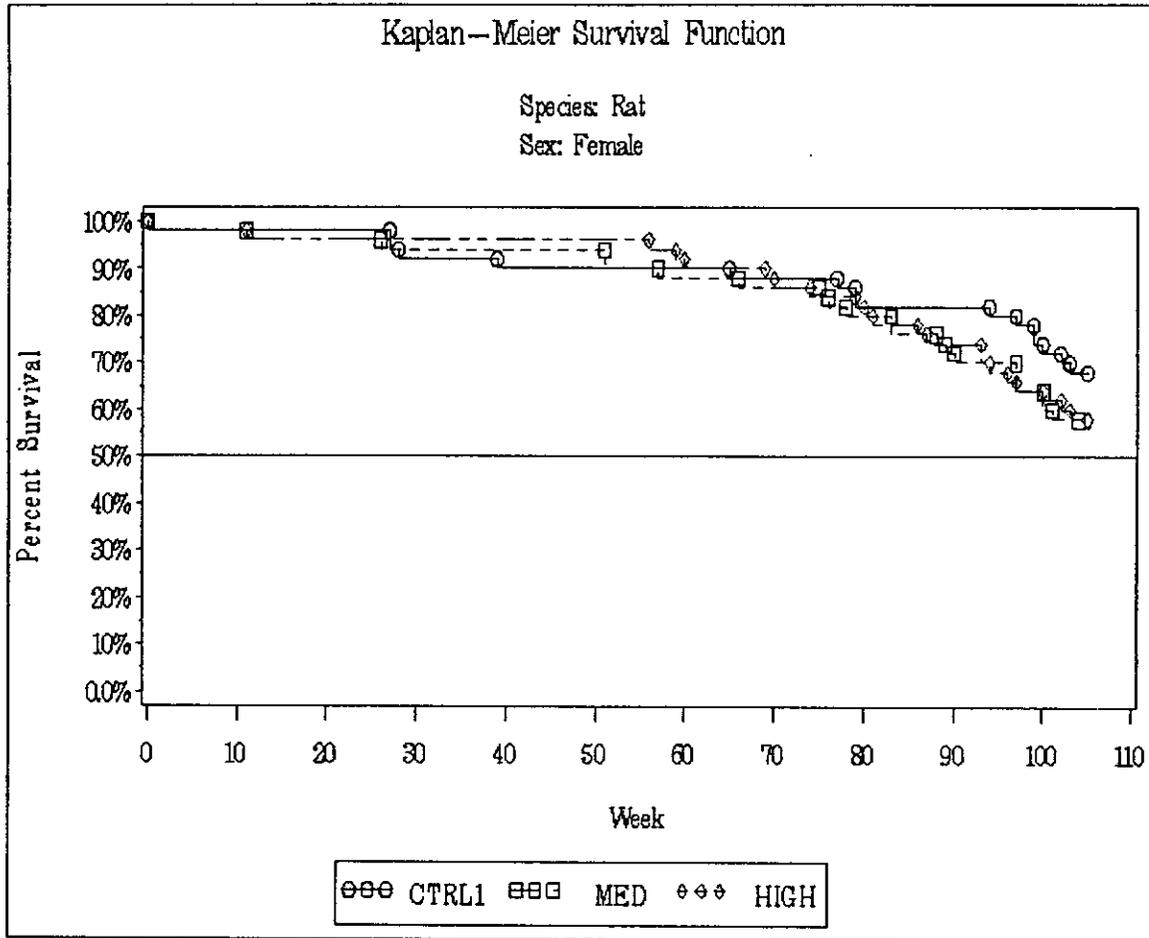
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

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

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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, follicular	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 tumor	G44	6%	3	0	0	IN	1.0000	0.9230
Ovaries	G31	Sex cord stromal tumor,	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)	CTR LI	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

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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	6.12	0.0774

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

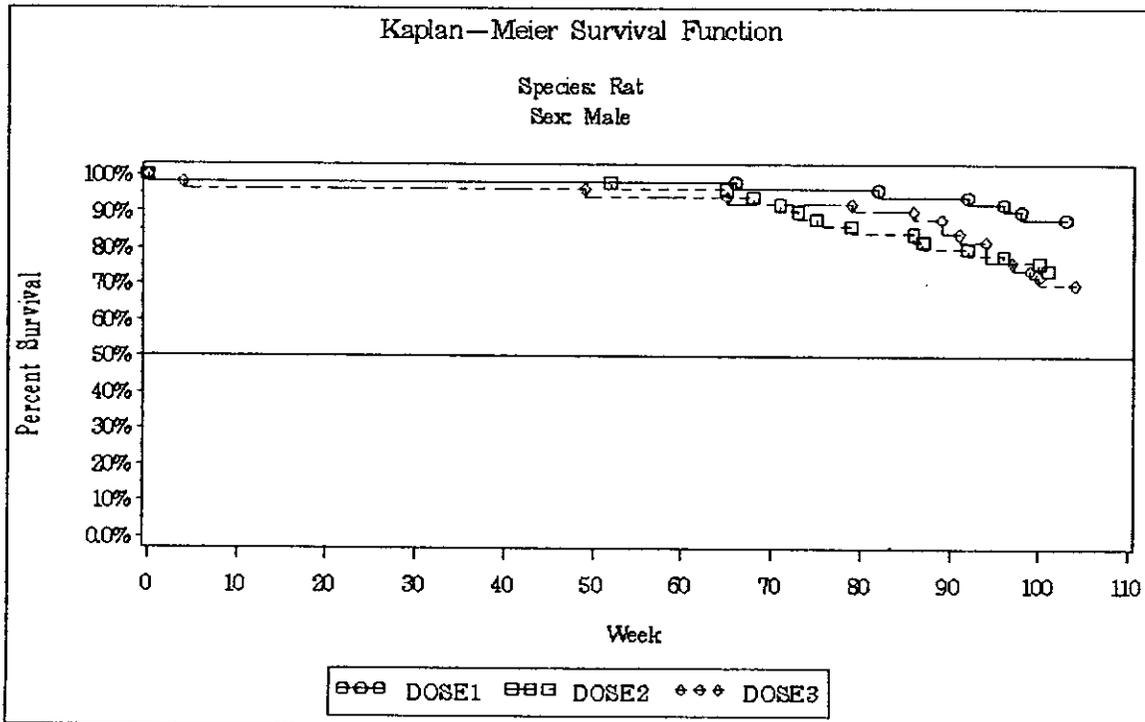


Table 11: Tumor Trend among Male Rats, Saline Control

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

Week	Treatment Group			
	CTRL2	MED	HIGH	Total
	N	N	N	N
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

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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

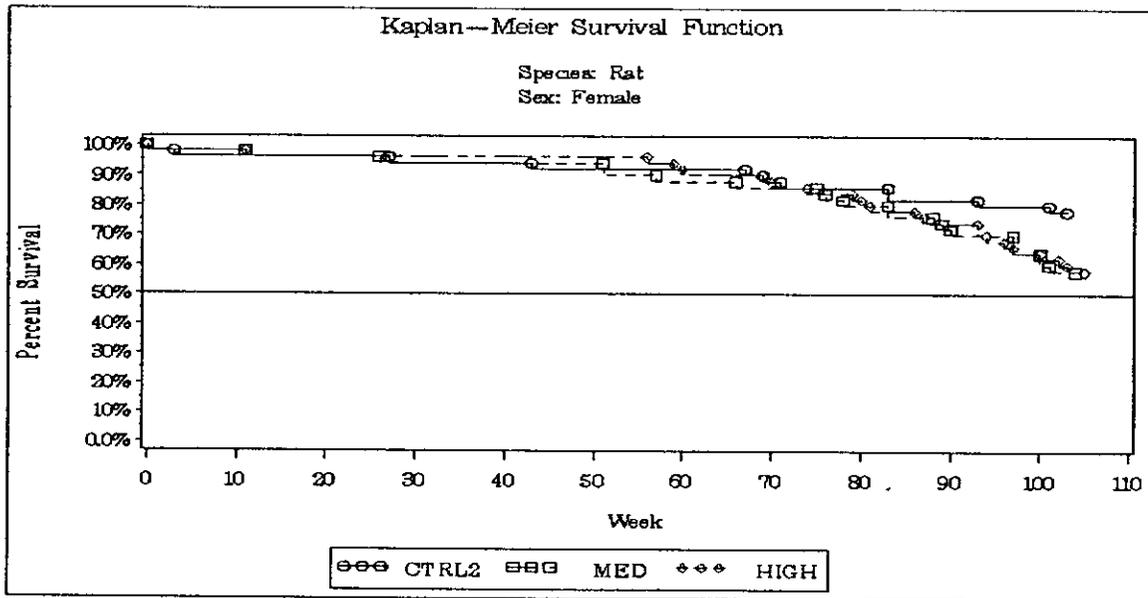


Table 15: Tumor Trend for Female Rats, Vehicle Control

Test for Dose-Tumor Positive Linear Trend

Source: Female Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTR L2	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	10%	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	10%	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	10%	0	1	0	IN	0.8000	0.7963
Ovaries	G31	Adenoma, tubulostromal	452	10%	0	1	0	IN	0.5979	0.6960
Ovaries	G31	Sertoli cell tumor, benign	G21	2%	1	0	0	IN	1.0000	0.7879
Ovaries	G31	Granulosa-theca cell tumor	G44	2%	1	0	0	IN	1.0000	0.7879
Ovaries	G31	Fibroma	M21	10%	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	10%	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 lymph	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 lymph	H154	2%	1	2	0	IN	0.7923	0.8488
Skin	I1	Keratoacanthoma	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

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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, follicular	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

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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
79-94	3	3	5	11
92-104	4	4	7	15
105-106	41	37	35	113
Total	50	50	50	150

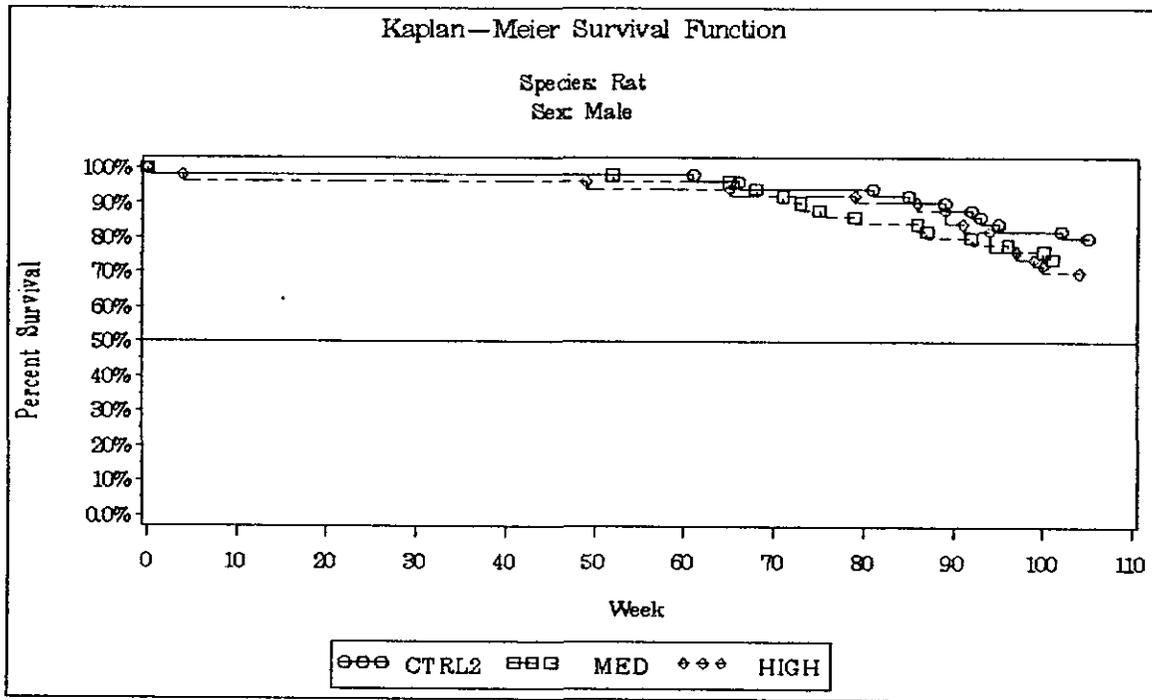
Table 18: Mortality Trend for Male Rats, Vehicle Control

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, follicular	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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