CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20658

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA:	**20-658**
Sponsor:	**SmithKline Beecham**
Drug:	**Ropinirole (Requip) Tablets**
Indication:	**Symptomatic treatment of Parkinson's disease**
Original Receipt Date:	**12/29/95**
Medical Reviewer:	**Janeth Rouzer-Kammeyer, M.D.**
Statistical Reviewer:	**Kun Jin, Ph.D.**

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Summary

The clinical trial program has been designed to provide data from controlled trials to establish the efficacy of ropinirole as symptomatic treatment of Parkinson's disease. The efficacy of ropinirole has been examined as early primary therapy for Parkinson's disease in patients not treated with l-dopa, and as adjunct therapy in combination with l-dopa for the treatment of more advanced Parkinson's disease. A total of 2106 patients have been enrolled in therapeutic studies, 1364 have been treated with ropinirole, 298 with placebo and 444 with active comparators (bromocriptine or l-dopa). The program included:

- -two placebo controlled studies in early therapy (Study-032 and Study-054)
- -one comparative study against l-dopa in early therapy (Study-056)
- -one comparative study against bromocriptine in early therapy (Study-053)
- -six placebo controlled studies in adjunct therapy (Study-030,Study-034, Study-36, Study-038, Study-040 and Study-044)
- -one comparative study against bromocriptine in adjunct therapy (Study-043).

Monotherapy Studies

The Studies 032 and 054 were double-blind, placebo controlled, randomized studies for evaluating efficacy of ropinirole as early primary therapy for Parkinson's disease in patients not treated with l-dopa. The two are summarized in Table I.

The two active controlled studies were designed primarily for evaluation of the safety profile of ropinirole. The presented six-month interim analyses for efficacy provided no conclusive evidence for the efficacy of ropinirole in comparison to the comparators (l-dopa or bromocriptine). This reviewer sees little relevance of the results from these two active controlled studies to the results and conclusions from the two placebo controlled studies. Therefore, these two active controlled studies are not reported in this review.

Table I

SUMMARY OF CLINICAL PROGRAM
Early Therapy Studies

Protocol	Country/ Centers	Date started /status	Objectives	Study design	Efficacy Measures	Treatment	Dose (mg)	Duration	N
032	Belgium/1 France/1 Italy/1 Holland/1 UK/4 S Africa/1	25 JUN 90 Completed	Efficacy of ropinirole versus placebo as monotherapy in Parkinson's disease	Double-blind, placebo controlled, parallel group	UPDRS, CGE	Ropinirole Placebo Ratio 2:1	Titrated 0.5 to 5.0 bd	12 weeks	63
054	US/25	27 AUG 92 Completed	A study of oral doses of ropinirole for 6 months treatment as early therapy in patients not receiving dopaminergic therapy	Double-blind, placebo-controlled, parallel group study	UPDRS, CGE, l-dopa rescue	Ropinirole Placebo Ratio 1:1	Titrated 0.25 -8.0 tid	6 months	240

This reviewer has reanalyzed the datasets for Studies 032 and 054 provided by the sponsor. The results are reported separately in the following sections. This reviewer agrees with the sponsor's conclusion that ropinirole is significantly more effective than placebo in terms of reduction in UPDRS total motor scores. The improvement in UPDRS total motor scores in ropinirole patients was estimated as more than 20% reduction in Study 054.

This reviewer also investigated a possible interaction of ropinirole and selegiline reported by sponsor. For Study 054, six patients out of 240 were identified as possible "outliers" who appeared to be the main source of interaction. A bootstrap (or empirical) evaluation was conducted to show that these six outliers should not be included in the study of interaction of ropinirole and selegiline. For Study 032, bootstrap procedures were conducted to evaluate the subgroup analyses concerning several factors, including selegiline. There was no statistically significant interaction of ropinirole and selegiline to be found. This reviewer sees no credible evidence for existence of interaction of ropinirole and selegiline in these two studies. With excessive variations apparently existed in the datasets, this reviewer doubts whether the present studies could adequately address this issue.

Adjunct Therapy Studies

Studies 036 and 038 had small sample sizes, 29 and 36, respectively, and provided no results to contradict Studies 030, 034 and 044. The active controlled Study 043 was designed primarily for evaluation of a safety profile of ropinirole and provided little evidence for evaluating the efficacy of adjunct therapy. The Studies 036, 038 and 043 are omitted from this report.

Table II summarizes Studies 030, 034, 040 and 044. Among these studies, Study 044, with largest sample size and longest duration of treatment, was submitted by sponsor as the one showing a statistically significant treatment effect of ropinirole compared to placebo.

This reviewer has provided a detailed report for Study 044 in the following sections. This reviewer disagrees with the sponsor's

Table II

SUMMARY OF CLINICAL PROGRAM
Adjunct Therapy Studies

Protocol	Country/ Centers	Date started /status	Objectives	Study design	Efficacy Measures	Treatment	Dose (mg)	Duration	N
030	UK/1 France/1	26 MAR 90 Completed	Efficacy of ropinirole versus placebo as adjunct therapy in Parkinsonian patients not optimally controlled on l-dopa	Double blind placebo controlled parallel group	Reduction in 'off' time UPDRS CGE	Ropinirole Placebo Ratio 1:1	Titrated 0.5 to 4.0 bd	12 weeks	46
034	UK/6 Israel/2	28 AUG 90 Completed	Efficacy (l-dopa sparing effect) of ropinirole vs placebo as adjunct therapy in Parkinsonian patients not optimally controlled on l-dopa	Double blind placebo controlled parallel group	L dopa reduction Reduction in 'off' time UPDRS CGE	Ropinirole Placebo Ratio 2:1	Titrated 0.5 to 5.0 bd	12 weeks	68
044	US/16	24 SEP 92 Completed	A study of oral doses of ropinirole for 6 months treatment as adjunct therapy in Parkinsonian patients not optimally controlled on l-dopa (DCI)	Double blind placebo controlled parallel group	l-dopa reduction Reduction in 'off' time UPDRS CGE	Ropinirole Placebo Ratio 2:1	Titrated 0.25 to 8 tid	6 months	149
040	US/15	15 SEP 91 Completed	Ropinirole 0.5 mg b.i.d or 2.0 mg b.i.d versus placebo as adjunct to l-dopa in the treatment of Parkinson's disease	Double blind placebo controlled parallel group	Reduction in 'off' time UPDRS CGE	Ropinirole Placebo	0.5 bd or 1.0 bd or 2.0 bd	6 weeks	125

use of the modified primary efficacy parameter, a responder defined as at least 20% reduction in l-dopa dose and 20% reduction in awake time spent "off", and its interpretation. After reviewing the analyses of the original protocol primary parameter, percentage reduction in l-dopa use, and the other secondary parameters. This reviewer thinks that this study shows that there is a statistically significant reduction in l-dopa redaction in ropinirole patient group. There is no evidence found that the patients in ropinirole group have worsened clinical outcomes compared with the placebo patients. There is a greater, although non-statistically significant, reduction in percentage awake time spent "off" in ropinirole patients. There is a statistically significant improvement in CGE measurement in ropinirole patients. There is no difference found in UPDRS total motor scores between ropinirole and placebo groups.

These conclusions are supported by Studies 030 and 034 as well. In Study 030, the primary efficacy parameter was the responder rate, defined as at least 30% reduction in awake time spent "off". The ITT-LOCF analysis showed there was a 65.2% responder rate in ropinirole group vs. 39.1% in placebo group. The result is in favor of ropinirole, although statistically non-significant. The analysis of the secondary endpoints showed that there were significantly more patients improving from baseline in Clinician's Global Evaluation, 78.% in ropinirole vs. 34.8% in placebo. The mean percentage changes in UPDRS total motor score in patients with same pre-dose state were -36.6% in ropinirole group and -15.1% in placebo group. It is still in favor of ropinirole, but statistically non-significant.

In Study 034, the primary efficacy parameter was the reduction in l-dopa use. The ITT-LOCF analysis showed that there was a 48.8% responder rate (at least 20% reduction in l-dopa) in ropinirole group compared with 36.4% in placebo group. There was no statistical difference between the two groups. The analyses of secondary parameters showed that 66.7% of ropinirole patients improved from baseline in Clinician's Global Evaluation compared to 54.5% in placebo group. The mean percentage changes in UPDRS total motor score in patients with same pre-dose state were -10.6% in ropinirole group and -27.4% in placebo group. The mean percentage reductions in l-dopa were -22% in ropinirole group and -2.53% in placebo group. All of the results are non statistically significant, but generally in favor of ropinirole.

Study 040 was the only fixed-dose parallel group trial in this program. The primary efficacy parameter was the reduction in the proportion of awake time spent "off". The statistical analyses of the primary and secondary efficacy parameters are summarized in the following table

	Treatment				
Primary Efficacy Parameter	**Placebo**	**1 mg**	**2 mg**	**4 mg**	**P-value**
% patients with 20% reduction in awake time "off"	33.3%	28.6%	36.7%	50.0%	0.392
Secondary Parameters					
mean % changes in total UPDRS motor scores	-20.9	-2.6	15.2	-20.7	0.311
% patients CGE improvement	53.3%	28.6	32.3	65.5	NS

These result do not contradict the conclusion reached in Study 044.

Conclusion

There is strong evidence from studies 054 and 032 that ropinirole provides efficacious dopaminergic therapy for patients with early symptoms of Parkinson's disease. When assessing improvement in motor score, ropinirole was statistically significantly superior to placebo in both studies. In Study 054 the ITT-LOCF analysis shows that there was an average improvement of 23.89% reduction in total motor scores in the ropinirole group, compared with -1.05% in placebo group, the p-value for testing difference was less than 0.001. In Study 032, the ITT-LOCF analysis shows that there was an average improvement of 43.37% reduction in total motor scores in the ropinirole group, compared with 20.99 in placebo group, the p-value for testing difference was less than 0.05.

In adjunct therapy study 044 significantly more patients on ropinirole achieved a 20% reduction of l-dopa dose compared with placebo. The treatment difference observed in ITT-LOCF analysis was statistically significant with an odds ratio of 6.059 (95% CI of 2.492, 14.730). There is no evidence found that the patients in ropinirole group had worsened clinical outcomes compared with the placebo group. Studies 030 and 034 support the findings in study 044.

In summary, ropinirole improved the motor function in patients with early disease. In patients with more advanced disease, ropinirole permitted a significantly greater reduction in l-dopa dose.

US Monotherapy Study 054*

1. Introduction

This study was designed to investigate the anti-Parkinson efficacy and safety of ropinirole in patients with early Parkinson's disease. Patients who had not previously received dopaminergic therapy for more than 6 weeks were stratified according to concomitant use of selegiline. A total of 241 patients was randomized at 25 study centers geographically distributed throughout the United States during a period from August 1992 to September 1994.

2. Objectives

The primary objective of this study was to evaluate the efficacy of ropinirole in early Parkinsonian patients not receiving dopaminergic therapy. The secondary objectives were: to evaluate the safety profile of ropinirole in early Parkinsonian patients; to assess the pharmacokinetic profile of ropinirole in early Parkinson's disease; and to assess the number of patients who required l-dopa rescue and the time to l-dopa rescue.

3. Study Design

This was a randomized multicenter, double-blind, placebo controlled assessment of six month's treatment in early Parkinsonian patients not receiving dopaminergic therapy. Patients were randomized in a 1:1 fashion to ropinirole or placebo. Randomization was stratified within each center according to concomitant use of selegiline. Patients had to remain on a stable dose of selegiline throughout the study. All patients started on the first dose level (0.25 mg t.i.d.) of study medication and received weekly increases until an optimal dose was achieved. Patients could then be maintained on the optimal dose level for the remainder of the study.

Study visits were scheduled at weekly intervals for the first month, every other week for the next 2 months and at monthly intervals for the remaining 3 months. At each study visit, vital signs, adverse experience monitoring and CGI were assessed. The UPDRS was performed at the week 4, week 12 and week 24 visits.

*In this report, the reviewer's analyses are in *Italic* font.

Patients who required additional symptomatic treatment during the study could be "rescued" with open-label l-dopa. The motor examination of the UPDRS was to be performed prior to the initiation of l-dopa rescue. Observations collected after l-dopa rescue were not used in the data analysis.

4 Patient Population

A total of 241 patients were randomized to study medication; 116 (48.1%) in the ropinirole group and 125 (51.9%) in the placebo group. A total of 58 of 116 patients (50.0%) in the ropinirole group were stratified to the selegiline group. Sixty-one (61) of 125 patients (48.8%) in the placebo group were stratified to the selegiline group. The following table shows the demographic characteristics for the Intention to Treat Population by selegiline strata.

	Ropinirole Non-Selegiline (n=58)		Placebo Non-Selegiline (n=64)		Ropinirole Selegiline (n=58)		Placebo Selegiline (n=61)	
	N	(%)	N	(%)	N	(%)	N	(%)
Sex								
Male	34	(58.6)	35	(54.7)	36	(62.1)	45	(73.8)
Female	24	(41.4)	29	(45.3)	22	(37.9)	16	(26.2)
Age (years)								
Mean SD	64.9+9.8		65.9+10.3		59.1+10.6		61.1+10.6	
Min, Max								
Race								
Black	4	(6.9)	2	(3.1)	0	(0.0)	1	(1.6)
White	52	(89.7)	60	(93.8)	58	(100)	59	(96.7)
Other	2	(3.5)	2	(3.1)	0	(0.0)	1	(1.6)

5. Efficacy Variables and Data Sets

The primary efficacy variable in this study was improvement in motor function as measured by the motor examination of the Unified Parkinson's Disease Rating Scale (UPDRS). The mean percentage reduction from the baseline in motor scores was the protocol defined primary analysis.

Secondary efficacy variables for this study were: the number of responders in each treatment group, defined as at least a 30% reduction from the baseline in the total motor score of the UPDRS; patient improvement, defined as a score of 1 or 2 on the global improvement item of the Clinical Global Impression; and the number of patients who required l-dopa rescue and time to

l-dopa rescue. The number of patients with an insufficient therapeutic response and time to insufficient response were also assessed.

Two patient populations were evaluated for the efficacy analysis: intention to treat population and the efficacy evaluable population. The primary inferences concerning the efficacy of ropinirole were made using the last observation carried forward data set (LOCF) of the intention to treat population. Two additional data sets were considered to ensure the robustness of the results: a) an LOCF data set using the latest time point where at least 70% of the patients in a study population remained in the study (defined as the 70% endpoint). For the analysis within each selegiline stratum, the 70% endpoint was calculated separately in each stratum; b) an observed cases (OC) data set at 6 months (24 weeks). For patients rescued with l-dopa prior to the 24 week observation, efficacy assessments made at this visit were censored from the analysis.

6. Dropout and Missing Data

To assess any potential bias in results caused by patients withdrawing from the study, the week 24 completers and LOCF endpoints in the ITT population were investigated for the mean percentage reduction in total motor scores of the UPDRS and the number of responders. The relative performance of drop-outs over time was also investigated for the number of patients with clinical improvement. There was little improvement in motor score for patients who withdrew prematurely.

The following procedure was employed in the event of missing item scores. For those items which were independent of the side of the patient (items 18, 19, 20-face, lips, chin, 22-neck, 27-31), the mean of all the scores across patients was calculated and substituted for the missing item score. For those items measured on the left side of the patient (20-26, excluding 20-face, lips and chin and 22-neck), the mean of the scores for the items on the left side only was used. For items measured on the right side, the mean of the non-missing right side scores was substituted for any missing items. This procedure was used only if 10% or fewer of the item scores were missing, i.e. only if 2 or fewer items were missing.

7. Primary Efficacy Analysis

7.1 Sponsor Analysis

The analysis of the mean percentage change from baseline in the UPDRS motor score was defined in the protocol as the primary efficacy analysis. The mean percentage change was defined as 100*(endpoint total motor score - baseline)/baseline. In the protocol, the mean percentage change from baseline was to be analyzed as a generalized linear model with treatment, selegiline and center effects. The mean percentage change from baseline in the UPDRS motor score for the ITT population is presented in the following table. There was a larger mean percentage change in the UPDRS motor score in the ropinirole treatment group compared to placebo at the week 4, week 12 and week 24 assessments.

Table 7.1.1

Mean SD
(n)

	Week 4	Week 12	Week 24	LOCF
Ropinirole	-6.3 37.6 (106)	-25.6 35.6 (93)	-29.6 45.6 (68)	-21.5 45.4 (107)
Placebo	-3.7 37.5 (114)	-3.5 37.2 (101)	4.7 55.2 (70)	3.57 47.8 (118)

The following Table 7.1.2 revealed a significant treatment by selegiline strata interaction which suggested that there was a difference in the treatment effect within strata.

Table 7.1.2
Mean Percent Change for ITT

	Selegiline	Non-selegiline
Ropinirole	-28.2	-14.7
Placebo	11.5	-4.1.

The mean baseline UPDRS motor scores for the intention to treat population were comparable between the two treatment groups;

17.9± 8.8 in the ropinirole treatment group and 17.7±8.1 in the placebo group. Based on these results, the placebo treatment group concomitantly treated with selegiline experienced a worsening of motor impairment during the study. In contrast, the placebo treatment group not concomitantly treated with selegiline experienced a slight improvement in motor function.

The sponsor stated that there was some evidence of violations in normality assumptions and they proposed an alternative analysis approach. The sponsor informed the FDA on this matter at the pre-NDA meeting on April 25, 1995. The sponsor's plots of motor score confirmed that there was a strong relationship between endpoint and baseline, that regression lines could be fit through the origin, and that an analysis of the endpoint total motor score adjusted for baseline motor score would be more appropriate. UPDRS motor score ranges from 0-108, where 0 is healthy. On the assumption that treatment effect will be proportional to baseline score, models fitted as regression lines through the origin will provide a clinically relevant interpretation of the data. A regression coefficient of 1.0 would indicate there was no change in motor score during the study. The chosen method was to fit the ratio of total motor score at endpoint (y) to total motor score at baseline (x), weighted by the baseline squared. The model was fit with effects for treatment, center, selegiline, sex, and treatment by sex interaction.

This model provided the following regression coefficients for the LOCF ITT data set:

Table 7.1.3

	Estimate	SE (Estimate)
Ropinirole	0.756	0.0309
Placebo	1.026	0.0295

This represents an average improvement of 24% in the ropinirole group. The difference between ropinirole and placebo was statistically significant ($p<0.001$). The model fitted with the protocol spedified effects treatment, center and selegiline yielded the similar results. In addition, regression coefficients were obtained for each treatment group and selegiline stratum constrained such that the difference between treatments was constant across strata:

Table 7.1.4

	Estimate	SE (Estimate)
Ropinirole - Selegiline	0.762	0.0387
Ropinirole - Non-Selegiline	0.749	0.0359
Placebo - Selegiline	1.032	0.0361
Placebo - Non-Selegiline	1.019	0.0363

This analysis also indicated that there was no significant difference in the treatment group regression lines in the separate selegiline strata.

The model was also fitted to the 70% endpoint and the week 24 OC. All estimates are similar to those obtained in the ITT LOCF data. The magnitude of the ropinirole response in the week 24 OC data set was larger with an average improvement of 34% compared to 24% in the ITT LOCF data set. The results in the efficacy evaluable population were also similar to the ITT population.

Table 7.1.5

Data set	Treatment Group	Coefficient (Estimate)	SE (Estimate)	Percentage Improvement
ITT 70% Endpoint	Ropinirole	0.745	0.0289	25.5%
	Placebo	0.964	0.0276	3.6%
ITT Week 24 OC	Ropinirole	0.658	0.0369	34.2%
	Placebo	1.008	0.0387	-0.8%*
Efficacy Eval. (LOCF)	Ropinirole	0.727	0.0342	27.3%
	Placebo	1.009	0.0329	0.9%

*Negative values indicate a worsening of motor function

There was a statistically significant treatment by sex interaction.

7.2 **Reviewer Analysis and Comments:**

The first question this reviewer raised was Is Table 7.1.1 an accurate picture? This question arose due to a concern about the way the missing data was handled. First, imputing missing items by mean of observed items might not be appropriate since this method ignored entirely the trend in individual patient data. Second, the imputation was only done for the observations with two or fewer missing items, and the

observations with more than two missing items were deleted from analysis. Considering there were 27 items of UPDRS motor score, this approach could yield a substantial loss of information.

The reviewer has proposed the following approach to assess the impact of missing data. We can compute the percentage changes in Table 7.1.1 by using only observed, partial motor scores without imputing missing items. This yielded the following table similar to Table 7.1.1

Table 7.2.1

Mean SD
(n)

	Week 4	Week 12	Week 24	Endpoint
Ropinirole	-7.26 36.4 (107)	-27.65 34.9 (95)	-32.11 44.5 (72)	-21.97 44.4 (107)
Placebo	-3.87 37.1 (118)	-4.83 36.9 (103)	-0.18 53.6 (73)	3.67 47.8 (118)

Table 7.2.1 had more patients than Table 7.1.1. All other missing patients were accountable from the known censored patients. There was no substantial difference between Table 7.1.1 and 7.2.1. We concluded that there was no evidence for missing data bias. The following analysis was done with the sponsor's data sets for which some items were imputed.

What happened to the "selegiline interaction?" This reviewer was particularly concerned about the apparent treatment and selegiline interaction that appeared in Table 7.1.2. The sponsor stated that the alternative approach was proposed because of the violation of normality assumption in the protocol specified analysis. They did not, however, show that the alternative approach provided a "better fit" for the data. The real reason for the alternative method, this reviewer thinks, was that the alternative method made the interaction "disappear" by their model. However, if the interaction had existed, it would be hard to believe that the interaction could go away by a different "modeling" method. Understanding the sponsor's SAS programs was difficult for this reviewer. This reviewer simply reanalyzed the data set.

First, the sponsor's model was fit. To see how well the model fit the data, the Q-Q plot was employed in which the quantiles of the residuals are plotted against normal quantiles. If the model is fit adequately, the points should be around the 45° diagonal line. From Figure 54-1 in appendix A54-1, it was clear that the model did not fit the data adequately. It appeared that there were six outliers that looked problematic. After removing these six outliers, the model was fitted and the Q-Q plot was drawn again (Figure 54-2). It appeared that the model fit very well. The table similar to Table 7.1.2 after removing the outliers was then

Table 7.2.2
Mean Percent Change for ITT
(after removing outliers)

	Selegiline	Non-selegiline
Ropinirole	-28.2	-23.3
Placebo	2.1	-4.1

It looks like the interaction no longer exists after the outliers were removed. The brief profiles of these six patients were as follows:

Table 7.2.3

ID	Treatment	Sex	Seleg.	Centre	Age	Hoehn& Yahr	% Change in Total Motor
054.002.00029	Ropinirole	Male	No	2	69	II.5	94.7
054.002.00209	Ropinirole	Male	No	2	80	I	160.7
054.023.00042	Ropinirole	Male	No	23	64	I	133.3
054.002.00032	Placebo	Male	Yes	2	63	I.5	122.2
054.002.00280	Placebo	Male	Yes	2	38	I	180.0
054.013.00071	Placebo	Male	Yes	13	68	II.5	250.0

Among these six patients, four were from Center 2. The finding was communicated to the medical officer, but nothing specific was found in the case reports.

<u>Were they really outliers?</u> How could we determine whether these six patients were indeed "outliers"? There is no standard answer to this problem, but we offered an "educated guess." What we could ask was "Is the result obtained by removing these six

Sponsor's Model

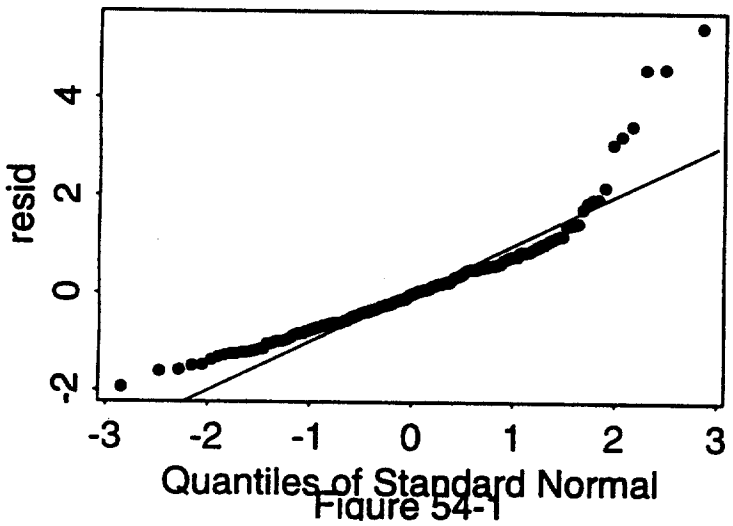


Figure 54-1

Remove Outliers

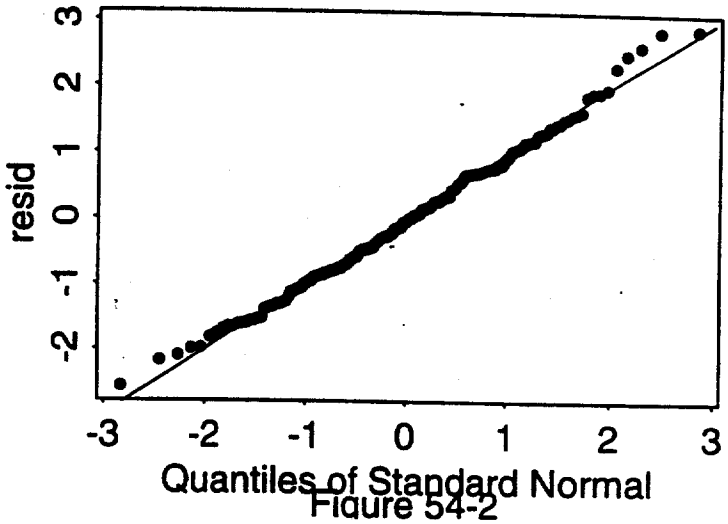


Figure 54-2

Final Model, LOCF

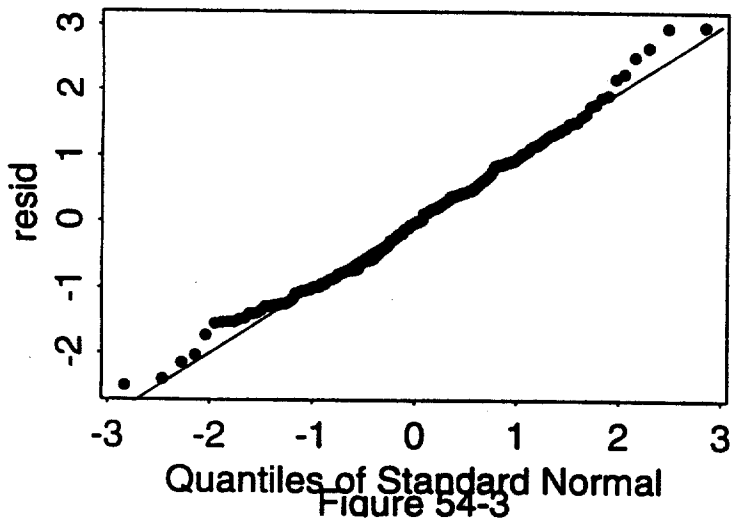


Figure 54-3

Final Model, Week 24

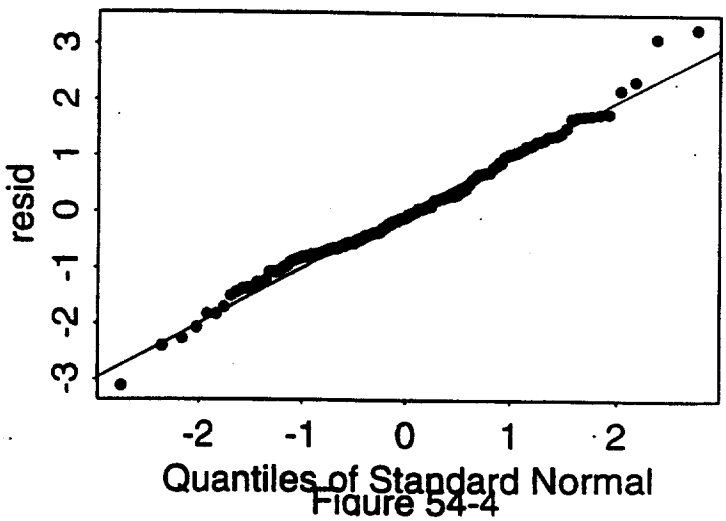


Figure 54-4

patients significantly different from the results obtained by removing any other six patients?" The positive answer will assure us that these six patients should not be included in reaching our final conclusion.

We employed a bootstrap resampling, or empirical approach. Let X_{11}, X_{12}, X_{21}, *and* X_{22} *be random variables defined as the mean percentage change for ITT as follows*

Table 7.2.4
Mean Percent Change for ITT

	Selegiline	Non-selegiline
Ropinirole	X_{11}	X_{12}
Placebo	X_{21}	X_{22}.

Define a test statistic as $Y=|X_{12} - X_{11}|/(|X_{12}|+|X_{11}|) + |X_{22} - X_{21}|/(|X_{22}|+|X_{21}|)$, *which is designed to detect the average discrepancies between selegiline strata. We had y=2.190274 for the data with the six outliers removed. We then randomly removed any six patients from the entire dataset with the six "outliers" included, and computed the test statistic y from the remaining patients. The process was then repeated 4999 times. These 5000 simulated y's formed an empirical distribution of Y under the null hypothesis that removing the six patients was the same as removing any other six patients. The p-value for y with the six outliers removed was <0.0001. This again strongly suggests that these six patients were significantly different from the entire population.*

<u>Final Model</u> *The mean percentage reduction in motor score was modeled as a linear combination of treatment, center, selegiline and sex with the six outliers removed from the data set. The modeling was done for the ITT LOCF data set and ITT completers (week 24). The Q-Q plots (Figure 54-1,2) suggested that the fits were adequate. The testing for the difference of treatment effect between ropinirole and placebo was highly significant for both data sets:*

Table 7.2.5
Testing of difference of treatment effect

	F statistic	d.f	p-value
LOCF Endpoint	31.19	1	<0.001
Week 24	20.72	1	<0.001

The estimated percentage improvement of motor score were given as follows:

Table 7.2.6

		% Improvement	SE
LOCF Endpoint	Ropinirole	23.89	3.61
	Placebo	-1.05*	3.08
Week 24 OC	Ropinirole	35.29	4.20
	Placebo	7.96	3.38

*Negative values indicate a worsening of motor function

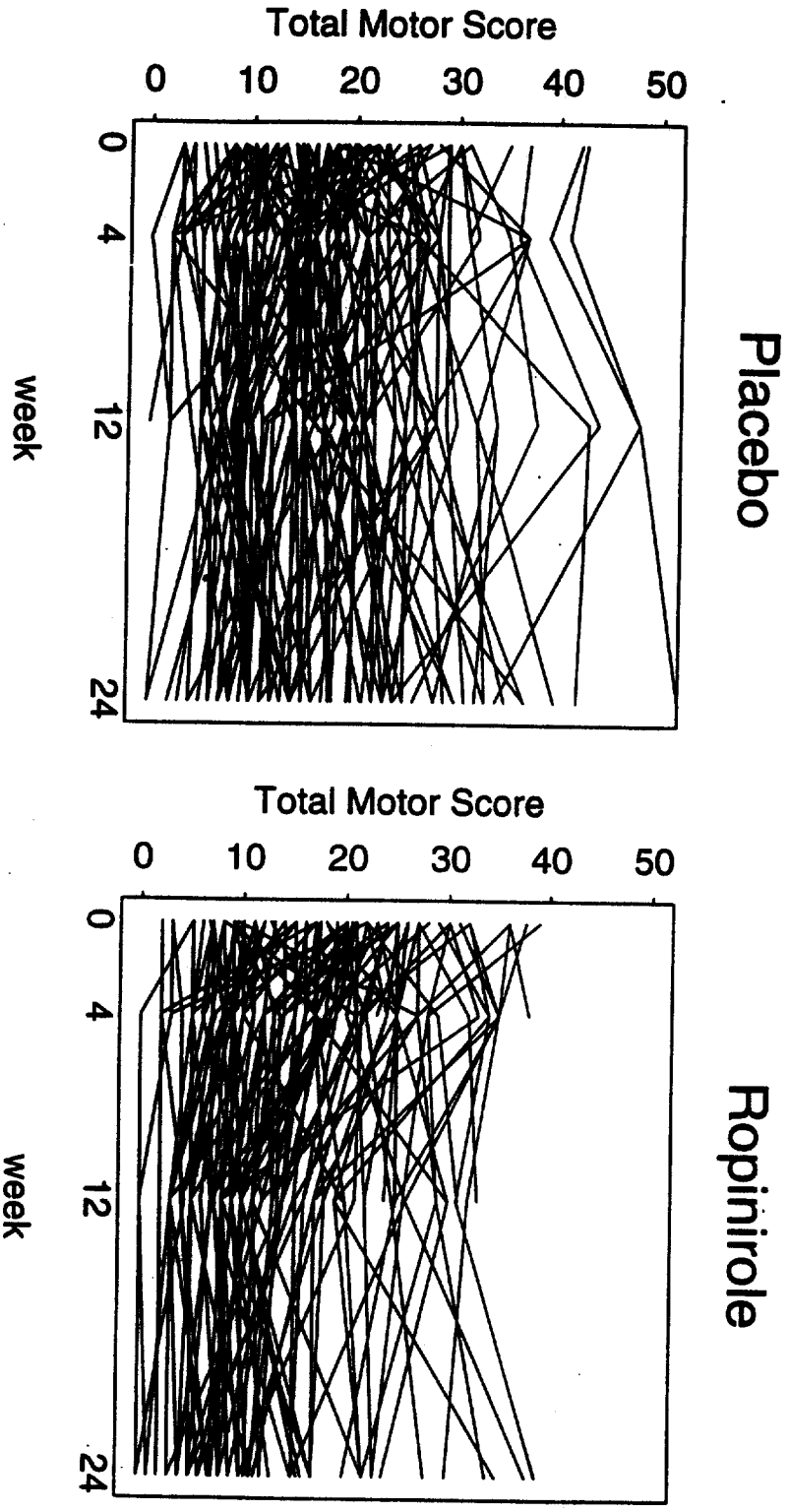
The results suggested that there was an average improvement of more than 20% reduction in total motor scores in the ropinirole group. The model fitted with the protocol spedified effects treatment, center and selegiline yielded the similar results.

Full View of the Data

We plotted all individual patient total motor scores at baseline, weeks 4, 12 and 24 in placebo and ropinirole groups, separately (see A54-2). Although we might not be able to fully fit a statistical model to this type of data concurrently, we nonetheless see a decreasing trend in total motor scores in the ropinirole group, but not in the placebo group.

8. Secondary Efficacy Endpoints

Here only the intention to treatment population LOCF analysis was summarized in this report.


Total Motor Score
0
10
20
30
40
50
week
0
4
12
24
Placebo
Total Motor Score
0
10
20
30
40
50
week
0
4
12
24
Ropinirole

A54-2

8.1 Sponsor's Analysis

Patient Response (30% reduction in UPDRS motor score)

Table 8.1.1 presents the number and percentage of patients who achieved at least a 30% reduction from the baseline in the total motor score of the UPDRS at endpoint in the intention to treat population. There were a significantly greater percentage of patients in the ropinirole treatment group who met criteria for response compared to the placebo group.

Table 8.1.1

Number and Percent of Patients with at least a 30% reduction in UPDRS Motor Score - Intention to Treat Population

	Ropinirole		Placebo		Odds ratio (95%CI)	
All Strata	47%	(50/107)	20%	(23/118)	4.45	(2.26, 8.78)
Selegiline	56%	(30/54)	14%	(8/58)	12.13	(4.14,30.53)
Non-Selegiline	38%	(20/53)	25%	(15/60)	1.87	(0.75,4.40)

There was a significant treatment by selegiline interaction (p=0.008). Analysis of the separate strata resulted in a statistically significant treatment effect in favor of ropinirole in the selegiline stratum but not in the non-selegiline stratum.

Patient Improvement (Score of 1 or 2 on CGI Improvement Item)

Thirty-three percent (38/115) of ropinirole patients and 12% (15/123) of placebo patients achieved a CGI improvement item score of 1 or 2 at endpoint. There was a significant treatment effect favoring ropinirole over placebo (odds ratio :4.06, 95% CI: 2.00,8.22). In the selegiline stratum, 37.9% (22/58) ropinirole treated patients and 11.5% (7/61) placebo treated patients achieved improvement on the CGI and in the non-selegiline stratum, 28% (16/57) of ropinirole treated patients and 13% (8/62) of placebo treated patients were improved on the CGI. There was no significant interaction between selegiline strata and treatment. Therefore, the treatment effect was similar in both selegiline strata.

Number of Patients Requiring l-dopa Rescue

In the ITT Population, 29% (36/125) of placebo treated patients

required rescue with l-dopa during the study as compared with 11% (13/116) of ropinirole treated patients. The odds ratio was 0.3 with a 95% confidence interval of 0.14 and 0.61 indicating a statistically significant treatment difference in favor of ropinirole. Similar proportions of patients were rescued in the separate selegiline strata and similar results were seen in the efficacy evaluable population.

Number of Patients with Insufficient Therapeutic Response

There was also a statistically significant treatment difference in favor of ropinirole treatment in the number of patients with an insufficient therapeutic response. Age of onset was found to have a significant effect and was thus included in the final model. In the ITT Population, 12% (14/116) ropinirole treated patients compared with 30% (37/125) of placebo treated patients met the criteria for insufficient therapeutic response (odds ratio:0.31, 95% CI:0.15,0.63). Similar proportions of patients had an insufficient therapeutic response in the separate selegiline strata and similar results were seen in the efficacy evaluable population.

8.2 **Reviewer's Comments**

Patient Response

This endpoint was actually a transformation of the primary endpoint, i.e., the mean percentage reduction in motor score. Transformation of random variables and related analysis are quite controversial issues in statistics. Once the efficacy testing was done for the primary endpoint, it seems to make little sense to carry out the hypothesis testing for the transformed one. The tabulated percentage results might be helpful for some clinical interpretation. The reviewer saw no need for the hypothesis testing.

All Other Endpoints

Besides that they all showed results favorable to ropinirole, it was worth noting that there was no treatment by selegiline interaction found in these non-motor score related endpoints.

9. Efficacy Subgroup Analysis

9.1 Sponsor's Analysis

Presentation of analyses on selegiline strata were included with the primary and secondary efficacy analysis. Since the majority of patients are Caucasian, the subgroup analysis for race was not carried out. Subgroup analyses for sex and age were descriptive only.

The mean baseline UPDRS motor score was slightly lower for males compared to females in both treatment groups (males: 17.3 ± 8.6 ropinirole and 16.8 ± 7.9 placebo; females: 18.7 ± 9.0 ropinirole and 19.2 ± 8.4 placebo). The mean percentage change from baseline in UPDRS motor score in male patients and female patients for the ITT population is presented in Table 9.1.1.

Table 9.1.1
Mean Percent Change for ITT

	Female	Male
Ropinirole	-26.0	-18.4
Placebo	8.6	0.8.

The sponsor also reported in the analysis of the total motor score at endpoint, adjusted for differences in the baseline motor score, there was a statistically significant treatment by sex interaction.

The mean UPDRS motor score at baseline was slightly lower for patients ≤ 65 years of age compared to patients >65 years of age (≤ 65 years: 17.3 ± 8.8 ropinirole and 17.3 ± 8.6 placebo; >65 years: 18.6 ± 8.7 ropinirole and 18.0 ± 7.7 placebo). There was a similar difference between ropinirole and placebo treatment in the two age groups (≤ 65 years: -25.3 ropinirole, +0.8 placebo; >65 years:-16.1 ropinirole, +6.2 placebo). Ropinirole treated patients in both age groups reported a decrease in the total motor score indicating an improvement at endpoint compared to the increase in the placebo group.

9.2 **Reviewer's Comments**

We concluded in the previous section that the six outliers should be excluded from the final analysis. Since all outliers were males, one would like to find out the impact of removing outliers to the sex subgroup analysis. With the six outliers removed, Table 9.1.1 was changed to

Table 9.1.2
Mean Percent Change for ITT

	Female	Male
Ropinirole	-26.0	-25.8
Placebo	8.6	-6.8.

The reported interaction of treatment by sex could be due to a large random variation. There was no meaningful interpretation for such interaction based on the data.

10. The Effect of Censoring

Nearly 30% of patients were censored at the end of the study (week 24). Out of 241 randomized patients, 225 (107 in ropinirole group, 118 in placebo group) had at least one post-drug UPDRS measurement (week 4). At week 24, there were only 72 patients in ropinirole group and 73 patients in placebo group left for statistical analysis. The sponsor's "dropouts" did not account for all censoring since some patients with l-dopa rescue were also classified as "completers." The reviewer produced the following table for all censored observations:

Table 10.1.1
Number of censored patients

	Ropinirole	Placebo
L-dopa rescue only	5	29
Sponsor's Dropouts only	28	15
Both	2	1
Total Censoring	35	45

Most of censoring in ropinirole was due to adverse experiences,

and most of censoring in placebo was due to insufficient therapeutic response (including those receiving l-dopa rescue).

To see the possible effect of censoring on final analysis, we made the following table of the mean percentage changes of UPDRS motor score stratified by censoring for each group:

Table *10.1.2*

Mean percentage changes at week 4, 12 and 24

	Ropinirole		*Placebo*	
	Censored	*Non-censored*	*Censored*	*Non-censored*
Week 4	*2.2*	*-10.5*	*-5.3*	*-3.3*
Week 12	*-14.7*	*-29.4*	*-6.0*	*-4.4*
Week 24	*N/A*	*-29.0*	*N/A*	*-5.1*

There was no evidence suggesting that the censoring in placebo group introduced a bias favorable to treatment. In ropinirole group, censoring seemed to occur for patients not responding to treatment, and introducing a bias favorable to treatment was possible. However, a trend was suggesting the effectiveness of treatment in those censored patients. The ITT LOCF analysis also reached the same conclusion as that for the "completers." There was no evidence that the censoring in ropinirole group distorted the conclusion of effectiveness of ropinirole in improving patients UPDRS motor function.

11. Conclusion

This reviewer thinks that this study provides statistical evidence showing that ropinirole treatment is effective in improving motor function in early Parkinsonian patients not receiving concomitant l-dopa therapy.

Non-U.S. Monotherapy Study 032*

1. Introduction

This study was designed to investigate the anti-Parkinson efficacy and safety of ropinirole in patients with early Parkinson's disease. Sixty-three patients were randomized at nine study centers geographically distributed throughout the United Kingdom, Belgium, Holland, S. Africa, Italy, and France during a period from June 1990 to October 1991.

2 Objectives

The primary objective of this study was to evaluate the anti-Parkinson efficacy of ropinirole versus placebo as monotherapy in de-novo Parkinsonian patients. The secondary objective was to evaluate a safe and tolerable dosing regimen for ropinirole.

3 Study Design

This was a randomized, multicenter, double-blind, placebo controlled study of 12 weeks' treatment duration. Patients were randomly allocated to receive treatment for 12 weeks with either ropinirole or placebo, using a 2:1 randomization in favor of ropinirole.

Assessments of efficacy and safety were undertaken after 1, 2, 3, 4, 6, 8, 10 and 12 weeks of treatment. The study allowed for ropinirole to be taken at doses in the range 1.0 mg to 10.0 mg daily, in two divided doses. All patients started at a dose of 0.5 mg b.i.d. (day 1) followed by incremental dose increases, in 0.5 mg steps, on days 8, 15, 22, 29 and 43. On days 57 and 71 the dose could be increased in increments of 0.5 mg or 1.0 mg at the discretion of the investigator.

*In this report, the reviwer's analyses are in Italic font.

4. Patient Disposition

A total of 63 patients was recruited into the study from nine centers in six countries. Most patients (34, 54.0%) were recruited at study centers in the UK. The distribution of patients by center is shown in Table 4.1.1.

Table 4.1.1
Number of patients by country and center

Center Details			Treatment Group		Total
Center No	Country	Investigator	Ropinirole	Placebo	
1	UK	Abbott	6	4	10
2	UK	Brooks	3	1	4
3	UK	Lees	6	3	9
4	UK	Sagar	8	3	11
5	Belgium	Ebinger	0	1	1
6	Holland	Roos	4	2	6
7	S. Africa	Philcox	4	3	7
8	Italy	Nappi	3	2	5
9	France	Rascol	7	3	10
Total			41	22	63

The numbers of patients randomized and the number who completed treatment with either ropinirole or placebo are shown in Table 4.1.2.

Table 4.1.2
Number of patients randomized and completing the study

Study Stage	Treatment Group		Total
	Ropinirole	Placebo	
Randomized	41	22	63
Completed Study	36 (87.8%)	19 (86.4%)	55
Valid for Efficacy Analyses	30 (73.2%)	16 (72.7%)	46

Table 4.1.3 presents demographic details of the study population.

Table 4.1.3 Demographic details

Demographic Parameter	Treatment Group	
	Ropinirole	Placebo
Total number of patients	41	22
Males	18 (43.9%)	14 (63.6%)
Females	23 (56.1%)	8 (36.4%)
Mean age ± SD (years)	59.2 ± 9.4	56.5 ± 10.3

Age range (years)	38-74	36-72
Mean height ± SD (cm)	166.6 ± 7.9	168.5 ± 10.3
Height range (cm)	150-179	150-191
Mean weight ± SD (kg)	69.2 ± 12.6	71.7 ± 12.5
Weight range (kg)	38-102	46-98

The mean duration of Parkinson's Disease was 28.3 months (SD 23.9, range: 4 to 109 months) for ropinirole group patients, compared with a mean duration of 25.8 months (SD 17.6, range: 5 to 77 months) for patients in the placebo group.

5. Efficacy Parameters

The assessment of anti-Parkinsonian activity was primarily by use of the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS). A responder was defined as a patient with at least a 30% reduction in UPDRS motor score.

Secondary measures of efficacy were the finger taps test, the Clinician's Global Evaluation (CGE), and scores for the mental section of UPDRS and Activities of Daily Living (ADL) section of the UPDRS.

6. Concomitant Medications

Concomitant medications taken most frequently (in > 10% of patients) during the study are shown in Table 6.6.1.

Table 6.1.1

Concomitant medication received by >10% of patients in either group

Medication	Treatment Group	
	Ropinirole (n=41)	Placebo (n=22)
Selegiline	8 (19.5%)	7 (31.8%)
Amantadine	6 (14.6%)	8 (36.4%)
Paracetamol	5 (12.2%)	2 (9.1%)

L-dopa was taken by one patient in the placebo group.

7. Sponsor's Efficacy Results

7.1 Data Sets:

Data from the intention-to-treat and efficacy-evaluable populations were analyzed. The intention-to-treat population LOCF analysis was the primary analysis that included all patients. In the efficacy-evaluable population, 46 patients (30 in the ropinirole treatment group and 16 in the placebo group) were included in the (post-dose) analysis at visit 10.

7.2 Primary Analysis

7.2.1 Protocol Specified Analysis

In the protocol last modified by 4th January, 1991, the sponsor stated that the ITT LOCF analysis and the week 12 OC analysis would be carried out for response rate. Response rates would be presented with 95% confidence intervals for differences in response rates.

The sponsor did not specify any statistical methods in the protocol.

7.2.2 Response Rate Analysis

The total motor examination score was calculated as the sum of the 14 individual motor examination components (numbers 18-31) of the UPDRS. For those parameters measured on both sides of the body, the side with the worst score at baseline was used in the analyses. In analyses investigating the chronic effect of study medication on motor score, the parameters were calculated on the same side throughout the study. If both sides had the same score at baseline, then the reduction in the total motor score was calculated for both sides and the patient was classified as a responder if he or she showed sufficient improvement (at least 30% reduction in score) on either side.

Intention-to-treat Population

Twenty-nine patients (70.7%) in the ropinirole treatment group achieved a 30% redection in motor score at the endpoint compared with 9 (40.9%) in the placebo group. This difference was

significantly in favor of ropinirole (p=0.021, chi-square test; C.I. (5.0%, 54.6%)). The numbers of patients classified as responders at the time of each visit are summarized in Table 7.2.1.

Table 7.2.1

Number of patients responding to treatment (intention-to-treat population)

Visit	Treatment Group				p-value at LOCF endpoint
	Ropinirole		Placebo		
	n (%)	N	n (%)	N	
Visit 6(week 4)	21 (52.5%)	40	9 (40.9%)	22	
Visit 10(week 12)	24 (72.7%)	33	8 (47.1%)	17	
LOCF endpoint	29 (70.7%)	41	9 (40.9%)	22	p=0.021

Key: n (%) = number and percentage of patient responding; N = total number of patients evaluated.

Efficacy-evaluable Population

Forty-six patients (30 in the ropinirole treatment group and 16 receiving placebo) were included in the efficacy evaluable analysis at visit 10. Eleven (26.8%) ropinirole-treated patients and six (27.3%) placebo group patients were excluded from the analysis of the primary efficacy parameter at visit 10 (post dose). At visit 10 (post-dose), 23 (76.7%) of the 30 evaluable patients on ropinirole were classified as responders compared with 8 (50.0%) of the 16 evaluable patients in the placebo group. The difference between treatment groups was not statistically significant (p = 0.066, chi-square test) (C.I. (-2.1%, 55.5%)). The numbers of patients classified as responders at the time of each visit are summarized in Table 7.2.2.

Table 7.2.2

Number of patients responding to treatment (efficacy-evaluable population)

Visit	Treatment Group				p-value at Visit 10
	Ropinirole		Placebo		
	n (%)	N	n (%)	N	
Visit 6(week 4)	21 (55.3%)	38	8 (40.0%)	20	
Visit 10(week 12)	23 (76.7%)	30	8 (50.0%)	16	p=0.066

Key: n (%) = number and percentage of patient responding; N = total number of patients evaluated.

Formal model fitting was carried out using logistic modeling. The chosen model contained the following terms: treatment and selegiline. The treatment by selegiline interaction could not be investigated because all the ropinirole patients treated with

selegiline were classified as responders. The odds ratio after fitting this model is shown below.

Log Odds	Odds Ratio	95% C.I. for Odds Ratio
1.57	4.83	(1.44, 16.20)

The sponsor reported a significant treatment by country (UK vs. non-UK) interaction in the efficacy-evaluable population. The odds ratio from fitting the model: treatment + selegiline + country for the efficacy-evaluable population is shown below.

Log Odds	Odds Ratio	95% C.I. for Odds Ratio
1.67	5.32	(1.13, 24.84).

7.2.3 Total Motor Score Analysis

In this analysis, total motor score was calculated by using both the left and right side scores.

Intention-to-treat Population

At the end of baseline period, the mean total motor score in the ropinirole group was 18.6 compared with 19.9 in the placebo group. At the LOCF endpoint, the mean change in the total motor score from baseline was -43.4% in the ropinirole group compared with -21.0% in the placebo group. There was a statistically significant difference between the two treatment groups (p=0.018, F-test; C.I. (-40.8%, -4.0%)). The mean percentage changes from baseline at each visit are shown in Table 7.2.3.

Table 7.2.3

Mean percentage change from baseline in total motor score (intention-to-treat population)

Visit	Ropinirole Score	n	Placebo Score	n	p-value
Visit 6(week 4)	-31.69	40	-16.62	22	
Visit 10(week 12)	-45.83	33	-32.75	17	
LOCF endpoint	-43.37	41	-20.99	22	p=0.018

Efficacy-evaluable Population

At visit 10 (post dose), the mean change in the total motor score from baseline in the efficacy-evaluable population was -49.5% in the ropinirole group, compared with -35.3% in the placebo group, giving a non-statistically significant difference between the two

treatment groups (p = 0.117, F-test; C.I. (-32.1%, 3.7%)). The mean percentage changes from baseline at each visit are shown in Table 7.2.4.

Table 7.2.4
Mean percentage change from baseline in total motor score (efficacy-evaluable population)

Visit	Ropinirole Score	n	Placebo Score	n	p-value at Visit 10
Visit 6(week 4)	-32.70	38	-15.24	20	
Visit 10(week 12)	-49.53	30	-35.30	16	0.117

Similar to Study 54, the sponsor stated that the plots of motor score confirmed that there was a strong relationship between endpoint and baseline motor score, and that regression lines could be fitted through the origin. On the assumption that treatment effect will be proportional to baseline score, models fitted as regression lines through the origin will provide a clinically relevant interpretation of the data, as healthy individuals would not be expected to get worse. A regression coefficient of 1.0 would indicate no change in motor score during the study. If the degree of improvement is measured by the reduction compared with 1.0, an improvement of 30% or more is equivalent to a regression coefficient of 0.7 or less.

The sponsor reported there was a significant treatment by selegiline interaction in the final model. The final model consisted of the following terms: treatment, selegiline, treatment by selegiline interaction. Due to the significant treatment by selegiline interaction (which was not seen in the original analysis), the results are now presented separately for each selegiline stratum.

	Ropinirole Ratio	SE	Placebo Ratio	SE
Selegiline	0.158	0.1133	0.792	0.0841
Non-selegiline	0.692	0.0448	0.881	0.0612

Treatment effects and 95% confidence intervals (C.I.) were calculated within each selegiline stratum. For the selegiline group the treatment difference was -0.634 (95% C.I. (-0.915, -0.353)) and for the non-selegiline group the treatment

difference was -0.189 (95% C.I. (-0.329, -0.049)). The improvement was considerably larger for patients treated with both ropinirole and selegiline (84%, compared with 31% in the ropinirole/non-selegiline group, 21% in the placebo/selegiline group and 12% in the placebo/non-selegiline group). The combined analysis in the intention-to-treat population at endpoint are shown below.

Treatment	Ratio Estimate	SE
Ropinirole	0.425	0.0610
Placebo	0.837	0.0519

7.2.4 Additional Subgroup Analysis

In addition to the interactions reported in 7.2.2 and 7.2.3, the sponsor reported the following:

Use of Selegiline

For response rates analysis, there was no significant treatment by selegiline interaction in either the intention-to-treat population or the efficacy-evaluable population.

By Country Analysis

Here only UK and non-UK were considered. In the ITT population, there was no significant treatment by country interaction for both response rate analysis and percentage change from baseline analysis.

In the efficacy-evaluable population, there was a significant treatment by country interaction for the response rate analysis. There was no significant treatment by country interaction for the percentage change from baseline in the total motor score analysis.

7.3 Secondary Efficacy Parameters

7.3.1 Finger Taps

The mean percentage change from baseline in the number of finger taps at week 4 and 12 and at endpoint is shown in Table 7.3.1.

Table 7.3.1

Mean percentage change from baseline in number of finger taps

(intention-to-treat population)

Visit Number	Treatment Group Ropinirole n	Placebo n	p-value
Visit 6 (week 4)	14.72 37	16.92 22	
Visit 10(week 12)	24.38 32	18.23 17	
LOCF endpoint	20.94 40	17.47 22	NS (0.85)

(efficacy-evaluable population)

Visit Number	Treatment Group Ropinirole n	Placebo n	p-value at Visit 10
Visit 6 (week 4)	14.96 35	14.16 20	
Visit 10(week 12)	25.03 29	20.02 16	NS

There was no statistically significant difference between the two treatment groups (p=0.850, Mann Whitney test).

7.3.2 Clinician's Global Evaluation

For the Intention-to-treat population, twenty-nine of the 41 patients (70.7%) receiving ropinirole showed an improvement in their Parkinson's disease symptoms at endpoint, compared with 9 of the 22 patients (40.9%) receiving placebo. There was a statistically significant difference between the two treatment groups (p=0.021, Chi-square test).

For the efficacy-evaluable population, twenty-six of the 33 patients (78.8%) receiving ropinirole showed an improvement at visit 10 compared with 9 of the 18 patients (50.0%) receiving placebo giving a statistically significant difference between the two treatment groups (p=0.034, Chi-square test).

7.3.3 Other Secondary Efficacy Parameters

For the mental component and activities of daily living component of UPDRS, there were no statistically significant differences between the two treatment groups.

8. Reviewer's Analysis and Comments

8.1 Sample Size

The number of patients, 63, is relatively small. The sponsor calculated the sample size aiming to detect 40% difference in response rate between treatment groups. With large variations observed in the data, the sample size might not be large enough to address the issues concerning some confounding factors, such as treatment by selegiline, or treatment by country interactions.

8.2 Inconsistency in Primary Efficacy Analysis

The sponsor did not use the UPDRS motor scores consistently. In the response rate analysis, the sponsor only used worst sides for those scores with right and left sides. While in the total motor score analysis, the sponsor used all measurements.

The responder variable in response rate analysis was simply a transformation of the mean percentage reduction of total motor scores from baseline. As this reviewer pointed out in the Review of Study 54, the transformation of a random variable and its related analyses are controversial issues in statistics. Simultaneous use of both original variable and its transformation in testing the same hypothesis could produce conflicting results. The present study provides an example to illustrate this point. The following are summaries of the interactions reported by the sponsor.

Table 8.2.1
Interactions in Efficacy Evaluable (OC) Analysis

	Interactions of treatment by Selegiline	Country
Response Rate	No	Yes
Total Motor Score Analysis	Yes	No

The response rate analysis and the total motor score analysis were both based on the same total motor score measurements. It is clear to see that the above results are nothing but sporadic.

This reviewer decided to review and analyze the efficacy result based on total motor score analysis, which uses all 27 UPDRS motor scores. The mean percentage reduction of total motor scores from baseline will be studied. Since this was a primary analysis in Study 54, the two studies would be more comparable.

8.3 Checking the Data Set

The stem-leaf plot of ITT LOCF data set revealed that there might be an outlier with the mean percentage reduction as high as 127.27.

Table 8.3.1

```
N = 63    Median = -40
Quartiles = -62.5, -8.51064

Decimal point is 1 place to the right of the colon

  -10 : 0
   -9 : 620
   -8 : 90
   -7 : 999610
   -6 : 9873
   -5 : 764000
   -4 : 7666210000
   -3 : 999652
   -2 : 521
   -1 : 442220
   -0 : 9644
    0 : zzz58
    1 : 2337
    2 : 0
    3 :
    4 : 5

High: 127.2727
```

The patient profile is as follows

ID	Treat.	Sex	Race	Dur.Dis.	H&Y	Age	Country	Concom. Med.
68	Placebo	F	Cau	46 mos	II	66	Holland	None

In the following sections, the main analyses will be done with and without this possible outlier.

8.4 Interaction and Subgroup Analysis

This reviewer was puzzled by the high mean percentage reduction of total motor score in the placebo group. They are -20.99 % for ITT LOCF data and -35.30% for efficacy-evaluable OC data set (Tables 7.2.3 and 7.2.4). These improvements are even better than the treatment group in Study 54 (around -20%).

8.4.1 Concomitant Medications

A noticeable difference between this study and Study 54 is that there were a considerable number of patients on Amantadine, see Table 6.1.1. After consultation with the medical officer, this reviewer decided to look into this matter further. There were no records of ID of those patients on Amantadine in the sponsor's report and electronic data sets. This reviewer called the sponsor and received a fax of those patients' ID's from the sponsor. The following table presents the mean percentage reductions of total motor scores in two treatment groups stratified by the Amantadine use for ITT LOCF data set.

Table 8.4.1

	Amantadine Use	
	No	Yes
Ropinirole	-40.01	-56.75
Placebo	-12.56	-28.54

Although it seems that Amantadine patients have high percentage reductions in total motor scores, a further analysis is needed to see whether this is possible due to chance. There is a similar question related to selegiline use.

8.4.2 Evaluations of Subgroup Analyses

Similar to the bootstrap method proposed in Review of Study 54, we will evaluate the subgroup analyses concerning concomitant medications empirically. We will also evaluate the possible interaction of treatment by country reported by sponsor.

Similar to what we did in the review of Study 54, let X_{11}, X_{12}, X_{21}, and X_{22} be random variables as follows

Mean Percent Changes

	Stratum 1	Stratum 2
Ropinirole	X_{11}	X_{12}
Placebo	X_{21}	X_{22}.

Define the test statistic as $Y=|X_{12} - X_{11}|/(|X_{12}|+|X_{11}|) + |X_{22} - X_{21}|/(|X_{22}|+|X_{21}|)$, which is designed to detect the average discrepancies between strata. The bootstrap samples x^*_{11}, x^*_{12}, x^*_{21}, and x^*_{22} were generated under the null hypothesis that there was no difference between strata, and y^* was then calculated. This procedure was repeated 4999 times. The 5000 y^*s formed an empirical distribution under the null hypothesis and the p-value for observed y was calculated with this empirical distribution. This method was applied to evaluate the subgroup analyses concerning interaction of treatment by amantadine, selegiline, and country. The following table presents the results

Table 8.4.2

Mean percentage change for ITT LOCF

	Amantadine		Selegiline		Country	
	No	Yes	No	Yes	UK	Non-UK
Ropinirole	-40	-58	-35	-75	-42	-43
Placebo	-13	-27	-13	-29	-30	-5
y =	1.078		1.522		1.888	
Bootstrap p-value	0.516		0.292		0.126	

* The values of mean percentage changes are rounded.

The same analyses with the outlier (see 8.3) removed yielded similar results.

Although we have no evidence for the existence of interactions of treatment by amantadine, selegiline and country, these non-significant results should be interpreted cautiously due to the small sample size of the trial. We probably cannot address these

issues adequately due to the lack of power of these tests. Since the high mean percentage reduction in placebo group is likely related to some confounding factors, we probably cannot address this matter adequately either.

There is a large imbalance in male and females patients between groups (see Table 4.1.3). The sponsor did not provide the related subgroup analysis. This reviewer carried out additional subgroup analysis concerning sex. There are similar mean percentage reductions in motor score in ropinirole patients (-42.8% in the females, -42.3% in the males). In placebo patients, males have higher percentage reductions (-25.6%) than females (-3.6%). This difference, however, is not statistically significent by a similar empirical evaluation.

8.5 Efficacy Evaluation

We will evaluate efficacy by the similar empirical methods to produce the result in contrast to those in Section 8.4.2.

8.5.1 Intention-to-Treat LOCF Analysis

Overall Test

To test overall difference between the two treatment groups regardless of covariates, we take a test statistic as the difference of means of percentage reductions of total motor score of two groups. The empirical distribution is generated under the null hypothesis that there is no difference between two groups. The p-values for the full data and one with the outlier removed are 0.012 and 0.0434, respectively.

Stratified Test

To allow for covariates, we carry out the stratified empirical test for covariates amantadine, selegiline, and country.

Let X_{11}, X_{12}, X_{21}, and X_{22} be those defined in Section 8.4.2, define a new test statistic $Z = |X_{11} - X_{21}|/(|X_{11}|+|X_{21}|) + |X_{12} - X_{22}|/(|X_{12}|+|X_{22}|)$, which is designed to detect the average difference between the two treatment groups across strata. The bootstrap samples x^*_{11}, x^*_{12}, x^*_{21}, and x^*_{22} were generated under the null hypothesis that there was no difference between two

treatment groups within each stratum, and z^* was then calculated. This procedure was repeated 4999 times. The 5000 z^*s formed an empirical distribution under the null hypothesis and the p-value for observed z was calculated with this empirical distribution. The results are summarized in the following

Table 8.5.1

Stratified Efficacy Test for ITT LOCF

	Amantadine		Selegiline		Country	
	No	Yes	No	Yes	UK	Non-UK
Ropinirole	-40	-58	-35	-75	-42	-43
Placebo	-13	-27	-13	-29	-30	-5
z =	1.784		1.837		1.888	
Bootstrap p-value	0.0086		0.004		0.0096	

The results with the outlier removed are

Table 8.5.2

Stratified Efficacy Test for ITT LOCF (outlier removed)

	Amantadine		Selegiline		Country	
	No	Yes	No	Yes	UK	Non-UK
Ropinirole	-40	-58	-35	-75	-42	-43
Placebo	-23	-27	-23	-29	-30	-19
z =	1.2674		1.3235		1.1324	
Bootstrap p-value	0.0386		0.0138		0.049	

Conclusion

There is a statistically significant difference between treatment groups in favor of ropinirole based on the ITT LOCF data set.

8.5.2 Efficacy-evaluable OC Analysis

Overall Test

The p-value for the efficacy evaluable population OC data is 0.1328.

Stratified Test

Table 8.5.3
Stratified Efficacy Test for Eff.Eval. OC

	Amantadine		Selegiline		Country	
	No	Yes	No	Yes	UK	Non-UK
Ropinirole	-46	-62	-41	-79	-48	-79
Placebo	-33	-34	-26	-50	-43	-21
z =	0.9067		0.9050		0.9176	
Bootstrap p-value	0.1632		0.0426		0.1132	

The significant testing result with the selegiline strata is likely due to a multiplicity effect. There is no statistically significant difference between two the treatment groups. However, small sample size (30 in ropinirole group and 16 in placebo group) might reduce the power of the test to detect the treatment difference. The censoring might also introduce a bias not favorable to ropinirole.

8.6 Censoring effect in Efficacy Evaluable OC Analysis

To look at the possible censoring effect in the efficacy-evaluable OC analysis, we produced the following table showing the mean percentage changes in total motor score at each visit

stratified by the treatment and censoring, where "non-censored" patients refer to those in efficacy-evaluable OC data set, "censored" patients refer to those patients eventually censored including the four protocol violators.

Table 8.6.1
Mean percentage changes at each visit

Visit	Ropinirole				Placebo			
	Censored eventually		Non-censored		Censored eventually		Non-censored	
	%	n	%	n	%	n	%	n
2	1.71	11	-7.33	30	3.60	6	-14.52	16
3	-22.27	11	-10.61	30	15.63	6	-21.37	16
4	-21.45	10	-17.09	30	-4.12	6	-23.86	16
5	-18.95	10	-25.24	30	21.08	6	-25.54	15
6	-27.51	10	-30.79	30	27.83	6	-29.28	16
7	-29.64	7	-38.24	28	30.65	6	-31.55	16
8	-31.32	6	-43.32	30	15.38	5	-33.41	16
9	-24.76	5	-46.93	29	-16.76	3	-32.64	15
10	-8.18	3	-48.33	30	5.26	1	-33.26	16

It seems that the censoring in placebo group introduced substantial bias not favorable to ropinirole. The high mean percentage reductions in total motor score in placebo group might be attributed to the bias, too.

To have a closer look, we plotted the percentage reductions vs. visits for the patients in four groups, see A-32. Figure 32-3 shows that there might be one outlier in censored placebo patients. This patient is the same patient classified as outlier in Section 8.3. Removing this patient, Table 8.6.1 becomes

Table 8.6.2

Mean percentage changes at each visit **(outlier removed)**

	Ropinirole				*Placebo*			
Visit	*Censored eventually*		*Non-censored*		*Censored eventually*		*Non-censored*	
	%	n	%	n	%	n	%	n
2	1.71	11	-7.33	30	-1.14	5	-14.52	16
3	-22.27	11	-10.61	30	-3.06	5	-21.37	16
4	-21.45	10	-17.09	30	-8.58	5	-23.86	16
5	-18.95	10	-25.24	30	-5.61	5	-25.54	15
6	-27.51	10	-30.79	30	-6.60	5	-29.28	16
7	-29.64	7	-38.24	28	2.23	5	-31.55	16
8	-31.32	6	-43.32	30	-12.59	4	-33.41	16
9	-24.76	5	-46.93	29	-16.76	3	-32.64	15
10	-8.18	3	-48.33	30	5.26	1	-33.26	16

We conclude that the censoring in placebo group introduced a bias not favorable to ropinirole. The bias, however, might not be the only reason for the high mean percentage reductions in total motor score in the placebo group.

8.7 Conclusion

Ropinirole is shown to be significantly more effective than placebo, as determined by the intention-to-treat analysis of reduction in motor score of the Unified Parkinson's Disease Rating Scale. The efficacy of ropinirole is also shown by the Clinician's Global Evaluation of efficacy, while with the Finger Tap test, the improvement with ropinirole is less marked. There is concern on possible interactions of treatment by some covariates. The sample size of the trial is too small to warrant a further investigation.

Figure 32-2

Figure 32-4

Figure 32-1

Figure 32-3

U.S. Adjunct Therapy Study 044

1. Introduction

This double-blind, placebo-controlled study was conducted to investigate the anti-Parkinson efficacy and safety of ropinirole as adjunct to l-dopa preparations in patients not optimally controlled on l-dopa. The study was conducted in the continental USA at sixteen investigational centers during a period from September 1992 to September 1994. One hundred forty nine (149) patients were randomized in this trial.

2. Objectives

- -To evaluate the anti-Parkinson efficacy of ropinirole as adjunct to l-dopa in Parkinsonian patients;
- -To evaluate the safety profile of ropinirole as an adjunct to l-dopa in Parkinsonian patients;
- -To assess the pharmacokinetic profile of ropinirole under multiple dosing steady state conditions in Parkinson's disease.

3. Study Design

This was a multicenter, double-blind, randomized, placebo controlled, parallel group assessment of six months' treatment with ropinirole as an adjunct to l-dopa in Parkinsonian patients not optimally controlled on l-dopa. Patients were randomly assigned at a ratio of 2 : 1 to receive either ropinirole or placebo orally following a 1 week placebo run-in phase. Randomization was stratified within each center according to concomitant use of selegiline.

4. Efficacy Variables

The primary efficacy endpoint in this study was at least a 20% reduction in l-dopa dose in conjunction with at least a 20% reduction in awake time spent "off" from baseline. Patients meeting both of these criteria were defined as responders. The primary efficacy endpoint originally described in the protocol was the mean percentage change from baseline in the total daily dose of l-dopa. In response to the FDA's concern that the reduction in l-dopa on its own was not an optimum endpoint, the

primary efficacy parameter was modified to the responder analysis stated above to include a measure of l-dopa sparing (reduction) and improvement in motor fluctuations. This was discussed at the end of phase 2 meeting in June 1993. The reviewer sees no protocol amendment submitted on this change.

Secondary efficacy variables for this study were: mean percentage reduction in l-dopa dose; the number of patients who maintained a 20% or more reduction from baseline in the total daily dose of l-dopa; mean reduction in percentage of awake time spent "off"; the number of patients with at least a 20% reduction in percent awake time spent "off"; the number of patients requiring reinstatement with l-dopa and time to reinstatement following reduction in l-dopa dose. Patients were defined as having been reinstated with l-dopa if, at any time during the trial, their l-dopa dose was reinstated up to or above their baseline level. In addition, the changes in the severity of Parkinson's disease signs and symptoms were assessed by the UPDRS and CGI.

5. Study Medication

Study medication was administered on a t.i.d. schedule with or immediately after meals. The starting dose (Level 1) was 0.25 mg t.i.d. followed by dose increases that were separated by a one week interval. The maximum dose was 8 mg t.i.d. (Level 13). All patients had to be titrated to at least 2.5 mg t.i.d. (Level 7). At Level 7 the level of l-dopa dose was reduced in all patients. This reduction was accomplished by lowering the Sinemet or Sinemet CR by ½ or 1 tablet (Sinemet CR being lowered before Sinemet). The l-dopa dose was reduced by an additional ½ or 1 tablet with each subsequent upward titration of study medication.

In the event that symptom control was lost, upward titration of the study medication was continued without reduction in l-dopa dose. Patients experiencing no improvement following two upward titrations of study medication warranted reinstatement of l-dopa. In the event of dopaminergic adverse experiences, the following sequence of events was recommended: first, the l-dopa unit dose was lowered while maintaining the ropinirole dose; second, the frequency of the l-dopa dose was reduced while maintaining the ropinirole dose; and third, the ropinirole dose was reduced. If an unacceptable loss of efficacy resulted from the above actions, the l-dopa dose was returned to baseline level and, if necessary,

was increased above the baseline level to maintain adequate clinical control.

6. Patient Disposition and Key Demographic Data

No. of Patients	Ropinirole		Placebo	
	n	%	n	%
-randomized	95	100.0	54	100.0
-completed trial	74	77.9	35	64.8
-premature discontinuations	21	22.1	19	35.2
-evaluated for ITT	94	98.9	54	100.0
-evaluated for forced l-dopa ITT	83	87.4	45	83.3
-evaluated for efficacy evaluable	72	75.8	42	77.8
-evaluated for safety	95	100.0	54	100.0
-in selegiline stratum	48	50.5	30	55.6
-in non-selegiline stratum	47	49.5	24	44.4
Demography				
-percentage of males (%)		63.2		68.5
-percentage of whites (%)		92.6		96.3
	mean ±SD		mean ±SD	
-mean age (years)	63.4 ± 9.4		63.4 ± 11.1	
-duration of Parkinson's disease (years)	8.6 ± 4.7		9.4 ± 6.3	
-duration of l-dopa (years)	7.3 ± 4.3		7.5 ± 5.6	
-l-dopa dose at baseline (mg)	758.5 ± 421.6		842.6 ± 516.9	

Sponsor's Efficacy Evaluation

7. Data Sets Analyzed

The sponsor performed the statistical analysis on the ITT population using the LOCF, 70% endpoint and week 24 observed cases (OC) datasets. The forced l-dopa reduction ITT population (83/95 (87%) ropinirole; 45/54 (83%) placebo) and the efficacy evaluable population (72/95 (76%) ropinirole; 42/54 (78%) placebo) were also analyzed using the LOCF datasets to check the robustness of the results.

8. Primary Efficacy Parameters

Table 8.1 displays the number and percentage of patients who were classified as responders in the ITT population. A patient was defined as a responder if they had at least a 20% reduction from baseline to endpoint in l-dopa dose and at least a 20% reduction from baseline to endpoint in percentage awake time spent "off".

More patients in the ropinirole group were classified as responders compared to the placebo group at every week and at endpoint (27.7% ropinirole vs. 11.1% placebo). The treatment effect observed at endpoint was statistically significant with an odds ratio of 4.406 and a 95% CI of 1.533, 12.658. The odds ratio is based on the odds of being a responder in the ropinirole group relative to the odds in the placebo group. The 95% confidence intervals did not include 1, indicating a statistically significant difference between ropinirole and placebo.

Table 8.1

Number (%) of patients with at least a 20% reduction in l-dopa* dose and at least a 20% reduction in the percent awake time spent "off"

Week	Ropinirole No. of Responders	%	Placebo No. of Responders	%
6	0/90	0	1/43	2.3
8	10/79	12.7	2/44	4.6
10	27/81	33.3	6/43	14.0
12	31/80	38.8	4/40	10.0
16	28/77	36.4	5/40	12.5
20	28/72	38.9	5/33	15.2
24	24/75	32.0	6/34	17.7
LOCF endpoint	26/94	27.7	6/54	11.1

*Reductions due to adverse experiences were not included.

The statistical model used to analyze these data was composed of treatment, selegiline stratum, center and Parkinson's disease stage. In the analysis, a significant treatment by selegiline interaction (p=0.013) was observed which could not be retained in the model due to a zero responder rate in the placebo, non-selegiline group

	Ropinirole n	%	Placebo n	%
Non-Selegiline	13/46	28	0/24	0
Selegiline	13/48	27	6/30	20

which caused difficulties in the PROC LOGISTIC procedure in SAS. Exploratory analyses were undertaken with different responder definitions. These analyses resulted in the disappearance of the zero-cell, which when analyzed, resulted in a non-significant treatment by selegiline interaction. This indicated that the interaction seen in the original analysis was probably an artifact of the zero responder rate observed in one group.

The ITT endpoint analysis was supported by analyses of the 70% endpoint dataset and by endpoint analysis of the forced l-dopa reduction ITT and efficacy evaluable populations. Analysis of the week 24 OC dataset showed that the treatment effect was not statistically significant (p=0.062). The odds ratios and 95% CI's for these analyses are displayed below.

Table 8.2

	Odds Ratio	95% CI
ITT-LOCF	4.406	1.533 , 12.658
Forced l-dopa Reduction ITT-LOCF	3.547	1.224 , 10.199
Efficacy Evaluable-LOCF	4.688	1.520 , 14.454
ITT-70% Endpoint	6.230	2.061 , 18.832
ITT-Week 24 OC	2.697	0.908 , 8.014

9. Secondary Efficacy Parameters

Formal hypothesis testing was performed on the LOCF intention to treat population for the secondary efficacy parameters described below. The 70% endpoint and week 24 OC datasets were also analyzed for the ITT population to check the robustness of the results. Terms for treatment, center and selegiline strata were always in the final models for the analysis of the secondary efficacy variables. Other terms were included where discussed.

9.1 20% Reduction in l-dopa Dose

Table 9.1.1 displays the number (%) of patients, by selegiline strata, who achieved at least a 20% reduction in l-dopa dose from baseline to endpoint for both treatment groups at endpoint. Overall, there were more ropinirole patients (48.9%) who achieved at least a 20% reduction in l-dopa dose compared to the placebo group (16.7%). The treatment difference observed for all patients was statistically significant with an odds ratio of 6.059 (95% CI of 2.492, 14.730). The percentage of patients with at least a 20% reduction in l-dopa dose was slightly higher for patients receiving selegiline (52.1% ropinirole, 20.0% placebo) compared to non-selegiline patients (45.7% ropinirole, 12.5% placebo).

Table 9.1.1

The number (%) of patients achieving at least a 20% reduction in l-dopa dose from baseline to LOCF endpoint

	Ropinirole		Placebo	
	n	%	n	%
Selegiline	25/48	52.1	6/30	20.0
Non-Selegiline	21/46	45.7	3/24	12.5
All Patients	46/94	48.9	9/54	16.7

The reduction in l-dopa dose excludes reductions due to adverse experiences.

The robustness of the ITT LOCF analysis was supported by analysis of the forced l-dopa reduction ITT population, the efficacy evaluable population, the week 24 OC, and the 70% endpoint, all of which indicated a statistically significant treatment effect. The odds ratio and 95% CI for each of these analyses is shown below.

	Odds Ratio	95% CI
ITT-LOCF	6.059	2.492, 14.730
Forced l-dopa Reduction ITT-LOCF	5.380	2.202, 13.143
Efficacy Evaluable-LOCF	6.737	2.632, 17.247
ITT-70% Endpoint	12.177	4.610, 32.164
ITT-Week 24 OC	3.956	1.550, 10.098

9.2 Mean Percentage Change in l-dopa Dose

The mean percentage changes in l-dopa dose from baseline to endpoint for all patients across selegiline strata and treatment groups are displayed in Table 9.2.1. Patients in the ropinirole group had a larger percentage reduction in l-dopa dose from baseline compared to the placebo group. This reduction was consistent across selegiline strata. The observed treatment difference was statistically significant ($p < 0.001$). The estimate of treatment difference was -18.858 with a 95% CI of -28.778, -8.937. The final model included terms for treatment, selegiline, center group, and PD stage.

Table 9.2.1

The mean percentage change from baseline in l-dopa dose at endpoint

	Ropinirole		Placebo	
	Mean	SD	Mean	SD
Selegiline	-21.9	37.1	0.4	22.6
Non-Selegiline	-16.9	28.8	-6.9	25.6
All Patients	-19.4	33.2	-2.8	24.0

All reductions in l-dopa dose exclude reductions due to adverse experiences.

The robustness of the endpoint analysis on the intention to treat population for mean percentage change was supported by analysis of the 70% endpoint and week 24 OC datasets, and the forced l-dopa reduction intent to treat and efficacy evaluable populations. The estimates of treatment difference and 95% CI for each of these analyses is shown below:

Table 9.2.2

	Treatment Difference	95% CI
ITT-LOCF	-18.858%	-28.778 , -8.937
Forced l-dopa Reduction ITT-LOCF	-20.050%	-31.332 , -8.768
Efficacy Evaluable-LOCF	-21.071%	-33.381 , -8.761
ITT-70% Endpoint	-21.441%	-33.493 , -9.388
ITT-Week 24 OC	-17.599%	-26.437 , -8.761

9.3 20% Reduction in Percentage Awake Time Spent "Off"

Table 9.3.1 displays the number of patients with at least a 20% reduction in the percent awake time spent "off" at the LOCF endpoint for the intention to treat population, as well as for the four datasets used to test the robustness of the analysis. There was a more favorable response in the ropinirole group compared to the placebo group for all datasets and populations examined.
The treatment effect observed in the intention to treat population was found not to be statistically significant. The odds ratio was 1.817 with a 95% CI of (0.891, 3.702).

Table 9.3.1

The number (%) of patients with at least a 20% reduction in the percent awake time spent "off" at endpoint

	Ropinirole		Placebo	
	N	%	N	%
ITT-LOCF	52/88*	59.1	23/52**	44.2
ITT-70% Endpoint	52/88	59.1	22/52	42.3
ITT-Week 24 OC	39/68	57.4	13/24	54.2
Forced l-dopa Reduction ITT-LOCF	49/80	61.3	19/44	43.2
Efficacy Evaluable-LOCF	44/69	63.8	17/41	41.5

*Six patients had either a missing baseline score for % awake time spent "off" or a zero % awake value which resulted in a total of 88 patients rather than 94

**One patient had a zero % awake value and one patient had no post baseline awake data which resulted in a total of 52 patients, rather than 54

The week 24 OC showed no significant treatment effect when using the same model as the ITT endpoint analysis.

9.4 Mean Percentage Awake Time Spent "Off"

Table 9.4.1 displays baseline and endpoint values for the mean percent awake time spent "off" and the percentage change from baseline to endpoint. The percentage change was calculated by the formula 100*(endpoint % - baseline %)/baseline %. In the overall population, there were reductions in mean percentage awake time spent "off" from baseline to endpoint in both groups. The mean percentage change from baseline to endpoint in percent awake time spent "off" was 9.2% for the ropinirole group and 4.3% for the placebo group, which would indicate a slight increase in percent awake time spent "off". This discrepancy between mean percent awake time spent "off", and percentage change from baseline was due to the fact that several patients had low baseline values which led to large positive percentage changes.

Table 9.4.1

Baseline and endpoint values for mean percent awake time spent "off" and % change from baseline to endpoint

	Ropinirole			Placebo		
	Mean	SD	mean % change*	Mean	SD	mean % change*
All Patients						
Baseline	39.3	23.3		43.4	21.6	
Endpoint	29.3	19.9	+9.2	37.8	20.0	+4.3
Selegiline						
Baseline	38.3	22.3		41.3	20.1	
Endpoint	25.5	20.3	-13.7	37.1	21.2	+15.1
Non-Selegiline						
Baseline	40.3	24.4		46.1	23.6	
Endpoint	33.1	18.9	+32.0	38.8	18.8	-10.5

* +indicates an increase percentage awake time spent "off" from baseline to endpoint and patient worsen clinically; - indicates a reduction from baseline to endpoint and patient better clinically.

As a result, the model fitting process included the change from baseline as the response variable with the baseline percent awake time spent "off" as a covariate in order to account for those patients entering the study with a low percent awake time spent "off". This model gave the following estimate (adjusted means) of change from baseline in percent awake time spent "off":

	Estimate	Standard Error
Ropinirole	-11.706	1.921
Placebo	-5.090	2.569

with a significant treatment difference of -6.617 with a 95% CI of (-12.883, -0.350). Analysis of the week 24 OC dataset did not result in a statistically significant treatment effect, due to placebo patients with large increases in percentage awake time spent "off" withdrawing or being reinstated above baseline l-dopa dose before week 24. Thus, these patients contribute to the differences in the LOCF analyses, but not in the week 24 OC analysis. The estimates of treatment difference and 95% CI for these analyses are displayed below:

	Treatment Difference	95% CI
ITT-LOCF	-6.617	-12.883 , -0.350
Forced l-dopa Reduction ITT-LOCF	-7.304	-14.006 , -0.602
Efficacy Evaluable-LOCF	-8.704	-15.961 , -1.446
ITT-70% Endpoint	-8.682	-15.334 , -2.029
ITT-Week 24 OC	-0.356	-8.587 , 7.876

9.5 Patients Response on CGI Global Improvement Item

The number (%) of patients in each of the individual categories of the CGI improvement score indicated that more ropinirole patients were 'much improved' compared to placebo patients and, conversely, more placebo patients were 'minimally worse' compared to ropinirole patients (Table 9.5.1).

Table 9.5.1

The number of patients in each category of the CGI improvement score at endpoint

	Ropinirole		Placebo	
	N	%	N	%
Very Much improved	2	2.1	0	0
Much Improved	23	24.5	6	11.3
Minimally Improved	30	31.9	11	20.8
No Change	27	28.7	21	39.6
Minimally Worse	8	8.5	11	20.8
Much Worse	4	4.3	4	7.6
Very Much Worse	0	0	0	0

Patients were classified as having an improvement if their CGI score was minimally improved or better and were classified as no improvement if otherwise. The odds ratio and 95% CI for the

analysis of CGI improvement are shown below.

Table 9.5.2

	Odds Ratio	95% CI
ITT-LOCF	2.981	1.462 , 6.080
Forced 1-dopa Reduction ITT-LOCF	2.846	1.333 , 6.079
Efficacy Evaluable-LOCF	3.061	1.372 , 6.831
ITT-70% Endpoint	4.185	1.974 , 8.873
ITT-Week 24 OC	2.236	0.862 , 5.799

The sponsor reported the significant treatment by selegiline interaction in these analysis.

9.6 Patients Reinstated Back Up To or Above Their Baseline 1-dopa Dose

Table 9.6.1 displays the number of patients who were reinstated back up to or above their baseline 1-dopa dose for all patients and across selegiline strata. Overall, there were fewer patients reinstated in the ropinirole group compared to the placebo group. The treatment effect observed for all patients was statistically significant ($p<0.0001$). The odds ratio was 0.229 with a 95% interval of 0.097, 0.545. The fitted model contained terms for treatment, selegiline, center grouping, disease duration, PD stage, and the selegiline by center grouping interaction. There were some differences in the percentage of patients reinstated back up to or above the baseline 1-dopa dose across the selegiline strata, but in both strata fewer ropinirole treated patients were reinstated compared with placebo treated patients.

Table 9.6.1

The number (%) of patients reinstated back up to or above their baseline 1-dopa dose

	Ropinirole		Placebo	
	N	%	N	%
Selegiline	12/48	25.0	14/30	46.7
Non-Selegiline	10/47	21.3	9/24	37.5
All Patients	22/95	23.2	23/54	42.6

9.7 Efficacy Subgroup Analysis

Descriptive subgroup analyses for gender and age were provided for the primary and secondary efficacy variables. The results were consistent with those in the ITT LOCF analyses. Age group and gender were considered as covariates in analyses of primary

and secondary efficacy variables. There were no statistically significant treatment by age or treatment by gender interactions identified in these analyses.

10. Reviewer's Analysis and Comments

10.1 Question on Primary Efficacy Parameter

This reviewer extracted the relevant components from the sponsor's datasets and carried out a hypothesis testing on whether the two factors, 20% reduction in l-dopa and 20% reduction in awake time spent "off", are independent. The p-values are 0.6361 for the ropinirole group and 0.129 for the placebo group, respectively. The independence hypothesis of the two factors is not rejected. Under the assumption of the independence, the proportion of patients with 20% reduction in l-dopa and 20% reduction in awake time spent "off" will be the product of the proportion of patients with 20% l-dopa reduction and the proportion of patients with 20% reduction in awake time spent "off". In this study, the proportion of patients with 20% reduction in l-dopa in ropinirole group is significantly higher than the placebo group (48.9% ropinirole vs. 16.7% placebo.) There is no significant difference between proportions of ropinirole and placebo patients with 20% reduction in awake time spent "off" (59.1% ropinirole vs. 44.2% placebo.) The significant testing result of compound parameter is mainly due to the large difference in l-dopa reduction. It is easy to see that even if we hypothetically let ropinirole group worsen than placebo group in reduction of awake time spent "off" , say 30% ropinirole vs. 50% placebo, the proportions from modified responders would still be favorable to ropinirole.

After consultation with Drs. Katz, Rouzer-Kammeyer and Chi, this reviewer decided to review this trial in two aspects separately: 1) Whether the ropinirole group had a significant reduction in l-dopa use; 2) Whether ropinirole group was clinically worse than the placebo group.

10.2 Reduction in L-dopa Use

The sponsor provided evidence showing that there was a

significant reduction in l-dopa from baseline in ropinirole group, see Sections 9.1 and 9.2.

The mean percentage change in the total daily dose of l-dopa in Section 9.2 was the primary efficacy parameter in protocol amendment 3 dated on August 7, 1992. In the protocol, the sponsor proposed that the efficacy parameter would be analyzed as a generalized linear model to take account of treatment, selegiline strata and center. In this NDA submission, the sponsor included the Parkinson's disease status in the final model. The similar efficacy conclusion, however, still holds (with p-value < 0.001) if only those protocol specified factors are included.

10.3 Comparing Clinical Outcomes

Besides sponsor's secondary endpoints, reduction in awake time spent "off" and the CGI improvement, this reviewer also examined the total motor scores of UPDRS that was a primary efficacy parameter in monotherapy study.

10.3.1 Reduction in Percentage Awake Time Spent "off"

Define a responder as at least 20% reduction in percentage awake time spent "off", the sponsor's analysis shows that the ropinirole group has a high rate of response although it is not statistically significant, see Section 9.3.

In Section 9.4, the sponsor analyzed the percentage awake time spent "off" in its original continuous form. Table 9.4.1 shows that there is an inconsistency in percentage reductions in different selegiline strata. The ropinirole group did little worse than the placebo group (9.2% vs. 4.3%.) The sponsor did an analysis with a covariate adjustment to show that the ropinirole group was better in ITT LOCF analysis. This reviewer would not comment on the merit of this analysis. This reviewer, however, agrees with the sponsor that the conflicting picture in Table 9.4.1 was mainly due to several patients with large positive percentage changes. This is similar to the situation in Study 54 where a few outlier produced a conflicting picture on interaction of treatment by selegiline. Since the mean is not robust to some extreme values of outliers, we calculated the median of the percentage awake time spent "off", the result is in the following,

Table 10.3.1

Median of % change in awake time spent "off" from baseline to endpoint

	Ropinirole	Placebo
Selegiline	-35.35	-15.08
Non-Selegiline	-28.39	-15.08

Based on the medians of the percentage changes in awake time spent "off", we see that ropinirole group is no worse than the placebo group.

10.3.2 CGI Global Improvement

The sponsor showed that the ropinirole group did better than placebo group in CGI improvement item, see Section 9.5.

10.3.3 Total UPDRS Motor Scores

Patients have different total UPDRS motor scores when they are in "on" or "off" status. The means of total UPDRS motor scores were calculated for "on" and "off" statuses separately.

Table 10.3.3

Means of total UPDRS scores at baseline and LOCF endpoint for ITT population

	Ropinirole		Placebo	
	On	Off	On	Off
Baseline	20.13	38.12	18.58	33.80
LOCF endpoint	18.07	30.16	17.71	32.33

Figures 44-1 to 44-4 are the plots of total UPDRS motor scores at week 0, 4, 12, and 24 for all patients. From the table and the plots, we see no trend of increasing total UPDRS motor scores in both ropinirole and placebo groups.

10.4 Selegiline Interaction

No significant interaction of treatment by selegiline was seen in this study. For the discrepancy of mean percentage changes of awake time spend "off" between selegiline and non-selegiline group (Table 9.4.1), this reviewer provided alternative calculation by using median instead of mean. The observed

discrepancy was then no longer existed. This reviewer thinks that the observed discrepancy is mainly due to the excessive variations presented in the data.

10.5 Conclusion

There is a statistically significant reduction in l-dopa dosage in ropinirole group. There is no evidence found that the patients in ropinirole group have worsened clinical outcomes compared with the placebo group.

Ropinirole, ON

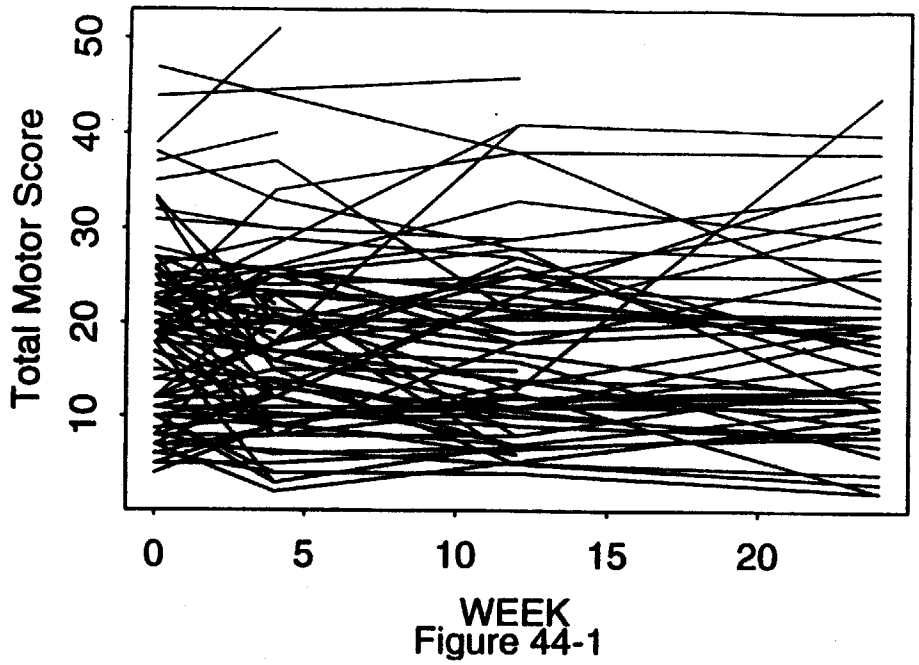


Figure 44-1

Placebo, ON

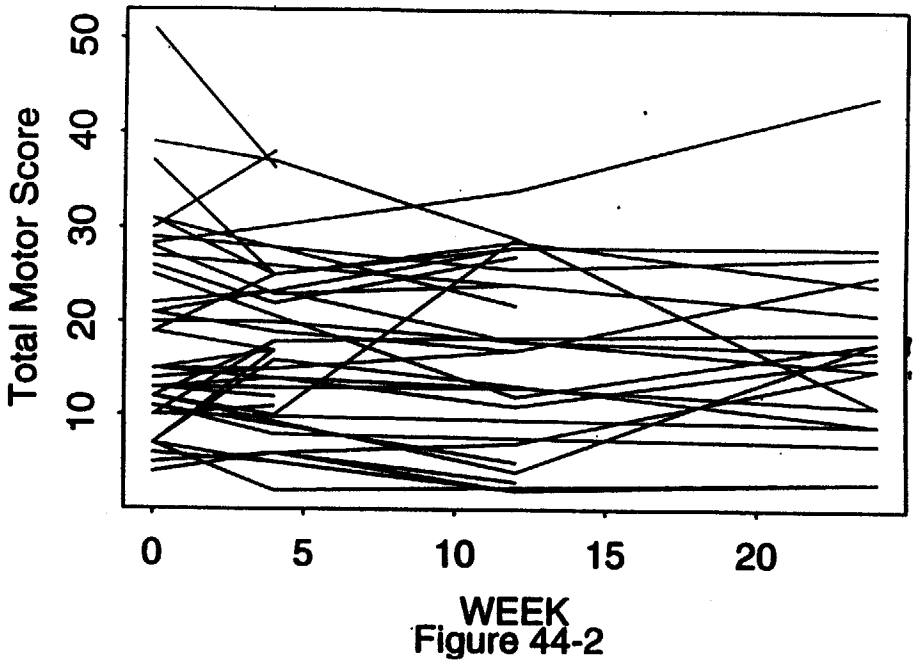


Figure 44-2

Ropinirole, OFF

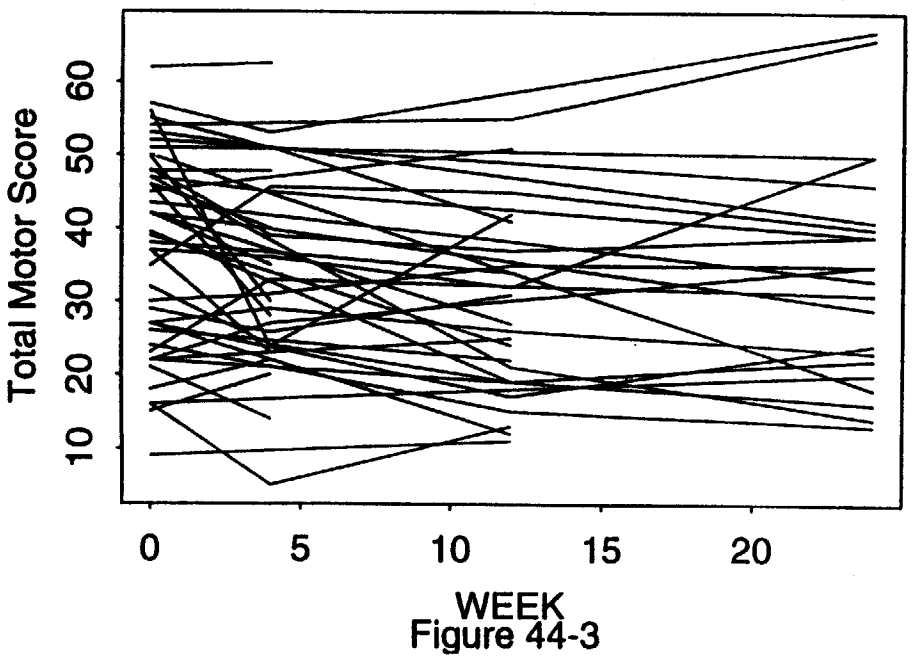


Figure 44-3

Placebo, OFF

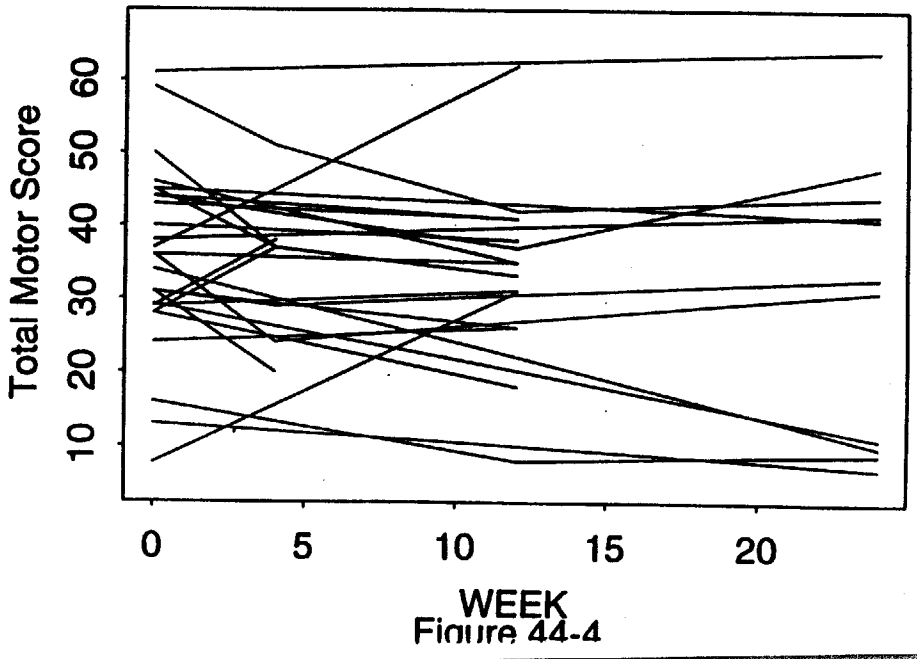


Figure 44-4

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APPEARS THIS WAY
ON ORIGINAL

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10/9/96

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10/15/96

cc: Archival NDA 20-658, Requip (ropinirole hydrochloride), SmithKline Beecham

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RETURN

Statistical Review and Evaluation of Carcinogenicity

JUN 11 1996

JUN 11 1996

NDA:	NDA 20-658
Applicant:	SmithKline Beecham
Name of Drug:	Requip (ropinirole hydrochloride) Tablets
Documents Reviewed:	TP-1005/SKF-101468/1 Two year carcinogenicity study of SK&F 101468-A in the Sprague-Dawley rat, Volumes 1 and 4 dated May, 1993; TP-1004/SKF-101468/2 A oral carcinogenicity study of SK&F 101468-A in CD-1 mice, Volumes 1 and 9 dated May 10, 1993; Data on floppy diskettes supplied by the sponsor
Statistical Reviewer:	Kun Jin, DOBI/OEB, HFD-710
Pharmacologist:	Brian Ault, ODE I, HFD-120

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1. Introduction

In this NDA submission two animal carcinogenicity studies, one in rats and one in mice, were included. The objective of these studies was to evaluate the carcinogenic potential of ropinirole in rats and mice when administered orally at some selected dose levels. The length of these studies is 2 years for both rats and mice. The entire study was done by species and by sex.

2. The Rat Study

The Sponsor's Analysis

2.1 Design

Two separate experiments, one in female and one in male rats, were conducted. In these experiments, ropinirole was given daily, by oral gavage, to male and female (70/sex/group) rats at dosages of 1.5, 15 or 50 mg/kg/day (doses expressed as the base) for approximately 23 months (706-709 days). Two additional groups (70/sex) received an equivalent volume (10 ml/kg) of vehicle (purified water). The rats were randomly assigned by rank body weight to one of the 5 groups. All surviving animals were necropsied over a 4-day period (days 707 to 710).

All rats were observed at least once daily for mortality, convulsions and morbidity. A palpable mass examination was performed monthly. The selected tissues (see sponsor's report for the list) were examined microscopically for all rats in both control groups and the high-dose group and for all decedent rats in the low- and mid-dose groups. For low- and mid-dose group rats in the terminal kill, the following tissues only were examined: eye, liver, ovaries, pituitary, testes with epididymides and macroscopic lesions.

2.2 Survival Data Analysis

The probability of survival was estimated using the product-limit method of Kaplan and Meier. The survival curves were compared using the log-rank test, firstly to test for an overall difference among all five groups and secondly to compare pairwise the treated groups to the combined controls.

Survival times in male and female rats receiving ropinirole did not differ significantly from those in the control groups, with the exception of the female 15 mg/kg dose group. When compared to the combined controls the female 15 mg/kg dose group's survival rates were significantly higher than that of the controls ($p < 0.001$).

2.3 Tumor Data Analysis

The analysis of incidental tumors was done by using the Hoel Walburg method. For fatal tumors, the data was analyzed by the log-rank test. For each tumor where lesions were recorded as incidental in some rats and fatal in others, Peto's method is used to combine the results of analyzing tumors using the Hoel Walburg method and fatal tumors using the log-rank test. See Gart et. al (1986) for details of these methods.

When the total numbers of observed lesions were between 3 and 10, analysis was only performed on the overall incidence, not adjusting for any differences in survival. A Cochran-Armitage linear trend test was performed using an exact permutation distribution and pairwise comparison between groups were made using a Fisher's exact test. Tumors with an incidence of two or less, across all five groups, were not formally tested.

The test did not show statistically significant positive trend in incidence of any of the tested tumor types for female rats. There were two individual tumors types in males for which the test for trend were statistically significant ($p < 0.05$): Skin: fibroma [B] and Testicular interstitial cell tumor [B]. The sponsor stated that the significant testing result for skin fibromas was marginal.

The Reviewer's Analysis

The reviewer independently performed analysis on the survival and tumor data. All data used in the reviewer's analysis were provided by the sponsor on the floppy diskettes in the "Biometrics" format, except for the body weight data that were taken from the sponsor's hard copy submission.

2.4 Survival Data Analysis

The purposes of the survival data analysis were: (1) to examine the significance of the differences in survival among the treatment groups (i.e., homogeneity test), and (2) to determine the significance of positive or negative dose-mortality trend (i.e., dose-mortality trend test). The Cox test statistic and the generalized Kruskal-Wallis test statistic were used. The background for these tests is found in Lin et. al. (1994) and Thomas et. al. (1976).

The intercurrent mortality data of rat study are given in Table 1. The plots of Kaplan-Meier estimates of the survival probabilities of female and male rats are given in Figures 1 and 2, respectively. The result of the homogeneity test and dose-mortality trend test for comparing four groups of survival distributions (Control, Low, Medium and High) are given in Table 2. The results of pairwise comparisons among those groups are given in Table 3.

For female rats, the medium dose group had a better survival rate compared with the other groups (Figure 1), and the homogeneity test was significant ($p < 0.05$, Table 2). However, there were no significantly positive dose-mortality trends being detected. For male rats, although it looks like the medium dose group had a high earlier mortality rate, the differences in survival among the four groups were not statistically significant, and there were no significant dose-

mortality trends. In the analysis, the reviewer has combined the two control groups since they are not statistically significantly different.

2.5 Tumor Data Analysis

In the tumor data analysis, the tumors were classified as either fatal (lethal) or non-fatal (non-lethal) type. In the analysis for a selected tumor, the significance of dose-tumor positive linear trend was our primary interest. Using the method of Peto et al (1980), the reviewer applied the death-rate method to fatal tumors and prevalence method to non-fatal tumors. The p-values of these tests were evaluated by an exact permutation method. For tumors that caused deaths for some, but not all rats, a combined test was performed. The combined test used the Z-statistic which was assumed to follow a standard normal distribution. This test was referred to as the asymptotic test in the following context. The details of these tests can be found in Lin et. al. (1994). For those types of tumors not examined in the terminal kill (low and medium dose groups), additional pairwise tests (control vs high dose) were performed. To adjust p-values for the effect of multiple testing, a rule proposed by the Division of Biometrics, CDER/FDA was used in the review. This rule says that in order to keep the false-positive rate at the nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of $\leq$ 1% (rare tumor) should be tested at a 0.025 significance level, otherwise (common tumor) a 0.005 significance level should be used.

The p-values of the tested tumor types for female and male rats are given in Tables 4 and 5, respectively. The time intervals used were 0-370, 371-552, 553-643, 644-706 days and terminal sacrifice. Note that the reviewer's decision on significance of trend for tumors that were either fatal or non-fatal to all rats (MSFLG=s) relied on the p-values of exact permutation tests. For other tumors (MSFLG=m), the p-values of asymptotic tests were used.

There were no statistically significant positive linear trends detected in female rats. For male rats, there was one tumor type, Testicular interstitial cell tumor [B], showing a significant positive linear trend, which was also reported by the sponsor. The testing result is as follows:

Sex	Tumor/Site	Tumor Incidence			
Male	Testicular interstitial cell tumor				
Exact p-value	Asymptotic p-value	Ctrl	Low	Med	High
0.0000	0.000	5/140	2	12	32

For skin fibromas reported by the sponsor, the testing result is given as follows,

Sex	Tumor/Site	Tumor Incidence			
Male	Skin fibroma				
Exact p-value	Asymptotic p-value	Ctrl	Low	Med	High
0.0168	0.01155	4/140	4	7	7
0.0156	0.00510	Pairwise comparison between control and high dose groups			

Since the spontaneous tumor rate in the control group was 2.857% (4/140), the cut-off p-value of 0.005 was used to determine that there was no statistically significant dose-tumor positive trend for this type of tumor.

2.6 Reviewer's Comments

The results of reviewer's analysis were consistent with that of the sponsor's. For the male rats, a positive linear trend for testicular interstitial cell tumor was highly significant with p-value of 0.0000. None of the other tested tumor types showed a statistically significant positive linear trend in either sex.

3. The Mouse Study

The Sponsor's Analysis

3.1 Design

Two separate experiments, one in female and one in male mice, were conducted. In these experiments, ropinirole (Lot No. P9-JSD-811) were given orally by gavage to 6-week-old CD-1 mice (, weighing between 17.4 and 32.4 grams, at dosages of 5, 15 or 50 mg/kg daily for 104 weeks. Two control groups received deionized water. Each group consisted of 60 mice/sex. The mice were randomly assigned to one of the five groups.

All animals were examined twice daily for mortality. Detailed clinical examinations, including palpation for masses, were performed once weekly as of Week 26. Histopathological examinations were performed on the selected tissues (see sponsor's report for the list) in high

dose and control groups and all mice in the low and medium dose groups that died or were sacrificed before study termination. All gross findings in all groups were examined microscopically.

3.2 Survival Data Analysis

The two control groups were combined for statistical comparisons of the survival data. Statistical procedures used for analysis of survival data included: a one-tailed Fisher's exact test ($P = 0.05$) for the overall incidence of mortality, the Kaplan-Meier method for computing survival curves and the Cox's test for comparing survival distributions.

The sponsor stated that there was a statistically significant decrease in mortality for the medium dose group when compared to control males. Statistical comparison of the survival distributions of drug-treated groups against the combined control groups revealed no intergroup differences.

3.3 Tumor Data Analysis

Statistical evaluation of the tumor data was not performed for low and medium dose groups since microscopic examination was not performed on all tissues. The Fisher's exact test was performed for all tumor types observed in this study. The sponsor stated that the analysis of tumor incidences was not time adjusted since no intergroup differences of mortality were observed. The nominal level for the tests is 0.05.

The sponsor concluded that administration of ropinirole at 5, 15 50 mg/kg/day for 104 weeks was not associated with any significant increase in neoplastic lesions in the organs and tissues examined with the exception of an increase in the incidence of benign uterine endometrial stromal polyp in high dose females when compared to combined control females.

The Reviewer's Analysis

The reviewer independently performed analysis on the survival and tumor data. All data used in the reviewer's analysis were provided by the sponsor on the floppy diskettes in the "Biometrics" format, except for the body weight data that were taken from the sponsor's hard copy submission. The descriptions of the reviewer's methods are given in the last section of the rat study.

3.4 Survival Data Analysis

The intercurrent mortality data of the mouse study are given in Table 6. The plots of Kaplan-Meier estimates of the survival probabilities of female and male mice are given in Figures 3 and 4, respectively. The result of the homogeneity test and dose-mortality trend test for comparing four groups of survival distributions (Control, Low, Medium and High) are given in

Table 7. The results of pairwise comparisons among those groups are given in Table 8.

For female mice, the differences in survival among all groups were not statistically significant, and there were not significant dose-mortality trends. For male mice, however, the high dose group appeared to have a high mortality rate in comparison with others(see Figure 4). The p-values of the homogeneity test are 0.0527 for the Cox test and 0.0344 for the Kruskal-Wallis test. The p-values of the dose-mortality trend test are 0.0505 for the Cox statistic and 0.0232 for the Kruskal-Wallis statistic (Table 7). The Kruskal-Wallis test gives more weight to the earlier deaths, which appears to be the case here(see Figure 4). The reviewer concludes that the high dose male group suffered a statistically significant high mortality rate in comparison with others.

3.5 Tumor Data Analysis

The reviewer applied the time adjusted methods to the tumor incidence data for control and all drug-treatment groups. (See the last section for the details of these tests.) The p-values of these tests are reported in Tables 9 and 10. In order to overcome the possible missing data problem in low and medium dose groups, the reviewer also carried out the similar test for control and high dose groups. (The result is not reported here.) The time intervals used were 0-52, 53-78, 79-91, 92-104 weeks and terminal sacrifice. Note that the reviewer's decision on significance of trend for tumors that were either fatal or non-fatal to all rats (MSFLG=s) relied on the p-values of exact permutation tests. For other tumors (MSFLG=m), the p-values of asymptotic tests were used.

There were no statistically significant positive linear trends detected in the male mice. For the female mice, there was one tumor type, benign uterine endometrial stromal polyp, showing a significant linear positive trend. This result is also reported by the sponsor. The testing result for this tumor type is as follows:

Sex	Tumor/Site	Tumor Incidence			
Female	Uterine endometrial stromal polyp [B]				
Exact p-value	Asymptotic p-value	Ctrl	Low	Med	High
0.0011	0.00055	10/120	5	6	14
0.0039	0.00150	Pairwise comparison between control and high dose groups			

The cut-off p-value of 0.005 was used to determine the testing significance.

3.6 Reviewer's Comments

The sponsor failed to point out the statistically significant high mortality rate occurred in male high dose (50 mg/kg/day) group. The sponsor's non-time adjusted method, Fisher exact test, is not appropriate for this type of tumor data. However, there is no discrepancy between the conclusion of the reviewer and that of the sponsor on the tumor data analysis. The only tumor type showing a significant linear positive trend was benign uterine endometrial stromal polyp in female mice.

4. Evaluation of Validity of the Design

To evaluate the validity of experimental design of carcinogenicity studies, the CDER statistician usually considers the following issues: (1) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor? (2) Were dose levels high enough to pose a reasonable tumor challenge to the animals? There has been no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with 50 animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by the experts in this field.

Haseman (1985) investigated the first issue. Based on the data from twenty one studies using Fisher 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP), he found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. In a personal communication with Dr. Karl Lin, Division of Biometrics II, CDER, FDA, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, after 80-90 weeks, would be considered as a sufficient number and adequate exposure. However, the percent could be lower or higher if the number of animals used in each treatment/sex group is larger or smaller than 50 so that there would be 20-30 animals still alive after the 80-90 weeks. In addition, Chu, Cueto and Ward (1981) suggested that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year." It appears that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and the number of animals at risk.

As far as the adequacy of dose level is concerned, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). Chu, Cueto and Ward proposed the following criteria for the dose adequacy.

(1) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(2) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(3) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

Based on the above suggestions and recommendations, the reviewer now examines the validity of experimental design of rat and mouse studies.

4.1 The Rat Study

The following are the summary of survival data of rats in high dose group.

Survivals at	End of 52nd week	End of 90th week
Female rat	88.57%	48.57%
Male rat	92.86%	42.86%

Although the survival rate of male rat at the end of 90th week was lower than 50%, there were 30 survivals out of the total of 70 rats. From the summary data, and the survival criteria mentioned above, it can be concluded that there were enough number of rats exposed for sufficient amount of time to the drug in both sexes.

The following are summary body weight gains of the rats (data from the sponsor's report).

Sex	Group	Mean body weigh (gms)		Percentage of weight gain
		Beginning of study	End of Study	
Female rat	Control	156	594	280.77%
	Low	157	561	257.32%
	Med	154	561	264.29%
	High	155	521	236.13%
Male rat	Control	197	871	342.13%
	Low	197	848	330.46%
	Med	194	760	291.75%
	High	195	728	273.33%

Relative to the control, decrement of body weight gain in the high dose group is 15.90% for females and 20.11% for males. Thus, from the weight gain criteria it appears that the high dose used in rat study is greater than the MTD.

From Table 1 (Appendix), the mortality rates of controls at the end of study are higher than that of the high dose groups for both sexes. These data do not support the finding in the previous paragraph. The reviewer has a concern on the validity of the experiment. To draw any conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

4.2 The Mouse Study

The following are the summary of survival data of mice in high dose group.

Survivals at	End of 52nd week	End of 90th week
Female mouse	91.67%	60.00%
Male mouse	85.00%	51.67%

From the summary data, and the survival criteria mentioned above, it can be concluded that there were enough number of mice exposed for sufficient amount of time to the drug in both sexes.

The following are summary body weight gains of the mice (data from the sponsor's report).

Sex	Group	Mean body weigh (gms)		Weight gain
		Beginning of study	End of Study	
Female mouse	Control	20.59	33.51	62.75%
	Low	20.72	33.27	60.57%
	Med	20.63	32.68	58.41%
	High	20.62	33.12	60.62%
Male mouse	Control	25.29	38.29	51.40%
	Low	25.70	38.64	50.35%
	Med	25.44	37.61	47.84%
	High	25.37	36.58	44.19%

Relative to the control, decrement of body weight gain in the high dose group is 3.39% for females and 14.03% for males. Using the body weight gain criteria, it appears that the high dose is only slightly greater than the MTD in males. From Tables 6 and 7, Figure 4, the high dose group of males has a higher mortality rate compared to the controls. There is no differences of mortality rates among female groups. The high dose appears adequate in males, but not in females. To draw a final conclusion on whether the high dose is MTD, all clinical signs and histopathological effects in the treated mice should be taken into consideration.

5. Conclusions

Rat study: No statistically significant positive linear trend or differences in the mortality among control and treatment groups was detected in either sex. For the male rats, a positive linear trend for testicular interstitial cell tumor was highly significant with p-value of 0.0000. None of the other tested tumor types showed a statistically significant positive linear trend in either sex.

From the weight gain criteria, it appears that the high dose used in rat study is greater than the MTD. To draw any final conclusion in this regard, all clinical signs and histopathological effects in the treated rats should be taken into consideration.

Mouse study: No statistically significant positive linear trend or differences in the mortality among control and treatment groups was detected in female mice, but the high dose male group suffered a statistically significant high mortality mice in comparison with others. There were no statistically significant positive linear trends detected in all tested tumor types in the male mice. For the female mice, there was one tumor type, benign uterine endometrial stromal polyp, showing a significant linear positive trend.

From the weight gain criteria, it appears that the high dose used in mouse study is adequate in males, but not in females. To draw any final conclusion in this regard, all clinical signs and histopathological effects in the treated mice should be taken into consideration.

References:

1. Chu, Cueto and Ward (1981). "Factors in the evaluation of 200 national cancer institute carcinogen bioassay." Journal of Toxicology and Environmental Health. Vol. 8, pp. 251-280.

2. Gart, J.J., Krewski, D., Lee, D.N., Tarone, R.E., and Wahrendorf, J. (1986) "Statistical Methods in Cancer Research. Volume III--The design and analysis of long-term animal experiments", pp. 1-219, International Agency for Research on Cancer, Lyon

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4. Haseman, J. K. (1985). "Issues in carcinogenicity testing: Dose selection." Fundamental and Applied Toxicology, Vol. 5. pp. 66-78.

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6. Peto et al (1980). "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments. In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer, Lyon, France. IARC Monographs Supplement 2. pp. 311-426.

7. Thomas et al (1976). "Trend and Homogeneity Analyses of Proportions and Life Table Data." Computers and Biomedical Research. pp. 373-81.

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6/11/96

George Chi, Ph.D.
Director, DB I

cc: Archival NDA 20-658, Requip (ropinirole hydrochloride), SmithKline Beecham

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Appendix

Table 1
Intercurrent mortality rates in the rat study

Female Rat

		Ctrl		Low		Med		High	
		No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died
Sex	Time (days)								
Female	0-370	9	6.40	2	2.86	2	2.86	9	12.86
	371-552	45	38.57	21	32.86	12	20.00	14	32.86
	553-643	30	60.00	11	48.57	10	34.29	15	54.43
	644-706	17	72.14	14	68.57	11	50.00	9	67.14
	Term. Sac.	39	27.86	22	31.43	35	50.00	23	32.86
	Total	140		70		70		70	

Male Rat

		Ctrl		Low		Med		High	
		No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died
Sex	Time (days)								
Male	0-370	16	11.43	5	7.14	14	20.00	6	8.57
	371-552	36	37.14	16	30.00	12	37.14	23	41.43
	553-643	31	59.29	18	55.71	11	52.86	12	58.57
	644-706	21	74.29	13	74.29	13	71.43	7	68.57
	Term. Sac.	36	25.71	18	25.71	20	28.57	22	31.43
	Total	140		70		70		70	

Female Rat Survival Curves

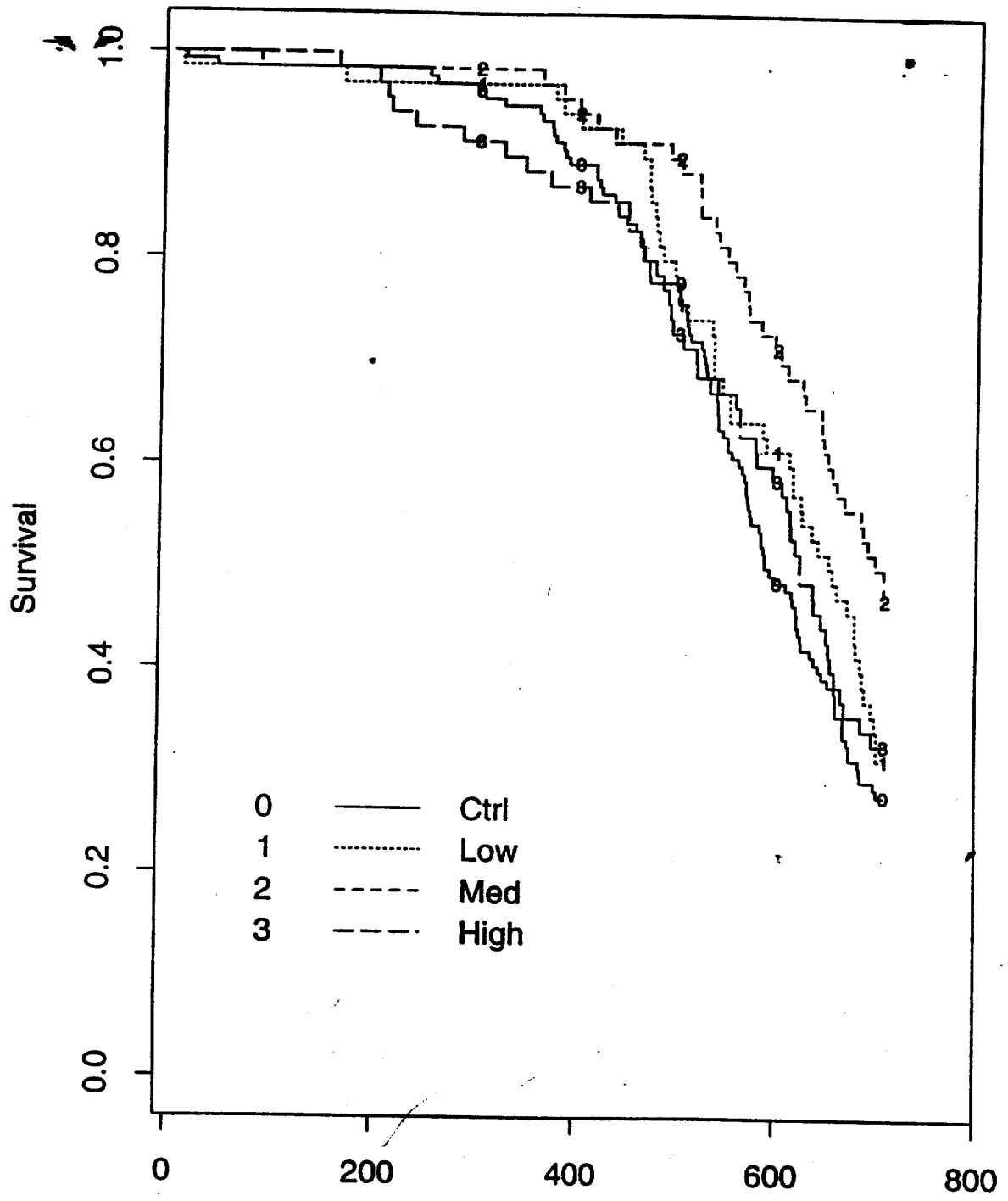

Figure 1

Male Rat Survival Curves

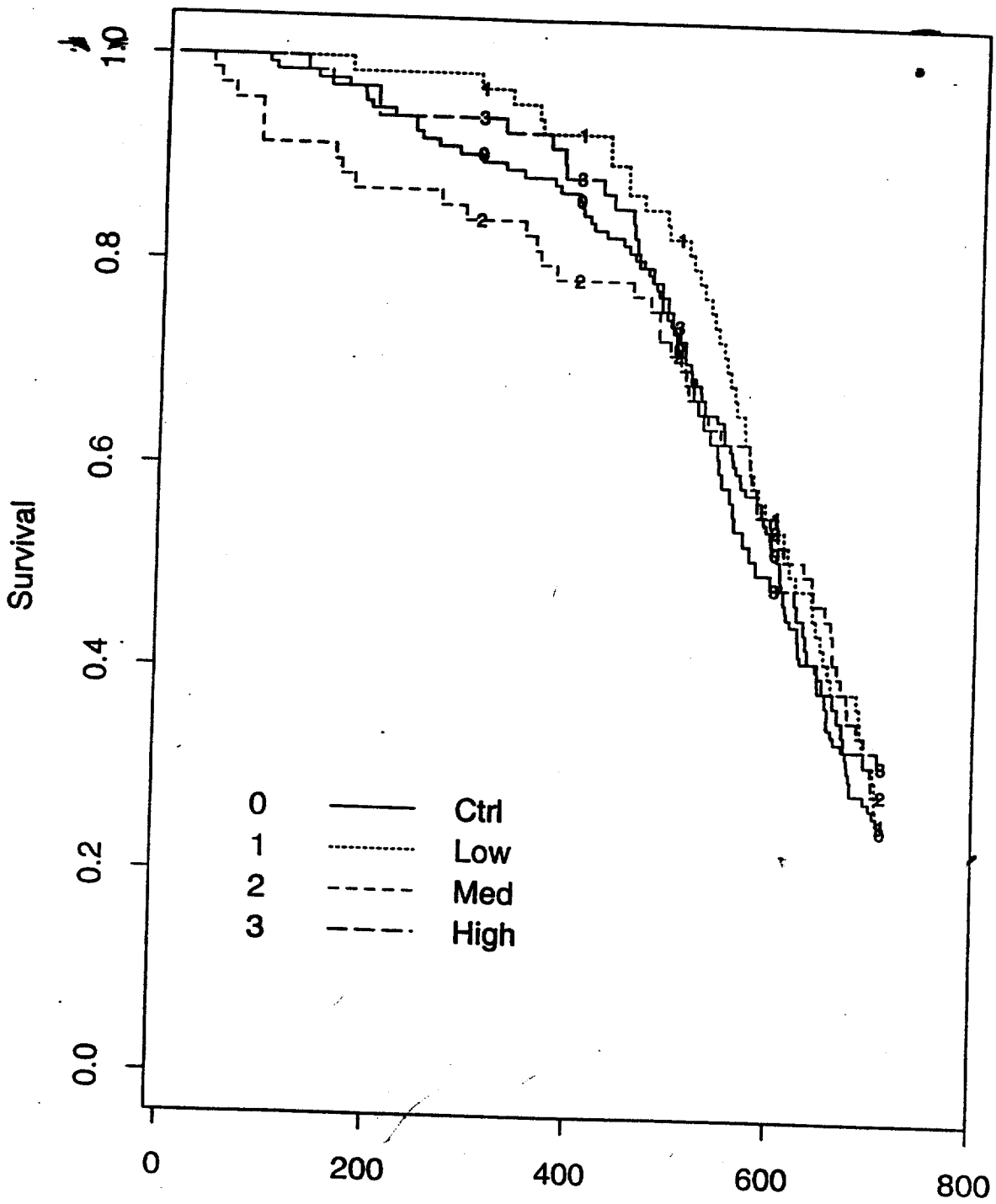

Figure 2

Table 2

P-values of tests for positive linear trend in mortality in the rat study

Female Rat

	Test	P-value
Homogeneity	Cox	0.0145*
	Kruskal-Wallis	0.0095*
Dose-mortality trend	Cox	0.5926
	Kruskal-Wallis	0.7600

Male Rat

	Test	P-value
Homogeneity	Cox	0.8965
	Kruskal-Wallis	0.7873
Dose-mortality trend	Cox	0.6695
	Kruskal-Wallis	0.9573

* $p < 0.05$

Table 3

P-values of pairwise tests for the differences in mortality between treatment groups in the rat study

Female Rat

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE CONSERVATIVE	GENERALISED K/W ANALYSIS EXACT	GENERALISED K/W ANALYSIS INVERSE CONSERVATIVE
0 VS. 1	CHISQ		.1415	NEG	.9816	.9791	1.7214	1.7185
	PROB	.3511	.7068		.3218	.3224	.1895	.1899
0 VS. 2	CHISQ		7.9398	NEG	9.7927	9.7236	10.9970	10.9399
	PROB	.0026**	.0048**		.0018**	.0018**	.0009**	.0009**
0 VS. 3	CHISQ		.3461	NEG	.3352	.3348	.2331	.2328
	PROB	.2767	.5563		.5626	.5628	.6293	.6294
1 VS. 2	CHISQ		3.6012	NEG	3.8237	3.8134	4.0935	4.0851
	PROB	.0286*	.0577		.0505	.0508	.0430*	.0433*
1 VS. 3	CHISQ		.0000	NEG	.0444	.0444	.4079	.4076
	PROB	.5000	1.0000		.8331	.8331	.5230	.5232
2 VS. 3	CHISQ		2.9592	POS	4.5326	4.5155	6.0154	5.9973
	PROB	.0425*	.0854		.0333*	.0336*	.0142*	.0143*

Male Rat

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE CONSERVATIVE	GENERALISED K/W ANALYSIS EXACT	GENERALISED K/W ANALYSIS INVERSE CONSERVATIVE
0 VS. 1	CHISQ		.0126	NEG	.3155	.3153	1.1135	1.1130
	PROB	.5186	.9106		.5743	.5744	.2913	.2914
0 VS. 2	CHISQ		.1509	NEG	.1506	.1503	.0182	.0181
	PROB	.3462	.6977		.6979	.6982	.8928	.8929
0 VS. 3	CHISQ		.6772	NEG	.2289	.2287	.0685	.0685
	PROB	.2046	.4105		.6323	.6325	.7935	.7935
1 VS. 2	CHISQ		.0361	NEG	.0071	.0071	.4029	.4024
	PROB	.4247	.8493		.9329	.9329	.5256	.5259
1 VS. 3	CHISQ		.3150	NEG	.0030	.0030	.4975	.4970
	PROB	.2875	.5746		.9566	.9566	.4806	.4808
2 VS. 3	CHISQ		.0340	NEG	.0007	.0007	.0261	.0260
	PROB	.4269	.8537		.9796	.9796	.8717	.8718

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Test of trend based on the tumor data

Female Rat

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ABDOMINAL CAVITY	FIBROSARCOMA [M]	S	0.1923	0.02530	0	0	0	1
ADRENAL	CORTICAL ADENOMA [B], unilater	S	0.7384	0.73820	2	0	1	0
ADRENAL	PHEOCHROMOCYTOMA [B], unilater	S	1.0000	0.92170	4	0	0	0
ADRENAL	PHEOCHROMOCYTOMA [M], unilater	S	1.0000	0.71255	1	0	0	0
BRAIN	ASTROCYTOMA [M]	S	1.0000	0.75365	1	0	0	0
BRAIN	MIXED GLIOMA [M]	S	1.0000	0.75550	1	0	0	0
JEJUNUM	OSTEOSARCOMA [M]	S	0.2273	0.03720	0	0	0	1
KIDNEY	LIPOMA [B]	S	0.8485	0.81885	1	1	0	0
KIDNEY	TUBULAR CELL ADENOMA [B]	S	1.0000	0.78055	1	0	0	0
LIVER	CHOLANGIOMA [B]	S	1.0000	0.78055	1	0	0	0
LIVER	HEPATOCELLULAR ADENOMA/ADENOMA	S	0.2986	0.28205	1	0	4	1
LIVER	KUPFFER CELL SARCOMA [M]	S	0.4451	0.46545	0	0	1	0
MAMMARY GLAND	ADENOCARCINOMA [M]	S	0.9999	0.99960	20	9	9	0
MAMMARY GLAND	CYSTADENOMA [B], papillary	S	1.0000	0.78055	1	0	0	0
MAMMARY GLAND	FIBROADENOMA [B]	S	1.0000	1.00000	74	41	32	18
MULTIPLE ORGANS	HISTIOCYTIC SARCOMA [M]	S	1.0000	0.77515	1	0	0	0
MULTIPLE ORGANS	MALIGNANT LYMPHOMA [M]	S	0.7315	0.77220	1	1	1	0
MULTIPLE ORGANS	MYELOMONOCYTIC LEUKEMIA [M]	M	0.8469	0.84795	3	1	2	0
OVARY	GRANULOSA CELL TUMOR [B]	S	0.9926	0.94165	4	1	0	0
OVARY	MESOTHELIOMA [M]	S	0.6667	0.72560	0	1	0	0
OVARY	TUBULAR ADENOMA [B]	S	0.1933	0.02725	0	0	0	1
PANCREAS	ACINAR CELL ADENOMA [B]	S	1.0000	0.78055	1	0	0	0
PANCREAS	ISLET CELL ADENOMA/ADENOMATA [	S	0.5266	0.58070	6	0	0	2
PANCREAS	ISLET CELL CARCINOMA [M]	S	1.0000	0.71255	1	0	0	0
PITUITARY	ADENOMA/ADENOMATA [B], pars di	M	0.9999	0.99980	110	58	54	40
PITUITARY	CARCINOMA [M], pars distalis	M	0.9952	0.94985	4	1	0	0
SKELETAL MUSCLE	HEMANGIOSARCOMA [M]	S	0.4874	0.48610	0	0	1	0
SKIN	BASAL CELL TUMOR [B]	S	1.0000	0.78055	1	0	0	0
SKIN	FIBROMA [B], dermal/subcutaneo	S	0.2870	0.28650	2	2	4	2
SKIN	FIBROSARCOMA [M], subcutaneous	S	0.3231	0.35850	1	1	2	1
SKIN	LIPOMA [B], subcutaneous	S	0.3853	0.38255	1	1	1	1
SKIN	SARCOMA, NOS [M], subcutaneous	S	1.0000	0.88625	2	0	0	0
SKIN	SCHWANNOMA [B], subcutaneous	S	0.4874	0.48610	0	0	1	0
SKIN	SQUAMOUS CELL PAPILLOMA/PAPILL	S	0.1507	0.08225	0	0	1	1
SKIN	TRICHOFOLLICULOMA / TRICHOEPIT	S	0.0484	0.02615	0	1	0	2
THYMUS	SQUAMOUS CELL CARCINOMA [M]	S	0.4874	0.48610	0	0	1	0
THYROID	C-CELL ADENOMA/ADENOMATA [B]	S	0.4020	0.41565	8	2	2	4
THYROID	C-CELL CARCINOMA [M]	S	0.1267	0.12420	7	1	1	5
THYROID	FOLLICULAR CELL ADENOMA [B]	S	1.0000	0.75365	1	0	0	0
URETHRA	SQUAMOUS CELL CARCINOMA [M]	S	0.6857	0.74510	0	1	0	0
URINARY BLADDER	TRANSITIONAL CELL CARCINOMA [M	S	1.0000	0.75345	1	0	0	0
UTERUS	ENDOMETRIAL CARCINOMA [M]	S	0.1897	0.02545	0	0	0	1
UTERUS	ENDOMETRIAL STROMAL POLYP [B]	S	0.3286	0.30570	3	0	2	2
UTERUS	ENDOMETRIAL STROMAL SARCOMA [M	S	1.0000	0.71255	1	0	0	0
UTERUS	LEIOMYOMA [B]	S	0.4874	0.48610	0	0	1	0
VAGINA	LEIOMYOSARCOMA [M]	S	0.4196	0.46140	0	0	1	0

Note: MSFLG=M indicates that the tumor is fatal to some but not all animals;
MSFLG=S indicates that the tumor is either fatal or non-fatal to all animals;
An '*' indicates a significant linear dose-tumor trend.

Table 5

Test of trend base[illegible] the tumor data

Ma[illegible]t

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ABDOMINAL CAVITY	ADENOCARCINOMA [M], accessory	M	0.1139	0.04115	1	0	0	2
ABDOMINAL CAVITY	LIPOMA [B]	S	0.4375	0.49730	0	0	1	0
ADRENAL	CORTICAL ADENOMA [B], unilater	S	0.3695	0.37870	2	0	2	1
ADRENAL	PHEOCHROMOCYTTOMA [B], unilater	S	0.8900	0.88210	11	3	4	2
ADRENAL	PHEOCHROMOCYTTOMA [M], unilater	S	0.6458	0.65505	1	0	1	0
BONE	OSTEOMA [B]	S	1.0000	0.72740	1	0	0	0
BRAIN	ASTROCYTOMA [M]	M	0.9462	0.88675	2	1	0	0
BRAIN	GRANULAR CELL TUMOR [B]	S	0.6111	0.70725	0	1	0	0
BRAIN	OLIGODENDROGLIOMA [M]	S	1.0000	0.75260	1	0	0	0
EAR	FIBROSARCOMA [M]	S	0.4023	0.51060	0	0	1	0
EAR	ZYMBAL'S GLAND CARCINOMA [M]	M	1.0000	0.84155	2	0	0	0
HEART	SCHWANNOMA [B], endocardial	S	1.0000	0.73785	1	0	0	0
KIDNEY	LIPOMA [B]	S	0.1467	0.08705	2	0	0	2
KIDNEY	TUBULAR CELL ADENOCARCINOMA [M	S	1.0000	0.77155	1	0	0	0
KIDNEY	TUBULAR CELL ADENOMA [B]	S	0.6973	0.76695	1	1	1	0
LIVER	CHOLANGIOMA [B]	S	1.0000	0.73785	1	0	0	0
LIVER	HEPATOCELLULAR ADENOMA/ADENOMA	S	0.0720	0.05785	5	1	3	5
LIVER	HEPATOCELLULAR CARCINOMA [M]	S	0.5524	0.51115	2	1	0	1
LUNG	OSTEOSARCOMA [M], metastatic s	S	1.0000	0.78840	1	0	0	0
LYMPH NODE - MESENTER	HEMANGIOMA [B]	S	0.8542	0.82150	1	1	0	0
MAMMARY GLAND	ADENOCARCINOMA [M]	S	0.6250	0.74820	0	1	0	0
MAMMARY GLAND	CYSTADENOMA [B], papillary	S	1.0000	0.72740	1	0	0	0
MAMMARY GLAND	FIBROADENOMA [B]	S	0.4995	0.52115	4	3	1	2
MULTIPLE ORGANS	HISTIOCYTTIC SARCOMA [M]	M	0.9669	0.92810	3	2	0	0
MULTIPLE ORGANS	MALIGNANT LYMPHOMA [M]	S	1.0000	0.83280	2	0	0	0
MULTIPLE ORGANS	MYELOMONOCYTTIC LEUKEMIA [M]	M	0.7942	0.79685	5	1	0	1
PANCREAS	ACINAR CELL ADENOMA [B]	S	0.6983	0.70270	3	2	0	1
PANCREAS	ACINAR CELL CARCINOMA [M]	S	0.5694	0.69935	0	1	0	0
PANCREAS	ISLET CELL ADENOMA/ADENOMATA [	S	0.9427	0.93720	12	3	1	2
PANCREAS	ISLET CELL CARCINOMA [M]	S	0.3454	0.34820	3	2	0	2
PERIPHERAL NERVE	PARAGANGLIOMA [M]	S	0.4375	0.49730	0	0	1	0
PITUITARY	ADENOMA/ADENOMATA [B], pars di	M	1.0000	1.00000	77	46	29	12
PITUITARY	CARCINOMA [M], pars distalis	S	0.3869	0.44525	0	0	1	0
SALIVARY GLAND	SCHWANNOMA [B]	S	0.6111	0.70725	0	1	0	0
SKIN	BASAL CELL TUMOR [B]	S	1.0000	0.83395	2	0	0	0
SKIN	FIBROMA [B], dermal/subcutaneo	S	0.0168	0.01155	4	4	7	7
SKIN	FIBROSARCOMA [M], subcutaneous	S	0.7489	0.78985	2	4	1	1
SKIN	KERATOACANTHOMA [B]	S	1.0000	0.76840	1	0	0	0
SKIN	LIPOMA [B], subcutaneous	S	0.9384	0.92750	4	2	2	0
SKIN	SARCOMA, NOS [M], subcutaneous	S	0.4482	0.41420	2	0	1	1
SKIN	SCHWANNOMA [M], subcutaneous	S	0.6370	0.74000	0	1	0	0
SKIN	SEBACEOUS ADENOMA [B]	S	0.1119	0.06245	0	0	1	1
SKIN	SQUAMOUS CELL CARCINOMA [M]	S	0.8542	0.82150	1	1	0	0
SKIN	SQUAMOUS CELL PAPILLOMA/PAPILL	S	0.8624	0.88545	2	2	1	0
SKIN	TRICHOFOLLICULOMA / TRICHOEPIT	S	0.4370	0.43540	4	1	4	2
SPLEEN	HEMANGIOSARCOMA [M]	S	0.6904	0.80225	0	3	1	0
SPLEEN	SARCOMA, NOS [M]	S	0.5862	0.74630	0	1	0	0
STOMACH	SQUAMOUS CELL PAPILLOMA [B]	S	1.0000	0.73785	1	0	0	0
TESTIS	INTERSTITIAL CELL TUMOR [B], u	S	0.0000*	0.00000	5	2	12	32
TESTIS	MESOTHELIOMA [B]	S	1.0000	0.77155	1	0	0	0
TESTIS	MESOTHELIOMA [M]	S	1.0000	0.85175	2	0	0	0
THYROID	C-CELL ADENOMA/ADENOMATA [B]	S	0.1211	0.11775	10	0	2	6
THYROID	C-CELL CARCINOMA [M]	S	0.2585	0.27300	3	4	1	3
THYROID	FOLLICULAR CELL ADENOMA [B]	S	0.9763	0.89905	3	1	0	0

Note: MSFLG=M indicates that the tumor is fatal to some but not all animals; MSFLG=S indicates that the tumor is either fatal or non-fatal to all animals;
An '*' indicates a significant linear dose-tumor trend.

Table 6

Intercurrent mortality rates in the mouse study

Female Mouse

		Ctrl		Low		Med		High	
		No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died
Sex	Time (weeks)								
Female	0-52	4	3.33	1	1.67	2	3.33	5	8.33
	53-78	22	21.67	8	15.00	12	23.33	9	23.33
	79-91	23	40.83	12	35.00	5	31.67	12	43.33
	92-104	24	60.83	10	51.67	9	46.67	8	56.67
	Term. Sac.	47	39.17	29	48.33	32	53.33	26	43.33
	Total	120		60		60		60	

Male Mouse

		Ctrl		Low		Med		High	
		No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died	No. Died	Cumul. Pct. Died
Sex	Time (weeks)								
Male	0-52	9	7.50	2	3.33	1	1.67	9	15.00
	53-78	18	22.50	9	18.33	6	11.67	11	33.33
	79-91	12	32.50	7	30.00	10	28.33	9	48.33
	92-104	30	57.50	8	43.33	14	51.67	9	63.33
	Term. Sac.	51	42.50	34	56.67	29	48.33	22	36.67
	Total	120		60		60		60	

Female Mouse Survival Curves

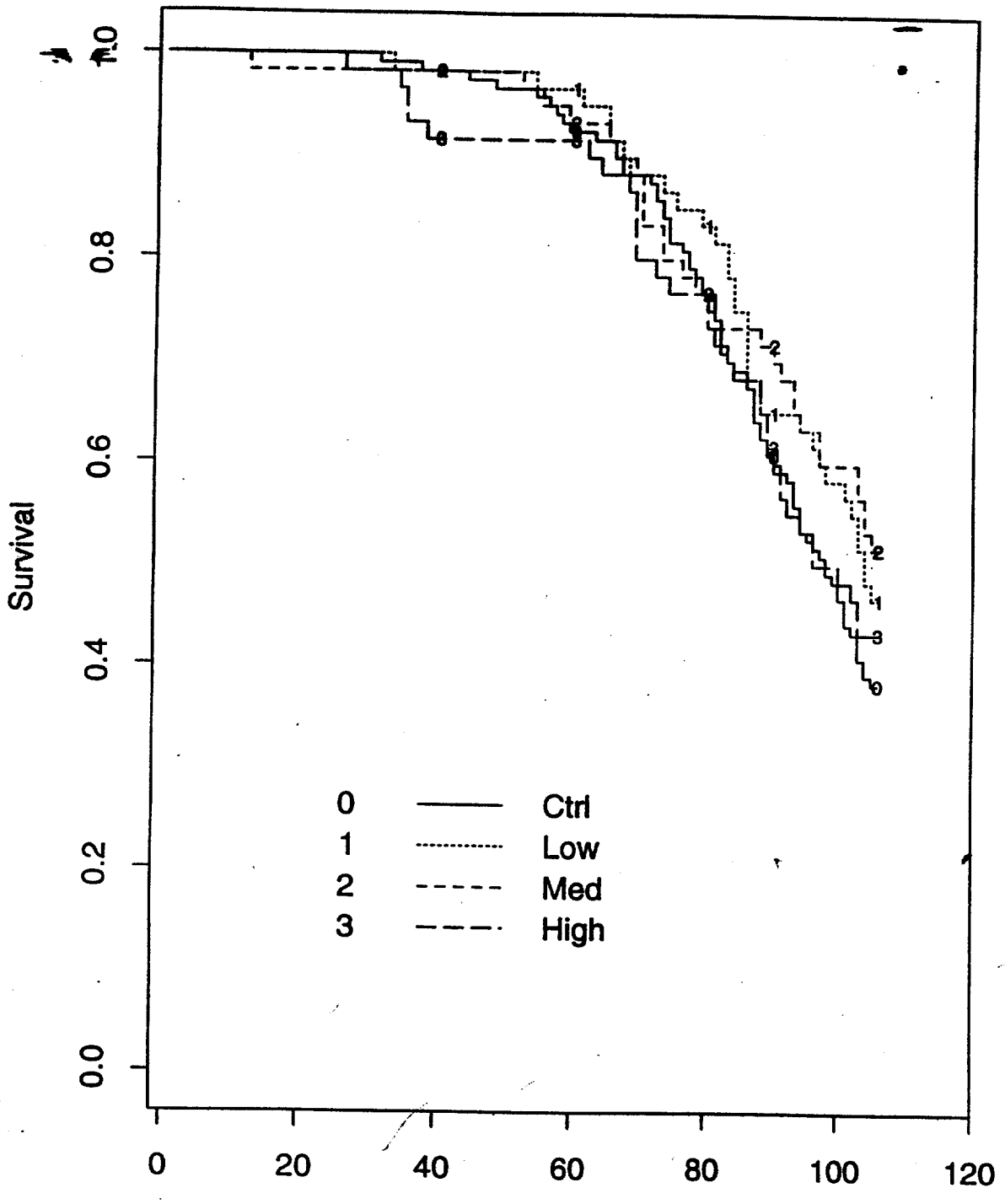

Figure 3

Male Mouse Survival Curves

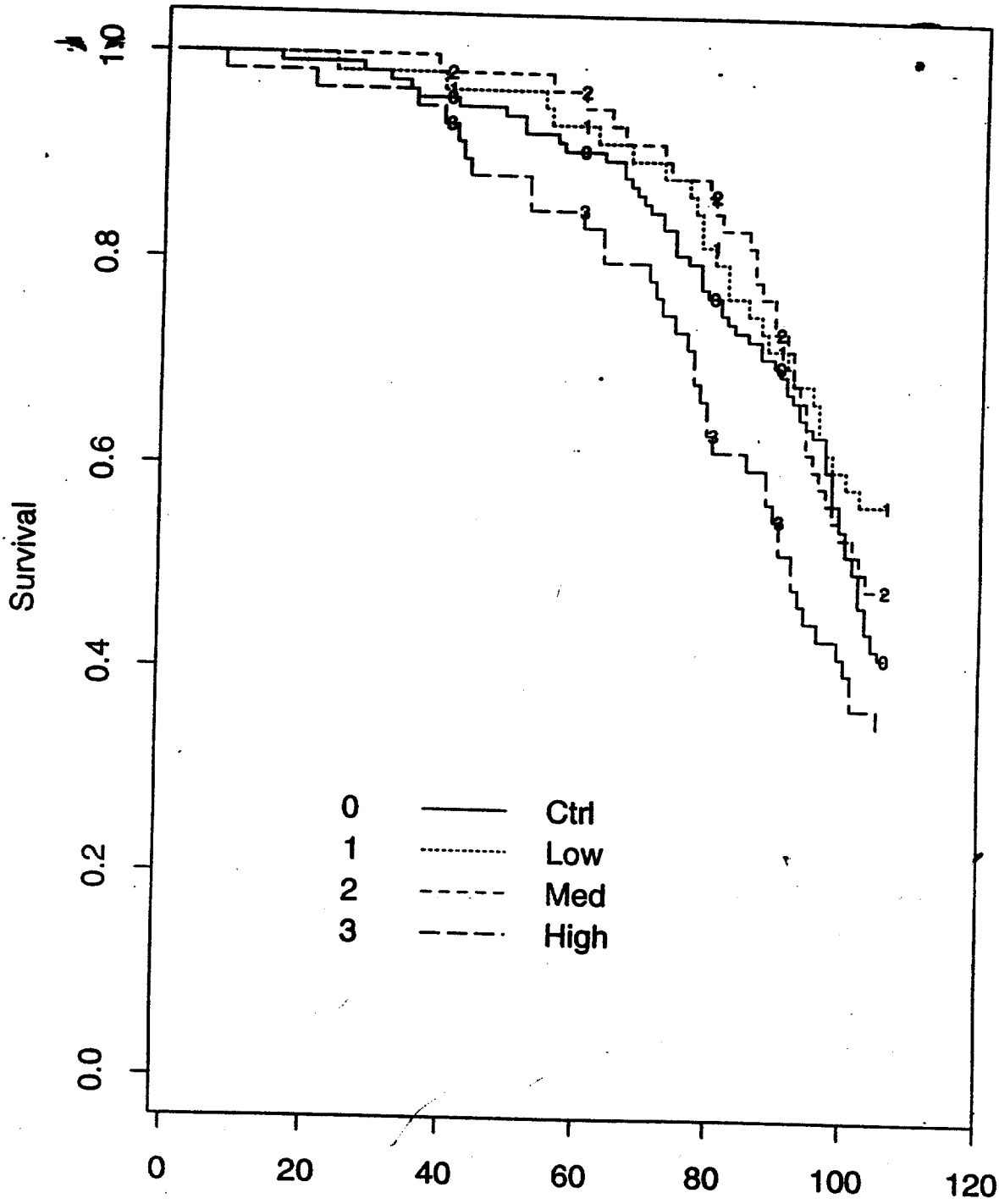

Figure 4

Table 7

P-values of tests for positive linear trend in mortality in the mouse study

Female Mouse

	Test	P-value
Homogeneity	Cox	0.3879
	Kruskal-Wallis	0.4545
Dose-mortality trend	Cox	0.8808
	Kruskal-Wallis	0.8882

Male Mouse

	Test	P-value
Homogeneity	Cox	0.0527
	Kruskal-Wallis	0.0344*
Dose-mortality trend	Cox	0.0505
	Kruskal-Wallis	0.0232*

* $p < 0.05$

Table 8

P-values of pairwise tests for the differences in mortality between treatment groups in the rat study

Female Mouse

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE CONSERVATIVE	GENERALIZED K/N ANALYSIS EXACT	GENERALIZED K/N ANALYSIS INVERSE CONSERVATIVE
0 VS. 1	CHISQ		.8290	NEG	1.1484	1.1388	1.3887	1.3793
	PROB	.1812	.3626		.2856	.2889	.2488	.2402
0 VS. 2	CHISQ		2.3859	NEG	2.1084	2.1014	1.6934	1.6898
	PROB	.0615	.1224		.1465	.1472	.1931	.1936
0 VS. 3	CHISQ		.2344	NEG	.0712	.0712	.0058	.0058
	PROB	.3133	.6283		.7896	.7896	.9392	.9392
1 VS. 2	CHISQ		.1334	NEG	.0733	.0732	.0531	.0531
	PROB	.3576	.7150		.7866	.7867	.8177	.8178
1 VS. 3	CHISQ		.0337	POS	.2498	.2496	.6616	.6611
	PROB	.4273	.8544		.6172	.6174	.4160	.4162
2 VS. 3	CHISQ		.5347	POS	.0287	.0272	1.1767	1.1752
	PROB	.2324	.4647		.3626	.3631	.2780	.2783

Male Mouse

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE CONSERVATIVE	GENERALIZED K/N ANALYSIS EXACT	GENERALIZED K/N ANALYSIS INVERSE CONSERVATIVE
0 VS. 1	CHISQ		3.0385	NEG	2.1507	2.1491	1.7020	1.7013
	PROB	.0407*	.0813		.1425	.1427	.1920	.1921
0 VS. 2	CHISQ		.4766	NEG	.4267	.4264	.5735	.5732
	PROB	.2447	.4900		.5136	.5138	.4489	.4490
0 VS. 3	CHISQ		.4913	POS	1.7855	1.7813	3.1571	3.1502
	PROB	.2424	.4833		.1815	.1820	.0756	.0759
1 VS. 2	CHISQ		.5347	POS	.2959	.2956	.1797	.1796
	PROB	.2324	.4647		.5865	.5867	.6716	.6717
1 VS. 3	CHISQ		4.8336	POS	5.6806	5.6605	6.4367	6.4171
	PROB	.0137*	.0279*		.0172*	.0174*	.0112*	.0113*
2 VS. 3	CHISQ		1.6800	POS	3.3757	3.3677	5.4227	5.4077
	PROB	.0974	.1949		.0662	.0665	.0199*	.0200*

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Test of trend base. on the tumor data

Female Mouse

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ADRENAL	CORTICAL ADENOMA	S	0.4476	0.59100	0	1	1	0
BONE	OSTEOSARCOMA	S	0.5950	0.48065	2	0	0	1
BONE MARROW	MYELOID LEUKEMIA	S	0.2214	0.21745	2	1	2	2
BRAIN	GLIOMA	S	0.1875	0.02340	0	0	0	1
CECUM	LEIOMYOMA	S	0.4328	0.48625	0	0	1	0
CECUM	SEBACEOUS GLAND ADENOCARCINOMA	S	0.5577	0.67515	0	1	0	0
HARDERIAN GLAND	ADENOCARCINOMA	S	1.0000	0.76675	1	0	0	0
HARDERIAN GLAND	ADENOMA	S	0.9066	0.87260	2	2	0	0
JEJUNUM	ADENOCARCINOMA	M	0.3246	0.17110	1	0	0	1
LIVER	HEMANGIOMA	M	0.8906	0.88565	4	1	2	0
LIVER	HEMANGIOSARCOMA	S	1.0000	0.75890	1	0	0	0
LIVER	HEPATOCELLULAR ADENOMA	S	0.9128	0.89830	8	0	1	1
LIVER	HEPATOCELLULAR CARCINOMA	S	0.3481	0.30330	1	1	0	1
LUNG	ALVEOLAR/BRONCHIOLAR ADENOMA	M	0.9557	0.95020	19	20	12	6
LUNG	ALVEOLAR/BRONCHIOLAR CARCINOMA	M	0.6524	0.64735	3	1	0	1
LYMPH NODE	HISTIOCYTIC SARCOMA	M	0.7803	0.77975	9	5	0	3
LYMPH NODE	LYMPHOSARCOMA	M	0.1531	0.14580	11	4	7	8
MAMMARY GLAND	ADENOCARCINOMA	M	0.8857	0.87405	3	3	3	0
MAMMARY GLAND	ADENOMA	S	0.3333	0.41995	0	0	1	0
MESENTERY	MESOTHELIOMA	S	0.6500	0.69120	0	1	0	0
OVARY	ADENOMA	S	0.1483	0.13740	3	1	3	3
OVARY	BENIGN LUTEOMA	S	0.3855	0.33870	1	1	0	1
OVARY	GRANULOSA-THECA CELL TUMOR	S	0.3697	0.31785	1	1	0	1
PANCREAS	ISLET CELL ADENOMA	S	1.0000	0.76675	1	0	0	0
PITUITARY	ADENOMA, PARS DISTALIS	S	0.4142	0.44020	1	2	1	1
PITUITARY	ADENOMA, PARS INTERMEDIA	S	0.5687	0.67405	0	1	0	0
SKIN MISCELLANEOUS	FIBROMA	S	0.6492	0.69480	0	1	0	0
SPLEEN	HEMANGIOMA	S	0.5687	0.67405	0	1	0	0
SPLEEN	HEMANGIOSARCOMA	S	0.6802	0.70205	1	0	1	0
STOMACH	ADENOMA	S	0.6492	0.69480	0	1	0	0
STOMACH	SQUAMOUS CELL CARCINOMA	S	0.4328	0.48625	0	0	1	0
SUBCUTANEOUS TISSUE	FIBROSARCOMA	M	0.3860	0.33390	1	1	0	1
SUBCUTANEOUS TISSUE	LIPOMA	S	0.4118	0.45890	0	0	1	0
SUBCUTANEOUS TISSUE	LIPOSARCOMA	M	0.8642	0.81245	1	1	0	0
SUBCUTANEOUS TISSUE	UNDIFFERENTIATED SARCOMA	M	0.8951	0.87365	3	1	1	0
URINARY BLADDER	LEIOMYOSARCOMA	S	1.0000	0.75890	1	0	0	0
UTERUS	ADENOCARCINOMA	S	1.0000	0.77175	1	0	0	0
UTERUS	BENIGN ENDOMETRIAL STROMAL POL	S	0.0011*	0.00055	10	5	6	14
UTERUS	ENDOMETRIAL STROMAL SARCOMA	M	0.5941	0.60045	9	1	6	3
UTERUS	GRANULAR CELL TUMOR	S	1.0000	0.75890	1	0	0	0
UTERUS	HEMANGIOMA	S	0.4476	0.59100	0	1	1	0
UTERUS	HEMANGIOSARCOMA	M	0.5818	0.56620	3	0	0	1
UTERUS	LEIOMYOMA	S	0.9527	0.93710	4	5	4	0
UTERUS	LEIOMYOSARCOMA	S	0.4261	0.43085	4	2	4	2
UTERUS	UNDIFFERENTIATED CARCINOMA	S	1.0000	0.78275	1	0	0	0

Note: MSFLG=M indicates that the tumor is fatal to some but not all animals; MSFLG=S indicates that the tumor is either fatal or non-fatal to all animals.
An '*' indicates a significant linear dose-tumor trend.

Test of trend ba. i the tumor data

Male Mouse

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ADRENAL	CORTICAL ADENOMA	S	0.2984	0.15410	1	0	0	1
BONE	OSTEOSARCOMA	S	0.1518	0.01285	0	0	0	1
BONE MARROW	MYELOID LEUKEMIA	S	0.1645	0.01655	0	0	0	1
CAVITY NASAL	ADENOCARCINOMA, RESPIRATORY EP	S	0.5909	0.69730	0	1	0	0
CAVITY ORAL	SQUAMOUS CELL CARCINOMA	S	1.0000	0.77670	1	0	0	0
CAVITY PELVIC	LEIOMYOSARCOMA	S	1.0000	0.76485	1	0	0	0
HARDERIAN GLAND	ADENOMA	S	0.3740	0.37705	4	2	2	2
HEART	HEMANGIOSARCOMA	S	0.3864	0.51110	0	0	1	0
JEJUNUM	ADENOCARCINOMA	S	1.0000	0.74905	1	0	0	0
JEJUNUM	ADENOMA	S	0.1618	0.01550	0	0	0	1
KIDNEY	TUBULAR CELL ADENOMA	S	1.0000	0.74905	1	0	0	0
KIDNEY	TUBULAR CELL CARCINOMA	S	0.1279	0.09060	0	1	0	1
LIVER	HEMANGIOMA	S	0.7657	0.76490	2	0	1	0
LIVER	HEMANGIOSARCOMA	M	0.6154	0.65835	1	0	1	0
LIVER	HEPATOBLASTOMA	S	0.6842	0.72685	0	1	0	0
LIVER	HEPATOCELLULAR ADENOMA	S	0.9590	0.95475	36	18	12	10
LIVER	HEPATOCELLULAR CARCINOMA	M	0.9911	0.98160	8	7	4	0
LUNG	ALVEOLAR/BRONCHIOLAR ADENOMA	S	0.4256	0.42145	35	18	25	15
LUNG	ALVEOLAR/BRONCHIOLAR CARCINOMA	M	0.6804	0.67830	4	0	0	1
LYMPH NODE	HISTIOCYTIC SARCOMA	M	0.7835	0.79190	3	1	3	0
LYMPH NODE	LYMPHOSARCOMA	M	0.7876	0.78840	5	4	3	1
LYMPH NODE MESENTERIC	HEMANGIOMA	S	1.0000	0.76485	1	0	0	0
PANCREAS	HEMANGIOSARCOMA	S	0.1618	0.01550	0	0	0	1
PANCREAS	ISLET CELL ADENOMA	S	0.0947	0.05135	0	0	1	1
PITUITARY	ADENOMA, PARS DISTALIS	S	1.0000	0.76485	1	0	0	0
PITUITARY	ADENOMA, PARS INTERMEDIA	S	1.0000	0.76485	1	0	0	0
SEMINAL VESICLE	ADENOMA	S	1.0000	0.76485	1	0	0	0
SKIN MISCELLANEOUS	PAPILLOMA	S	1.0000	0.76485	1	0	0	0
SKIN MISCELLANEOUS	SQUAMOUS CELL CARCINOMA	S	1.0000	0.75635	1	0	0	0
SPLEEN	HEMANGIOMA	S	1.0000	0.84730	2	0	0	0
SPLEEN	HEMANGIOSARCOMA	S	0.9038	0.86685	2	2	0	0
STOMACH	SQUAMOUS CELL CARCINOMA	S	0.5000	0.53510	0	0	1	0
SUBCUTANEOUS TISSUE	HEMANGIOMA	S	0.6435	0.71740	0	2	0	0
TESTIS	HEMANGIOMA	S	1.0000	0.74905	1	0	0	0
TESTIS	INTERSTITIAL CELL ADENOMA	S	0.3227	0.35265	1	2	2	1
URINARY BLADDER	HEMANGIOMA	S	0.3750	0.44360	0	0	1	0
URINARY BLADDER	LEIOMYOSARCOMA	S	0.6250	0.66790	0	1	0	0

Note: MSFLG=M indicates that the tumor is fatal to some but not all animals; MSFLG=S indicates that the tumor is either fatal or non-fatal to all animals.
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