Primary efficacy analysis

A summary of percentage change in partial seizure frequency from baseline and seizure frequency per 28 days in the baseline phase and the double-blind phase is presented in Exhibit 8.1.-1.

Exhibit 8.1.-1 Summary of percentage change in partial seizure frequency from baseline* (ITT population), and seizure frequency per 28 days in the Baseline Phase and the Double-blind Treatment Phase

Treatment group	OXC 600 mg/day	OXC 1200 mg/day	OXC 2400 mg/day	Placebo**
Number of patients	**168**	**177**	**174**	**173**
Baseline seizure frequency (median)	9.59	9.78	9.96	8.58
Double-blind treatment seizure frequency (median)	8.15	6.93	4.67	9.33
Percentage change in seizure frequency (median)	-26.45	-40.22	-49.95	-7.59
P-value	0.0001	0.0001	0.0001	

* Percentage change in seizure frequency is 100 (seizure frequency in the Double-blind Treatment Phase - seizure frequency in the Baseline Phase) / seizure frequency in the Baseline Phase

** Although, for the placebo group, the median of the seizure frequency in the Double-blind Treatment Phase was higher than that in the Baseline Phase, the median of the within-patient % change showed a reduction in seizure frequency.

The sponsor reported that the comparisons with placebo for OXC 1200 mg/day and 2400 mg/day both resulted in significance levels of p=0.0001 according to Bonferroni-Hilm procedure, and each was associated with a reduction in seizure frequency from baseline (40% and 50%, respectively, compared with 7.6% for placebo).

The comparisons between each dose of OXC and placebo resulted in p-values of 0.0001. Also each dose group displayed a larger decrease in seizure frequency per 28 days: 26%, 40%, and 50% for the 600 mg/day, 1200 mg/day, and 2400 mg/day OXC group respectively, compared with 7.6% for placebo.

Secondary efficacy variable

Variable 1: Seizure frequency per 28 days in the double-blind treatment phase

Seizure frequency per 28 days (log-transformed) in the double-blind treatment phase was analyzed for both the ITT and Steady-state population using a multiple linear regression model assuming Normal errors. The results were in favor of OXC and similar to those of the primary analysis.

Variable 2: Response to treatment

Response to treatment was defined as having at least 50% reduction in 28-day seizure frequency. The treatment responder rates together with unadjusted p values for the

comparisons between each dose and placebo (logistic regression) are summarized in Exhibit 8.1.-5 for the ITT population.

The percentage of responders in the ITT patient population increased from 13% in the placebo group to 50% in the OXC 2400 mg/day group. Each OXC group had a statistically significantly higher percentage of responders than placebo group ($p<0.001$). Results using the steady-state population were similar.

Exhibit 8.1.-5 Percentage of patients in each treatment group who responded to treatment (50% reduction or more in seizure frequency from baseline; ITT population)

Population	Treatment group	OXC 600 mg/day	OXC 1200 mg/day	OXC 2400 mg/day	Placebo
ITT	Number of patients	n=168	n=177	n=174	n=173
	≥50% reduction	26.8	41.2	50.0	12.7
	P-value*	0.0008	0.0001	0.0001	n.a.

Variable 3: Global Assessment of Therapeutic Effect (GATE)

Of the 692 patients in the ITT population, 637 supplied data on the GATE. For the 600 mg/day, 1200 mg/day, and 2400 mg/day OXC group, the percentage of patients with a "very good" rating was 10.8%, 18.5%, and 28.0%, respectively, compared with 7.1% for placebo. Using the complete 4-level response, each dose of OXC was compared with placebo using separate, pairwise Wilcoxon rank-sum tests. The 1200 mg/day and 2400 mg/day OXC groups were both significantly different from placebo ($p=0.0083$ and $p=0.0001$, respectively). The difference between OXC 600 mg/day and placebo just failed to reach significance ($p=0.0597$). The p values were not adjusted for multiple tests.

6.5 Reviewer's Findings/ Comments

Primary efficacy variable

The primary analysis of the percentage changes in total seizure frequency per 28 days was performed using Wilcoxon rank-sum test. It was found that the overall differences between the treatment groups were statistically significant at 0.0001 level. Further comparisons between each dose and placebo revealed that the treatment effect was significant for each dose level with p-values of 0.0001 (Wilcoxon rank-sum test). Dose response was found in the increasing reduction of the seizure frequency by increasing dose.

Differentials of treatment effect on gender and age were also examined. The Wilcoxon rank-sum test for the overall difference on the primary efficacy variable across the four dose groups was performed by gender and by age groups of <=35 years old and > 35 years old. The analyses showed that the treatment effect is significant on both gender groups ($p<.0001$) and both age groups ($p<.0003$).

Secondary efficacy variable

The secondary efficacy variables and their corresponding statistical analysis for this study were not clearly stated in the protocol, statistical analysis plan or amendments. Therefore, no analyses were performed to secondary efficacy variables.

III Reviewer's Overall Comments

In this NDA submission 8 studies (6 main studies and 2 active controlled studies) were reviewed. These trials cover a wide range of patient population (pediatric and adult patients), disease stages (newly diagnosed patients, patients with uncontrolled partial seizures and patients who had completed presurgical diagnostic evaluation), and dosage (300 mg/day, 600 mg/day, 1200 mg/day and 2400 mg/day). The lengths of these studies range from 10 days for Study 004 to 7 months for Study OT/PE1.

As pointed in the Introduction, the six key studies differ in their design:

- Studies 004 and 025 are mono-therapy and placebo controlled.
- Studies 026 and 028 are mono-therapy and dose controlled.
- Studies 011 and OT/PE1 are adjunctive therapy and placebo controlled.
- Studies OT/F02 and OT/F04 are mono-therapy and active controlled (not reported above but their results will be discussed later).

In the following sections various issues such as deviations from protocol and impact of dropouts are discussed. The efficacy results are summarized and concluded. The results of two active controlled studies, which are not reported in the above sections, will also be discusses.

1. Deviations from protocols

Among the six key studies most primary efficacy variables reported by the sponsor are the ones that were specified in the protocol and analyzed using the protocol specified methods. The primary efficacy variable and its analysis of the Study OT/PE1 were changed from protocol in its Amendment V. Center pooling was not specified in protocols or statistical analyses plans, but used in one primary analysis (Study 028) and most secondary efficacy variable. The method of center pooling is based on the order of the center number consistent across all studies and is considered reasonable.

2. Validity of primary efficacy measures and primary analyses

The efficacy measures for the 6 key studies are time to (or percentage of patients) meeting one of the exit criteria and seizure frequency. These efficacy variables are considered typical and agree with the study objectives. The statistical methodologies used in the primary analysis of each study are generally standard. Log-rank test was used in all time to event data, CMH test was used in all frequency data, and Wilcoxon test was used in all continuous data.

3. Summary of Premature discontinuation/ Adverse experience

The following table displays the number of patients prematurely discontinued treatment and break down to adverse experience, treatment group and study.

Table 7. Number of premature discontinuation by treatment group and study.

Study	Length of DB phase	Treatment	# of patients	Dropout		# of deaths
				Total	Adverse	
004	10 days	Placebo	51	2	0	
		2400 mg/day	51	3	2	
025	90 days	Placebo	35	4	2	
		1200 mg/day	32	10	3	
026	126 days	Non-randomized	47	47	24	
		300 mg/day	45	5	0	
		2400 mg/day	51	5	0	1[1]
028	126 days	300 mg/day	46	1	1	
		2400 mg/day	41	7	6	
011	16 weeks	Placebo	129	10	4	
	(112 days)	900-1800 mg/day	136	21	14	1
OT/PE1	7 months	Placebo	173	49	15	2[2]
	(196 Days)	600 mg/day	168	38	20	3
		1200 mg/day	177	80	64	
		2400 mg/day	174	128	116	1

1. Death occurred due to ischemic heart failure.
2. Deaths occurred in this trial may or may not related to the study drug.

Note that in Study 026 all patients started treatment with OXC 2400 mg/day, and then patients who were assigned to OXC 300 mg/day group were titrated down from OXC 2400 mg/day. Forty-seven of the 143 patients who were enrolled prematurely discontinued either in Open-label Conversion Phase or in Open-label Baseline Phase.

Study 025 had a high dropout rate (21% in total and 31% in the OXC group). The primary efficacy variable, time to first seizure, was examined in those dropout patients. Among the 4 discontinued patients in the placebo group, one discontinued before having his/her first seizure. Among the 10 discontinued patients in OXC group, 4 discontinued before having their first seizure. The median duration for those 4 patients from their first dose is 13 days. This finding indicates that the time to first seizure for those 4 patients would be at least 13 days, which is larger than the median survival time of 11.67 days for the whole OXC group, were they not dropped out.

Study 028 had 17% and 2% premature discontinuation in the OXC 2400 mg/day and the placebo groups, respectively. Although the discontinuation rate for OXC group is large and is much high than the placebo group, the efficacy results from the primary analysis (percentage of exit) should be considered valid since a worst case scenario was used in

the primary analysis. For studies 011 and OT/PE1, the method of last observation carry forward was used in the analyses for premature discontinuations.

In summary, the impact of premature discontinuation to the efficacy results for each study has been examined. It was found that the effect of premature discontinuation on the efficacy results, if any, was not substantial. The efficacy results obtained should be considered valid.

4. Choice of effective and safe dose

In four of the six key studies the highest dose level was 2400 mg/day, and in the pediatric study 011, the maximum dose of 1800 mg/day was used. A substantial number of patients who were randomized to 2400 mg/day dose group either had reduction in their dose to 1800 mg/day or 1200 mg/day, or had never reached the dose level 2400 mg/day. The following table lists the number of patients who were randomized to OXC 2400 mg/day and who had dose reduction or withdrawal prematurely.

Table 8. Occurrence of dose reduction or withdrawal among OXC 2400 mg/day treated patients

Protocol #	Length of DB phase	Total # of patients randomized to 2400 mg/day	# of Premature discontinuation	# of patients had dose reduction
004	10 days	51	3	7
026	126 days	143 [1]	5 randomized, 47 non-randomized [2]	
028	126 days	41	7	11
OT/PE1	196 days	174	128	47

1. The number represents the total number of subjects received OXC 2400 mg/day before randomization.
2. The number represents the total number of subject who received OXC 2400 mg/day and then withdrew before entering the double-blind treatment phase.

In Study 04 seven patients randomized to OXC 2400 mg/day required dosage reduction to 1800 mg/day. Two patients needed an additional reduction to 1200 mg/day. In Study 026, all subjects who met enrollment requirement received OXC 2400 mg/day before randomization. The patients who entered double-blind treatment phase were those who were able to tolerate OXC 2400 mg/day. In Study 028, eleven patients in the OXC 2400 mg/day group had reductions made to their drug during the double-blind treatment phase. In Study OT/PE1 43 of the 174 patients randomized to the high-dose group were titrated to 1800 mg/day instead of 2400 mg/day (those patients had never reached the dose 2400 mg/day). Additional four patients who were titrated to 2400 mg/day had a subsequent dose reduction to 1800 mg/day during the double-blind treatment.

It appears that the longer the duration of patients receiving OXC 2400 mg/day, the fewer the patients who could complete the trial at this dose, and very few, if any, patients could complete the trial at the 2400 mg/day dose in Study OT/PE1.

It should be noted that in Study 026, even though that the death occurred after the randomization and before the patient received the double-blind trial medication, that patient had received OXC 2400 mg/day on days 21 to 84 during the open-label conversion phase and open-label baseline phase prior to randomization.

In the adjunctive therapy pediatric study (Study 011), The protocol specified that all patients were to be titrated with an initial daily dose of 10 mg/kg to a daily dose of 30-46 mg/kg or to their maximum tolerated dose within the 30-45 mg/kg/day dosage range. However, 44.9% (62/138) of the OXC-treated patients received <=30 mg/kg/day by the end of the titration period. In addition, 51 (37%) OXC-treated patients made adjustment to their dosage during the maintenance period of the double-blind treatment phase.

5. Summary and conclusion of efficacy results

For all of the 6 key studies, the primary analyses showed significant treatment effect in favor of OXC vs. placebo or in favor of high dose vs. low dose. Table 5 summarizes the efficacy of the six studies. The results presented are based on reviewer's analysis. In most of the studies, when the number of partial seizure counts per 28 days is used as a primary or main secondary efficacy variable, the p-values from CMH test are obtained using a worst case scenario. The results from these six key studies have provided sufficient evidence that the study drug is effective in reducing the partial seizure frequency. I would therefore conclude that the efficacy of OXC versus placebo in treating epilepsy patients with partial seizures is established.

Table 5. Summary of efficacy results, all six studies

Study #	Primary Efficacy/ Main Secondary	Dose	# of Patients	p-value Primary/Secondary
004	Time to exit/	2400 mg/day	51	.0001 (log-rank)/
	Percentage of exit	Placebo	51	.0010 (CMH)
025	Time to 1st seizure/ #	1200 mg/day	32	.0476 (log-rank)/
	of seizures per 28 days	Placebo	35	.0307 (Wilcoxon)
026	Time to exit/	2400 mg/day	51	.0001 (log-rank)/
	Percentage of exit	300 mg/day	45	.0110 (CMH)
028	Percentage of exit/	2400 mg/day	41	.0010 (CMH)/
	Time to exit	300 mg/day	46	.0001 (log-rank)
011	Percentage change in seizure frequency/ # of	900-1800 mg	136	.0001 (Wilcoxon)/
	seizures per 28 days	Placebo	128	.0020 (Wilcoxon)
OT/PE1	Percentage in seizure -	600 mg/day	168	Primary only
	frequency/ # of	1200 mg/day	177	Overall: p= .0001
	seizures per 28 days	2400 mg/day	174	Pairwise: p=.0001
		Placebo	173	(Wilcoxon)

The effect of OXC on secondarily generalized seizure was studied in one study as a secondary variable. Generally, none of the studies was designed to incorporate secondarily generally seizure in the study objectives. In five of the six key studies, measures of secondarily generalized seizure were not included in the efficacy variables. Therefore, no conclusions regarding to the secondarily generalized seizure can be reached.

Efficacy of the individual dose level of OXC

Next, I would discuss the efficacy of the individual dose level. The 300 mg/day dose was used as controls in Study 026 and Study 028, and the efficacy of this dose level was not studied.

Dose 600 mg/day was used in one study, Study OT/PE1. The target population in this study was patients with refractory partial seizures who were being treated up to 3 AEDs. Although the results showed that the difference in the change of percentage of seizure frequency between the OXC 600 mg/day group and the placebo group was highly significant (p=.0001) in favor of OXC 600 mg/day, based on the pairwise comparison (without adjustment for multiple comparisons), the interactions of OXC with AEDs are not clear and the net benefit of OXC 600 mg/day needs to be further studied.

The effectiveness of OXC 2400 mg/day was well established in 4 of the 6 key studies. However, larger percentage of dropout due to adverse experience among the OXC 2400 mg/day treated patients compared to other patients indicated that the dose might be high enough to raise the safety concern, as discussed above in section 4. Choice of effective and safe dose. In addition, a substantial number of patients who were assigned to OXC 2400 mg/day treatment had dose reduction to OXC 1800 mg/day or 1200 mg/day, due to the non-tolerability. Furthermore, patients who entered double-blind treatment phase in Study 026 are selective toward those who were able to tolerate the high dose of OXC 2400 mg/day. The efficacy result from this study may not apply to the target patient population. The number of OXC 2400 mg/day treated patients who completed trial without dose reduction is not reported. Based on these reasons, I would NOT conclude that OXC 2400 mg/day is an effective and safe dose.

Dose 1200 mg/day has been studied in two trials, one mono-therapy and one adjunctive therapy. In the mono-therapy trial Study 025, the patients were newly treated with recent onset of partial seizures. The efficacy significance of the study was marginal on the primary efficacy and was not reached in secondary efficacy variables. It was a small study that consisted of 67 patient. The dropout rate in this study is relatively high (21%). Dose 1800 mg/day was not specifically studied, but were used as reduced dose for some patients who were assigned to OXC 2400 mg/day treatment and who could not tolerate 2400 mg/day.

Efficacy results from subgroups of demographic characteristics

Differentials of treatment effect on demographic characteristics have been examined. For all six key studies significant treatment effect based on protocol specified primary analysis was shown in both male subjects and female subjects. In order to examine the treatment effect on age differential, subjects were divided into two age groups of <= 35 year old and > 35 years old in five studies with the exception of the pediatric study 011, in which the age was divided by 3 to 7 and 8 to 17. Except for the pediatric study 011, treatment effect was shown to be significant or at least shown numerically in both age groups.

In the pediatric study 011, it was found that the treatment effect, although was significant overall, was mainly came from subjects 8 to 17 years old. The younger age group among the two age groups contained 61 patients with 30 patients in the OXC group and 31 patients in the placebo group. In this younger age group, both OXC-treated and placebo-treated patients showed improvement in the percentage change of total partial seizure frequency (primary efficacy variable) at the end of the study, with slightly better improvement in numerical value from placebo group. Therefore, the treatment effect seems entirely came from the older age group of patients 8 to 17 years old. Although the analysis is post-hoc, cautious should be taken when applying the drug to very young pediatric patients.

The majority of the patient population is white and the analysis on the racial differential was not performed.

6. Efficacy of OXC compared to phenytoin (PHT) monotherapy

In studies OT/F02 and OT/F04, OXC monotherapy was compared to PHT monotherapy in adult and pediatric patients. These two studies had identical design except that Study OT/F02 was aimed at adult patients while Study OT/F04 was aimed at pediatric and adolescent patients. A total of 480 patients were enrolled in the two studies, 287 in Study OT/F02 and 193 in Study OT/F04. A maximum of 2400 mg/day was compared to a maximum of PHT 800 mg/day.

Treatment difference was not significant in both active controlled studies. Numerical measures of the primary efficacy variables for the two studies were very close based on the sponsor's reported numbers. The p-values for the primary analyses of the two studies are both above 0.9. The sponsor concluded that OXC was equally effective as PHT with respect to the seizure types in the population studied.

/S/

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This review consists of 60 pages. 6/17/99

APPEARS THIS WAY
ON ORIGINAL

Statistical Review and Evaluation

Review of Carcinogenicity Data

NDA#: 21-014

Applicant: Novartis

Name of Drug: Trileptal (oxcarbazepine) Tablets

Documents Reviewed: Volumes 23, 30, 34, 35, 55, and 56 Containing One Mouse and Two Rat Study Reports and the Data Diskettes, as well as One Unnumbered Volume of the Supplement Filed 06/25/99.

Pharmacology Reviewer: J. Edward Fisher, Ph.D. (HFD-120)

I. Background

The Division of Biometrics 1 was requested to evaluate the three oncogenicity studies, two in rats, one in mice. The results were discussed with the reviewing pharmacologist, Dr. Ed Fisher.

II. The Rat Study

II.1 Sponsor's Findings

This is a two-year carcinogenicity study in Sprague-Dawley CD albino rats. There were 60 animals per treatment group per sex. Trileptal was administered in the diet at doses of 0, 25, 75, and 250 mg/kg/day.

The sponsor observed no significant differences in survival rates between the control and treated groups.

Average body weights and growth rates were suppressed early in the trial in the high dose (HD) males and in the mid- and HD females when compared to the controls and remained such throughout the study (Figures 1, 2).

Organs from all control and HD animals were microscopically examined. In addition, liver, gross lesions, and tissue masses were examined for all animals. For terminally sacrificed females there was a compound related increase in hepatocellular carcinomas. Other changes occurred with higher frequency in the treated groups, but no other tumor finding was statistically significant for either sex.

II.2 Reviewer's Findings

This reviewer included accidental deaths in her analyses which resulted in minor differences in totals but not in any conclusions. There were no statistically significant differences in the mortality experience of the male or female rats ($p=0.9949$ and $p=0.1744$, respectively; Tables 1-4, Figures 3,4).

From the data it appears that the tissues of all terminally sacrificed (TS) animals were microscopically examined. Therefore, trend tests are appropriate when events were observed only on terminally sacrificed animals or for liver, gross lesions, and tissue masses, for which all animals were examined. Otherwise, pairwise comparisons between controls and high dose animals are appropriate. This reviewer did not run separate analyses on decendents and TS animals, but combined the findings from before and after the terminal sacrifice.

Among the males, interstitial cell tumor of the testes reached statistical significance for the trend test ($p=0.0031$, $\alpha=0.005$ for common tumors, Table 5). This may be an underestimate as low and mid dose animals were only examined microscopically if surviving till terminal sacrifice. The p-value of the pairwise comparison between controls and HD animals was 0.009 (statistically significant for $\alpha=0.01$ for common tumors) and may be the more appropriate test. The incidences were 1, 2, 4, 8 for the controls, low, mid, and high doses, respectively. The sponsor apparently did not combine the pre-TS (0, 0, 0, 2) with the post-TS findings (1, 2, 4, 6). No other tumor trends or pairwise comparisons between controls and HD reached statistical significance among the males.

Among the females, hepatocellular carcinoma approached statistical significance with a p-value of 0.0295 for trend ($\alpha=0.025$ for rare tumors, Table 6) when considering **all** animals. The incidences were 0, 3, 7, 7 for the controls, low, medium and high doses, respectively. The p-value for the pairwise comparison between the control and HD was 0.0159, again based on all animals, not just those which completed the study. As the latter test was performed conditional on a (almost) significant trend test, its α-value is not established. The α-level for unconditional pairwise comparisons is 0.05 for rare tumors. No other trend or pairwise comparison tests approached statistical significance.

II.3 Validity of the Rat Study

As there were no clear statistically significant (positive) trends in tumors among female rats, the validity of this portion of the study needs to be evaluated. Two questions need to be answered (Haseman, Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984):

(i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?

(ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following rules of thumb are suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol5, pp 66-78, 19985) had found that in his experience on the average, approximately 50 % of the animals in the high dose group survived a two-year study. In a personal communication with Dr. Karl Lin (HFD-720), he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed 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'. From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

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

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

(iii) 'In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls'.

In another paper, Bart, Chu and Tarone (Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, pp 957-974, 1979), stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, 'Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD.'

With 29 controls and 39 HD female rats being terminally sacrificed, it is clear that there were sufficient numbers of animals surviving a sufficient length of time to allow for late developing tumors.

The sponsor reports that mean body weight and growth rates of the mid- and HD females were suppressed at weeks 13, 23, and 52, when compared to the controls. The average body weights of the HD females were lower than the controls as early as Week 1, though they had a small numeric advantage at the start of the study. After week 18 the differential seems to be greater than 10 percent. It appears that the HD females were substantially leaner than their controls indicating that the MTD might have been exceeded. As the mortality experience was worse for the controls than for the treated animals, it is another indication that the HD was not close to the MTD. The evaluation of clinical signs or severe histopathologic toxic effects by the pharmacologist should be used to determine whether the HD was close to the MTD.

III. The Second Rat Study

III.1 Sponsor's Findings

This study was conducted on the active monohydroxy derivative of Trileptal and was administered via gavage to Sprague-Dawley rats at doses of 0, 75, 250, 600 mg/kg/day. There were sixty animals of each sex per group. The treatment lasted at least 104 weeks.

Survival was not affected negatively by treatment. As a matter of fact, the high dose of either sex had the best survival.

The high dose affected the average bodyweight and bodyweight gain of both sexes (Figures 5, 6). The reduction was seen from the early days on treatment and lasted the whole period. At the end of two years, the high

dose males had a 20 % lower average body weight than the controls and the females had a 52% lower average body weight than the controls.

The sponsor discussed increases in numerous neoplastic and non-neoplastic lesions. Of the neoplastic lesions the following were considered to show a statistically significant trend: hepatocellular adenoma, hepatocellular adenoma and carcinoma combined, and interstitial-cell tumor of the testes, all among the males; among the females, hepatocellular adenoma, hepatocellular carcinoma, hepatocellular adenoma and carcinoma combined, and combined benign and malignant granular cell tumor of the vagina.

III.2 Reviewer's Findings

The sponsor submitted additional ten volumes in a supplement on 6/25/99. This reviewer evaluated one volume (unnumbered) which contained the re-analysis of the granular cell tumors among the females and an investigation into the causes for the observed interstitial cell tumors among the males. The re-analyses changed the gross incidences for granular cell tumors of the vagina and cervix from 0, 4, 5, 7 to 7, 9, 14, 17 for controls, low, medium, and high dose females. These new findings are not incorporated below, because the sponsor did not submit the time intervals in which the many additional tumors were found. Therefore, no mortality adjusted analysis can be performed by this reviewer and we have to accept the sponsor's results on face value. From Section 5 it appears that the sponsor adjusted for intercurrent mortality but used only the simple scale of 0, 1, 2, 3 instead of the actual doses when computing the p-value for trend. It can be presumed that the use of the actual doses as weights would lower the p-value, but based on the sponsor's findings, the p-value of 0.026 is not statistically significant (α=0.005).

The doses administered are reported as 0, 75, 250, and 600 mg/kg in volume 1.55. However, in the 'readme' file on the diskette the doses are specified as 0, 0.6, 6.0, and 60 mg/kg. The doses are used as weights in the trend tests for mortality and for tumors and using different sets of doses would result in different statistics and associated p-values. In this review the doses 0, 75, 250, and 600 mg/kg were used. Otherwise, this appears to be a well conducted study. All identified tissues were microscopically examined in all animals. This reviewer reproduced the sponsor's numbers of animals surviving till the end of the study as well as the number of tumor incidences. This reviewer's p-values are somewhat different than the sponsor's. It appears that the sponsor did not adjust for intercurrent mortality in tumor findings. In order to control the overall false positive rate to about 10 percent despite the many tests performed, only trend tests with p-values less than or equal to 0.025 for rare tumors and 0.005 for common tumors are considered statistically significant. This approach is standard by the Office of Biometrics in the review of carcinogenicity studies.

As reported by the sponsor, survival was best among the high dose animals, resulting in statistically significant trends (p(males)=0.0161, p(females)=0.0001, Tables 7-10, Figures 7, 8).

Hepatocellular adenoma showed a highly statistically significant trend (p=0.0000) among the males, and hepatocellular adenoma (p=0.0000) and hepatocellular carcinoma (p=0.0000) were equally statistically significant among the females (Tables 11, 12). Combining the

hepatocellular adenomas with the carcinomas would also result in highly statistically significant trends. However, interstitial-cell tumors of the testes, which was a statistically significant finding for the sponsor, was not so for this reviewer (p=0.0590). The difference in p-values is due to the fact that the sponsor failed to adjust for intercurrent mortality and may have used different weights. Furthermore, the sponsor's observed p-value of 0.021 would not pass the statistical criterion for common tumors (α=0.005) and would not be considered statistically significant. Similarly, the combined benign and malignant granular cell tumors of the vagina would not be considered statistically significant by these criteria (p=0.0401). When including the granular cell tumors observed in the cervix, the p-value is No other tumor trends reached statistical significance.

IV. The Mouse Study

IV.1 Sponsor's Findings

In this study 80 animals per dose group per sex were treated with Trileptal in the diet at doses of 0, 10, 40, 70, and 100 mg/kg/day. Terminal sacrifice was started on day 728 for the males and on day 735 for the females. Some animals of each group of 80 were used for interim sacrifice.

The sponsor reports that there was a transient drop in survival among the males during weeks 71-74, when 18 treated mice died, of which 10 had myocardial hemorrhage and necrosis. For the females, the survival rates of the treated animals were similar to the controls.

Bodyweight gain of the males was not affected by treatment (Figure 9). Bodyweights of the treated females dropped after week 15 as compared to the controls (Figure 10). The sponsor does not consider this of toxicological significance because there was no between group variation among the treated animals.

The sponsor observed a statistically significant increase in benign hepatomas for the mid and high dose males and for the high dose females. The reported p-values are 0.0002 for the males and 0.0330 for the females. For combined benign hepatomas, carcinomas, and hepatoblastoma, the p-values are 0.0016 for the males and 0.0369 for the females.

There were a total of 11 high dose and two mid dose males with myocardial hemorrhage and necrosis. The sponsor did not analyze these findings.

IV.2 Reviewer's Findings

It was difficult to produce the exact number of animals terminally sacrificed. The sponsor reported only **percent** of animals censored:

SEX/DOSE	CONTROL	10 MG	40 MG	70 MG	100 MG
MALES	57%→45 or 46	53%→42	58%→46	60%→48	47%→37 or 38
FEMALES	62%→49 or 50	66%→53	60%→48	67%→53 or 54	67%→53 or 54

However, 57, 47, 62, and 67 % out of 80 animals appear to be improperly rounded. E.g., 45 animals represent 56.25 or 56 % and 46 animals represent 57.5 or 58 % censored. There are no whole numbers of animals that compute to 57, 47, 62, or 67 percent.

Besides the day of death, the data contain a code that reflects that an animal was terminally sacrificed. The beginning of terminal sacrifice was day 728 for the males and day 735 for the females. However, some animals died naturally before being sacrificed. As these animals were intended for terminal sacrifice this reviewer re-coded them as such. With this approach this reviewer computed 150 males (versus the sponsor's estimated 180) and 180 females (versus the sponsor's estimated 141) as terminally sacrificed. These differences affect the magnitude of the statistics and of the p-values, but appear not to affect the conclusions.

Mortality among either sex was not affected by treatment. The p-value for dose related trend was 0.1757 for the males and 0.5590 for the females (Tables 13-16, Figures 11, 12).

Investigating dose related increases in tumor incidences showed a highly significant (p=0.0005) increase in benign hepatoma of the liver among the males as the only significant finding (Table 17). Among the females neither this nor any other tumor finding reached statistical significance (Table 18). Pairwise comparisons between the incidences of control and high dose hepatomas produced a p-value of 0.0067 for the males and 0.0716 for the females. It is noted that there are no established α-levels for conditional pairwise comparisons (males: significant trend test; females: a significant finding among the males).

Analyzing the incidence of mycardial hemorrhage and necrosis produced a p-value of 0.0002. The sponsor's table on p. 107 of volume 1.34 was used in this calculation:

Days/Dose	Controls	10 MG	40 MG	70 MG	100 MG
1-359	0/8	0/6	0/6	0/5	0/10
360-369	0/4	0/4	0/4	0/6	1/5
370-489	0/5	0/3	0/9	0/5	0/2
490-519	0/4	0/3	0/5	2/6	10/18
520-736	0/59	0/64	0/56	0/58	0/45

As there were no statistically significant tumor findings among the females, this part of the study was evaluated with respect to its validity using the same criteria outlined above for the first rat study. Despite the difficulties in establishing the precise number of animals at terminal sacrifice, it is clear that there were sufficient numbers of animals living long enough to manifest late developing tumors if the drug causes them. The mean body weights of the high dose seem to be less than 10 percent lower than that of the controls. A similar effect was seen for all treated groups. Going strictly by the criterion of a small suppression in body weights, the high dose appears to be close to the MTD.

V. Summary

V.1 First Rat Study

In this two year study, 60 animals of each sex were dosed at 0, 25, 75, and 250 mg/kg/day in the diet. Survival was good and similar across groups. Among the males, interstitial cell tumor of the testes reached statistical significance in a pairwise comparison of controls and HD. Among the females, hepatocellular carcinoma approached statistical significance in a trend test. Evaluating the validity of the female

portion of the study gave no statistical support (body weights sharply decreased, no depressed survival) that the HD was close to the MTD.

V.2 Second Rat Study

In this two year study, 60 animals per sex were dosed with 0, 75, 250, and 600 mg/kg/day of the active monohydroxy derivative of Trileptal. Survival was not affected by the treatment, as the high dose animals experienced the best survival. Average body weights and body weight gains were depressed for both sexes, starting early in the study and lasting the whole treatment period. This reviewer observed highly statistically significant trends in hepatocellular adenoma among the males and hepatocellular adenoma and carcinoma among the females. No other tumor incidences reached statistical significance at the usual criteria set up for common and rare tumors.

V.3 Mouse Study

In this two year study, 80 animals per group received doses of 0, 10, 40, 70, and 100 mg/kg/day. Mortality was not affected by the treatment with Trileptal. Among the males there was a statistically significant trend in benign hepatomas. No other tumor incidences reached statistical significance. Among the females, no trend test reached statistical significance. This reviewer could not reproduce the numbers of terminally sacrificed mice reported by the sponsor but all tumor incidences were identical. The differences in the number of TS animals changed the magnitude of the statistics and the associated p-values, but not the conclusions. Mycardial hemorrhage and necrosis were observed among the HD males to a highly statistically significant level. Investigating the validity of the female section of the study showed sufficient numbers of animals surviving till the end of the study to manifest late developing tumors. The high dose seemed to be close to the MTD based on the depression of average body weights after week 15 when compared to the controls. Therefore, this study section appears to be a valid study based on statistical criteria.

/S/

Roswitha Kelly, M.S.
Mathematical Statistician

/S/

Kun Jin, Ph.D.
Team Leader

APPEARS THIS WAY
ON ORIGINAL

/S/

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

Cc: Archival NDA 21-014, Trileptal (oxcarbazepine) Tablets, Novartis
CARCINOGENICITY

HFD-120/Ms. Mallandrucco, CSO
HFD-120/Dr. Fisher
HFD-120/Dr. Fitzgerald
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Ms. Kelly
HFD-710/Chron.
This review consists of 9 pages, 1 addendum, 18 tables, 12 figures.
MSWord: trileptal.doc/08/03/99

ADDENDUM

In these studies there are several occasions where the gross incidences of tumors (e.g., 0, 3, 2, 6, for control, low, medium, and high dose groups) would suggest a statistically significant finding, but the p-value for trend does not reach statistical significance. This phenomenon is basically due to the fact that the test performed by this reviewer adjusts for intercurrent mortality and that the test is the exact permutation trend test, not based on the normal approximation. Adjusting for intercurrent mortality implies not only adjusting for any differential mortality among treatment groups, but also, that the denominators are much less than the total groups size; because the tumors are evaluated within the time intervals in which they occurred. Using an example taken from the second rat study, namely benign granular cell tumors of the vagina, the gross (unadjusted) rates are 0/60, 3/60, 2/60, 6/60. The p-value for the exact permutation trend test (unadjusted for intercurrent mortality) is 0.0128 and for the asymptotic test, it is 0.0089. Both results would be considered statistically significant but the asymptotic results are much more so. In reality, most events were found during terminal sacrifice and are based on roughly only half the animals, namely 0/17, 2/24, 2/31, and 6/38 for controls, low, mid and high dose groups. There was one more event in the previous time interval with the following rates: 0/10, 1/13, 0/11, 0/6. The p-value for the exact permutation trend test adjusted for intercurrent mortality is 0.0622, which is not statistically significant. The adjusted asymptotic test has a p-value of 0.0542, which is also not statistically significant, but lower than the one for the exact test. In general, adjusting for intercurrent mortality may decrease the apparent significance of the finding and using asymptotic methods when the incidence of tumors is small tends to give falsely significant results.

Table 1.

Number of . ıls
Species: Hat
Sex: Male

Time Interval	Treatment Group CTRL Count	LOW Count	MED Count	HIGH Count	Total Count
0-52	.	.	3		5
53-78	2		7		13
79-91	4		3		19
92-105	11		8		35
106-106	43		39		168
Total	60	60	60	60	240

Table 2. Dose-Mortality nd Tests

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

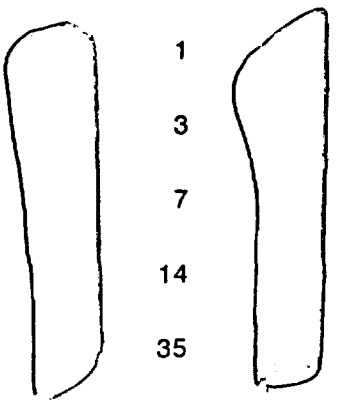
Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.00	0.9949
	Depart from Trend	1.31	0.5182
	Homogeneity	1.31	0.7256
Kruskal-Wallis	Dose-Mortality Trend	0.01	0.9431
	Depart from Trend	1.69	0.4306
	Homogeneity	1.69	0.6391

Table 3:

Number of Animals
Species: Rat
Sex: Female

Week	Treatment Group CTRL N	LOW N	MED N	HIGH N	Total N
0-52	5		1		10
53-78	3		3		12
79-91	9		7		35
92-105	14		14		44
106-106	29		35		139
Total	60	60	60	60	240



Source: C:\TRILEPT\rat11.dat

Table 4: Dose-Mortality nd Tests

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

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.85	0.1744
	Depart from Trend	1.89	0.3885
	Homogeneity	3.74	0.2914
Kruskal-Wallis	Dose-Mortality Trend	1.56	0.2120
	Depart from Trend	2.27	0.3208
	Homogeneity	3.83	0.2803

Source: C:\TRILERT\rat11.dat

Table 5: Test for Positive Dose-Response (Tumor) Linear Trend
Species: Rat
Sex: Male
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
1	ADRENALS	44	PHEOCHROMOCYTOMA [B]	0.1279	0.1207	0.1209
1	ADRENALS	19	GANGLIONEUROMA [B]	0.2560	0.0503	0.0508
1	ADRENALS	11	CORTICAL CARCINOMA [M]	0.8038	0.8165	0.8173
1	ADRENALS	10	CORTICAL ADENOMA [B]	0.8926	0.8804	0.8807
1	ADRENALS	37	MALIG PHEOCHROMOCYTOMA [M	1.0000	0.8130	0.8144
2	BONE	43	OSTEOSARCOMA [M]	0.2551	0.0501	0.0506
3	BRAIN	6	ASTROCYTOMA [M]	0.0512	0.0062	0.0062
3	BRAIN	20	GRANULAR CELL TUMOR [M]	0.1662	0.1259	0.1263
6	KIDNEYS	55	TUBULE CELL CARCINOMA [M]	0.1621	0.0829	0.0834
6	KIDNEYS	36	MALIG MIXED TUMOR [M]	0.4881	0.5516	0.5536
6	KIDNEYS	51	TRANSITIONAL CELL CARCINO	0.6113	0.7003	0.7014
6	KIDNEYS	54	TUBULE CELL ADENOMA [B]	1.0000	0.8130	0.8144
7	LIVER	41	NEOPLASTIC NODULE [B]	0.1702	0.1634	0.1635
7	LIVER	23	HEPATOCELLULAR CARCINOMA	0.4478	0.4455	0.4460
8	LUNG	4	ALVEOLAR/BRONCHIOLAR CARC	0.4881	0.5516	0.5536
9	LYMPH NODE - MANDIB/CERV	43	OSTEOSARCOMA [M]	0.6923	0.5399	0.5424
10	MAMMARY GLAND	2	ADENOCARCINOMA [M]	0.2892	0.2869	0.2877
[illegible]	MAMMARY GLAND	14	FIBROADENOMA [B]	0.8603	0.8644	0.8650
	PANCREAS	25	ISLET CELL ADENOMA [B]	0.2504	0.2448	0.2455
12	PANCREAS	26	ISLET CELL CARCINOMA [M]	0.4382	0.4148	0.4159
12	PANCREAS	1	ACINAR CELL CARCINOMA [M]	1.0000	0.7871	0.7887
13	PARATHYROIDS	3	ADENOMA [B]	0.2407	0.0440	0.0444
14	PITUITARY	3	ADENOMA [B]	0.0628	0.0577	0.0578
14	PITUITARY	9	CARCINOMA [M]	0.8613	0.8548	0.8548
15	SALIVARY GLAND	47	SARCOMA [M]	1.0000	0.8130	0.8143
16	SKIN	53	TRICHOEPITHELIOMA [B]	0.2560	0.0503	0.0508
16	SKIN	45	PILOMATRICOMA [B]	0.2953	0.3053	0.3063
16	SKIN	48	SQUAMOUS CELL CARCINOMA [	0.4881	0.5516	0.5536
16	SKIN	49	SQUAMOUS CELL PAPILLOMA [	0.8038	0.8165	0.8173
16	SKIN	27	KERATOACANTHOMA [B]	0.8275	0.8410	0.8416
17	SPLEEN	22	HEMANGIOSARCOMA [M]	1.0000	0.8130	0.8144
18	STOMACH	48	SQUAMOUS CELL CARCINOMA [	0.4881	0.5516	0.5536
5	SYSTEMIC	30	LEUKEMIA [M]	0.4916	0.5460	0.5480
5	SYSTEMIC	13	ERYTHROLEUKEMIA [M]	0.4979	0.5484	0.5504
5	SYSTEMIC	40	MYELOMONOCYTIC LEUKEMIA [	0.5008	0.5112	0.5118
5	SYSTEMIC	33	MALIG LYMPHOMA, HISTIOCYT	0.8124	0.8247	0.8255
5	SYSTEMIC	39	MYELOGENOUS LEUKEMIA [M]	1.0000	0.8948	0.8954
19	TESTES	24	INTERSTITIAL-CELL TUMOR [	0.0031	0.0017	0.0016
21	THYROID	17	FOLLICULAR CELL ADENOMA [	0.1854	0.0980	0.0986
21	THYROID	8	C-CELL CARCINOMA [M]	0.9994	0.9906	0.9906
	THYROID	7	C-CELL ADENOMA [B]	1.0000	0.9393	0.9397
	TISSUE MASS(ES)	15	FIBROMA [B]	0.4154	0.4345	0.4354
22	TISSUE MASS(ES)	43	OSTEOSARCOMA [M]	0.4364	0.2869	0.2882
22	TISSUE MASS(ES)	49	SQUAMOUS CELL PAPILLOMA [	0.4881	0.5516	0.5536
22	TISSUE MASS(ES)	47	SARCOMA [M]	0.4973	0.5505	0.5525
22	TISSUE MASS(ES)	5	AMELOBLASTOMA [B]	[illegible]	[illegible]	[illegible]

Table 5 cont'd: Test for Positive Dose-Response (Tumor) Linear Trend
Species: Rat
Sex: Male
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
22	TISSUE MASS(ES)	16	FIBROSARCOMA [M]	0.8829	0.8877	0.8881
22	TISSUE MASS(ES)	48	SQUAMOUS CELL CARCINOMA [	0.9200	0.8807	0.8813
22	TISSUE MASS(ES)	31	LIPOMA [B]	0.9218	0.8834	0.8840
22	TISSUE MASS(ES)	42	NEUROFIBROSARCOMA [M]	0.9320	0.8567	0.8575
22	TISSUE MASS(ES)	22	HEMANGIOSARCOMA [M]	1.0000	0.8142	0.8156
23	TRIGEMINAL GANG	42	NEUROFIBROSARCOMA [M]	0.4800	0.5452	0.5472

Table 6: Test for Positive Dose-Response (Tumor) Linear Trend
Species: Rat
Sex: Female
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
1	ADRENALS	10	CORTICAL ADENOMA [B]	0.4467	0.4533	0.4540
1	ADRENALS	11	CORTICAL CARCINOMA [M]	0.7914	0.7597	0.7612
1	ADRENALS	44	PHEOCHROMOCYTOMA [B]	0.9715	0.9602	0.9603
3	BRAIN	6	ASTROCYTOMA [M]	0.1736	0.1095	0.1102
4	CECUM	28	LEIOMYOMA [B]	1.0000	0.7984	0.7999
6	KIDNEYS	55	TUBULE CELL CARCINOMA [M]	0.0561	0.0074	0.0075
6	KIDNEYS	52	TRANSITIONAL CELL PAPILLO	0.2806	0.0611	0.0617
7	LIVER	23	HEPATOCELLULAR CARCINOMA	0.0295	0.0234	0.0234
7	LIVER	41	NEOPLASTIC NODULE [B]	0.7252	0.7230	0.7234
8	LUNG	48	SQUAMOUS CELL CARCINOMA [	0.2806	0.0611	0.0617
10	MAMMARY GLAND	2	ADENOCARCINOMA [M]	0.1729	0.1667	0.1668
10	MAMMARY GLAND	3	ADENOMA [B]	0.6168	0.6168	0.6169
10	MAMMARY GLAND	14	FIBROADENOMA [B]	0.9943	0.9926	0.9926
11	OVARIES	9	CARCINOMA [M]	1.0000	0.8303	0.8315
11	OVARIES	21	GRANULOSA-THECA CELL TUMO	1.0000	0.7984	0.7999
12	PANCREAS	1	ACINAR CELL CARCINOMA [M]	1.0000	0.7984	0.7999
12	PANCREAS	26	ISLET CELL CARCINOMA [M]	1.0000	0.8303	0.8315
	PITUITARY	3	ADENOMA [B]	0.7861	0.7826	0.7834
	PITUITARY	9	CARCINOMA [M]	0.9532	0.9467	0.9467
25	PRIMARY SITE UNDETERMINED	2	ADENOCARCINOMA [M]	1.0000	0.7886	0.7901
15	SALIVARY GLAND	2	ADENOCARCINOMA [M]	1.0000	0.8202	0.8215
18	STOMACH	49	SQUAMOUS CELL PAPILLOMA [	0.6818	0.7099	0.7117
18	STOMACH	2	ADENOCARCINOMA [M]	0.7914	0.7597	0.7612
18	STOMACH	48	SQUAMOUS CELL CARCINOMA [	1.0000	0.7984	0.7999
5	SYSTEMIC	40	MYELOMONOCYTIC LEUKEMIA [	0.2336	0.2425	0.2434
5	SYSTEMIC	33	MALIG LYMPHOMA, HISTIOCYT	0.3899	0.4150	0.4160
5	SYSTEMIC	34	MALIG LYMPHOMA, LYMPHOBLA	1.0000	0.8150	0.8163
5	SYSTEMIC	35	MALIG LYMPHOMA, LYMPHOCYT	1.0000	0.8303	0.8315
5	SYSTEMIC	38	MESOTHELIOMA [M]	1.0000	0.8303	0.8315
20	THYMUS	50	THYMOMA [B]	1.0000	0.8303	0.8315
21	THYROID	18	FOLLICULAR CELL CARCINOMA	0.0801	0.0467	0.0469
21	THYROID	7	C-CELL ADENOMA [B]	0.5777	0.5357	0.5369
21	THYROID	8	C-CELL CARCINOMA [M]	0.7714	0.7825	0.7835
22	TISSUE MASS(ES)	49	SQUAMOUS CELL PAPILLOMA [	0.1480	0.0757	0.0761
22	TISSUE MASS(ES)	42	NEUROFIBROSARCOMA [M]	0.3000	0.0672	0.0678
22	TISSUE MASS(ES)	15	FIBROMA [B]	0.5000	0.4949	0.4971
22	TISSUE MASS(ES)	32	MALIG FIBROUS HISTIOCYTOM	0.5235	0.5609	0.5628
22	TISSUE MASS(ES)	47	SARCOMA [M]	0.6659	0.7320	0.7331
22	TISSUE MASS(ES)	16	FIBROSARCOMA [M]	0.6818	0.7099	0.7117
22	TISSUE MASS(ES)	46	RHABDOMYOSARCOMA [M]	0.9451	0.8655	0.8663
	TISSUE MASS(ES)	29	LEIOMYOSARCOMA [M]	1.0000	0.7984	0.7999
--	TISSUE MASS(ES)	48	SQUAMOUS CELL CARCINOMA [	1.0000	0.8881	0.8888
24	UTERUS	48	SQUAMOUS CELL CARCINOMA [	0.1626	0.1253	0.1261
24	UTERUS	29	LEIOMYOSARCOMA [M]	0.2545	0.0499	0.0504
24	UTERUS	31	LIPOMA [B]	0.2806	0.0611	0.0617
24	UTERUS	3	ADENOMA [B]	0.7914	0.7597	0.7612

Table 6 cont'd

24	UTERUS	12	ENDOMETRIAL STROMAL POLYP	0.9319	0.9219	0.9222
24	UTERUS	2	ADENOCARCINOMA [M]	1.0000	0.7984	0.7999
24	UTERUS	15	FIBROMA [B]	1.0000	0.8303	0.8315

Source: C:\TRILEPT\rat11.dat

Table 7: Number of Animals
Species: Rat
Sex: Male
Second Rat Study

Week	Treatment Group CTRL N	LOW N	MED N	HIGH N	Total N
0-52	1	9	5	37	
53-78	13	11	35	54	
79-91	8	16	54	109	
92-105	16	24	109	240	
106-106	22				
Total	60	60	60	60	

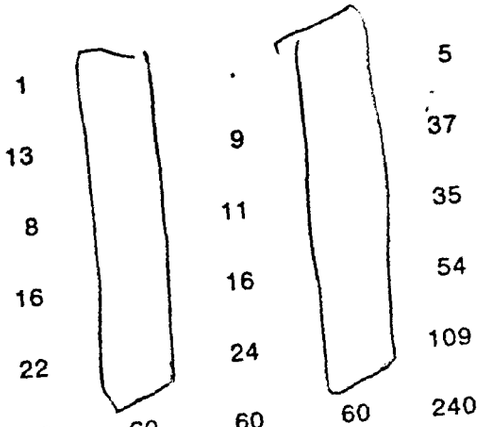


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Table 8. Dose-Mortality Trend Tests
Second Rat Study

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

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	5.79	0.0161
	Depart from Trend	0.71	0.7007
	Homogeneity	6.50	0.0895
Kruskal-Wallis	Dose-Mortality Trend	5.16	0.0231
	Depart from Trend	0.32	0.8503
	Homogeneity	5.48	0.1396

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Table 9: Number of Animals
Species: Rat
Sex: Female
Second Rat Study

Week	Treatment Group CTRL N	LOW N	MED N	HIGH N	Total N
0-52	2		1		8
53-78	15		7		40
79-91	16		10		42
92-105	10		11		40
106-106	17		31		110
Total	60	60	60	60	240

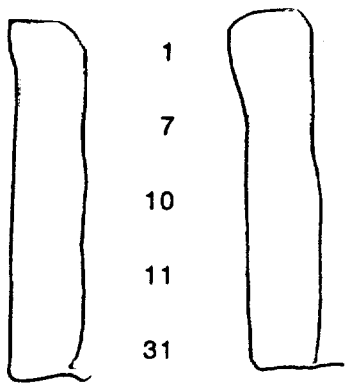

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Table10: Dose-Mortality Trend Tests
Second Rat Study

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

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	14.52	0.0001
	Depart from Trend	3.60	0.1650
	Homogeneity	18.13	0.0004
Kruskal-Wallis	Dose-Mortality Trend	13.21	0.0003
	Depart from Trend	3.70	0.1570
	Homogeneity	16.92	0.0007

Source: C:\TRILEPT\rat22.dat

Table 11: Test for Positive Dose-Response (Tumor) Linear Trend

Species: Rat

Sex: Male

Sorted by: Organ Name

Second Rat Study

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
1	ABDOMINAL CAVITY	39	LEIOMYOSARCOMA [M]	0.7598	0.7518	0.7525
2	ADRENAL GLAND	17	CORTICAL ADENOMA [B]	0.8473	0.8370	0.8373
2	ADRENAL GLAND	55	PHEOCHROMOCYTOMA [B]	0.8214	0.8222	0.8223
2	ADRENAL GLAND	56	PHEOCHROMOCYTOMA [M]	0.7995	0.7899	0.7902
4	BRAIN	9	ASTROCYTOMA [M]	0.7201	0.7173	0.7177
4	BRAIN	25	GRAN CELL TUM, BEN	0.7934	0.7899	0.7902
4	BRAIN	26	GRAN CELL TUM, MAL	0.2447	0.0534	0.0536
4	BRAIN	51	OLIGODENDROGLIOMA [M]	0.3303	0.0905	0.0908
6	EYE	39	LEIOMYOSARCOMA [M]	1.0000	0.8529	0.8534
7	HEART	46	NERVE SHEATH TUM, BEN, en	0.3303	0.0905	0.0908
8	KIDNEY	3	ADENOCARC	1.0000	0.8661	0.8665
8	KIDNEY	7	ADENOMA [B]	0.2642	0.2304	0.2309
8	KIDNEY	41	LIPOSARCOMA [M]	1.0000	0.8661	0.8665
9	LACRIMAL GLAND	28	HEMANGIOMA [B]	1.0000	0.8374	0.8380
10	LARGE INTESTINE	39	LEIOMYOSARCOMA [M]	0.3303	0.0905	0.0908
11	LIVER	30	HEPATOCELLULAR ADENOMA [B	0.0000	0.0000	0.0000
11	LIVER	31	HEPATOCELLULAR CARCINOMA	0.1023	0.0928	0.0928
	LIVER	32	HEPATOCHOLANGIOCELLULAR C	0.6487	0.6704	0.6713
	LUNG	1	ADENOCARC, alveolar/bronc	0.6487	0.6704	0.6713
12	LUNG	4	ADENOMA, alveolar/bronchi	0.6487	0.6704	0.6713
12	LUNG	54	PAPILLOMA [B]	0.2376	0.1933	0.1937
13	LYMPH NODE	21	FIBROSARCOMA [M]	0.3303	0.0905	0.0908
13	LYMPH NODE	28	HEMANGIOMA [B]	1.0000	0.8661	0.8665
13	LYMPH NODE	29	HEMANGIOSARCOMA [M]	0.2202	0.1418	0.1421
13	LYMPH NODE	42	LYMPHANGIOSARCOMA [M]	0.3303	0.0905	0.0908
14	MAMMARY GLAND	3	ADENOCARC	0.7910	0.7877	0.7880
14	MAMMARY GLAND	7	ADENOMA [B]	0.5667	0.5567	0.5575
14	MAMMARY GLAND	19	FIBROADENOMA [B]	0.3556	0.1018	0.1021
15	OTHER TISSUE(S)	24	GRAN CELL TUM, BEN, perio	0.7982	0.7888	0.7894
15	OTHER TISSUE(S)	44	MESOTHELIOMA [B], omentum	0.7982	0.7888	0.7894
16	PANCREAS	35	ISLET CELL ADENOMA [B]	0.5711	0.5653	0.5654
16	PANCREAS	36	ISLET CELL CARCINOMA [M]	0.9960	0.9940	0.9939
17	PARATHYROID	7	ADENOMA [B]	0.6463	0.6495	0.6496
18	PITUITARY	5	ADENOMA, pars distalis	0.9740	0.9726	0.9727
18	PITUITARY	6	ADENOMA, pars intermedia	0.7050	0.7316	0.7321
19	PROSTATE	7	ADENOMA [B]	0.3303	0.0905	0.0908
20	SKELETAL MUSCLE	20	FIBROMA [B]	0.7982	0.7888	0.7894
20	SKELETAL MUSCLE	60	RHABDOMYOSARCOMA [M]	0.9607	0.9126	0.9129
21	SKIN	10	BASAL CELL CARCINOMA [M]	0.9607	0.9126	0.9129
21	SKIN	11	BASAL-CELL EPITHELIOMA [B	0.8070	0.8032	0.8035
	SKIN	20	FIBROMA [B]	0.6230	0.6151	0.6156
21	SKIN	21	FIBROSARCOMA [M]	0.5372	0.4275	0.4280
21	SKIN	37	KERATOACANTHOMA [B]	0.7959	0.7948	0.7952
21	SKIN	40	LIPOMA [B]	0.2051	0.2060	0.2060
21	SKIN	47	NERVE SHEATH TUM, BEN	0.7836	0.7769	0.7775
21	SKIN	49	NERVE SHEATH TUM, MAL	0.5357	0.5008	0.5015

Table A cont'd: Test for Positive Dose-Response (Tumor) Linear Trend

Species: Rat

Sex: Male

Sorted by: Organ Name

Second Rat Study

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
21	SKIN	54	PAPILLOMA [B]	0.9127	0.9068	0.9070
21	SKIN	57	PILOMATRICOMA [B]	0.5185	0.4493	0.4501
21	SKIN	63	SQUAMOUS CELL CARCINOMA [	0.7653	0.7637	0.7644
21	SKIN	64	TRICHOEPITHELIOMA [B]	1.0000	0.8661	0.8665
22	SMALL INTESTINE	39	LEIOMYOSARCOMA [M]	0.7982	0.7888	0.7894
23	SPINAL CORD	9	ASTROCYTOMA [M]	0.6965	0.7237	0.7242
24	SPLEEN	29	HEMANGIOSARCOMA [M]	0.5505	0.5354	0.5362
25	STOMACH	54	PAPILLOMA [B]	0.5185	0.4493	0.4501
25	STOMACH	61	SARCOMA [M], stromal	0.2930	0.0747	0.0750
25	STOMACH	63	SQUAMOUS CELL CARCINOMA [	0.3303	0.0905	0.0908
26	SYSTEMIC	27	GRAN LEUKEMIA [M]	0.7982	0.7888	0.7894
26	SYSTEMIC	33	HISTIOCYTIC SARCOMA [M]	0.7932	0.7901	0.7905
26	SYSTEMIC	43	LYMPHOMA, MALIGNANT [M]	0.1296	0.0924	0.0925
27	TESTIS	34	INTERSTITIAL-CELL TUMOR [	0.0590	0.0520	0.0521
29	THYROID	12	C-CELL ADENOMA [B]	0.3366	0.3080	0.3084
29	THYROID	22	FOLLICULAR ADENOCARCINOMA	0.5505	0.5354	0.5362
29	THYROID	23	FOLLICULAR ADENOMA [B]	0.8086	0.8062	0.8063
34	ZYMBAL'S GLAND	3	ADENOCARC	0.3303	0.0905	0.0908

Table 12: Test for Positive Dose-Response (Tumor) Linear Trend

Species: Rat

Sex: Female

Sorted by: Organ Name

Second Rat Study

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
2	ADRENAL GLAND	17	CORTICAL ADENOMA [B]	0.9045	0.8958	0.8960
2	ADRENAL GLAND	55	PHEOCHROMOCYTOMA [B]	0.8078	0.8120	0.8122
2	ADRENAL GLAND	56	PHEOCHROMOCYTOMA [M]	0.1939	0.1178	0.1182
3	BONE	16	CHONDROMA [B]	0.6273	0.5735	0.5743
3	BONE	52	OSTEOMA [B]	0.1500	0.0180	0.0181
3	BONE	53	OSTEOSARCOMA [M]	0.2469	0.0542	0.0545
4	BRAIN	8	ASTROCYTOMA [B]	0.7753	0.7838	0.7843
4	BRAIN	9	ASTROCYTOMA [M]	0.6250	0.5627	0.5635
4	BRAIN	25	GRAN CELL TUM, BEN	0.8455	0.8212	0.8218
5	CERVIX	25	GRAN CELL TUM, BEN	0.7182	0.6928	0.6932
7	HEART	48	NERVE SHEATH TUM, MAL, en	0.3455	0.0995	0.0998
8	KIDNEY	40	LIPOMA [B]	0.8455	0.8212	0.8218
8	KIDNEY	41	LIPOSARCOMA [M]	0.7619	0.7569	0.7572
10	LARGE INTESTINE	38	LEIOMYOMA [B]	0.6273	0.5735	0.5743
11	LIVER	30	HEPATOCELLULAR ADENOMA [B	0.0000	0.0000	0.0000
11	LIVER	31	HEPATOCELLULAR CARCINOMA	0.0000	0.0000	0.0000
11	LIVER	59	RHABDOID TUMOR [M]	0.7230	0.7407	0.7411
	MAMMARY GLAND	3	ADENOCARC	0.9949	0.9942	0.9941
	MAMMARY GLAND	7	ADENOMA [B]	0.9407	0.9285	0.9285
14	MAMMARY GLAND	19	FIBROADENOMA [B]	0.9971	0.9966	0.9965
14	MAMMARY GLAND	60	RHABDOMYOSARCOMA [M]	0.7500	0.7069	0.7077
16	PANCREAS	14	CARCINOMA, atypical	0.2768	0.0681	0.0684
16	PANCREAS	35	ISLET CELL ADENOMA [B]	0.6273	0.5735	0.5743
16	PANCREAS	36	ISLET CELL CARCINOMA [M]	0.9079	0.8955	0.8958
17	PARATHYROID	7	ADENOMA [B]	0.9315	0.9150	0.9152
18	PITUITARY	5	ADENOMA, pars distalis	0.9999	0.9999	0.9999
18	PITUITARY	6	ADENOMA, pars intermedia	0.3455	0.0995	0.0998
18	PITUITARY	15	CARCINOMA, pars distalis	0.7337	0.7339	0.7343
20	SKELETAL MUSCLE	45	MYXOSARCOMA [M]	0.7700	0.7667	0.7672
21	SKIN	11	BASAL-CELL EPITHELIOMA [B	0.3455	0.0995	0.0998
21	SKIN	20	FIBROMA [B]	0.8566	0.8543	0.8546
21	SKIN	21	FIBROSARCOMA [M]	0.3388	0.3123	0.3127
21	SKIN	28	HEMANGIOMA [B]	0.6273	0.5735	0.5743
21	SKIN	39	LEIOMYOSARCOMA [M]	0.8455	0.8212	0.8218
21	SKIN	40	LIPOMA [B]	0.9740	0.9615	0.9617
21	SKIN	62	SEBACEOUS ADENOCARCINOMA	0.3455	0.0995	0.0998
22	SMALL INTESTINE	39	LEIOMYOSARCOMA [M]	0.8455	0.8212	0.8218
25	STOMACH	50	NEUROENDOCRINE CELL TUM,	0.6512	0.6038	0.6043
25	STOMACH	54	PAPILLOMA [B]	0.4250	0.3682	0.3691
	STOMACH	63	SQUAMOUS CELL CARCINOMA [	0.4286	0.3901	0.3909
	SYSTEMIC	33	HISTIOCYTIC SARCOMA [M]	0.7489	0.7500	0.7507
26	SYSTEMIC	43	LYMPHOMA, MALIGNANT [M]	0.6220	0.6143	0.6148
28	THYMUS	47	NERVE SHEATH TUM, BEN	0.6321	0.5774	0.5782
29	THYROID	12	C-CELL ADENOMA [B]	0.2054	0.1935	0.1938
29	THYROID	13	C-CELL CARCINOMA [M]	0.6191	0.6951	0.6958
29	THYROID	22	FOLLICULAR ADENOCARCINOMA	0.4865	0.4584	0.4589

Table 12 cont'd) Test for Positive Dose-Response (Tumor) Linear Trend

Species: Rat

Sex: Female

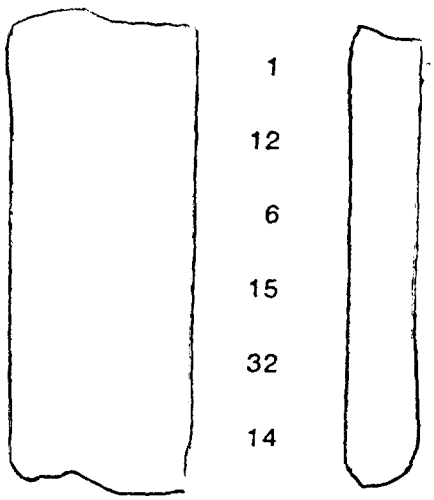
Sorted by: Organ Name

Second Rat Study

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
29	THYROID	23	FOLLICULAR ADENOMA [B]	0.2736	0.2185	0.2188
30	TONGUE	2	ADENOCARC, salivary, glan	0.8438	0.8096	0.8101
31	URINARY BLADDER	54	PAPILLOMA [B]	0.6273	0.5735	0.5743
32	UTERUS	18	ENDOMETRIAL STROMAL SARCO	0.7444	0.7384	0.7387
32	UTERUS	39	LEIOMYOSARCOMA [M]	0.8455	0.8212	0.8218
32	UTERUS	58	POLYP [B]	0.2112	0.2031	0.2031
33	VAGINA	18	ENDOMETRIAL STROMAL SARCO	0.6191	0.6951	0.6958
33	VAGINA	25	GRAN CELL TUM, BEN	0.0622	0.0543	0.0543
33	VAGINA	26	GRAN CELL TUM, MAL	0.3138	0.2174	0.2178
33	VAGINA	58	POLYP [B]	1.0000	0.8639	0.8644

Table 13: Number of Animals
Species: Mouse
Sex: Male

Week	Treatment Group CTRL N	LOW N	LOWMED N	MED N	HIGH N	Total N
0-52	4			1		17
53-78	10			12		72
79-91	6			6		28
92-104	17			15		73
105-105	32			32		150
INTERIM	11			14		60
Total	80	80	80	80	80	400



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Source: C:\TRILEPT\mouse3m.dat

Table 14: Dose-Mortality Trend Tests

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

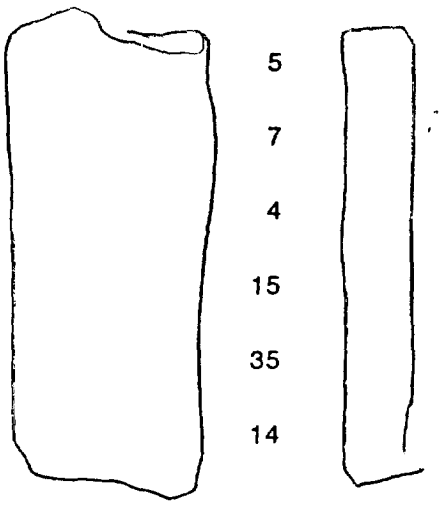
Species: Mouse
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.83	0.1757
	Depart from Trend	3.50	0.3214
	Homogeneity	5.33	0.2551
Kruskal-Wallis	Dose-Mortality Trend	3.14	0.0763
	Depart from Trend	4.41	0.2204
	Homogeneity	7.55	0.1094

Source: C:\TRILEPT\mouse3m.dat

Table 15 Number of Animals
Species: Mouse
Sex: Female

Week	Treatment Group					
	CTRL	LOW	LOWMED	MED	HIGH	Total
	N	N	N	N	N	N
0-52	3			5		16
53-78	6			7		35
79-91	8			4		35
92-104	15			15		67
105-106	33			35		180
INTERIM	15			14		67
Total	80	80	80	80	80	400



Source: C:\TRILEPT\mouse3f.dat

Table 1b : Dose-Mortality Trend Tests

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

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.34	0.5590
	Depart from Trend	2.14	0.5433
	Homogeneity	2.48	0.6475
Kruskal-Wallis	Dose-Mortality Trend	0.38	0.5354
	Depart from Trend	2.12	0.5471
	Homogeneity	2.51	0.6432

Source: C:\TRILEPT\mouse3f.dat

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ON ORIGINAL

Table 17: Test for Positive Dose-Response (Tumor) Linear Trend

Species: Mouse

Sex: Male

Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
1	ADRENAL GLAND	7	CORTICAL ADENOMA [B]	0.3648	0.2949	0.2984
4	HARDERIAN GLAND	2	ADENOMA [B]	0.9117	0.9085	0.9090
5	KIDNEY	2	ADENOMA [B]	0.7866	0.8110	0.8149
3	LARGE INTESTINE	6	CARCINOMA [M]	0.3712	0.3128	0.3162
6	LIVER	4	BENIGN HEPATOMA [B]	0.0005	0.0005	0.0005
6	LIVER	12	HEMANGIOMA [B]	0.1404	0.1277	0.1286
6	LIVER	14	HEPATOCELLULAR CARCINOMA	0.6311	0.6241	0.6254
6	LIVER	13	HEPATOBLASTOMA [M]	0.9622	0.9526	0.9534
7	LUNG	2	ADENOMA [B]	0.5608	0.5553	0.5561
7	LUNG	6	CARCINOMA [M]	0.8350	0.8330	0.8352
9	MEDIASTINUM	12	HEMANGIOMA [B]	0.1608	0.0512	0.0527
13	PREPUTIAL GLAND	8	CYSTADENOMA [B]	0.7857	0.8142	0.8180
14	PROSTATE	6	CARCINOMA [M]	0.1781	0.0557	0.0572
14	PROSTATE	2	ADENOMA [B]	0.7115	0.7132	0.7157
15	RETROPERITONEUM	18	LEIOMYOSARCOMA [M]	0.7671	0.7839	0.7878
16	SEMINAL VESICLE	18	LEIOMYOSARCOMA [M]	0.0495	0.0338	0.0342
16	SEMINAL VESICLE	12	HEMANGIOMA [B]	0.3667	0.2089	0.2130
	SEMINAL VESICLE	2	ADENOMA [B]	0.5934	0.5143	0.5199
	SKIN	12	HEMANGIOMA [B]	0.7011	0.6478	0.6514
17	SKIN	21	MALIGNANT FIBROUS HISTIOC	0.7671	0.7839	0.7878
17	SKIN	26	SARCOMA [M]	0.8758	0.8501	0.8523
19	SPLEEN	12	HEMANGIOMA [B]	0.2007	0.1238	0.1259
20	SYSTEMIC	23	MAST CELL TUMOR, MALIGNAN	0.5934	0.5143	0.5199
20	SYSTEMIC	15	HISTIOCYTIC SARCOMA [M]	0.8189	0.8088	0.8111
20	SYSTEMIC	26	SARCOMA [M]	0.8349	0.8397	0.8417
20	SYSTEMIC	20	LYMPHOMA, MALIGNANT [M]	0.9928	0.9911	0.9911
20	SYSTEMIC	18	LEIOMYOSARCOMA [M]	1.0000	0.8746	0.8774
20	SYSTEMIC	24	MYELOID LEUKAEMIA [M	1.0000	0.8777	0.8806
21	THYMUS	29	THYMOMA [B]	0.3611	0.2064	0.2104
21	THYMUS	28	THYMIC LYMPHOMA [M]	0.4333	0.3848	0.3880
22	URINARY BLADDER	30	TRANSITIONAL CELL CARCINO	0.3788	0.2152	0.2192

Table 18: Test for Positive Dose-Response (Tumor) Linear Trend
Species: Mouse
Sex: Female
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
1	ADRENAL GLAND	5	BENIGN MEDULLARY TUMOR [B	0.7636	0.7657	0.7686
2	BRAIN	22	MALIGNANT RETICULOSIS (C.	0.3607	0.1893	0.1933
4	HARDERIAN GLAND	2	ADENOMA [B]	0.7324	0.7263	0.7273
4	HARDERIAN GLAND	6	CARCINOMA [M]	1.0000	0.8804	0.8834
6	LIVER	4	BENIGN HEPATOMA [B]	0.0208	0.0196	0.0197
6	LIVER	14	HEPATOCELLULAR CARCINOMA	0.4049	0.3966	0.3984
6	LIVER	12	HEMANGIOMA [B]	0.9028	0.8900	0.8915
7	LUNG	6	CARCINOMA [M]	0.4071	0.3458	0.3493
7	LUNG	2	ADENOMA [B]	0.6087	0.6028	0.6029
8	MAMMARY GLAND	2	ADENOMA [B]	0.2123	0.0704	0.0721
8	MAMMARY GLAND	6	CARCINOMA [M]	0.4047	0.3962	0.3982
8	MAMMARY GLAND	1	ADENOACANTHOMA [M]	0.9970	0.9947	0.9947
10	OVARY	3	ANGIOSARCOMA [M]	0.4122	0.2454	0.2496
10	OVARY	12	HEMANGIOMA [B]	0.4176	0.2570	0.2612
10	OVARY	11	GRANULOSA CELL TUMOR [B]	1.0000	0.8869	0.8894
11	PANCREAS	16	ISLET CELL ADENOMA [B]	0.2167	0.0721	0.0739
12	PITUITARY	2	ADENOMA [B]	0.9031	0.8985	0.8989
[illegible]	SKIN	26	SARCOMA [M]	0.3333	0.1613	0.1654
[illegible]	SKIN	10	FIBROSARCOMA [M]	0.6154	0.5259	0.5315
17	SKIN	27	SQUAMOUS CELL CARCINOMA [	0.8395	0.8246	0.8270
17	SKIN	21	MALIGNANT FIBROUS HISTIOC	1.0000	0.8830	0.8857
18	SPINAL CORD	12	HEMANGIOMA [B]	0.2647	0.0801	0.0820
19	SPLEEN	12	HEMANGIOMA [B]	0.9577	0.9323	0.9335
19	SPLEEN	3	ANGIOSARCOMA [M]	1.0000	0.8840	0.8865
20	SYSTEMIC	18	LEIOMYOSARCOMA [M]	0.4130	0.2497	0.2539
20	SYSTEMIC	25	OSTEOGENIC SARCOMA [M]	0.4130	0.2504	0.2546
20	SYSTEMIC	15	HISTIOCYTIC SARCOMA [M]	0.4186	0.3854	0.3881
20	SYSTEMIC	24	MYELOID LEUKAEMIA [M	0.6570	0.6212	0.6242
20	SYSTEMIC	19	LYMPHATIC LEUKAEMIA [M]	0.7787	0.7705	0.7722
20	SYSTEMIC	20	LYMPHOMA, MALIGNANT [M]	0.8342	0.8305	0.8308
21	THYMUS	28	THYMIC LYMPHOMA [M]	0.4337	0.2609	0.2651
23	UTERUS	17	LEIOMYOMA [B]	0.2767	0.2638	0.2651
23	UTERUS	12	HEMANGIOMA [B]	0.4025	0.3726	0.3754
23	UTERUS	26	SARCOMA [M]	0.4927	0.4195	0.4231
23	UTERUS	18	LEIOMYOSARCOMA [M]	0.5030	0.4590	0.4619
23	UTERUS	9	FIBROMA [B]	0.7619	0.8106	0.8144
23	UTERUS	3	ANGIOSARCOMA [M]	0.8000	0.8387	0.8427

Figure 1

Mean Body Weight Data

104 Week Chronic Oral Administration of GP47680 in Rats

Males

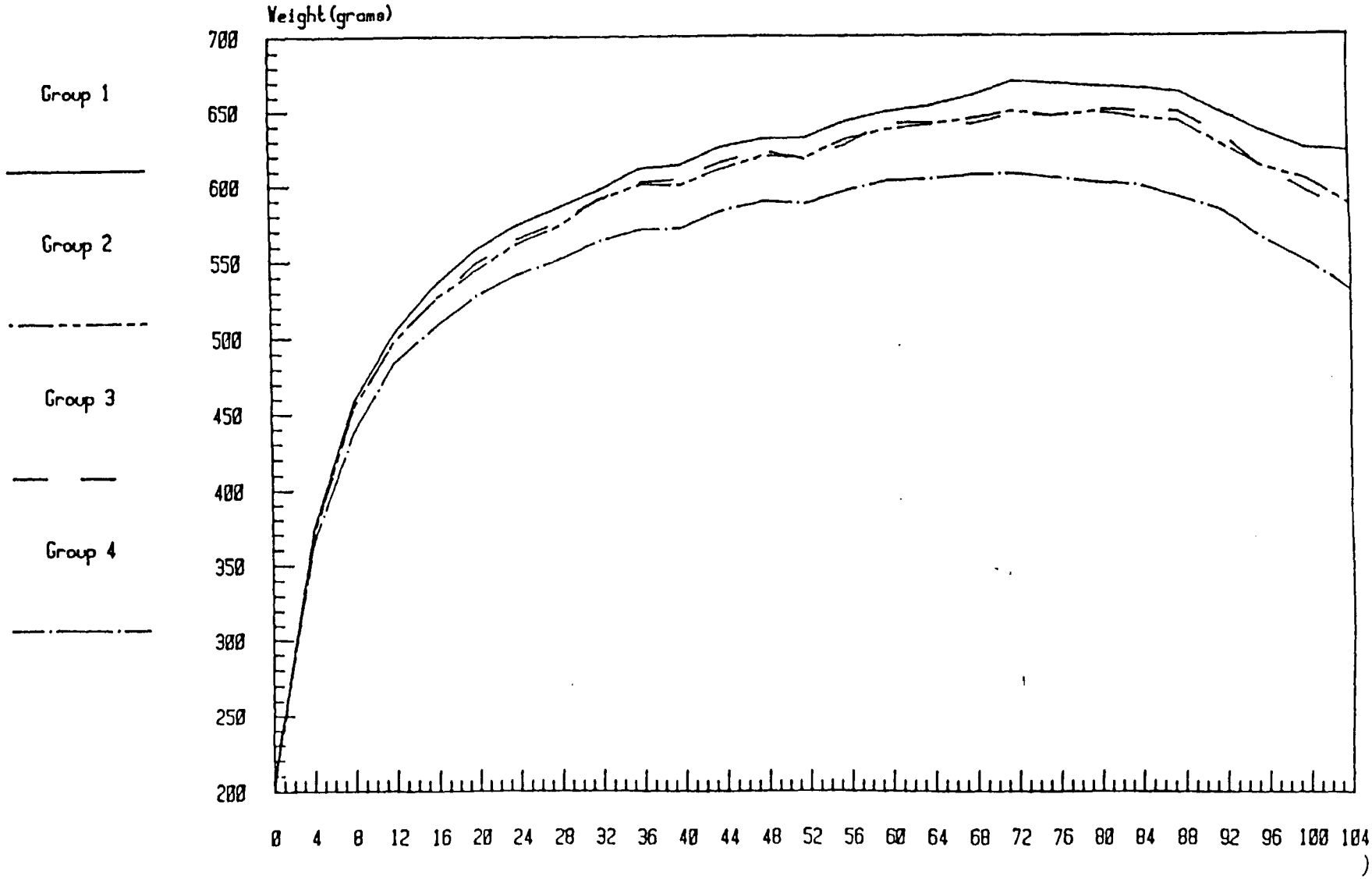
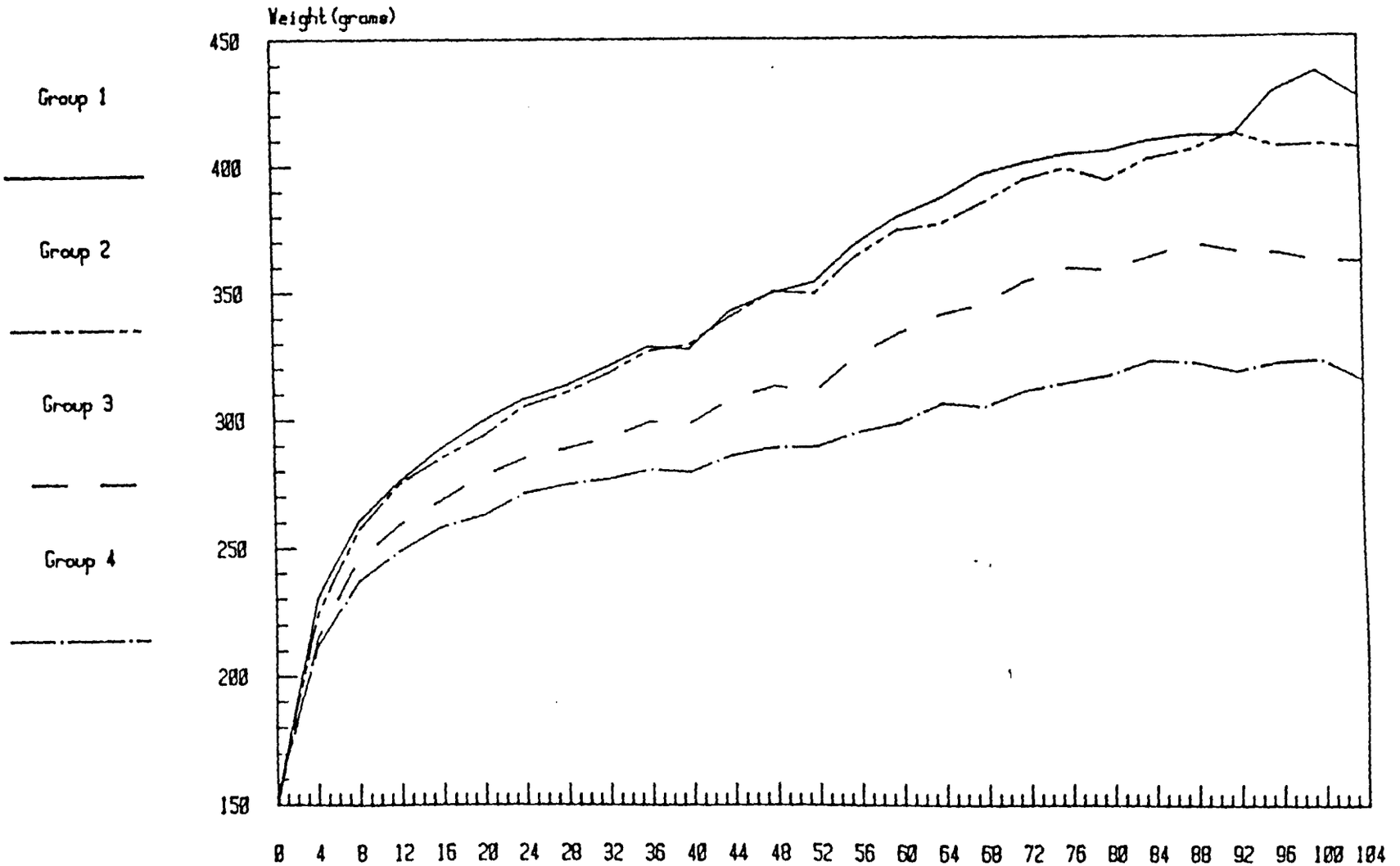


Figure 2
Mean Body Weight Data
104 Week Chronic Oral Administration of GP47680 in Rats
Females



Species: Rat

Sex: Male

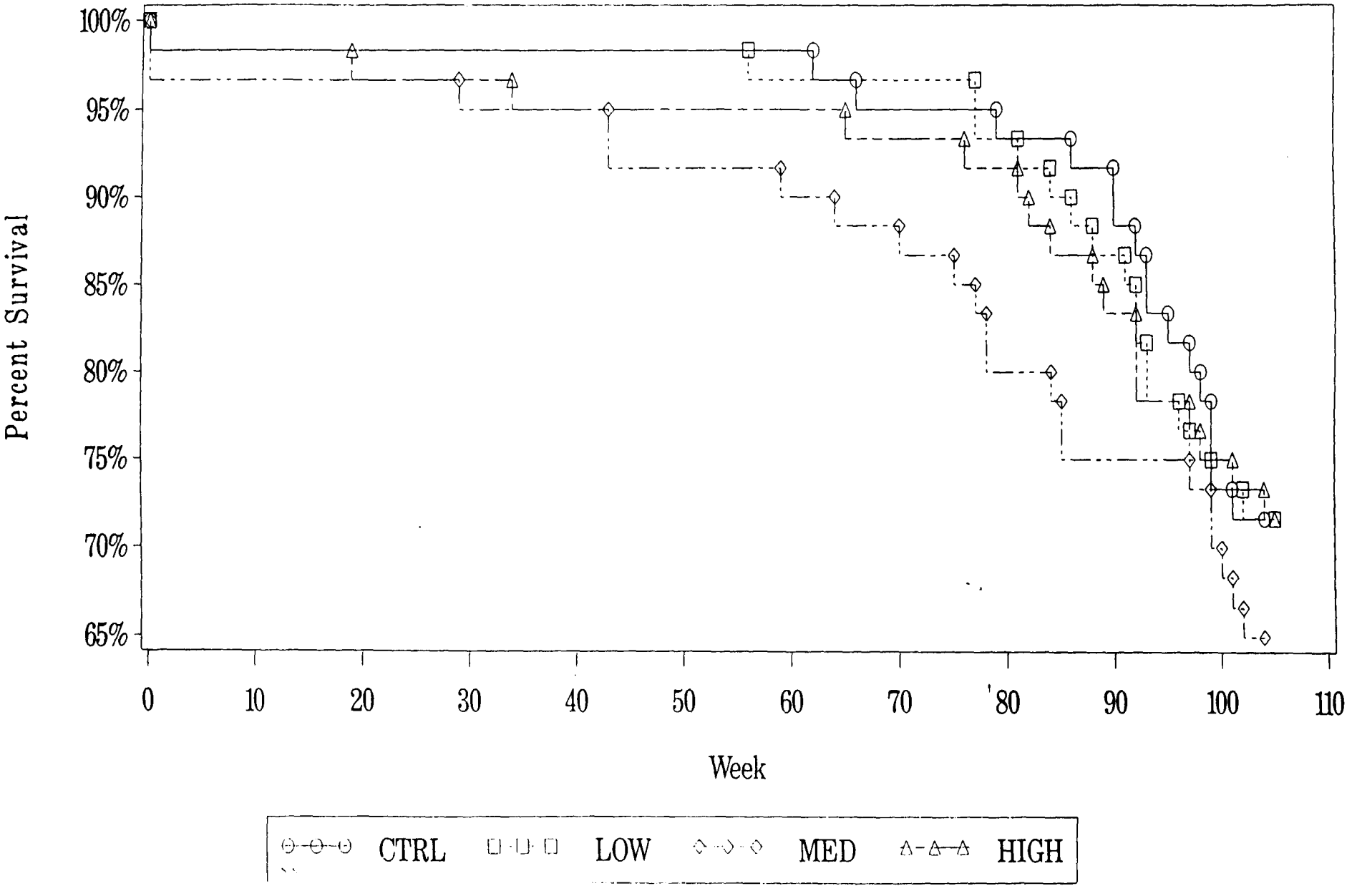


Figure 4: Kaplan–Meier Survival Function

Species: Rat
Sex: Female

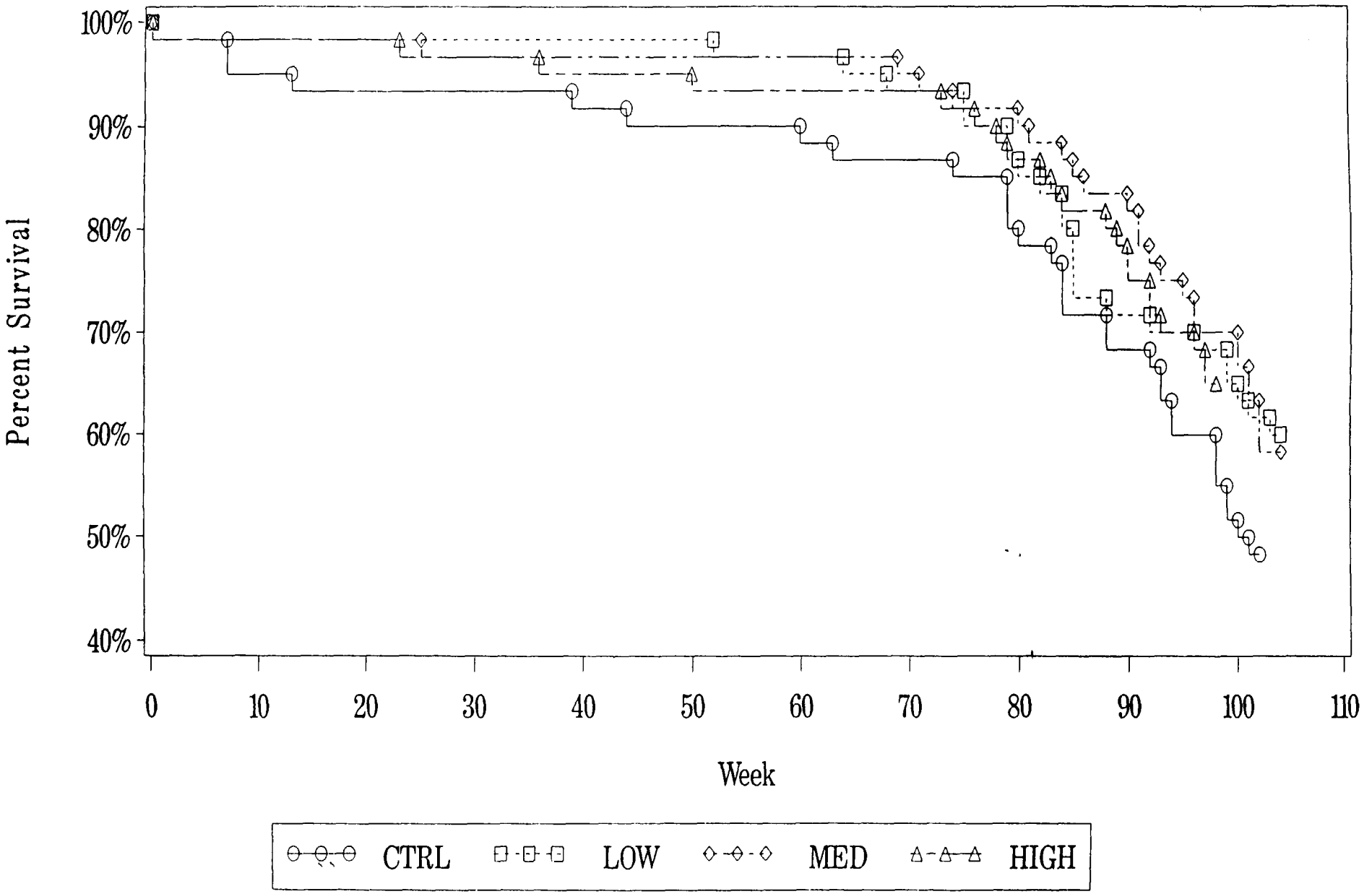
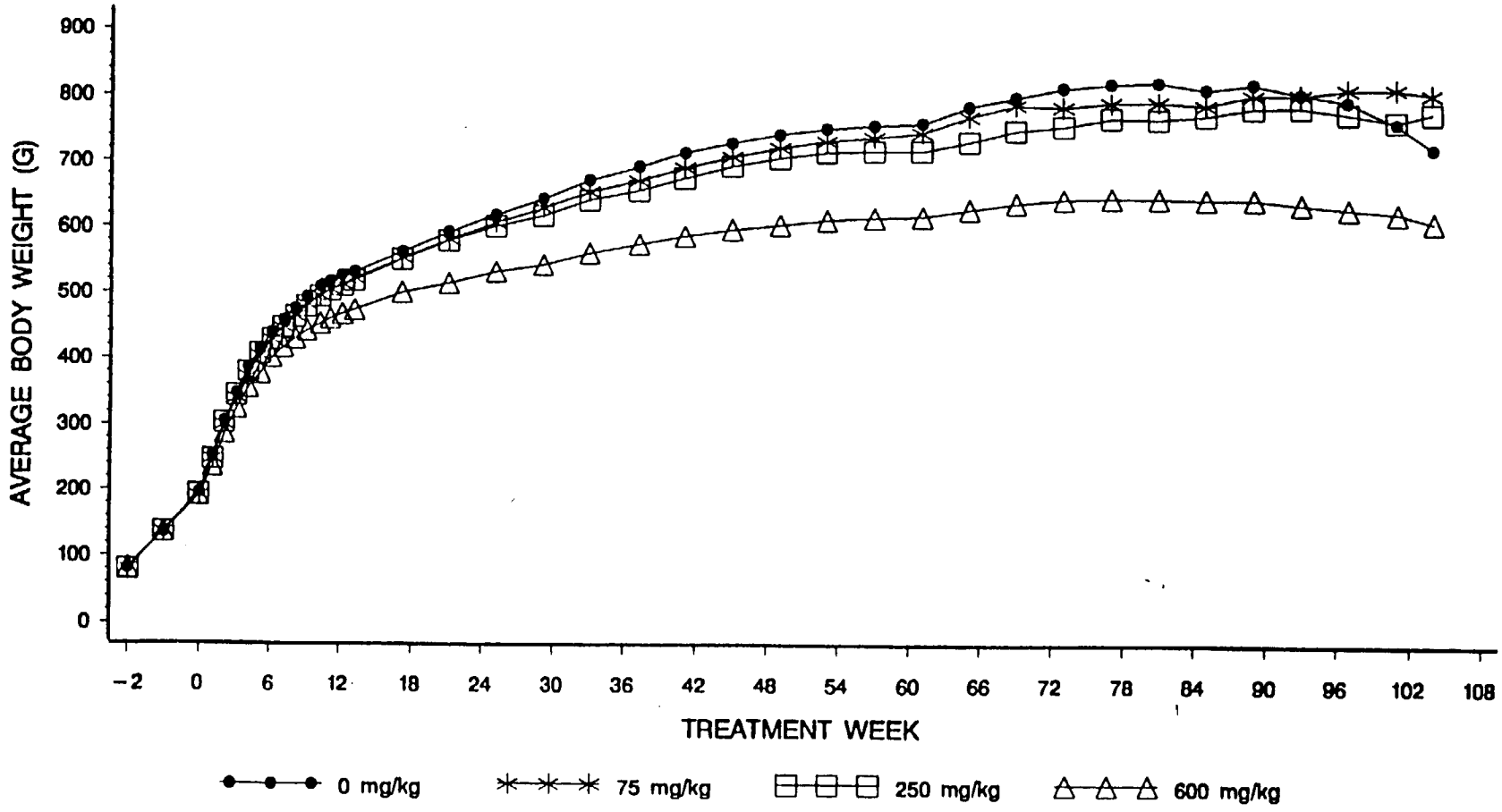


Figure 5:

BODY WEIGHT

GP 47779: 104-Week Oral (Gavage)
Carcinogenicity Study In Rats
MIN 951001
Males

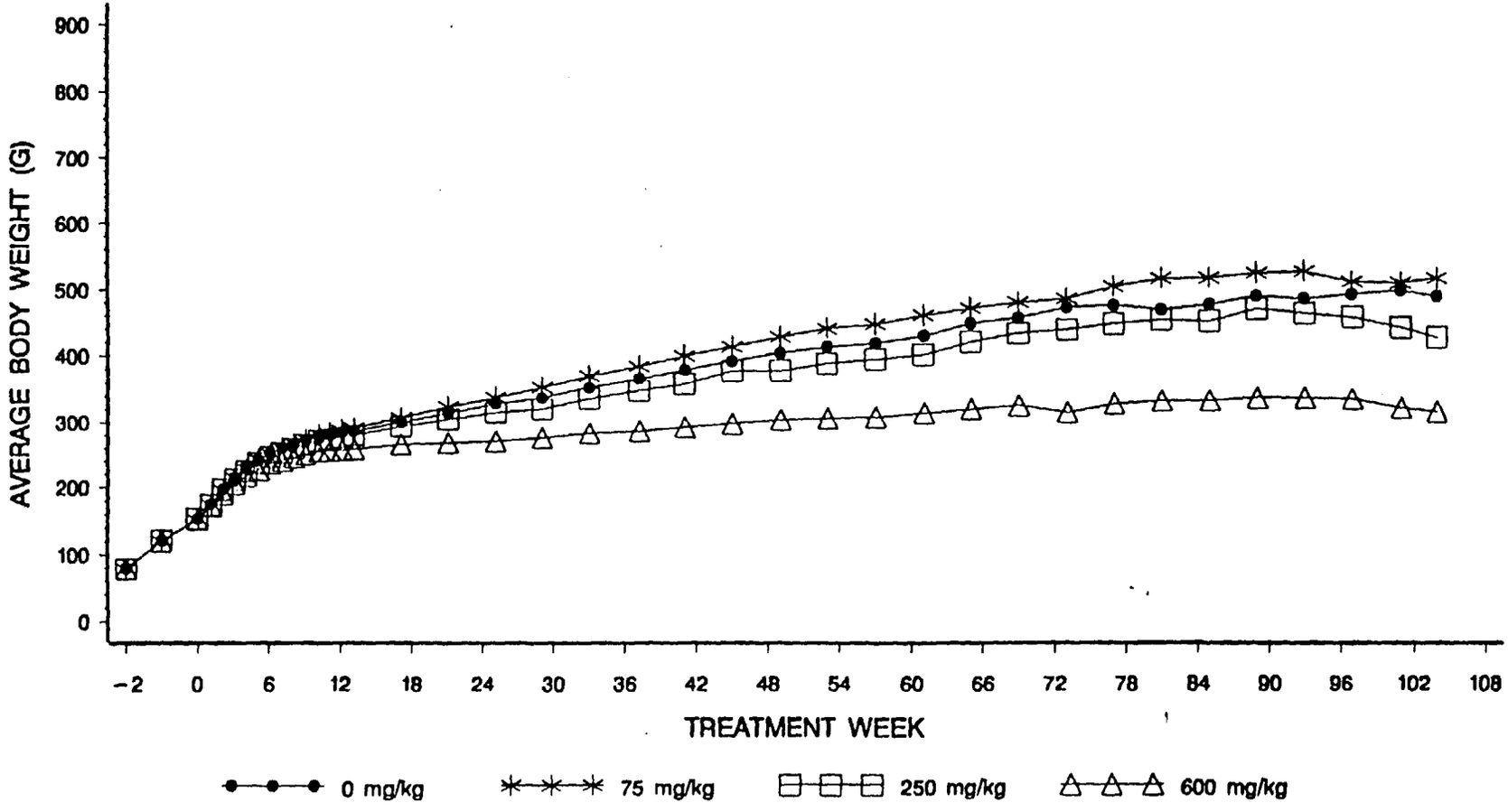


Pre-dose Time(weeks < 0) is not plotted in same scale as Post-dose Time

Figure 6:

BODY WEIGHT

GP 47779: 104-Week Oral (Gavage)
Carcinogenicity Study in Rats
MIN 951001
Females



Pre-dose Time(weeks < 0) is not plotted in same scale as Post-dose Time

Kaplan–Meier Survival Function

Species: Rat

Sex: Male

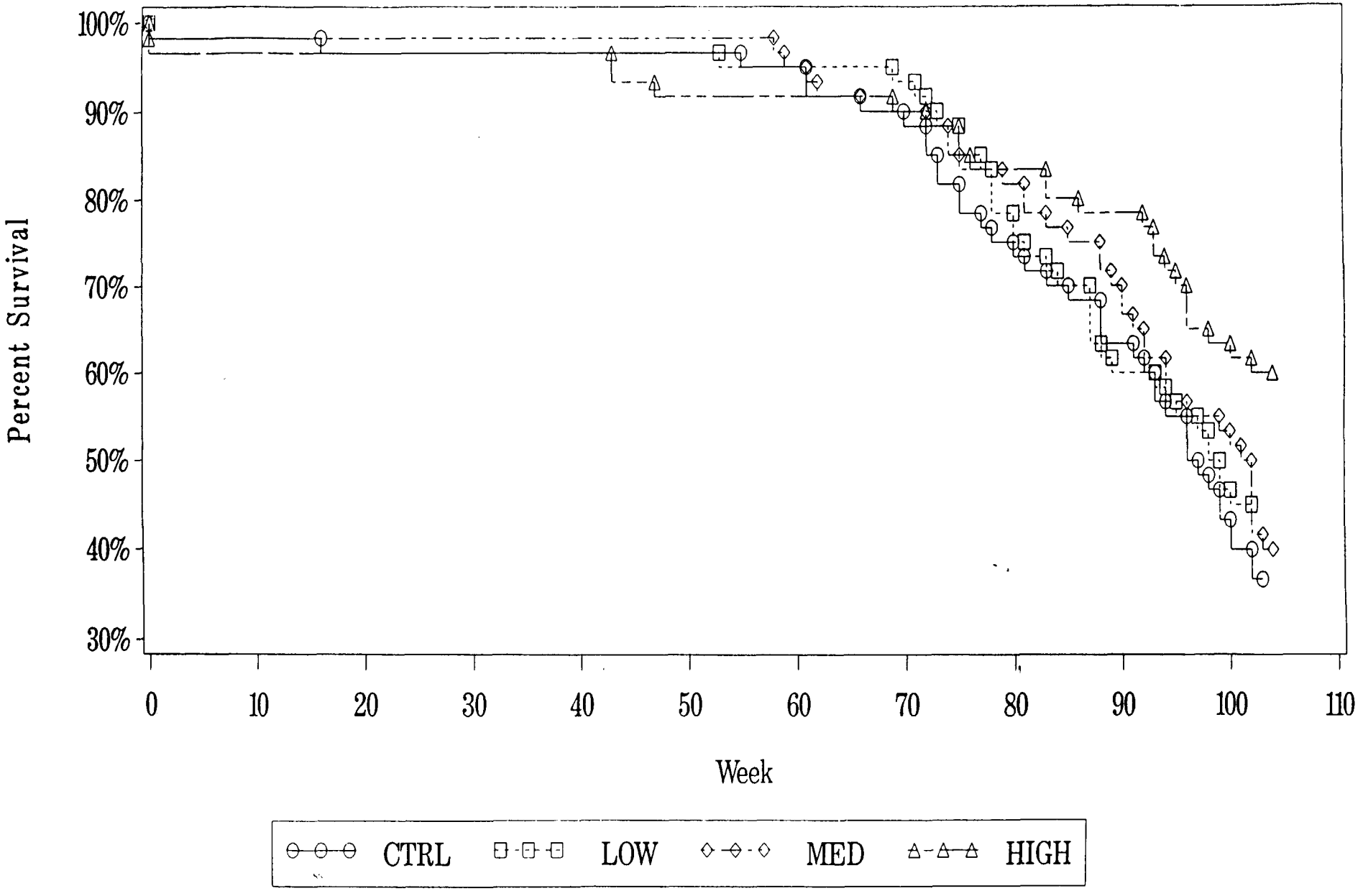


Figure 8: Kaplan–Meier vival Function

Species: Rat
Sex: Female

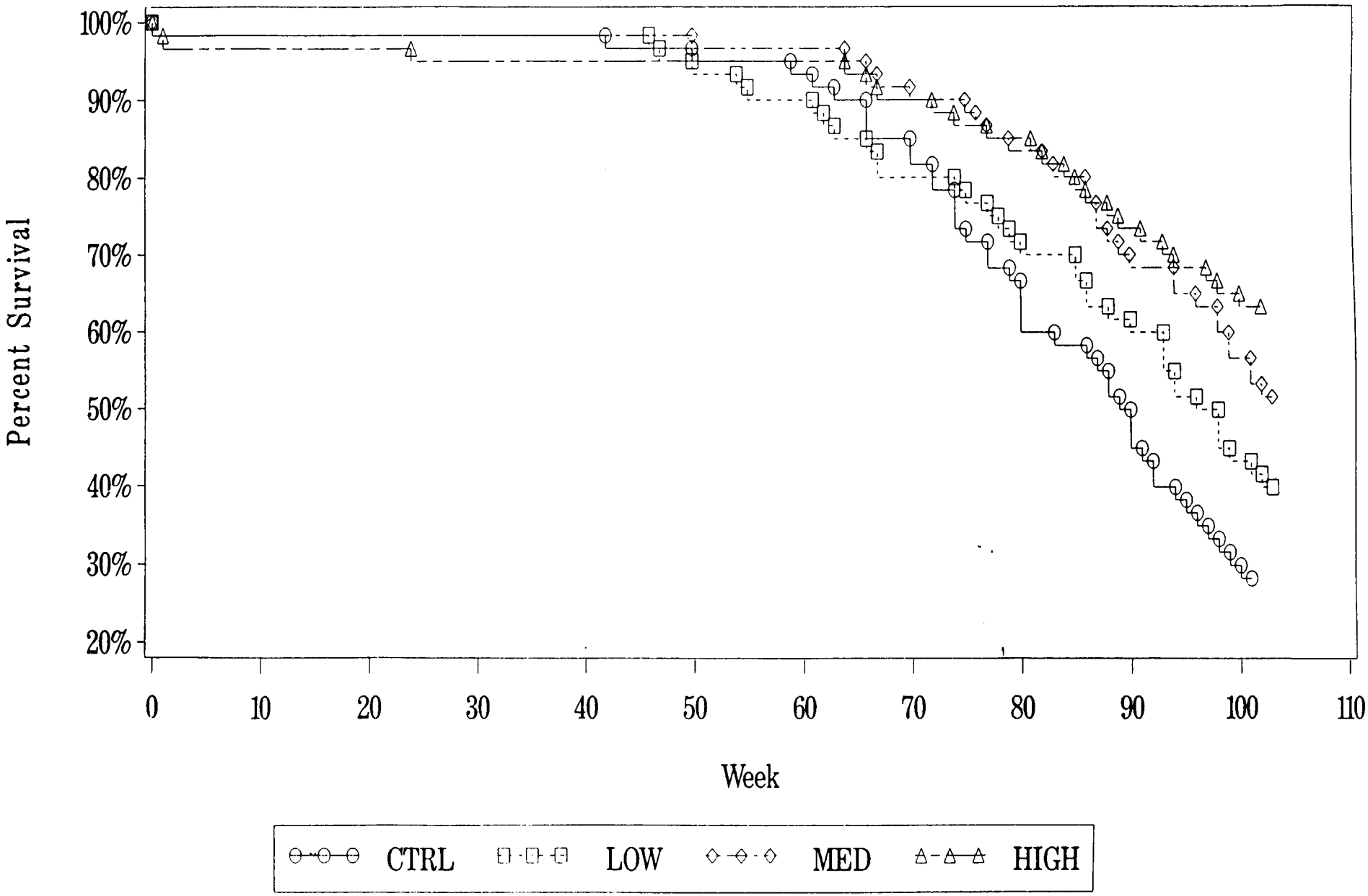


Figure 1: MEAN BODY WEIGHT / MALES
820939

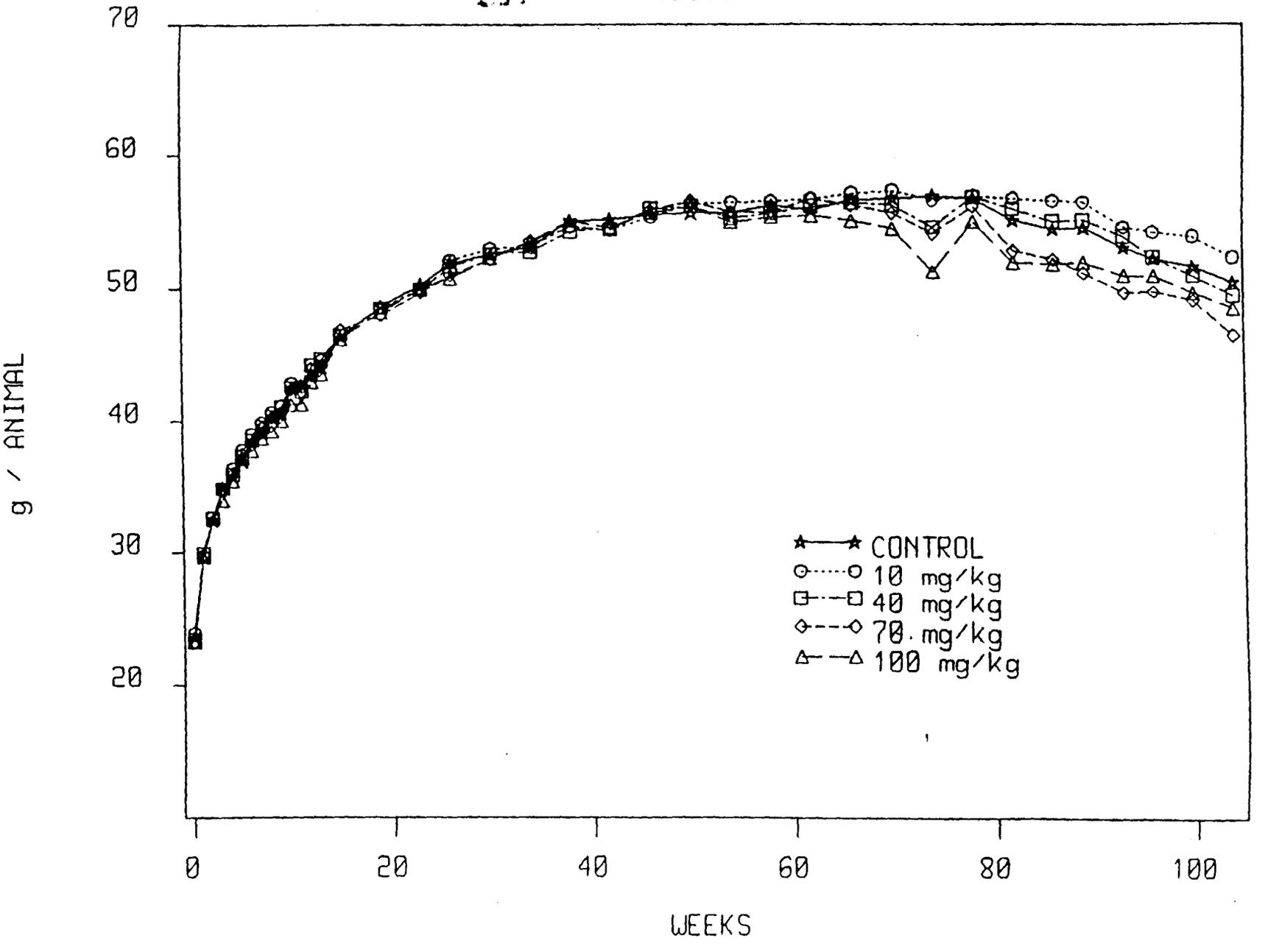


Figure 10

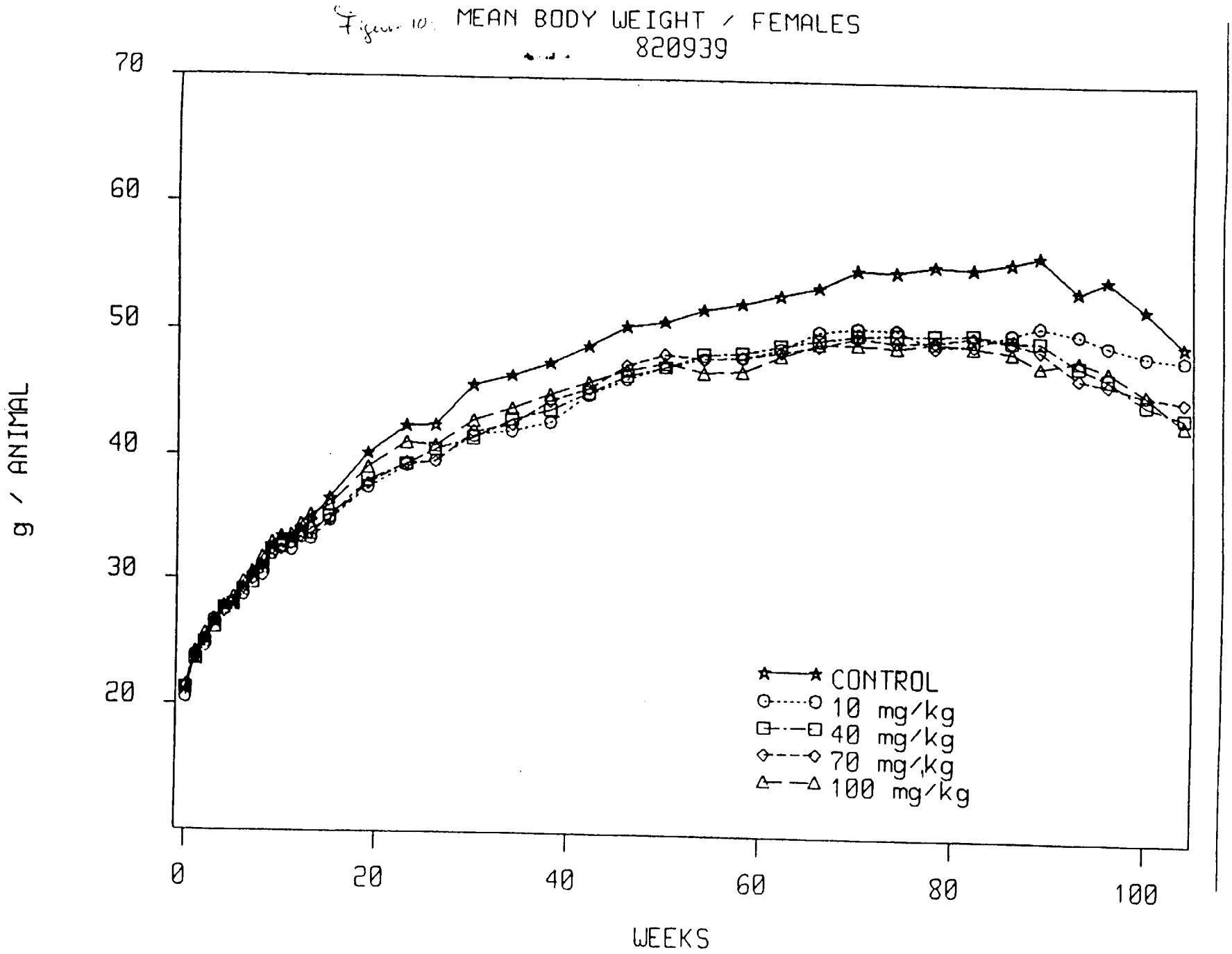

MEAN BODY WEIGHT / FEMALES
820939
g / ANIMAL
70
60
50
40
30
20
0
20
40
60
80
100
WEEKS
CONTROL
10 mg/kg
40 mg/kg
70 mg/kg
100 mg/kg

Figure 11: Kaplan–Meier Survival Function

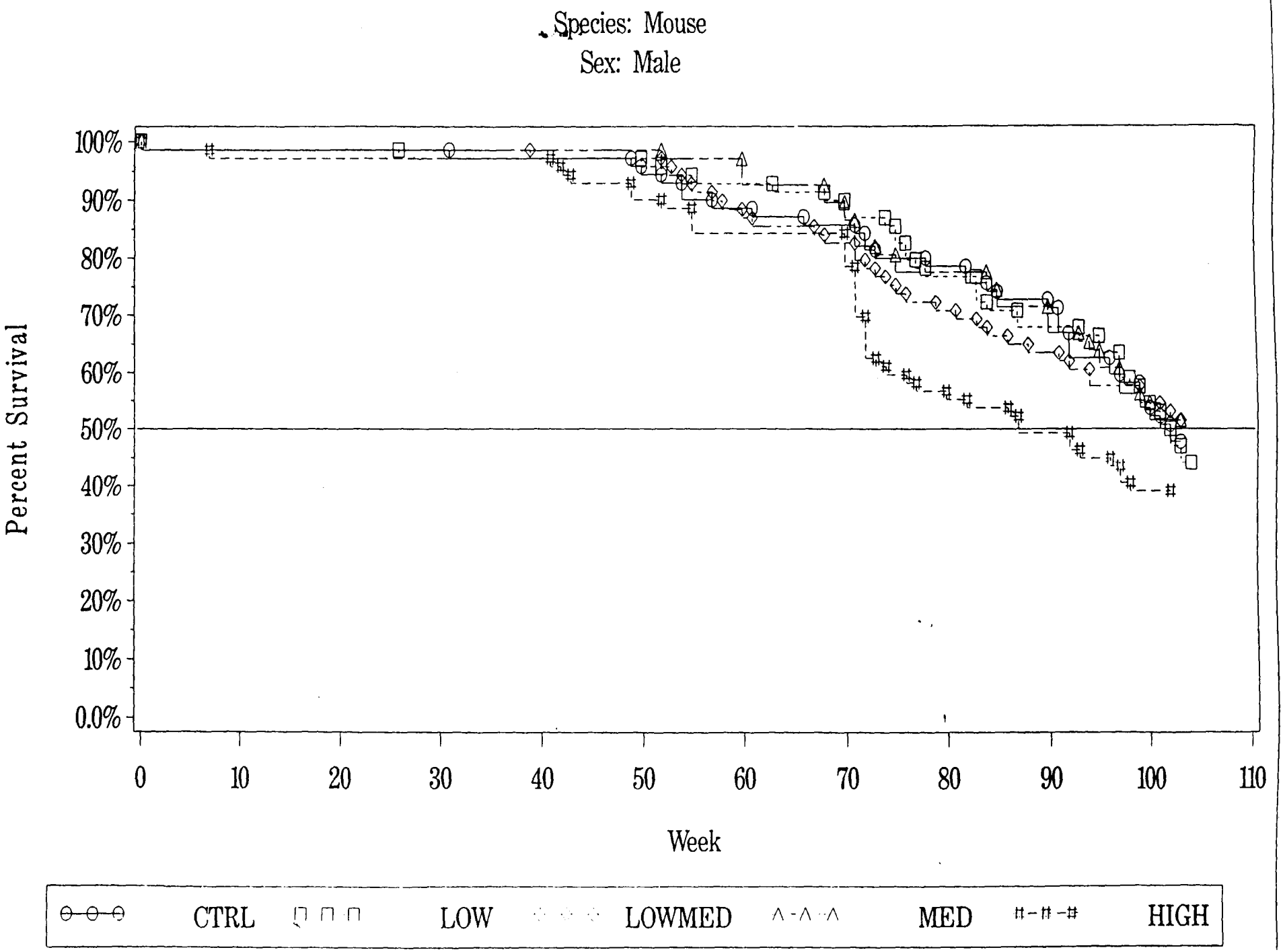


Figure 12: Kaplan–Meier rvival Function

Species: Mouse
Sex: Female