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Statistical Review and Evaluation

1. Introduction

1.1 Background

Eletriptan was approved for the acute treatment of migraine with or without aura. This NDA submission is to respond to the approvable letter issued by the FDA on December 1, 2000. It provides results of studies that measures the effect of eletriptan on the coronary artery at exposures achieved with therapeutic doses, particularly in the presence of concomitant CYP3A4 inhibition. The submission also includes updated safety data.

Two studies of effect of eletriptan on coronary artery were included in the submission. Study A1601072 was an acute, double-blind, placebo controlled, parallel group study of coronary vascular responsiveness during administration of the 5HT_{1B/1D} - receptor agonists, Eletriptan (IV) or Sumatriptan (SC), as determined using quantitative coronary angiography. This study was designed to demonstrate that high eletriptan concentration had no more effect on coronary arteries, or the clinical sequelae, than a therapeutic sumatriptan dose in subjects undergoing QCA.

Another study, Study 160-309, on the effects of intravenous eletriptan on the coronary circulation in subjects undergoing percutaneous transluminal coronary angioplasty for single vessel was not requested by FDA, but was conducted on the Sponsor's initiative.

Only Study A1601072 (referred as 1072 later on) is discussed in this statistical review.

1.2. Summary of Study 1072

In Study 1072 the sponsor compared geometric means of minimum mean segment diameter (MSD) post baseline divided by the mean segment diameter at baseline, both measured in the mid-LAD region, between eletriptan group and sumatriptan group. The sponsor used ratio of the two geometric means to set the non-inferiority margin at 10%. It was specified in the protocol that non-inferiority of eletriptan to sumatriptan could be concluded if the lower bound of the 95% confidence interval of the ratio (geometric mean of eletriptan to geometric mean of sumatriptan) is greater than 0.9.

Note that the protocol of the study was not reviewed by the Agency, and the choice of the margin was neither discussed with the Agency, nor agreed by the Agency. In this review I will present the results of the study without commenting on whether non-inferiority can be concluded or not.

2. Clinical Review of Study 1072

2.1. Objective

The objectives of this study were to:

- Determine any dose-dependent effects of eletriptan on coronary artery diameter;
- Assess changes, if any, in mid-LAD (1) and proximal circumflex (2) coronary artery mean segment diameter resulting from exposure to eletriptan;
- Allow safety determination of 80 mg PO dose if administered in the presence of a potent CYP3A4 inhibitor; and
- Compare effects of eletriptan with those of sumatriptan and placebo.

2.2. Study Design

This was a double-blind, double-dummy, placebo-controlled, 3-arm parallel comparison of the effects of IV eletriptan and subcutaneous sumatriptan on the coronary vasculature.

The intent was to rapidly achieve therapeutic plasma concentrations of the agents and obtain sequential images of the coronary tree. Serial images obtained at 5, 15, and 40 minutes after start of infusion, and 10 minutes after termination of infusion were to be compared to a pretreatment baseline.

Patients scheduled for diagnostic coronary angiography could elect to be screened for participation in this study. A pre-qualified patient was to undergo the scheduled diagnostic coronary angiography. If the results of this angiographic examination indicated that the patient met the inclusion criteria he/she was to be randomized into one of the three treatments of eletriptan i.v., sumatriptan s.c., or placebo of the study. An independent QCA laboratory, blinded to treatment group, was to measure QCA evaluations.

The study aimed to enroll 54 evaluable subjects at up to five study centers. Subjects were considered unevaluable if they met the criteria specified below. Additional subjects were recruited as replacements for unevaluable subjects to ensure that there were 18 subjects in each study drug group.

1. Subjects who did not complete the entire infusion for any reason;
2. Subjects who completed the entire infusion but did not have quantifiable angiographic data for the primary QCA parameter;
3. Subjects who completed the entire infusion but who had a vasodilator during the angiographic study;
4. Subjects whose QCAs were not obtained during the timing windows specified in the sponsor's statistical analysis plan; or

5. Subjects whose pharmacokinetic data was either unevaluable or indicated that the final target eletriptan concentration had not been reached.

2.3. Inclusion and Exclusion Criteria

Main Inclusion Criteria

- Subjects who were male or female aged 18 to 60 years;
- Subjects with coronary angiogram without evidence of $\geq 20\%$ stenosis or other multiple luminal irregularities that the investigator considered abnormal;

Main Exclusion Criteria

- Patients with unstable coronary artery disease, Prinzmetal's angina, history of MI, uncontrolled HTN, or significant valvular disease.

2.4. Dose of the Treatment

The sponsor aimed to produce the same mean maximum concentration of eletriptan as obtained after oral doses of 240 mg, equivalent to 80 mg in combination with a potent cytochrome P450 (CYP) 3A4 isosyme inhibitor. To achieve this, the sponsor chose an eletriptan 36 mg dose administered as a 40 minutes infusion. The first pharmacokinetic interim analysis showed that the eletriptan dose needed to increase to 52 mg to provide mean plasma concentration closer to the target. After a subsequent interim analysis, based on the observed safety and tolerability, the sponsor increased the eletriptan dose to 72 mg to ensure the target plasma concentrations were achieved. The sponsor chose the sumatriptan 6 mg dose because it was the standard migraine treatment.

2.5. Data Analysis and Statistical Considerations

2.5.1. Power and Sample Size

The sponsor calculated that eighteen evaluable patients per treatment group were to be studied giving a total study size of 54 evaluable patients. This number of patients per group would give a power of over 90% to detect non-inferiority of eletriptan to sumatriptan for the primary variable to be analyzed, the log of the minimum mean segment diameter post baseline minus the log of the mean segment diameter at baseline, both measured in the mid-LAD region. The power calculation assumed equal means for eletriptan and sumatriptan and a one-sided 2.5% significance level. The allowable margin of inferiority was defined as the ratio of, minimum postbaseline diameter divided by baseline diameter for eletriptan to minimum postbaseline diameter divided by baseline diameter for sumatriptan being no less than 0.9. The standard deviation used for this calculation was that observed in Study 160-211 for the proximal segment diameter and was equal to 0.081.

2.5.2. Interim Analysis

An independent statistician, unblinded with respect to study drug allocation, was to undertake a statistical interim analysis of the data from the first 10 eligible subjects in each of the treatment groups (30 subjects in total) to check that the sample size was large enough to analyze the primary endpoint with 80 and 90% power, respectively, for the eletriptan and sumatriptan groups. Subjects would need to have qualifiable post-dose QCA data and eletriptan subjects had to have at least the minimum eletriptan plasma concentration, to be eligible for the analysis. There was uncertainty surrounding the number of subjects in each study drug group because the sponsor was blind with respect to study drug allocation, including replacements, and did not have the pharmacokinetic data analyzed for all subjects. The sponsor sent data for 34 subjects because four were ineligible. When the blind was broken post-database release, the 30 subjects were found to split evenly between the three study drug groups.

The independent statistician completed the sample size recalculation on 30 November 2001 and calculated that the number of subjects required in each treatment group to have 80 and 90% power for the primary analysis of the primary parameter was 13 and 17, respectively. The independent statistician also signed an affidavit to confirm that he had conducted the analysis while the blind, with respect to the sponsor, was maintained.

2.5.3. Primary Analysis

The primary pharmacodynamic parameter to be analyzed was the log of the minimum mean segment diameter post baseline minus the log of the mean segment diameter at baseline, both measured in the mid-LAD region. When anti-logged, this difference became the ratio of the minimum mean segment diameter post baseline to the mean segment diameter at baseline. Multiplied by 100, this ratio gave the minimum post-baseline measurement as a percentage of the baseline value.

The primary analysis for the primary pharmacodynamic parameter was to be the calculation, for the ITT group, of a 95% confidence interval for the difference between the means for the eletriptan and sumatriptan treatment groups. The limits of this confidence interval were to be anti-logged to enable a comparison with the allowed margin of inferiority.

Should the concentration levels of eletriptan not reach the desired levels, as determined at the interim analysis of PE levels, a new infusion rate was to be used. Patients who did not achieve the target eletriptan concentration were not to be used in the primary analysis of the primary variable.

2.5.4. Analysis of Secondary Pharmacodynamic Parameters

The analysis described above was to be repeated for the corresponding measurements made in the proximal circumflex arterial region.

A secondary analysis was to calculate 95% confidence intervals for the difference between the mean of, the log of the ratio of the mean segment diameter at maximum concentration divided by baseline mean segment diameter for sumatriptan and the mean of the following:

1. The log of the ratio of mean segment diameter for eletriptan 5 minutes, 15 minutes, and 40 minutes after the start of infusion divided by the baseline mean segment diameter;
2. The log of the ratio of mean segment diameter 10 minutes post termination of cletriptan infusion divided by the baseline mean segment diameter.

These confidence intervals were to be calculated separately for measurements made in the mid-LAD region and for measurements made in the proximal circumflex region. The confidence intervals for the ITT population were to be calculated both by omitting missing values and by replacing them using the last-observation-carried-forward (LOCF) algorithm.

2.6. Sponsor’s Analysis Results

2.6.1. Subject Disposition

Of the 162 subjects screened, 60 were randomized, had study drug and were analyzed for safety. Of the 24 subjects who had eletriptan iv, 23 (96%), completed the study and one (4%) discontinued. All of the 18 subjects who had sumatriptan 6mg sc and 18 subjects who had placebo completed the study.

2.6.2. Demographic and Baseline Characteristics

The sponsor reported that demographic characteristics were similar between the study drug groups. There were more males than females (38 males and 22 females) and the females were generally slightly older. All subjects were white except eight who were black and two who were of another race. Ages ranged from 30 to 60 years (mean age 47 years) and weights ranged from 72 to 135kg for males and 60 to 137kg for females. The following table presents a demographic summary for all treated subjects.

	Eletriptan iv			Sumatriptan 6mg sc			Placebo		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of subjects	15	9	24	12	6	18	11	7	18
Age range (years)	33-58	43-57	33-58	36-53	38-59	36-59	30-57	32-60	30-60
Mean age (years)	45	52	48	43	51	46	44	49	46
Mean height (cm)	180	164	174	176	163	172	179	170	175
Mean weight (kg)	91	85	89	90	90	90	101	76	91

Source: Table 2.1

2.6.3. Efficacy Evaluation

Investigators performed QCA with a catheter and non-ionic contrast media to image the mid-LAD and the proximal circumflex coronary artery regions at pre-dose baseline and at 5, 15, and 40 minutes post-start of infusion and 10 minutes post-end of infusion. Investigators obtained multiple QCA images at each time point. An independent reader, blind with respect to study drug allocation, analyzed up to three consecutive images to calculate the MSD at each time point, and the sponsor took the mean of each measurement set.

The sponsor replaced subjects who had a plasma eletriptan concentration < 299 ng/ml at 40 minutes post-start of infusion. The minimum plasma concentration was determined before the study started and remained unchanged after the infusion rate increases.

The protocol stated that the sponsor would perform all analyses on an ITT population. The sponsor subsequently defined a subset of the ITT population, a modified ITT (MITT) population defined as subjects who had baseline and any on treatment data and who also had an eletriptan plasma concentration above the defined minimum at the last planned QCA. The sponsor also defined a MITT+ population defined as the MITT population and any subjects whose eletriptan plasma concentration at last planned QCA could not be determined. The sponsor only defined an MITT+ population for the primary analysis in the mid-LAD coronary artery region and corresponding analysis in the proximal circumflex coronary artery region.

2.6.3.1. Primary CAD Results

The sponsor reported that the effect of eletriptan iv on CAD was no more than that of sumatriptan in the mid- LAD region. The results met the pre-stated criterion in the protocol, for concluding non-inferiority of eletriptan iv compared to sumatriptan 6mg sc. The criterion required that the lower limit of the 95% CI was >0.90 for the MITT population. This was consistent for all the other three populations.

The table below shows the relative effect of eletriptan iv and sumatriptan sc on CAD in the mid-LAD region for the MITT population. The results from the ITT population were the same as from the MITT population.

Drug	Geometric mean CAD ratio ^a	Ratio ^b	95% CI
Eletriptan iv	0.78	0.96	0.91 to 1.02
Sumatriptan 6mg sc	0.81		

Source: Table 5.1.2.1; ^aantilog of the mean log (minimum MSD, post-start of infusion/baseline MSD); ^beletriptan iv/sumatriptan 6mg sc.

2.6.3.2. Secondary CAD Results

Proximal Circumflex Region

The sponsor reported that there was no difference between eletriptan iv and sumatriptan 6mg sc in effect on the proximal circumflex region for the MITT population. This was consistent with the results for the primary mid- LAD analysis and with the results across the different populations.

The table below shows the relative effect of eletriptan iv and sumatriptan 6mg sc on CAD in the proximal circumflex region for the MITT population.

Drug	Geometric mean CAD ratio ^d	Ratio ^b	95% CI
Eletriptan iv	0.81	0.97	0.93 to 1.02
Sumatriptan 6mg sc	0.83		

Source: Table 5.2.2.1; ^aantilog of the mean log (minimum MSD post-start of infusion/baseline MSD); ^beletriptan iv/sumatriptan 6mg sc.

Mid-LAD and Proximal Circumflex Regions by Time- point

The sponsor reported that CAD data by time-point was placebo corrected in both coronary artery regions because there was an important CAD effect noted in the placebo group.

The table below shows the comparisons of the placebo corrected effect of eletriptan iv, at 5, 15 and 40 minutes post- start of infusion and 10 minutes post-end of infusion, and the time of maximum sumatriptan 6mg sc effect (at mean concentration 67.9ng/ ml) on CAD in the mid-LAD region.

Drug	Time	Mean plasma concentration ng/ml ^a	Geometric mean CAD ratio ^b	Ratio ^c	95% CI
Eletriptan iv	5 mins post-start of infusion	186	0.96	1.00	0.96 to 1.05
Sumatriptan 6mg sc	Minimum MSD	67.9	0.96		
Eletriptan iv	15 mins post-start of infusion	297	0.99	1.02	0.98 to 1.07
Sumatriptan 6mg sc	Minimum MSD	67.9	0.96		
Eletriptan iv	40 mins post-start of infusion	660	0.95	0.98	0.93 to 1.04
Sumatriptan 6mg sc	Minimum MSD	67.9	0.96		
Eletriptan iv	10 mins post-infusion end	281	0.95	0.98	0.94 to 1.03
Sumatriptan 6mg sc	Minimum MSD	67.9	0.96		

Source: Tables 5.3.2 and 5.5; ^aMean peak plasma sumatriptan concentration at 15 minutes post-start of infusion; ^bthe ratio of the geometric means eletriptan iv:sumatriptan 6mg sc; ^cantilog of the mean log (minimum MSD post-start of infusion/baseline MSD).

2.7. Reviewer's Analysis

2.7.1. Analysis of Primary Parameter

The primary parameter to be analyzed was the difference between the logs of the minimum post-baseline MSD and the baseline MSD at the mid- LAD coronary artery region.

For each subject, the sponsor analyzed the log of the ratio of minimum MSD post-baseline divided by the MSD at baseline:

$$\text{Log} \left(\frac{\text{Minimum MSD}}{\text{MSD at baseline}} \right)$$

The primary analysis was to produce a 95% confidence interval (CI) for the difference between the means in the above variable for the eletriptan and sumatriptan groups. The difference between the means and the confidence interval when anti-logged produced the ratio of the geometric means:

$$\frac{\text{Eletriptan geometric mean} \left(\frac{\text{Minimum MSD}}{\text{MSD at baseline}} \right)}{\text{Sumatriptan geometric mean} \left(\frac{\text{Minimum MSD}}{\text{MSD at baseline}} \right)}$$

and the 95% CI of the ratio. The margin of the non-inferiority defined by the sponsor was that the above ratio should be greater than 0.90. Therefore, the criteria to determine the non-inferiority given by the sponsor was that the lower bound of the CI be greater than 0.90.

Note that the study protocol was not reviewed by the Agency. The choice of the margin was neither discussed with the Agency, nor agreed by the Agency. There were a number of changes through the trial conduct that makes the results difficult to be interpreted. For example, the dose of eletriptan iv and the infusion rate were changed after each of the interim analyses. The target plasma concentration was specified as 564 ng/mL, but only 11 subjects had reached this target plasma concentration. Therefore, I will only present the results of performed analyses without making any interpretation or conclusions.

There were 60 subjects in total in the ITT patient population (24 in eletriptan, 18 in sumatriptan, and 18 in placebo). Among the 24 subjects in the eletriptan group, two had unknown plasma concentration and two had concentration below the minimum target level of 299 ng/mL.

It was not specified what statistical model was to be used. However, it was specified in the

protocol that a non-parametric analysis was to be used if the data were not normal. Therefore, I analyzed the data use the simple parametric model of t-test. The residual of the model was analyzed to see if normality assumption was met. It was found that that the normal assumption was not violated ($p=0.9651$ from Shapiro-Wilk test).

The results from the t-test I obtained agree with the ones obtained by the sponsor. The overall difference among the three treatment groups is statistically significant with a p-value of 0.0339. The difference between the treatment groups of eletriptan and sumatriptan carries a p-value of 0.1677. The following table summarizes the results from different patient populations. Two subjects with unknown plasma concentration are excluded from ITT patient population to form the MITT population, and another two subjects with plasma concentration below 299 ng/mL are excluded from MITT population to form MITT+ population. The population MITT* consists of those 11 subjects whose plasma concentration reached target level of 564 ng/mL

Table 1. Geometric mean, ratio to sumatriptan and its confidence interval by treatment groups.

Treatment	Geometric Mean	Ratio to Sumatriptan (95% CI)	Ratio to Placebo (95% CI)
Eletriptan			
ITT (n=24)	0.777	0.96 (0.91, 1.02)	0.93 (0.88, 0.98)
MITT (n=20)	0.775	0.96 (0.91, 1.02)	
MITT+ (n=22)	0.772	0.96 (0.91, 1.01)	
MITT*	0.774	0.96 (0.91, 1.02)	
Sumatriptan (n=18)	0.806		0.96 (0.91, 1.02)
Placebo (n=18)	0.836		

The following table presents the geometric means and ratio of eletriptan to sumatriptan by demographic characteristics of age and gender. The median age of 44.5 years is used as a cut point for the two age groups presented.

Table 2. Geometric mean and ratio by demographic characteristics (ITT patient)

Characteristic	Geometric Mean		Ratio Ele/Sum (CI)	p-value (Ele vs. Sum)
	Eletriptan	Sumatriptan		
Age (years)				
<44.5 (n=21)	0.78	0.79	0.99 (0.91, 1.08)	0.7906
>=44.5 (n=21)	0.78	0.84	0.92 (0.86, 0.99)	0.0364
Sex				
Male (n=27)	0.78	0.79	0.99 (0.93, 1.05)	0.6878
Female (n=15)	0.77	0.84	0.92 (0.85, 1.00)	0.0889

Note that the difference in geometric means between the treatment of eletriptan and sumatriptan in the older age group has a nominal p-value below 0.05. The lower bound of CI is 0.86, and the upper bound of CI is just below 1. The difference in geometric mean in the female subgroup is similar to that of older age group. It should also be noted that the standard deviations (not presented) from the eletriptan group are always larger than the ones from the sumatriptan group, across the population and all subgroups.

2.7.2. Analysis of Secondary Parameters

Proximal Circumflex Region

The following table presents the results from analysis of CAD from proximal circumflex region. Results of CAD from proximal circumflex region by time points are presented in the Sponsor's Analysis Results section, and I have verified these results to be correct.

Table 3. Geometric mean and ratio for CAD at proximal circumflex region by treatment groups (ITT patient)

Treatment	Geometric Mean	Ratio to Sumatriptan (95% CI)	Ratio to Placebo (95% CI)
Eletriptan (n=24)	0.80		0.93 (0.88, 0.98)
Sumatriptan (n=18)	0.83	0.97 (0.93, 1.02)	0.95 (0.90, 1.01)
Placebo (n=18)	0.87		

2.7.3. Overall Review and Discussion of the Analysis

The sponsor concluded that the results of the study met the criteria to be concluded non-inferiority of eletriptan to sumatriptan. Based on the analysis on the statistical analysis, the lower bound of the confidence interval for the ratio of eletriptan to sumatriptan did meet the 10% margin set by the sponsor. However, the choice of the margin was not discussed with or accepted by the Agency. The lower bound of the confidence interval would not meet any margin below 10%.

In addition, various issues surrounding the conduct of the trial make the results difficult to interpret. For example, during the trial the sponsor increased dose and infusion rate after each interim analysis in order to reach the target plasma concentration level. The sponsor stated that patients who did not achieve the target eletriptan concentration were not be used in the primary analysis of the primary variable. The target plasma concentration specified in the protocol was 564 ng/mL. However, only 11 subjects reached this target level and the sponsor used minimum target plasma level of 299 ng/mL, not defined in the protocol, in order to include most subjects in the analysis.

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Statistical Review and Evaluation

NDA#: 21-016 AUG 5 1999

SPONSOR: Pfizer Inc.

NAME OF DRUG: RELPAX™ (eletriptan)

INDICATION: Treatment of Acute Migraine

DOCUMENTS REVIEWED: Initial NDA submission, electronic data files in SAS format

MEDICAL INPUT: HFD-120: Armando Oliva, M.D.

Background

The sponsor has identified six studies as pivotal and proposes describing these studies in the label. Two of these are single attack studies, 102 and 104, and four are multiple attack studies: 305, 307, 314 and 318. Additional studies have been described as supportive and will not be discussed in this review. The applicant has also submitted the results of a meta analysis which was discussed with the review division prospectively. This meta analysis has been submitted to support claims related to the treatment of initial non-response and recurrence. The results of this analysis will also be discussed.

Single Attack Studies

Study 307 - A double-blind, randomized, placebo-controlled parallel group comparative study of the efficacy and safety of eletriptan and cafergot when given for the treatment of acute migraine

Design

Nine-hundred subjects, otherwise healthy with a history of frequent (expected one attack each 6 weeks with no more than 6 per month) acute migraine (with or without aura), were to be assigned to one of the following treatment groups (1:1:1:5) using random permuted blocks (stratification was not discussed):

- 40 mg eletriptan
- 80 mg eletriptan
- cafergot (1 mg ergotamine + 100 mg caffeine)
- placebo.

The assigned treatment was to be taken within 6 hours of onset. A second dose of medication was to be taken at 2 hours for inadequate response or recurrence of migraine. Efficacy evaluations were to be recorded by the subject at 0, 1, 2, 4 and 24 hours after dosing. A migraine specific QOL questionnaire was to be completed at 24 hours. A clinic visit was to be made 7-14 days after treatment. Only one acute episode was to be treated.

For the second dose of medication, the following randomization was used:

1st dose	2nd dose
cafergot	cafergot
40 mg eletriptan	40 mg eletriptan or placebo
80 mg eletriptan	80 mg eletriptan or placebo
placebo	40 eletriptan or 80 eletriptan

It was anticipated that 900 subjects would be treated in approximately 50 centers to achieve 700 fully evaluable subjects. Self-dosing was to begin with a headache of moderate or severe intensity which was not improving and no analgesic or anti-emetic had been used within 6 hours, and no sumatriptan, ergotamine or ergotamine-like agent had been taken within 48 hours and the aura phase had ended.

Patients were to be screened no more than 12 weeks prior to taking study medication. Patients were trained to use their diary and filled out a QOL (SF-36) questionnaire at the screening visit.

The severity of headache was to be assessed by the patient on a 4-point scale (severe, moderate, mild and absent). A patient was to be treated as successfully responding at 2 hours if a moderate or severe score changed to mild or absent

The following were to be recorded as present or absent: nausea, vomiting, photophobia and phonophobia. Additionally, patients were to answer the following at 24 hours: "given the choice between this and any other medication to treat a migraine attack, would you take this again." Additional questions addressed functional impairment, migraine recurrence, QOL and health economics.

This study was powered to compare the response rates for headache at two hours after the first dose. A total of 12 pairwise comparisons are possible for this study. To minimize the multiple comparison adjustment required, tests were broken up into two groups: 1) the two eletriptan doses versus placebo and 2) the two eletriptan doses with cafergot. The protocol indicates that within the first group, a stepdown procedure was to be used to preserve the type I error at the .05 level for the first group. Within the second group, tests were to be made at the .025 level.

The intent-to-treat (ITT) population was defined as all subjects with baseline and any on-treatment data. Subjects without at least a moderate headache at baseline were to be excluded from the calculation of the response rate.

The primary analysis (yes/no on headache response) was to be based upon an analysis of covariance using the logit of the responder rate. The only covariate specified was baseline severity (moderate/severe).

Study Results

Nine hundred forty-eight (948) subjects were screened for eligibility. Of these, 937 were found to be eligible and randomized. Of the randomized subjects, 733 were treated and 204 were not treated. The following table contains the study status of all patients randomized.

	E40	E80	Cafergot	Placebo	Total
randomized	278	264	263	132	937
treatment recorded					
yes	210	214	203	106	733
no	68	50	60	26	204

source: Tables 1.1, V. 1.105

The majority of subjects were female (approximately 90% of subjects), white (close to 100%) with a mean age of about 40 years (17 to 65 years). Approximately two-thirds of subjects were without aura and typically experienced 7 attacks every 3 months.

The study report includes 732 subjects as making up the ITT population based upon those subjects known to have taken at least one dose of medication. The evaluable population is made up of subjects receiving non permitted medication and taking medication six hours after onset. In the discussion that follows, only the results of the ITT population will be presented.

	E40	E80	Cafergot	Placebo	Total
ITT	210	214	203	105	732
Evaluable	174	170	169	85	598

The applicant modified the protocol specified analysis plan after an examination of the data. The specified stepdown procedure for taking into account multiple comparisons among the treatment arms was not used for vomiting and recurrence due to a lack of monotonicity.

The proportion of subjects with headache response and key secondary endpoints (suggested by the medical reviewer) are summarized in the following table. The proportions are calculated for the subset with assessments at two hours with at least moderate severity at baseline. The applicant reported that the p-values from the analysis of covariance for headache relief at two hours were all less than .0001 for the pairwise comparisons between each dose of eletriptan and both Cafergot and placebo. Additionally, the two doses of eletriptan were found to differ with respect to headache relief with a p-value less than .0001.

With respect to nausea, there was no observed difference between the two doses of eletriptan. Both were reported as significantly better than cafergot ($p < .0001$) and placebo ($p < .0059$).

With respect to both photophobia and phonophobia, the 80 mg dose was observed to have a higher rate of photophobia absent than the 40 mg dose (not reported as significant). The 80 mg dose was found to be significantly ($p < .0001$) better than both placebo and cafergot. The comparisons involving the lower dose were more problematic. The comparison of 40 mg to placebo fails to reach

statistical significance based upon a Bonferroni adjustment, but are approximately at the traditional .05 level (.04 and .06, respectively) level based upon the applicant's original step-down procedure.

	E40	E80	Cafergot	Placebo
headache relief	54% (111/206)	68% (142/209)	33% (65/197)	21% (21/102)
photophobia absent	56% (115/206)	69% (143/208)	38% (75/197)	43% (44/102)
phonophobia absent	58% (119/206)	72% (148/206)	43% (84/194)	49% (50/102)
nausea absent	62% (129/207)	62% (129/206)	36% (70/197)	47% (47/101)

Based upon these findings, the applicant has concluded that both doses of eletriptan are effective with respect to headache relief. Similar conclusions were reached for the key secondary endpoints

Comments

The manner in which Cafergot was used in this clinical trial differs from the dosage and administration section of the current labeling for ergotamine tartrate plus caffeine tablets. The dosage and administration for this product allows for additional dosing every 1/2 hour if needed for up to six tablets. It is unclear how this dosing schedule has affected the comparison between eletriptan and cafergot.

The multiple comparison procedure specified is somewhat ambiguous with respect to the two sets of comparisons: the first between eletriptan and placebo and the second between eletriptan and Cafergot. It is likely that the intention was to only conduct the second set of comparisons if eletriptan was found to be significantly better than placebo. In which case, the proposed procedure would be technically valid. The primary difficulty with the applicant's approach is that it uses a stepdown procedure for the doses of eletriptan in which the low dose would only be compared to placebo if the high dose were significantly better than placebo. It has been this reviewer's experience that if a monotonic relationship is not seen the low dose comparison will still be made. In fact, the applicant did this in their analysis when a lack of monotonicity was detected for nausea. For these reasons, significance at the 5% level will be evaluated using a Bonferroni procedure for the comparison between the doses of eletriptan and placebo. When this standard is applied, both doses of eletriptan were found to have reached the 5% level of significance relative to both placebo and Carergot.

The ITT population was defined in the protocol as having a baseline attack and on-treatment data. The first restriction upon the ITT population appears reasonable and has been interpreted in the study analysis as having a moderate or severe event in 12 weeks of follow-up for which drug was taken. The second restriction (on-treatment data) is much more problematic. Ideally, all subjects randomized who have an attack should be included in the analysis regardless of treatment status and each such patient should have data recorded. The following table provides the final disposition for all 937 subjects assigned to therapy (948 screened minus 11 never randomized). This table has been constructed using files EFFICAF (variables HEADRESP for headache response, TPD to identify the 2 hour response and DOSENUM to identify the first attack) and SSUM (variables ITT to identify the ITT population, TRTSEQC to identify treatment group and FINALTXT for reason excluded from ITT) provided by the applicant.

	E40	E80	Cafergot	Placebo	Total
Total Randomized	278	261	263	132	937
ITT	208	210	202	103	723
In Analysis	207	209	200	102	718
Assessment Absent	0	0	1	1	2
Mild at Baseline	1	1	1	0	3
Excluded	70	54	61	29	214
Adverse Event*	0	2	1	2	5
Ineligible for Study	3	2	3	2	10
No Attack to Treat	39	32	37	13	121
Failed to Treat	8	2	7	3	20
Consent Withdrawn	2	3	4	3	12
No Efficacy Data	2	5	1	2	10
No Response Exp.	1	0	0	0	1
Loss to Follow-up	11	7	7	2	27
Other	4	1	1	2	8

*With the exception of patient #307 03000059 (receiving placebo), these events were pretreatment

The exclusion of the following subjects from the ITT population is problematic: did not treat an attack which occurred, no efficacy data recorded, no response expected, lost to follow-up and other. The first group, did not treat an attack, should not influence the treatment comparison since the decision not to treat was made without knowledge of treatment and prior to treatment initiation. The remaining 46 subjects should not have been excluded from the ITT population. Fortunately, this number of subjects is too small to effect the interpretation of the study results.

The stratification used to assign subjects to treatment is somewhat vague in the protocol and study report. Based upon an examination of the randomization codes provided in the application it is clear that subjects were stratified by center and order of enrollment (blocks of size 7). No adjustment was discussed for stratification by center. Since there is generally a positive correlation within center, ignoring center is likely to produce a conservative test of significance.

A Cochran-Mantel-Haenszel (CMH) test may have been preferable to the applicant's ANCOVA model since the model assumed in the ANCOVA explicitly makes the assumption that the treatment effect is constant for each level of baseline severity. The following table contains the distribution of subjects and outcome with respect to 2 hour headache response for subjects with moderate or severe headache at baseline and data recorded. It can be seen in this table that the response rates are considerably lower for patients with severe headache at baseline for both doses of eletriptan as well as for placebo. Cafergot was less affected by baseline severity. The Breslow-Day test for homogeneity was conducted for each pairwise difference. Only the comparison for E80 versus cafergot had a nominal p-value suggesting a lack of homogeneity ($p=.055$). Still, E80 had a higher response rate than cafergot ($p<.001$) for both levels of baseline severity. The overall CMH test found both doses of eletriptan to have greater headache relief than both placebo and cafergot ($p<.001$) when stratified by baseline severity. Due to the robustness of these findings no additional tests including subjects inappropriately excluded from the ITT analysis or center adjusted analyses have been conducted.

The p-value associated with the comparison of E80 to E40 is .003 (CMH stratified by baseline headache severity). There is little statistical evidence for an interaction with baseline severity, which indicates that E80 is consistently better than E40 for this study though numerically the effect is larger

for moderate baseline severity. The secondary endpoints with the exception of nausea support the overall advantage of E80.

Baseline Headache	E40	E80	Cafergot	Placebo
moderate	63% (70/111)	80% (90/113)	36% (39/107)	26% (14/54)
severe	43% (41/95)	54% (52/96)	29% (26/91)	15% (7/41)

Study 314 - A multicenter, double-blind, double-dummy, parallel group, placebo-controlled dose response study of oral UK-116,044 and oral sumatriptan (100mg) given for the acute treatment of migraine (with and without aura)

Design

Seven-hundred subjects, otherwise healthy with a history of frequent (expect one attack each 6 weeks with no more than 6 per month) acute migraine (with or without aura), were to be assigned to one of the following treatment groups (1:1:1:1:1) using random permuted blocks:

- 20 mg eletriptan
- 40 mg eletriptan
- 80 mg eletriptan
- 100 mg sumatriptan
- placebo.

The study design was comparable to that used for study 307. One major difference is that study 314 was designed to demonstrate equivalence between 80 mg eletriptan and sumatriptan. Equivalence was defined for the purpose of sample size calculation as 20%.

Interim data analyses were planned. No adjustment was proposed based upon an assertion that these looks were for administrative purposes only.

The primary analysis (yes/no on headache response) was to be based upon either Mantel-Haenszel testing or logistic regression. The ITT population was defined as requiring baseline and post-treatment data and at least moderate severity at baseline. Gender and center were specified as possible covariates.

No discussion of multiple comparisons was contained in the protocol.

Study Results

Eight hundred and fifty-seven (857) subjects were screened for eligibility. Of these, 849 were found to be eligible and randomized. Of the randomized subjects, 692 were treated at least once and 154 were not known to have been treated. The reasons for no treatment recorded were not described numerically but it was reported that the majority had not experienced an attack. The following table contains the study status of all patients randomized.

	E20	E40	E80	Sumatriptan	Placebo	Total
randomized	171	169	173	167	169	849
treatment recorded						
yes	144	136	141	129	142	692
no	27	33	32	38	27	154

source: V. 1.110 Table1.1

The majority of subjects were female (over 80% of subjects), white (approx. 100%) with a mean age of about 40 years (18 to 71 years). Almost 2/3 of subjects were without aura.

The original plan for assessing the equivalence of eletriptan 80 mg and sumatriptan was modified at the time of the interim data analysis after it was discovered that the two treatments might not be equivalent. Superiority testing was substituted.

The proportion of subjects with headache response and key secondary endpoints (recommended by the medical reviewer) are summarized below. Statistical analyses were conducted using dose as a continuous variable (logistic regression, interaction of treatment by baseline severity was initially included but then deleted after inspection). Additional analyses were conducted using dose as a categorical variable using pairwise comparisons (Wald statistic based upon analysis of variance for categorical data with a treatment by severity interaction included because it was "significant" at the .1 level). The proportions were calculated for the subset with assessments at two hours with at least moderate severity at baseline. The applicant reported that the p-values from the analysis of variance for headache relief at two hours were all less than .0001 for the pairwise comparisons between each dose of eletriptan and placebo. The 80 mg dose of eletriptan was reported as significantly better than sumatriptan ($p=.0002$), but the 40 mg dose was not statistically significant relative to sumatriptan ($p=.0532$). Additionally, a significant ($p=.0001$) dose relationship was found for eletriptan. The p-value associated with the comparison of eletriptan 80 mg and eletriptan 40 mg was not reported.

By examining the table below, it can be seen that subjects with severe headache at baseline did not respond as well as those with moderate headache at baseline for all doses of eletriptan. No corresponding difference was seen for placebo. It appears that the interaction reported is originating from this lack of observed difference in the placebo group relative to the difference seen for eletriptan. This suggests that the treatment effect is reduced for patients with severe headache at baseline.

With respect to nausea, phonophobia and photophobia at 2 hours, no significant differences were reported and statistical analyses were not presented in the body of the study report.

The study report did not discuss the relationship between treatment and gender, race or age.

headache relief	E20	E40	E80	Sumatriptan	Placebo
overall	54% (70/129)	65% (76/117)	77% (91/118)	55% (63/115)	24% (30/126)
baseline moderate	66%	76%	83%	not presented	24%
baseline severe	39%	53%	69%	not presented	24%

Source: overall response taken from text table section 7.4.1, V1.110
response by baseline severity taken from table 5.10.1, V1.110

Based upon these findings, the applicant has concluded that both doses of eletriptan are effective with respect to headache relief.

Comments

Sumatriptan is currently approved at doses of 25, 50 and 100 mg with the label describing repeated dosing at 2 hours if required. The label indicates that 100 mg sumatriptan may not provide additional efficacy relative to the 50 mg dose. It should be noted that the 55% response rate seen for sumatriptan in study 314 is slightly lower than the overall rate listed in the current labeling which is approximately 60% at 2 hours.

The original protocol has no statistical procedures described for multiple comparisons and interim data analysis. The particular data analysis technique to be used for the primary analysis was also not specified. These issues make it difficult to interpret the p-values reported though the comparisons of eletriptan to placebo are quite convincing and supported by the results of the other trials. It appears that this study was not originally anticipated for use to support approval and that it can be argued that this trial should be treated as supportive rather than as a phase III trial.

The use of a 20% delta to define equivalence was not justified based upon either clinical or statistical grounds. The trial was changed from an equivalence trial to a superiority trial after an examination of the data at an interim analysis though it was stated that the interim analysis would be strictly administrative.

A sizeable proportion (12%) of subjects were reported to have received treatment, but lacked headache assessments. Though the magnitude of the differences between the eletriptan doses relative to placebo suggest that this amount of missing should not have an impact upon the interpretation of the study results for eletriptan, the amount of missing data seriously compromises the comparisons to sumatriptan.

The protocol indicated that only the 80 mg dose of eletriptan was to be compared to sumatriptan. Based upon the observed results, the applicant made additional comparisons. This approach does not allow a valid statistical assessment to be made.

The use of the logistic regression model (i.e., dose as a continuous variable) utilized by the applicant is not appropriate unless the effect of baseline severity is identical for each of the treatment arms. The applicant reported that treatment by baseline severity interaction was not significant though an interaction was detected in the analysis of variance (i.e., dose as a categorical variable). It is difficult to reconcile these discrepant results and the applicant did not elaborate upon the inconsistencies. It seems plausible that there is a true interaction between baseline severity and treatment effect but that the logistic model with dose as a continuous effect may have been underpowered to detect such an effect. As such, the logistic regression model utilized may have been inappropriate.

Given the methodological flaws of this study, the statistical interpretation of study 314 is problematic. It appears to have shown that all three dose of eletriptan are effective, but it may not provide precise information regarding efficacy of the doses relative to each other, placebo or to sumatriptan.

Multiple Attack Studies

Study 102 - A multicenter, double-blind, placebo controlled parallel group, study of the efficacy and safety of oral eletriptan in subjects with acute migraine

Design

Twelve-hundred subjects, otherwise healthy with a history of frequent (expect one attack each 6 weeks with no more than 6 per month) acute migraine (with or without aura), were to be assigned to one of the following treatment groups (1:1:1:1) using random permuted blocks within center:

- 20 mg eletriptan
- 40 mg eletriptan
- 80 mg eletriptan
- placebo.

The study design was comparable to that used for study 307. One difference was that subjects were to take study medication again if an adequate response was not seen within 4 hours. Additionally, subjects were to treat up to 3 migraine attacks in this study over at most a 3 month period after randomization. Medication for attacks 2 and 3 were provided at the first post-treatment visit (after attack 1) and was identical to the treatment for attack 1. Efficacy assessments were to be made at 0, .5, 1, 2, 4, 6 and 24 hours after study treatment. A recurrence of headache was defined as a return to moderate or severe headache within 24 hours after an initial response. For each attack, patients were assigned study medication to take if they did not respond by 4 hours or experienced a recurrence. Patients assigned to one of the three doses of eletriptan were randomized either to the same dose of eletriptan or placebo. Patients assigned initially to placebo were assigned to either eletriptan 80 or placebo.

Interim data analyses were not discussed in the protocol.

The primary analysis (yes/no on headache response) was to be based upon logistic regression with dose as a continuous variable and the covariate of baseline severity (moderate or severe). Pairwise contrasts were to be used for each dose versus placebo. The comparisons to placebo will proceed from high to low with discontinuation of further testing for a result with p-value >.05. This method was to be abandoned if a lack of monotonicity was observed. The ITT population was defined as requiring baseline and post-treatment data and at least moderate severity at baseline.

Study Results

Sixteen-hundred and forty-nine (1649) subjects were screened for eligibility. Of these, 1334 were found to be eligible and randomized. Of the randomized subjects, 1190 were treated at least once and 144 were not treated. Nine-hundred eighteen (918) received 3 doses. Of those receiving at least one dose the proportion receiving all three doses ranged from 71% (placebo) to 85% (eletriptan 40). The following table contains the study status of all patients randomized. Subjects not treating three attacks within three months were considered withdrawn from the study.

	E20	E40	E80	Placebo	Total
randomized	333	333	335	333	1334
treatment					
recorded yes	290	296	312	292	1190
no	43	37	23	41	144

source: Table 1.1, V. 1.81

The majority of subjects were female (over 80% of subjects), white (100%) with a mean age of about 40 years (18 to 78 years). Approximately two-thirds of subjects were without aura.

The study report treats 1190 subjects as making up the ITT population for attack 1, 1018 for attack 2 and 915 for attack 3. Of these, 1120 had a headache assessment at 2 hours. An evaluable patient population analysis was also presented. In the discussion that follows, only the results of the ITT population will be presented. Analyses were not stratified by center due to the small number of subjects in some centers.

The proportion of subjects with headache response and key secondary endpoints (determined by medical reviewer) are summarized below. The p-values reported by the applicant were all <.0001 for the pairwise comparisons versus placebo. There was no apparent difference between the 40 and 80 mg doses of eletriptan.

With respect to nausea, photophobia and phonophobia, eletriptan was reported to have a higher proportion with the symptom absent at 2 hours. There were no apparent differences among the eletriptan doses.

The applicant identified significant interactions of treatment by gender and treatment by previous sumatriptan use for headache response at two hours for the first dose. It appears that the gender interaction is being driven by the better response by males to the lower dose of eletriptan. For the group previously receiving sumatriptan, the placebo group appears to have had a lower response rate with the converse true for eletriptan 40 and 80. No interaction was reported for race by treatment. The subgroup analyses are presented in the following table.

headache relief	E20	E40	E80	Placebo
overall	47% (129/273)	62% (174/281)	59% (170/290)	24% (30/126)
gender female	45%	67%	59%	23%
male	60%	43%	52%	26%
previous no	52%	56%	52%	29%
sumatriptan yes	45%	65%	62%	17%

text table p. 38, VI.81

Comments

The protocol did not specify how the results of the logistic regression were to be used. The pairwise comparisons were to be evaluated using a stepdown procedure. The procedure described by the

company is inappropriate because it allows for modification based upon the observed data. A Bonferroni procedure will be used for the purpose of this review. (.05/3=.017). The logistic regression analysis will be viewed as supportive. In fact, the applicant chose not to present the results of the logistic regression analyses due to the apparent lack of a linear dose relationship. Based upon the observed results there should be no statistical concern regarding the multiple adjustment procedures used. The results for all three doses of eletriptan clearly compare favorably with placebo.

The applicant's definition of the ITT population excluded subjects without postbaseline data. As indicated previously, this is not appropriate. Still, given the strength of the findings this issue will not be addressed further.

There was an apparent differential among the four arms with respect to subjects experiencing 3 attacks within 3 months. Since all subjects with a first attack were used in the primary analysis, this differential is of minimal consequence.

The applicant identified possible interactions by gender and previous sumatriptan use. The patterns seen were suggestive, but a clear pattern was not established. It would be of interest for the applicant to conduct an analysis for all studies submitted investigating these possible interactions.

This study did not establish a clear dose response relationship for eletriptan. It appears that the 40 mg and 80 mg doses may have greater efficacy than the 20 mg dose but this has not been clearly established. An analysis over all the trials submitted would be of interest in addressing the choice of dose. In particular, the relationship between dose and baseline headache severity has not been adequately established.

Study 104- A multicenter, double-blind, placebo controlled parallel group, study of two dose levels of oral eletriptan and two dose levels of oral sumatriptan given for the acute treatment of migraine

Design

Nine-hundred subjects, otherwise healthy, with a history of relatively frequent (expect one attack each 6 weeks with no more than 6 attacks per month on average) acute migraine (with or without aura) without prior sumatriptan use, were to be assigned to one of the following treatment groups (2:2:2:2:1) using random permuted blocks (no stratification discussed):

- 40 mg eletriptan
- 80 mg eletriptan
- 25 mg sumatriptan
- 50 mg sumatriptan
- placebo.

The study design was comparable to that used for study 102. The primary endpoint for this study was headache response at 4 hour. For each attack, patients were assigned study medication to take if they did not respond by 2 hours or experienced a recurrence. Patients assigned to one of the two doses of eletriptan were randomized either to the same dose of eletriptan or placebo. Patients assigned initially to sumatriptan or placebo were assigned to their initial medication.

Interim data analyses were not discussed in the protocol.

The protocol indicated that there would be six pairwise comparisons of interest; each dose of eletriptan versus the doses of sumatriptan and placebo. These comparisons were treated as two "families" of comparisons: (1) each dose of eletriptan versus placebo and (2) each dose of eletriptan versus each dose of sumatriptan. The multiple comparison procedure specified was to preserve the type I error for each family separately at the .05 level. It appears that the 40 mg dose of eletriptan would be compared to placebo only if the high dose was superior to placebo. It also appears that the second set of comparisons was to be made only if a dose of eletriptan was found to be superior to placebo. For the second family of comparisons, the applicant proposed testing high dose eletriptan (80) versus low dose sumatriptan (25). If this test reached the .05 level the comparable doses of eletriptan and sumatriptan (E40 vs. S25 & E80 vs S50) will be made at the .025 level. Finally, if either of these tests reached the .025 level the comparison of low dose eletriptan (40) will be compared to the high dose of sumatriptan (50).

Logistic regressions with treatment as both a categorical variable and as a continuous variable with baseline severity as a covariate were specified. Pairwise comparisons were to be conducted using contrasts within the model with dose as a categorical variable.

The ITT population was defined as requiring baseline and post-treatment data and at least moderate severity at baseline.

Study Results

Eighteen-hundred and ninety-six (1896) subjects were screened for eligibility. Of these, 1141 were found to be eligible and randomized. Of the randomized subjects, 818 were treated at least once and 323 were not known to have been treated. The reasons for no treatment recorded were listed by patient but not tabulated. It was reported that only 1/3 failed to have a treatable migraine. Four hundred sixty-five (465) received 3 doses. Of those receiving at least one dose, the proportion receiving all three doses was comparable over the study arms. The following table contains the study status of all patients randomized.

	E40	E80	S25	S50	Placebo	Total
randomized	254	253	254	253	127	1141
treated - yes	184	180	180	181	93	818
no	70	73	74	72	34	323

source: V. 1.91 Table1.1

The majority of subjects were female (over 80% of subjects), white (80%) with a mean age of about 35 years (18 to 65 years). Almost 90% of subjects were without aura.

The study report treats 818 subjects as making up the ITT population for attack 1, 577 for attack 2 and 628 for attack 3. For attack 1, 782 had a headache assessment at 2 hours. An evaluable patient population analysis was also presented. In the discussion that follows, only the results of the ITT population will be presented. Though the protocol and study report list the headache response at four hours as the primary analysis, in the following only the results at two hours will be discussed for

consistency with the other studies submitted in this NDA (the proposed label is based upon the 2 hour results).

The applicant chose not to present the results of the logistic regression analysis due to a lack of dose response.

The proportion of subjects with headache response and key secondary endpoints (determined by medical reviewer) are summarized below. The p-values reported by the applicant were all <.004 for the comparisons between eletriptan 80 and the other three treatment arms. Eletriptan 40 was reported to be significantly better than placebo (p=.001). The remaining comparisons involving eletriptan were not reported. The comparison of sumatriptan versus placebo was not reported. There is a relatively small difference between the 40 and 80 mg doses of eletriptan.

With respect to nausea at 2 hours, there were reported significant differences.

The applicant identified significant treatment by race and treatment by center interactions at two hours for the first dose. No other interactions were reported. The subgroup analyses with significant reported interactions are presented in the following table. The results for the test for interaction between baseline severity and dose were not shown in the study report. The interaction for race can be best understood by examining the placebo group. The race "Other" group has a much higher response rate than for race "White". There was no differential by race for the other treatment groups. For center 5091, both the placebo and sumatriptan arms did worse than in center 5090. The eletriptan arms had approximately the same response rates in both centers.

headache relief		E40	E80	S25	S50	Placebo
overall		62% (109/175)	70% (119/170)	53% (90/171)	56% (98/175)	40% (34/86)
race	White	63	71	49	57	30
	Other	60	66	64	54	70
center	5090	58	67	61	71	54
	5091	65	71	49	47	34

Source: Table 1.2 Appendix III V 1.96

Comments

The applicant has divided the tests into two families: those between eletriptan and placebo and those between eletriptan and sumatriptan. This seems appropriate from the standpoint of establishing the efficacy of eletriptan versus placebo. In effect, the relative efficacy of eletriptan and sumatriptan will only be of interest if eletriptan is established to be superior to placebo. Still, the procedure described by the company for taking into account multiple comparisons was inappropriate because it allows for modification based upon the observed data as was discussed with the other studies. A Bonferroni procedure with two comparisons will be used for the purpose of this review (.05/2=.025) for evaluating eletriptan versus placebo and a Bonferroni procedure with four comparisons (.05/4=.0125) will be used for the four comparisons among the doses of eletriptan and sumatriptan.

The results of the logistic regression analyses were not presented due to a lack of dose response. This raises the issue of multiplicity since it is likely that a significant dose response would have been used to support an indication even in the absence of a significant pairwise difference.

The applicant's definition of the ITT population excluded subjects without postbaseline data. As indicated previously, this is not appropriate. For this study, 323 subjects were excluded from the ITT population (818 included). Since it was reported by the applicant that only 1/3 failed to have a treatable migraine, almost 200 subjects may have had a migraine but were excluded from the data analysis. This is a very high proportion of subjects and is much greater than that seen in most of the other studies. This suggests that the results of this study should be viewed with considerable caution. This is especially true for the comparisons between eletriptan and sumatriptan for which the treatment difference is smaller.

There was an apparent differential among the four arms subjects not experiencing 3 attacks within 3 months. Since all subjects with a first attack were used in the primary analysis, this differential is of minimal consequence.

The applicant identified possible interactions by race and center. The patterns seen were suggestive, but a clear pattern was not established. It would be of interest for the applicant to conduct an analysis for all studies submitted investigating these possible interactions.

This study did not establish a clear dose response relationship for eletriptan. It appears that the 80 mg dose may have greater efficacy than the 40 mg dose but this has not been clearly established statistically.

Study 305 - A multicentre, double-blind, randomized, parallel group, placebo controlled study to assess the safety and efficacy of two oral dose levels of eletriptan given for the acute treatment of migraine (with and without aura)

Design

One-thousand three-hundred subjects, otherwise healthy, with a history of relatively frequent (expect one attack each 6 weeks with no more than 6 attacks per month on average) acute migraine (with or without aura), were to be assigned to one of the following treatment groups (2:2:1) using random permuted blocks (no stratification discussed):

40 mg eletriptan
80 mg eletriptan
placebo.

The study design was comparable to that used for study 102. The primary endpoint for this study was headache response at 2 hours. For each attack, patients were assigned rescue medication if they did not respond by 2 hours or experienced a recurrence after 2 hours. Subjects initially assigned to an eletriptan dose were randomized to receive either the same dose or placebo. For the second attack (three attacks were to be studied for each subject), subjects receiving placebo as their first dose were randomly assigned to one of the two doses of eletriptan. Rescue medication was not to include sumatriptan, ergotamine or any ergotamine-like substance.

Interim data analyses were not discussed in the protocol.

Logistic regressions with treatment as both a categorical variable and as a continuous variable with baseline severity as a covariate were specified. Interactions were tested at the .1 level for inclusion. Pairwise comparisons were to be conducted using contrasts within this model. A step-down procedure was specified to maintain an overall .05 level of significance.

The ITT population was defined as requiring baseline and post-treatment data and at least moderate severity at baseline.

Study Results

Thirteen hundred and sixty-five (1365) subjects were screened for eligibility. Of these, 1354 were found to be eligible and randomized. Of the randomized subjects, 1153 were treated at least once and 201 were not known to have been treated. The reasons for no treatment recorded were not tabulated. The following table contains the study status of all patients randomized.

	E40	E80	Placebo	Total
randomized	538	544	272	1354
treated - yes	453	462	238	1153
no	85	82	34	201

source: V. 1.98 Table 1.1

The majority of subjects were female (over 80% of subjects), white (approx. 100%) with a mean age of about 40 years (18 to 68 years). Almost 2/3 of subjects were without aura.

The study report treats 1151 subjects as making up the ITT population for attack 1, 1104 for attack 2 and 766 for attack 3. For attack 1, 1111 had a headache assessment at 2 hours. An evaluable patient population analysis was also presented. In the discussion that follows, only the results of the ITT population will be presented.

The applicant chose not to present the results of the logistic regression analysis due to a lack of dose response.

The proportions of subjects with headache response are summarized below. The p-values reported by the applicant were all <.001 for the comparisons between both doses of eletriptan and placebo. There was no apparent difference between the 40 and 80 doses of eletriptan. The results of the logistic regression were not presented due to a lack of dose response.

With respect to nausea, phonophobia and photophobia at 2 hours, there were reported significant differences for both doses of eletriptan versus placebo.

The applicant identified no significant interactions with gender, race or age. Results by baseline severity were not discussed in the study report.

headache relief	E40	E80	Placebo
	62% (265/430)	65% (288/446)	19% (44/432)

Source: text table section 7.4.1.1

Comments

The step-down procedure specified by the company is theoretically valid, but is difficult to apply in practice when there is a possible lack of monotonic response. The applicant's examination of the data for monotonicity is not statistically valid. As was done for the other studies, a Bonferroni procedure with two comparisons will be used for the purpose of this review ($.05/2=.025$) for evaluating eletriptan versus placebo.

The results of the logistic regression analyses were not presented due to a lack of dose response. This raises the issue of multiplicity since it is likely that a significant dose response would have been used to support an indication even in the absence of a significant pairwise difference.

This study did not identify a dose response relationship for eletriptan. The relationship between dose and baseline headache severity should be investigated.

Study 318 - A multicentre, double-blind, double-dummy, parallel group, placebo controlled, study of two dose levels of oral eletriptan and two doses of oral sumatriptan given for the acute treatment of migraine (with and without aura)

Design

Eleven hundred subjects, otherwise healthy, with a history of relatively frequent (expect one attack each 6 weeks with no more than 6 attacks per month on average) acute migraine (with or without aura) and no past sumatriptan use, were to be assigned to one of the following treatment groups (2:2:2:2:1) using random permuted blocks (no stratification discussed):

- 40 mg eletriptan
- 80 mg eletriptan
- 50 mg sumatriptan
- 100 mg sumatriptan
- placebo.

The study design was comparable to that used for study 102. The primary endpoint for this study was headache response at 1 hour. For consistency with the review of the other studies in this submission, the analysis at 2 hours will be considered primary for this review. Up to three attacks were to be treated. Subjects assigned initially to eletriptan were randomized to either their original dose of eletriptan or placebo if they required a second dose of medication for a particular attack.

The protocol indicated that there would be six pairwise comparisons of interest; each dose of eletriptan versus the doses of sumatriptan and placebo. These comparisons were treated as two "families" of comparisons: (1) each dose of eletriptan versus placebo and (2) each dose of eletriptan versus each dose of sumatriptan. The multiple comparison procedure specified was to preserve the

type I error for each family separately at the .05 level. It appears that the 40 mg dose of eletriptan would be compared to placebo only if the high dose was superior to placebo. It also appears that the second set of comparisons would be made only if a dose of eletriptan were found to be superior to placebo. For the second family of comparisons, the applicant proposed testing high dose eletriptan (80) versus low dose sumatriptan (50). If this test reached the .05 level, the comparable doses of eletriptan and sumatriptan (E40 vs. S50 & E80 vs S100) were to be made at the .025 level. Finally, if either of these tests reached the .025 level the comparison of low dose eletriptan (40) was to be compared to the high dose of sumatriptan (100).

Interim data analyses were discussed with respect to both safety and efficacy. Stopping for efficacy was not addressed.

Analysis of covariance was specified as the primary analysis technique. Baseline severity was treated as a categorical variable. Dose was treated both as a continuous and a categorical variable. Baseline severity by treatment interaction was tested at the .1 level.

The ITT population was defined as requiring baseline and post-treatment data and at least moderate severity at baseline.

Study Results

One thousand and thirteen (1013) subjects were screened for eligibility. Of these, 1008 were found to be eligible and randomized. Of the randomized subjects, 774 were treated at least once and 234 were not known to have been treated. The reasons for no treatment recorded were not tabulated but it was reported that the majority (60%) had not experienced an attack. The following table contains the study status of all patients randomized

	E40	E80	S50	S100	Placebo	Total
randomized	224	219	226	223	116	1008
treated - yes	175	164	181	170	84	774
no	49	55	45	53	32	234

source: V. I.115 Table1.1

The majority of subjects were female (over 85% of subjects), white (approx. 100%) with a mean age of about 40 years (17 to 76 years). Almost 2/3 of subjects were without aura.

The study report treats 773 subjects as making up the ITT population with 745 (96%) having headache assessments at 2 hours. An evaluable patient population analysis was also presented. In the discussion that follows, only the results of the ITT population will be presented.

The proportion of subjects with headache response is summarized below. The p-values reported by the applicant between the doses of eletriptan and placebo were both <.001 for the comparisons between all three doses of eletriptan and placebo. The p-values for the comparisons among the doses of eletriptan and sumatriptan were all less than .014 with the exception of eletriptan 40 mg versus sumatriptan 100 mg (p=.047). There is little apparent difference among the two doses of eletriptan.

A significant baseline severity by treatment interaction was reported. The response rates by baseline severity are presented in the following table. It can be seen that the response rate for the sumatriptan 100 mg dose group is roughly the same for both levels of baseline severity. For the other four treatment arms, the response rate is considerably lower for subjects with severe baseline headache.

With respect to nausea, phonophobia and photophobia at 2 hours, the treatment effects were consistent with those reported for headache.

The applicant identified a significant interaction between treatment and gender, but no interactions between treatment and race or age. Sample size was considered too small for these comparisons to be easy to interpret. The results for the gender interaction are presented in the following table.

headache relief	E40	E80	S50	S100	Placebo
overall	64% (108/169)	67% (107/160)	50% (88/176)	53% (85/160)	31% (25/80)
baseline severity					
moderate	77%	79%	60%	55%	36%
severe	46%	49%	36%	51%	26%
gender					
male	86%	62%	67%	45%	11%
female	61%	68%	48%	54%	34%

Source: text table section 7.4.1, text table section 7.4.3.1, table 1.2 appendix III

Comments

See comments for study 104 for a discussion of concerns regarding the multiple comparison procedure proposed by the applicant. Using the Bonferroni procedure, the comparison of eletriptan 40mg to sumatriptan 50mg would not be considered significant

As was discussed for a number of the other studies, the applicant needs to more clearly establish the relationship between baseline severity and treatment.

Meta Analysis

The applicant prespecified criteria for study inclusion in the meta analysis to allow comparisons to be made for the efficacy of repeat dosing of eletriptan (40 mg and 80 mg) after initial nonresponse and also for the treatment of recurrence after initial response. The dose of eletriptan (or placebo) to be taken after initial nonresponse or for recurrence was assigned at the time of initial randomization for each study. The studies agreed upon for the meta analysis are: 305, 307, 318, 102 and 104. Two primary endpoints were proposed: (1) change from moderate/severe to absent/mild at two hours post second dose and (2) change from moderate/severe to absent at two hours post second dose. Tests were to be conducted at the 2.5% level of significance to allow for two comparisons versus placebo (40 mg and 80 mg of eletriptan versus placebo). Baseline severity was to be included as a covariate. The medical division had recommended that non-compliers to the second dose be treated in the statistical analysis as treatment failures.

Treatment of initial nonresponders

The applicant reported the results of 860 subjects who did not initially respond to therapy and were initially assigned to 40 mg or 80 mg of eletriptan in the five studies. The following table lists the number of nonresponding subjects in the relevant dose groups by study taken from each of the individual study reports. It can be seen that 943 subjects failed to initially respond over the 5 studies. No significant differences were found between the two doses of eletriptan and placebo. The reported rates were 49% versus 51% and 48% versus 53% for the comparison to the relevant placebo arm.

Study	40 mg	80 mg
305	165	158
307	95	67
318	61	53
102	107	120
104	66	51
total	494	449

Treatment of relapse

Subjects were included in this analysis if they had initially responded to treatment (i.e., no headache with initial treatment or with retreatment) but had a headache recurrence within 24 hours. Headaches returning later than 24 hours were not treated as recurrences. Three hundred forty-two (342) patients were included in the analyses for treatment of relapse. The following table contains the distribution by study of the 377 subjects who were considered to have had a recurrence (taken from the individual study reports). Approximately 9% of the subjects with a recurrence are not included in the analysis of headache response. The reported response rates were 74% for eletriptan 40 mg and 33% for the placebo group initially assigned to eletriptan 40 mg. The corresponding rates for the 80 mg versus placebo comparison were 82% and 28%, respectively. Both comparisons were reported to be significant ($p < .0001$). The tests of significance were based upon logistic regression analysis with treatment, baseline severity, study, treatment by severity interaction and treatment by study interaction. Interactions were tested for inclusion in the model using a significance level of 10%.

Study	40 mg	80 mg
305	83	63
307	24	32
318	21	17
102	68	53
104	7	9
total	203	174

Comments on Meta Analysis

Treatment of Initial Nonresponders

There is a roughly 10% loss of subjects between the first failure to respond to treatment and retreatment. This lack of efficacy data was not adequately explained but was not explored further for this review due to the lack of apparent treatment effect.

Treatment of Recurrence

It is somewhat troubling that approximately 10% of subjects classified as having experienced a recurrence were not included in the efficacy analysis. Still, the treatment effect is large enough that this should not have had an impact upon the statistical conclusions reached by the applicant.

The applicant's analysis of recurrence based upon the logistic models picked and the practice of testing interactions and the refitting the model raises a number of statistical concerns. It would have been desirable to be able to review a Cochran-Mantel-Haenszel test stratifying by the original variates used to assign subjects to treatment (presumably center though this was not adequately addressed in the submission). This would have avoided the applicant's model based assumptions (and need for testing) that only the pairwise interactions of treatment by center and treatment by severity are possibly important. As with the concern regarding deletion of subjects, the large treatment effects relative to placebo makes it unnecessary to be able to review these alternative (and preferable) analyses.

Review Summary

The applicant has provided considerable statistical evidence that the 20 mg, 40 mg and 80 mg doses of eletriptan are effective relative to placebo for the initial treatment of migraine. The 20 mg dose was evaluated in studies 102 and 314 while the two higher doses were evaluated in all six trials considered in this review.

The 40 and 80 mg doses of eletriptan were shown to be effective for the treatment of a recurrence within 24 hours in the meta analysis provided. The use of either of these doses of eletriptan was shown to be ineffective for retreatment when a first dose failed to produce a response. It is not possible based upon the analyses considered for this review to conclude that the 20 mg dose is effective for the treatment of recurrence.

Interactions between baseline severity and treatment effect were reported for studies 314 and 318. The results for this interaction for the other studies was not discussed. It would be useful for the applicant to conduct an investigation of the relationship between dose of eletriptan and baseline severity over all the pivotal studies. It appears, based upon studies 314 and 318, that the effect of eletriptan is smaller for severe migraine.

Interactions between gender and treatment effect were reported in studies 102 and 318. The results presented were difficult to interpret due to the small samples sizes, but both studies seem to suggest a better response by males. It may be useful for the applicant to develop more extensive analyses for gender over the pivotal studies as a group to address this issue.

The individual study reports provide very limited statistical evidence that the 80 mg dose provides increased efficacy over the 40 mg dose. The following table shows the success rates calculated by the applicant for initial treatment for the six pivotal studies reviewed. It can be seen that there is considerable variation from study to study in the treatment effect. A Breslow-Day Test for interaction suggests that this may be reflecting real study to study variability in the treatment effect ($p=.067$). In trial 102 (the second largest trial), the 80 mg dose is 3% worse than the 40 mg dose. In trial 314 (the smallest study), the 80 mg dose is 12% better than the 40 mg dose. Study 305, which is by far the largest study, shows a 3% advantage (nonsignificant) for the 80 mg dose. The overall difference is 5% in favor of the 80 mg dose ($p=.01$ using a Cochran-Mantel-Haenszel test which is a

relatively weak result for a meta analysis with so many studies and subjects). The only study with clear evidence of an advantage of the 80 mg dose over the 40 mg dose is study 307 which seems to have shown an unusually large treatment effect (13%). The applicant should be encouraged to attempt to identify subpopulations (such as those formed by baseline severity) where the 80 mg dose provides a clear advantage over the 40 mg dose. It would also be useful if these analyses accounted for the relatively larger treatment effect seen in study 307.

Study	Dose	
	40 mg	80 mg
	Success Rate (n)	Success Rate (n)
102	62% (281)	59% (290)
104	62% (175)	70% (170)
305	62% (430)	65% (446)
307	54% (206)	67% (209)
314	65% (117)	77% (118)
318	64% (169)	67% (160)
Total	61% (1378)	66% (1393)

Study 314 suffered from a number of methodological flaws including an inadequate description in the protocol of the statistical analyses to be used and considerable loss to follow-up. The follow-up and rather sloppy trial design may account for the larger difference seen for study 314 between 40 mg and 80 than is seen in the other studies.

The secondary endpoints commented upon in this review include nausea, photophobia and phonophobia. Though the comparisons of eletriptan to placebo were not always statistically significant, the overall pattern of response was consistent with the results for headache response.

Three of the studies, 104, 314 and 318, contained comparisons between doses of sumatriptan and doses of eletriptan. As previously indicated, study 314 has serious methodological flaws and may not be adequate for comparative claims between eletriptan and sumatriptan. Similarly, study 104 excluded a relatively high proportion of subjects from the ITT population. For studies 104 and 318, only the 50 mg dose of sumatriptan was contained in both studies. In study 318 the 50 mg dose of sumatriptan had a numerically lower response rate; 14% lower than eletriptan 40 mg and 17% relative to eletriptan 80 mg. These reach the 5% level of significance even after adjustment for multiple comparisons. The results from study 104 are not consistent with the results from study 318. In study 104, there was little difference between the 40 mg dose of eletriptan and the 50 mg dose of sumatriptan. The comparison between the 80 mg dose of eletriptan and the 50 mg dose of sumatriptan reaches the 5% level of significance after adjustment for multiple comparisons. It should be noted that this study reported an interaction between center (there were two centers) and the treatment effect. Sumatriptin 50 mg was numerically superior to both doses of eletriptan in one of the centers, but only somewhat better than placebo in the other. The inconsistencies and the lack of replication over multiple doses of sumatriptan suggest that the applicant has failed to clearly establish the superiority of eletriptan over sumatriptan and that further studies should be conducted.

The applicant submitted a single study (307) that contained a comparison of eletriptan (40 mg and 80 mg) to cafergot (1 mg ergotamine + 100 mg caffeine). The comparisons were found to be statistically significant at the 5% level of significance after adjustment for multiple comparisons. As

was commented upon in the review for study 307, cafergot was used in a manner inconsistent with current labeling for ergotamine + caffeine which allows for repeat dosing earlier than that allowed in study 307.

/S/
Paul Flyer, Ph.D.
Statistical Team Leader, DB II

concur.

Dr. Kun Jin

Dr. George Ch' /S/

cc:

Archival NDA 21,016

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This review contains 22 page.

Statistical Review and Evaluation

Review of Carcinogenicity Data

JUL 2 1999

NDA#: 21-016
Name of Sponsor: Pfizer Inc.
Name of Drug: Relpax (eletriptan)

Documents Reviewed: Volumes 1.21 to 1.25 Containing the Mouse Study Reports, Volumes 1.28 to 1.31 Containing the Rat Study Reports, and Volume 1.156 Containing Data Diskettes and Data Listings. This Reviewer Had Access to the Electronic NDA.

Pharmacology Reviewer: Robin Huff, Ph.D. (HFD-120)

I. Background

The Division of Biometrics 1 was requested to review the rat and mouse data of the two year oncogenicity studies. The results were discussed with the reviewing pharmacologist, Dr. Robin Huff.

II. The Rat Study

II.1 Sponsor's Findings

Sixty-five Sprague-Dawley Crl:CD(SD)BR rats per group per sex received the drug in doses of 0, 0, 3, 15, and 75 mg/kg/day in the feed. The dose of the HD females was reduced to 50 mg/kg/day at about 8 months due to extreme weight loss. Terminal sacrifice began after 24 months.

The sponsor observed statistically significant increase in survival with dose. The p-value was < 0.001 for the males and 0.060 for the females.

The only tumor with statistically significant increase was benign testicular interstitial cell adenoma. However, after Bonferroni correction for multiplicity of testing these findings were no longer significant.

From the onset the treatment decreased body weight gains in the male and female high dose (HD) groups, reaching 24.1 and 33.6 percent less than the first control group (Figures 1 and 2). As mentioned above, the effect was so strong among the HD females that the dose was reduced to 50 mg/kg/day for the remainder of the study.

II.2 Reviewer's Findings

This reviewer excluded one animal (#556, HD male) from all analyses. It seemed to have been an accidental death, had 37 tissues listed, none with tumors. No other animal had that many tissues listed.

This reviewer could basically reproduce the sponsor's findings. There are minor differences in the number of animals at TS which are not of consequence. Besides the exclusion of the accidental death, other discrepancies are due to whether an animal died a natural death before being sacrificed. The trend statistic for survival of the males is highly significant for increased survival with dose (Tables 1-2, Figures 3-4). For the survival (and for the tumor) trend tests, this reviewer recalculated the high dose for the females to 58 mg/kg/day, which is the weighted average of the 75 and 50 mg/kg/day doses. Female survival is also best for the high dose, reaching statistical significance when early deaths are weighted more heavily (Kruskal-Wallis trend test) (Tables 3-4, Figures 5-6).

The sponsor analyzed only tumors with at least 5 occurrences. The exact permutation trend test used by this reviewer is not limited by a minimum number of observed tumors. With this approach, testicular interstitial cell adenoma is extremely close to the α -level for common tumors ($p=0.0051$ versus $\alpha=0.0050$, Table 5). This alpha level was established to limit the overall false positive rate for the two species-two sexes bioassay to about 10 percent. The sponsor's approach of a Bonferroni correction is considered too liberal. No tumor trends reached statistical significance for the females (Table 6).

III.3 Validity of the Rat Study

As there were no statistically significant (positive) trends in tumors among female rats, the validity of this study arm 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, Vol 5, pp 66-78, 1985) had found that 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.'

As mentioned above, survival was at least as good among the treated animals as among the controls. With 27 of the 65 HD animals surviving to terminal sacrifice, there was a sufficient number of animals exposed for a sufficient length of time to manifest late developing tumors. Assessing whether the high dose was close to the MTD is more complicated: average body weights were substantially lower than the controls' from early on, suggesting that the HD exceeded the MTD. Again, the effect of the drug on body weight was so strong that it necessitated a reduction of the high dose. It is left to the expertise of the pharmacologist to evaluate the clinical signs and severe histopathologic toxic effects to assess whether the HD was close to the MTD.

III. The Mouse Study

III.1 Sponsor's Findings

In this study, Crl:COBS-VAF-CD1(ICR)BR(France) mice were fed a diet supplemented with 0, 0, 20, 90, and 400 mg/kg/day eletriptan for 24 months. There were 50 animals per treatment group per sex. The control groups were combined for survival analysis. Survival was statistically significantly higher for mid and high dose females. There was little difference in survival among the male groups.

The treatment with eletriptan affected the average body weights of the mid and high dose groups of both sexes (Figures 7-8). At mid dose, there were small decreases (up to 6%) which persisted throughout the study for the females. At the high dose, the males experienced a decrease in average body weight of up to 8 % during the first two months, which leveled off to 5 % for the remainder of the study. The females' decrease started early (from first week) and reached a plateau of about 14 % after 17 months. The sponsor concluded that the changes observed for the high dose were toxicologically significant.

The sponsor observed treatment related effects in the liver and harderian glands. There was an increased incidence of adenomas of the liver among the males which was statistically significant at the $\alpha=0.01$ level. The increased incidence of adenoma of the harderian glands among the males reached statistical significance at the $\alpha=0.05$ level.

III.2 Reviewer's Findings

When reanalyzing the data on diskette, this reviewer obtained results very similar to the sponsor's. The mortality tables (Tables 7-10, Figures 9-12) have slightly different numbers for terminal sacrifice in some groups. This happens when animals are dying prior to being

terminally sacrificed and are treated as natural deaths by the sponsor but as TS by this reviewer. These differences have no effect on any conclusions. Survival was significantly better with dose for the females, but similar across the male groups.

This reviewer observed the same tumor incidences as the sponsor. The p-value for linear trend of hepatocellular adenoma among the males was 0.0017, which is considered statistically significant even after adjusting for the many tests performed (α for trend in common tumors is 0.005) (Table 11). The p-value associated with adenoma in the Harderian glands was 0.0348, which is not statistically significant for a common tumor. Among the females, no tumor incidence trends reached statistical significance (Table 12).

III.3 Validity of the Mouse Study

As there were no statistically significant tumor trends for the female mice, the validity of this study arm needs to be evaluated. Following the criteria outlined above for the rats, it is concluded, that there were sufficient numbers of animals at all dose levels at the end of the study. Whether the high dose presented a reasonable tumor challenge is more difficult to assess. Average body weights were suppressed by treatment with eletriptan, but beyond the limit of 10% recommended by the experts. Also, the survival was not affected negatively. As a matter of fact, there was a statistically significant increase in survival with dose. The final determination of the whether the high dose was close to the MTD is left to the expertise of the pharmacologist. From a statistical point of view the substantial suppression of average body weights seem to indicate that the high dose exceeded the MTD.

IV. Summary

Sixty-five rats per treatment group per sex received 0, 0, 3, 15, and 75 mg/kg/day of Relpax in the feed for two years. The treatment affected body weight gains, especially in the high dose groups. For the females this effect was so strong that the high dose was reduced to 50mg/kg/day at about eight months into the study. Survival was better in the high dose groups than in any other group, to a highly significant level among the males. A statistically significant increase in tumor incidence rates was seen only for testicular interstitial cell adenoma. When evaluating the validity of the female arm, this reviewer concluded that there were sufficient numbers of animals exposed for a sufficient length of time to manifest late developing tumors. However, based on the strong reduction in weight gain, it appears that the high dose exceeded the MTD.

Fifty mice per treatment group per sex received 0, 0, 20, 90, and 400 mg/kg/day of Relpax in the feed for two years. Survival of the male mice was not affected. Among the females, there was a statistically significant increase in survival with dose. Hepatocellular adenoma among the males showed a statistically significant increase with dose. Among the females, no tumor findings reached statistical significance. Evaluating the validity of the female arm, this reviewer concluded that there were sufficient numbers of animals exposed for a sufficient length of time to manifest late developing tumors. Average body weights were suppressed beyond the 10 percent differential from controls recommended by experts. As mortality was not affected either, it is this reviewer's opinion that the high dose may have exceeded the MTD.

/S/

~~Roswitha Kelly, M.S.~~
Mathematical Statistician

/S/

~~Kun Jin, Ph.D.~~
Team Leader

/S/

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

Cc: Archival NDA 21-016, Relpax (eletriptan), Pfizer
CARCINOGENICITY

HFD-120/Ms. Chen, CSO
HFD-120/Dr. Huff
HFD-120/Dr. Fitzgerald
HFD-710/Dr. Chi
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This review consists of 5 pages, 12 tables, and 12 figures.
MSWord: relpax.doc/07/01/99

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	23.16	0.0000
	Depart from Trend	3.32	0.3442
	Homogeneity	26.49	0.0000
Kruskal-Wallis	Dose-Mortality Trend	22.01	0.0000
	Depart from Trend	3.83	0.2799
	Homogeneity	25.85	0.0000

Species: at
Sex: Female

Treatment Group

	CTRL1	CTRL2	LOW	MED	HIGH	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-52	3	3	3	1	1	11
53-78	16	12	16	16	4	64
79-91	12	13	16	14	14	69
92-104	9	19	10	12	19	69
105-105	25	18	20	22	27	112
Total	65	65	65	65	65	325

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	3.47	0.0625
	Depart from Trend	1.03	0.7934
	Homogeneity	4.50	0.3423
Kruskal-Wallis	Dose-Mortality Trend	5.53	0.0187
	Depart from Trend	0.97	0.8081
	Homogeneity	6.51	0.1645

Sex: Mr
Sorted by: Org Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
2	Adrenal	192	B-PHEOCHROMOCYTOMA	0.3525	0.3536	0.3545
2	Adrenal	366	M-PHEOCHROMOCYTOMA, MALIG	0.5041	0.6593	0.6646
2	Adrenal	454	M-CORTICAL CARCINOMA	0.6859	0.7776	0.7819
2	Adrenal	183	B-CORTICAL ADENOMA	0.6954	0.7100	0.7114
5	Bone, sternum	235	M-OSTEOSARCOMA	1.0000	0.7437	0.7491
6	Brain	320	M-ASTROCYTOMA	0.4685	0.5310	0.5386
15	Heart	380	M-SCHWANNOMA, ENDOCARDIAL	0.2811	0.0574	0.0592
15	Heart	352	M-MESOTHELIOMA, ATRIOCAVA	0.2865	0.0598	0.0617
15	Heart	377	B-SCHWANNOMA, ENDOCARDIAL	0.4743	0.6179	0.6282
18	Kidney	393	M-NEPHROBLASTOMA	0.2020	0.0256	0.0266
18	Kidney	326	B-RENAL TUBULE ADENOMA	0.3037	0.1339	0.1368
18	Kidney	418	B-LIPOMA	0.3471	0.0874	0.0898
18	Kidney	428	M-RENAL MESENCHYMAL TUMOR	0.6778	0.7578	0.7625
18	Kidney	217	M-LIPOSARCOMA	1.0000	0.7768	0.7815
19	Liver	423	M-CHOLANGIOCARCINOMA	0.6859	0.7776	0.7819
19	Liver	75	B-HEPATOCELLULAR ADENOMA	0.9109	0.9133	0.9141
19	Liver	181	M-HEPATOCELLULAR CARCINOM	0.9504	0.9428	0.9432
20	Lung	113	B-BRONCHIOLAR-ALVEOLAR AD	0.7314	0.7141	0.7202
22	Lymphoreticular	211	M-LYMPHOMA, NOS	0.3630	0.3564	0.3599
22	Lymphoreticular	196	M-GRANULOCYTIC LEUKAEMIA	0.4013	0.2106	0.2141
22	Lymphoreticular	46	M-HISTIOCYTIC SARCOMA	0.4342	0.4572	0.4592
26	Pancreas	341	M-ISLET CELL CARCINOMA	0.6702	0.6892	0.6908
26	Pancreas	98	B-ISLET CELL ADENOMA	0.7444	0.7473	0.7483
26	Pancreas	291	B-MIXED ACINAR-ISLET TUMO	0.9434	0.8640	0.8663
27	Parathyroid	103	B-ADENOMA	0.4090	0.4221	0.4241
29	Pituitary	260	B-ADENOMA, PARS INTERMEDI	0.7063	0.7885	0.7915
29	Pituitary	16	B-ADENOMA, PARS DISTALIS	1.0000	1.0000	1.0000
33	Skeletal muscle	200	M-RHABDOMYOSARCOMA	1.0000	0.8293	0.8323
34	Skin and adnexa	300	B-SQUAMOUS CELL PAPILLOMA	0.3153	0.2788	0.2810
34	Skin and adnexa	156	M-ADENOCARCINOMA, MAMMARY	0.4167	0.5175	0.5251
34	Skin and adnexa	202	M-SEBACEOUS/SQUAMOUS CELL	0.4339	0.2382	0.2417
34	Skin and adnexa	344	B-BASAL CELL TUMOR	0.4811	0.4102	0.4140

Species: P
 Sex: Ma
 Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
34	Skin and adnexa	224	B-BASOSQUAMOUS TUMOR	0.6377	0.7196	0.7239
34	Skin and adnexa	373	M-SQUAMOUS CELL CARCINOMA	0.6528	0.6952	0.7019
34	Skin and adnexa	301	B-HAIR FOLLICLE TUMOR	0.7597	0.7779	0.7793
34	Skin and adnexa	119	B-FIBROADENOMA, MAMMARY G	1.0000	0.8030	0.8070
34	Skin and adnexa	367	B-SEBACEOUS GLAND ADENOMA	1.0000	0.6785	0.6882
34	Skin and adnexa	276	M-SEBACEOUS GLAND CARCINO	1.0000	0.8030	0.8070
35	Soft tissues	107	M-SCHWANNOMA; MALIGNANT	0.1146	0.0819	0.0832
35	Soft tissues	125	M-FIBROSARCOMA	0.3122	0.2946	0.2980
35	Soft tissues	339	B-LIPOMA	0.3471	0.0874	0.0898
35	Soft tissues	401	M-HEMANGIOSARCOMA	0.4731	0.6171	0.6230
35	Soft tissues	254	M-LEIOMYOSARCOMA	0.5041	0.6593	0.6646
35	Soft tissues	85	M-SARCOMA, N.O.S.	0.5049	0.3717	0.3755
35	Soft tissues	106	M-FIBROUS HISTIOCYTOMA, M	0.5302	0.5204	0.5237
35	Soft tissues	216	B-FIBROMA	0.7205	0.7411	0.7431
35	Soft tissues	342	B-HEMANGIOMA	1.0000	0.8341	0.8372
36	Spinal cord	371	B-ASTROCYTOMA	0.7768	0.8457	0.8483
38	Stomach	431	M-SQUAMOUS CELL CARCINOMA	0.4247	0.5292	0.5366
38	Stomach	349	B-SQUAMOUS CELL PAPILLOMA	0.5756	0.3601	0.3640
39	Testis	245	B-INTERSTITIAL CELL ADENO	0.0051	0.0032	0.0032
39	Testis	364	B-MESOTHELIOMA, BENIGN	1.0000	0.8030	0.8070
41	Thymus	448	B-THYMOMA	1.0000	0.8047	0.8088
42	Thyroid	167	B-C-CELL ADENOMA	0.3158	0.3172	0.3184
42	Thyroid	138	B-FOLLICULAR CELL ADENOMA	0.6001	0.6069	0.6086
42	Thyroid	275	M-C-CELL CARCINOMA	0.6695	0.6397	0.6426
42	Thyroid	470	M-FOLLICULAR CELL CARCINO	1.0000	0.7391	0.7452

Species: RAT
Sex: F
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
1	Abdomen	272	M-MESOTHELIOMA, MALIGNANT	0.5308	0.6926	0.6979
2	Adrenal	192	B-PHEOCHROMOCYTOMA	0.3451	0.3360	0.3391
2	Adrenal	183	B-CORTICAL ADENOMA	0.4497	0.4575	0.4591
2	Adrenal	366	M-PHEOCHROMOCYTOMA, MALIG	0.4501	0.2635	0.2683
2	Adrenal	454	M-CORTICAL CARCINOMA	0.5556	0.6369	0.6500
6	Brain	450	M-MALIGNANT RETICULOSIS	0.2754	0.0565	0.0588
6	Brain	400	B-GRANULAR CELL TUMOR	0.8451	0.8287	0.8324
6	Brain	320	M-ASTROCYTOMA	1.0000	0.8524	0.8558
15	Heart	380	M-SCHWANNOMA, ENDOCARDIAL	1.0000	0.7612	0.7680
18	Kidney	418	B-LIPOMA	0.5572	0.7191	0.7239
18	Kidney	326	B-RENAL TUBULE ADENOMA	0.6902	0.7362	0.7410
19	Liver	181	M-HEPATOCELLULAR CARCINOM	0.3578	0.3867	0.3914
19	Liver	75	B-HEPATOCELLULAR ADENOMA	0.9355	0.9280	0.9290
20	Lung	322	M-BRONCHIOLAR-ALVEOLAR CA	1.0000	0.7802	0.7861
22	Lymphoreticular	46	M-HISTIOCYTIC SARCOMA	0.1432	0.1126	0.1155
22	Lymphoreticular	196	M-GRANULOCYTIC LEUKAEMIA	0.4403	0.5397	0.5457
25	Ovary	338	B-SEX CORD/STROMAL TUMOR	1.0000	0.8538	0.8572
26	Pancreas	341	M-ISLET CELL CARCINOMA	0.2885	0.1190	0.1227
26	Pancreas	277	B-ACINAR ADENOMA	0.4058	0.5092	0.5182
26	Pancreas	98	B-ISLET CELL ADENOMA	0.7001	0.7015	0.7039
26	Pancreas	291	B-MIXED ACINAR-ISLET TUMO	1.0000	0.7583	0.7653
27	Parathyroid	103	B-ADENOMA	0.8220	0.8263	0.8294
29	Pituitary	16	B-ADENOMA, PARS DISTALIS	0.9589	0.9568	0.9570
34	Skin and adnexa	156	M-ADENOCARCINOMA, MAMMARY	0.3602	0.3633	0.3649
34	Skin and adnexa	276	M-SEBACEOUS GLAND CARCINO	0.4058	0.5092	0.5182
34	Skin and adnexa	447	M-CARCINOSARCOMA, MAMMARY	0.4269	0.2441	0.2488
34	Skin and adnexa	475	B-ADENOLIPOMA, MAMMARY GL	0.4281	0.5333	0.5420
34	Skin and adnexa	224	B-BASOSQUAMOUS TUMOR	0.4375	0.5418	0.5501
34	Skin and adnexa	270	B-ADENOMA, MAMMARY GLAND	0.8395	0.8600	0.8621
34	Skin and adnexa	119	B-FIBROADENOMA, MAMMARY G	1.0000	1.0000	0.9999
34	Skin and adnexa	300	B-SQUAMOUS CELL PAPILLOMA	1.0000	0.7802	0.7861
34	Skin and adnexa	202	M-SEBACEOUS/SQUAMOUS CELL	1.0000	0.7539	0.7609

Source: C:\RELPAX\rat2_tum.fil

cont'd.

Species: t

Sex: F

Sorted by: Organ Name

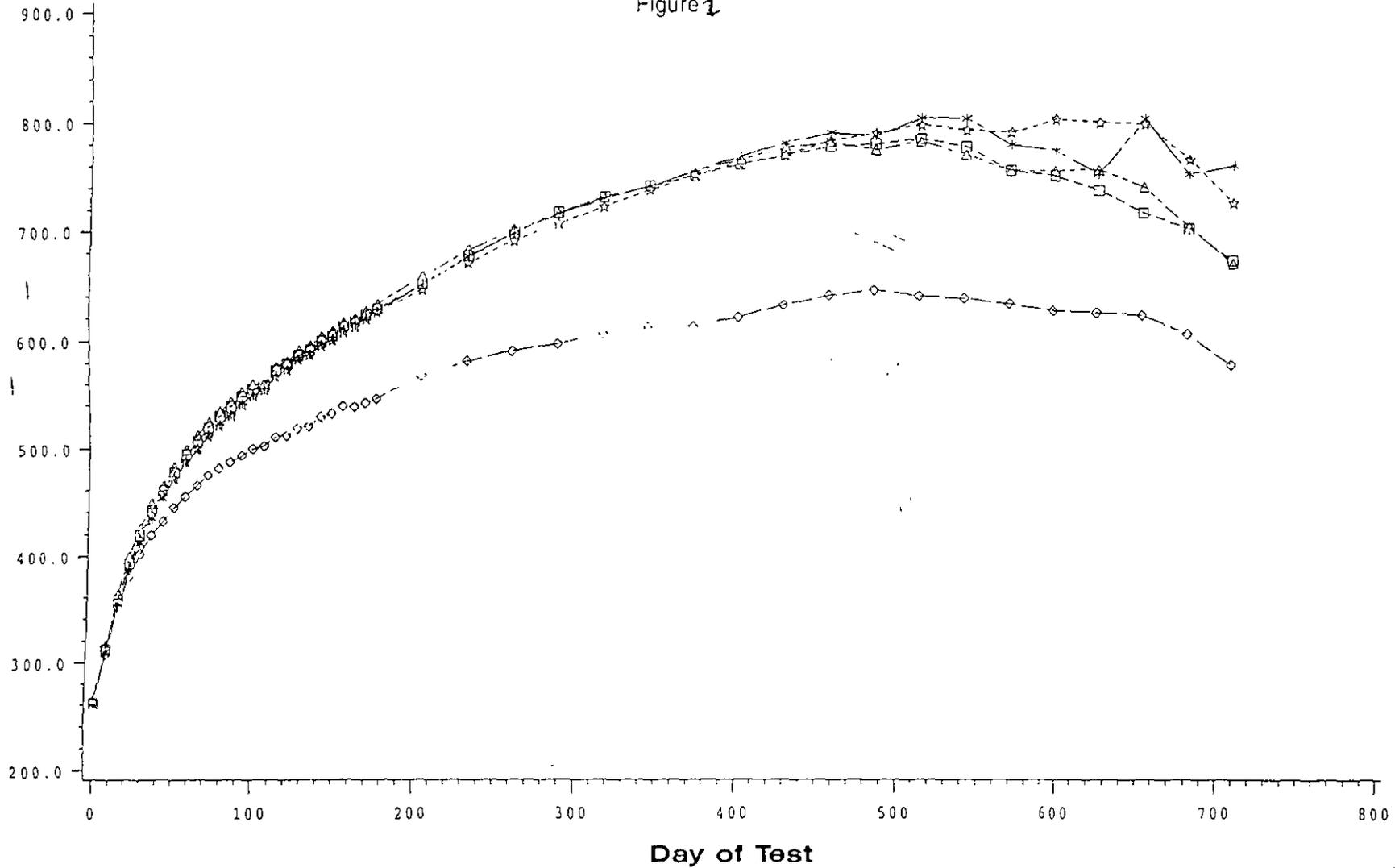
Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
35	Soft tissues	401	M-HEMANGIOSARCOMA	0.4212	0.2408	0.2455
35	Soft tissues	254	M-LEIOMYOSARCOMA	0.5875	0.6243	0.6314
35	Soft tissues	85	M-SARCOMA, N.O.S.	0.6782	0.7204	0.7255
35	Soft tissues	125	M-FIBROSARCOMA	0.7935	0.8329	0.8362
35	Soft tissues	106	M-FIBROUS HISTIOCYTOMA, M	0.9395	0.8760	0.8786
35	Soft tissues	339	B-LIPOMA	0.9745	0.9629	0.9635
35	Soft tissues	216	B-FIBROMA	1.0000	0.7687	0.7751
35	Soft tissues	342	B-HEMANGIOMA	1.0000	0.7714	0.7777
38	Stomach	315	B-NEUROENDOCRINE CELL TUM	1.0000	0.7802	0.7861
41	Thymus	448	B-THYMOMA	1.0000	0.7802	0.7861
42	Thyroid	275	M-C-CELL CARCINOMA	0.1371	0.1081	0.1110
42	Thyroid	167	B-C-CELL ADENOMA	0.2792	0.2819	0.2831
42	Thyroid	138	B-FOLLICULAR CELL ADENOMA	0.3050	0.2576	0.2606
44	Urinary bladder	476	B-SQUAMOUS CELL PAPILLOMA	0.4493	0.5648	0.5727
45	Uterus	249	M-STROMAL CELL SARCOMA	0.0764	0.0491	0.0503
45	Uterus	207	B-ENDOMETRIAL STROMAL POL	0.1193	0.1147	0.1157
45	Uterus	482	B-GRANULAR CELL TUMOR, CE	0.9617	0.9544	0.9551
45	Uterus	422	M-CARCINOMA	1.0000	0.7707	0.7772
46	Vagina	421	B-STROMAL POLYP	0.2432	0.0430	0.0449

Mean Body Weight Study - 9491203

UK-116044-04 Rat

Sex=Males

Figure 1

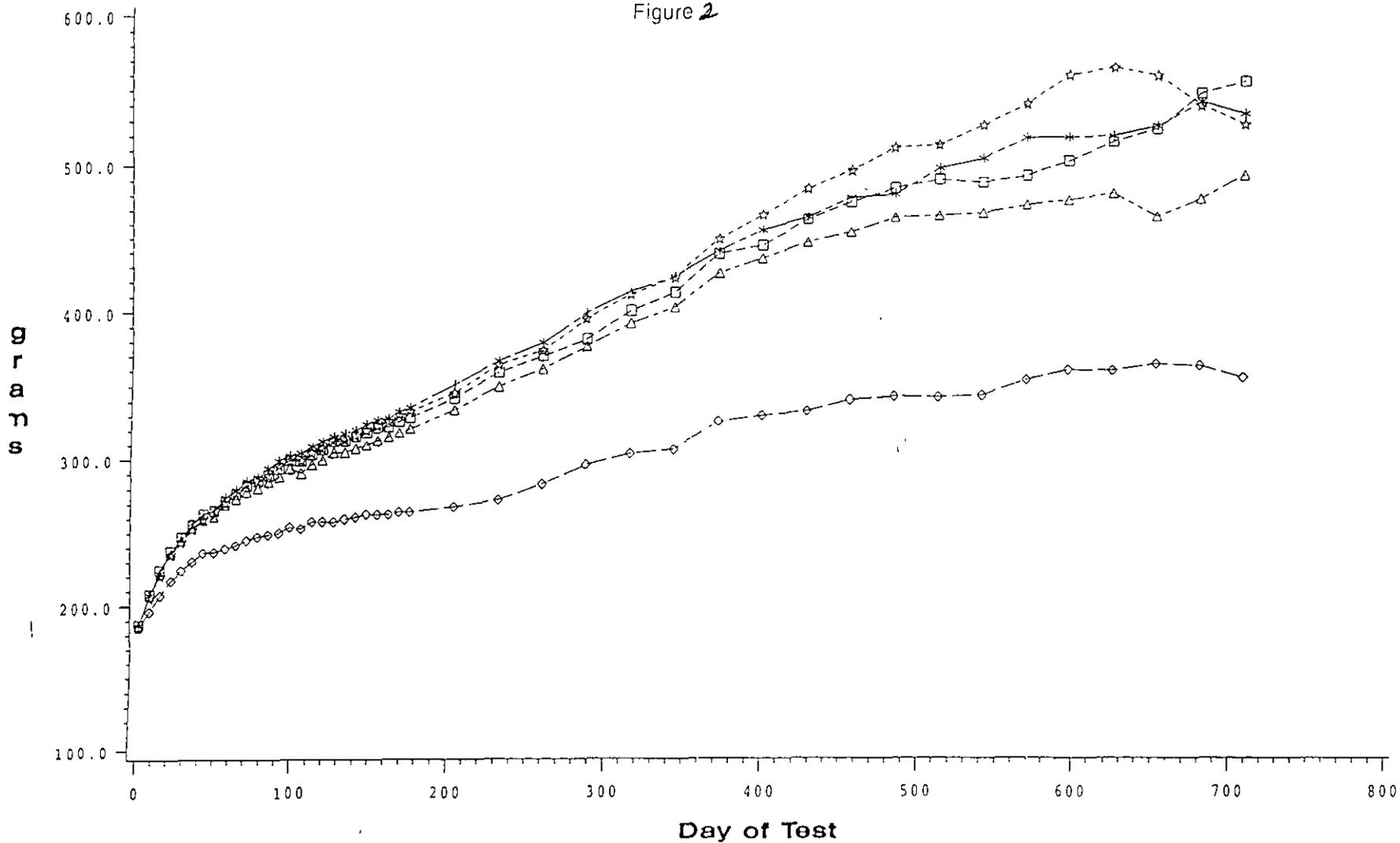


Group *-*-*-* 1 +--+ 2 □-□-□ 3 △-△-△ 4 ◇-◇-◇ 5

Mean Body Weight Study - 9491203

UK-116044-04 Rat
Sex=Females

Figure 2



Group + + + + * * * * □ □ □ □ △ △ △ △ * * * *

Cumulative Percentages of Death

Species: Rat

Sex: Male

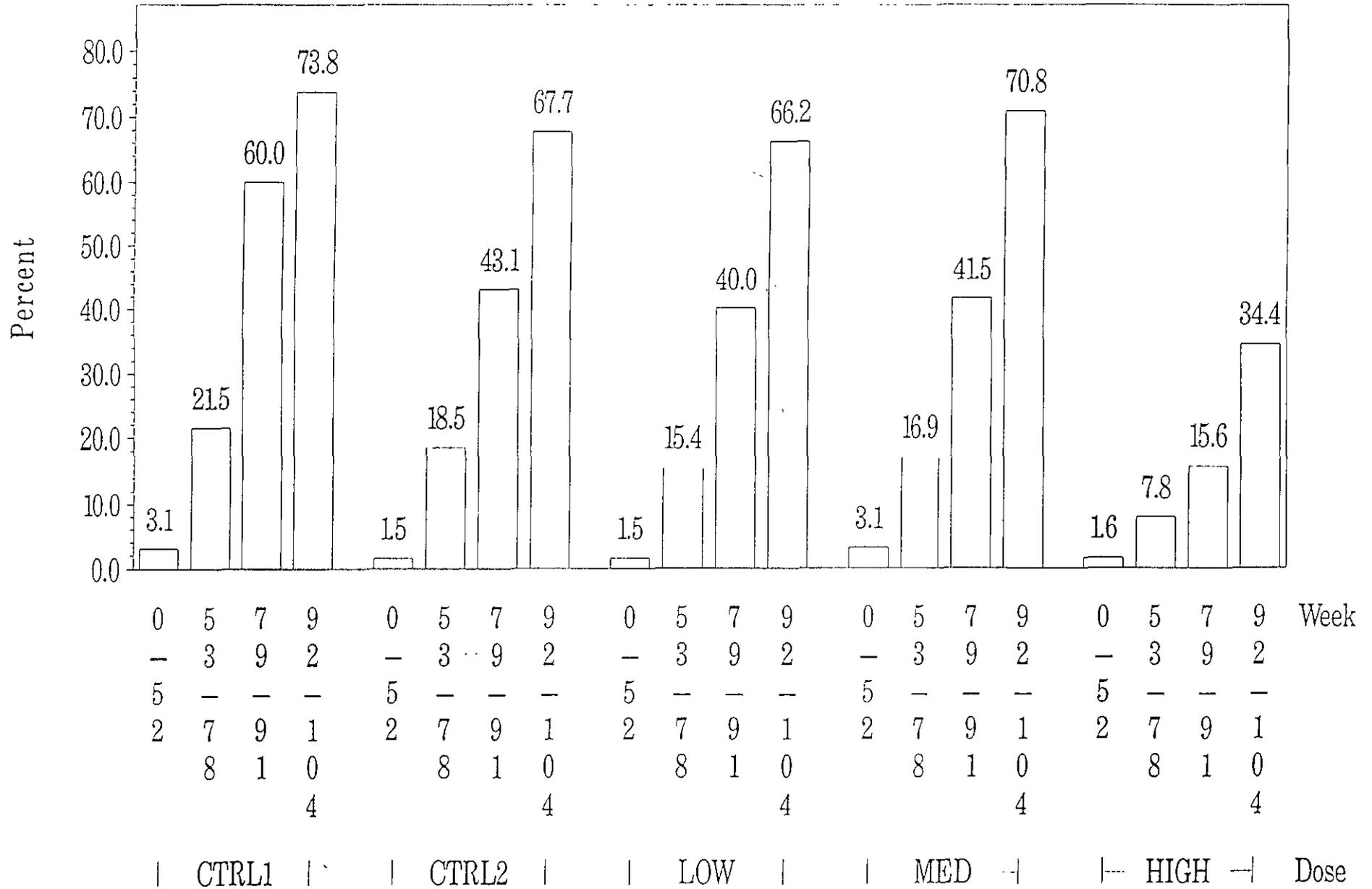
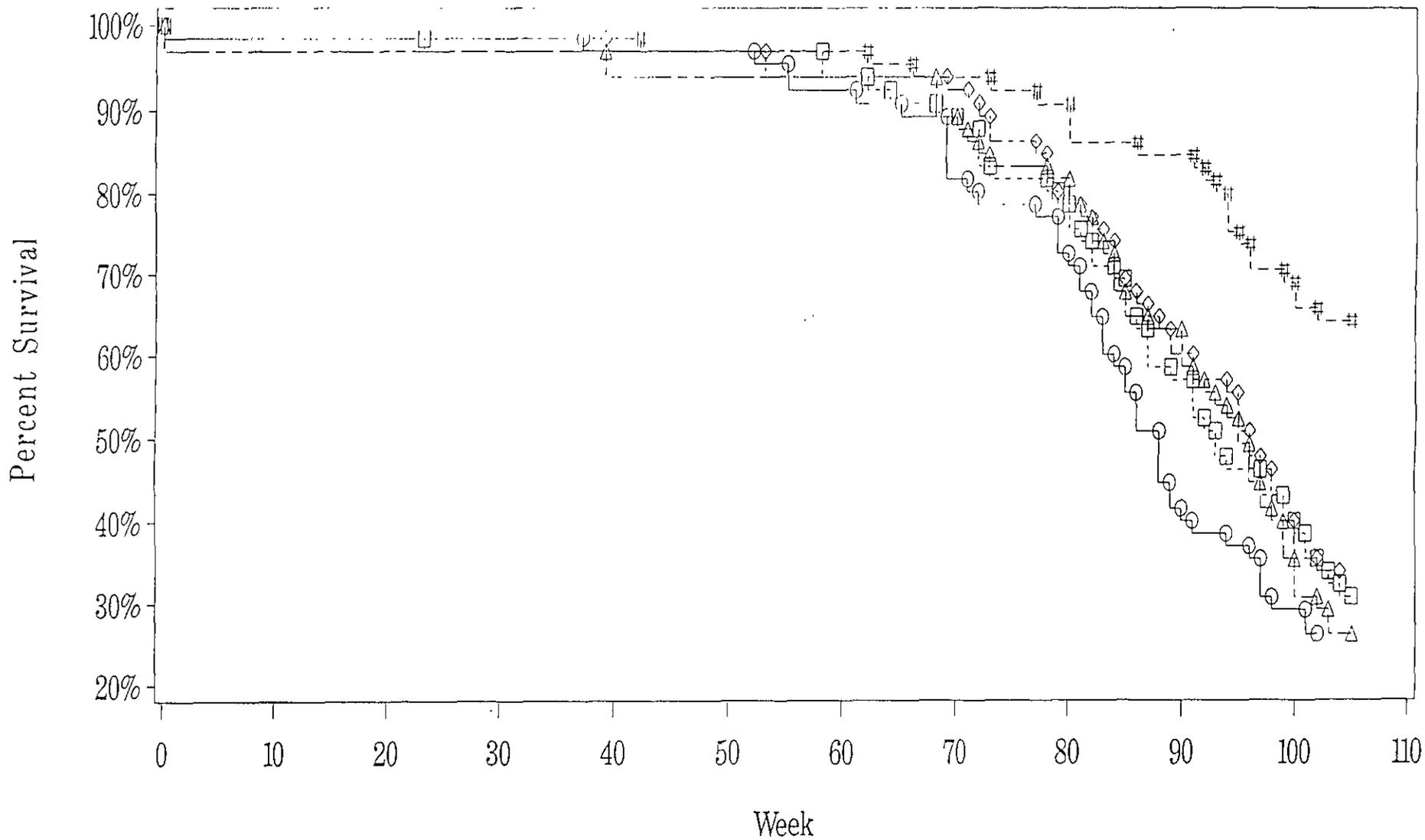


Figure 4: Kaplan-Meier Survival Function

Species: Rat

Sex: Male



○-○-○ CTRL1 □-□-□ CTRL2 ······ LOW △-△-△ MED #-#-# HIGH

Figure 5. Cumulative Percentages of Death

Species: Rat

Sex: Female

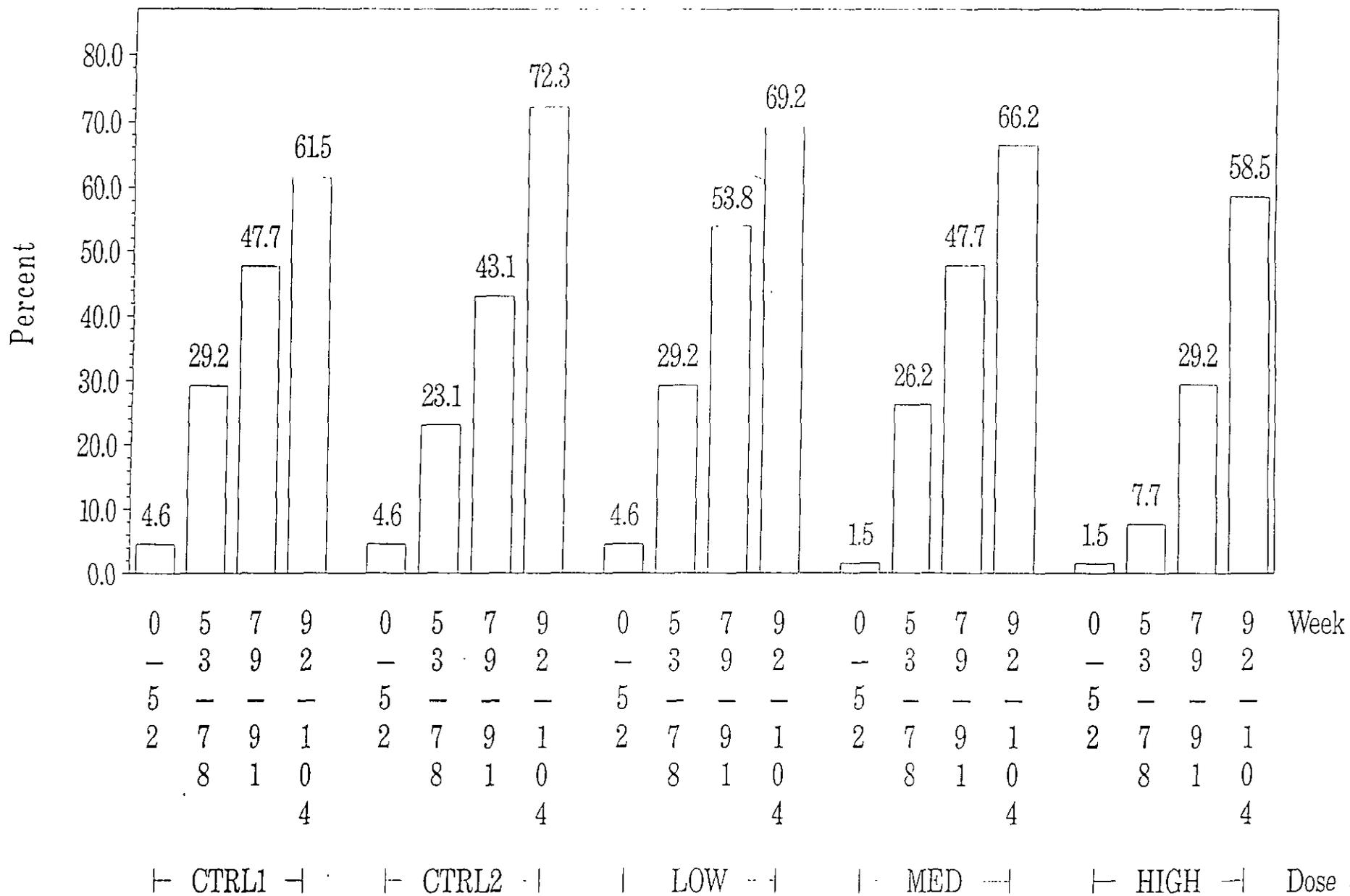


Figure 6 Kaplan-Meier Survival Function

Species: Rat

Sex: Female

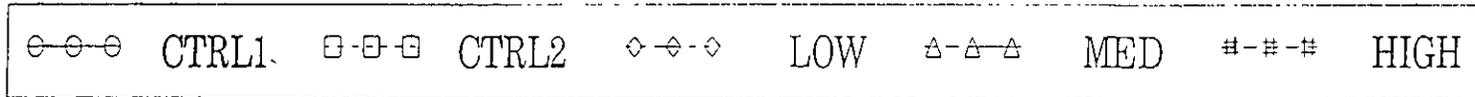
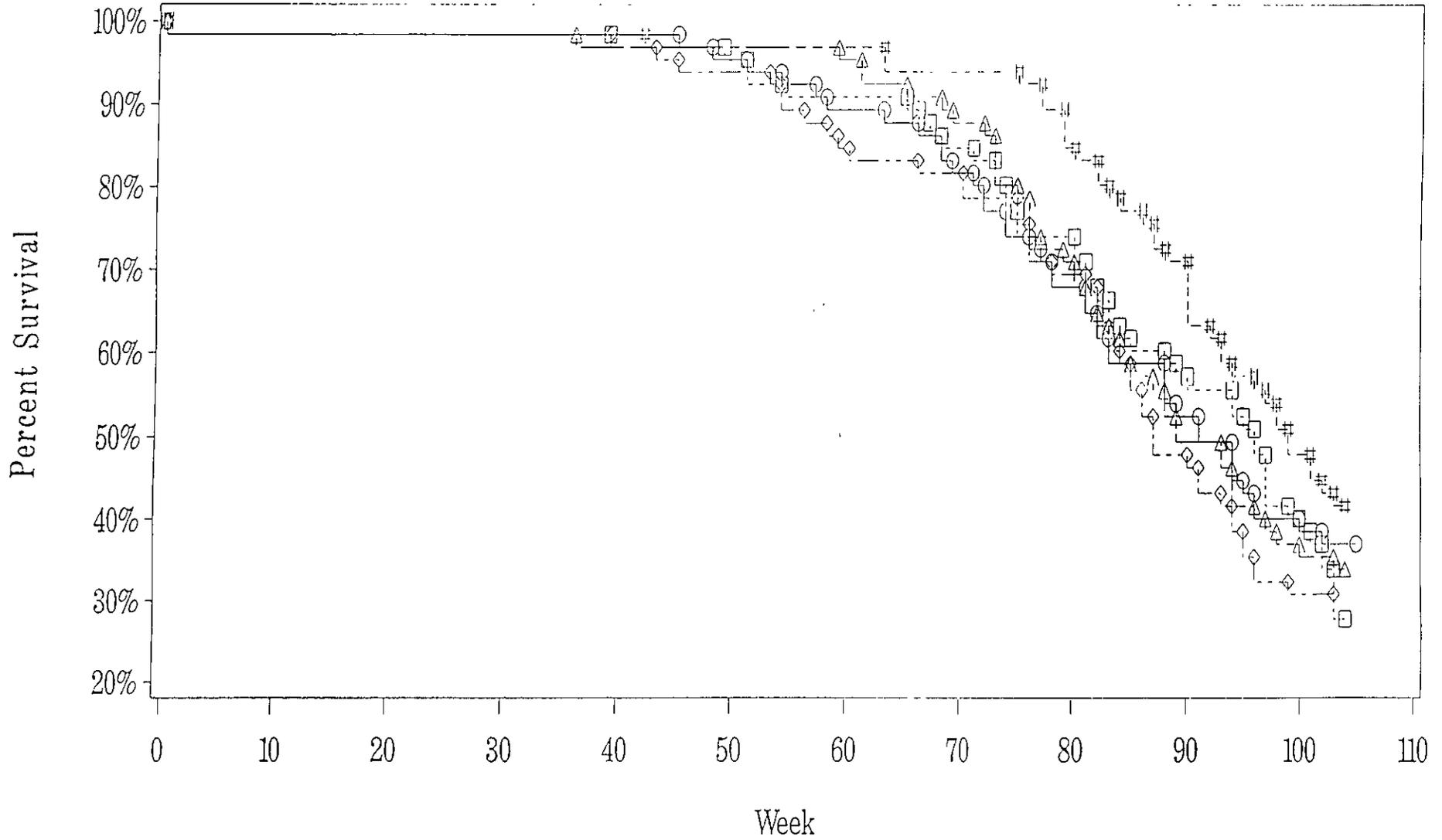


Table 7. NUMBER OF Animals
 Species: se
 Sex: Male

Time Interval	Treatment Group					Total Count
	CTRL1	CTRL2	LOW	MED	HIGH	
	Count	Count	Count	Count	Count	
0-52	4	5	4	.	2	15
53-78	7	8	2	4	4	25
79-91	2	1	3	4	1	11
92-104	9	10	9	8	14	50
105-106	28	26	32	34	29	149
Total	50	50	50	50	50	250

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: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.10	0.7496
	Depart from Trend	3.47	0.3246
	Homogeneity	3.57	0.4669
Kruskal-Wallis	Dose-Mortality Trend	0.31	0.5785
	Depart from Trend	3.64	0.3035
	Homogeneity	3.94	0.4135

Species: Mouse

Sex: e

11
12

Treatment Group

	CTRL1	CTRL2	LOW	MED	HIGH	Total
	Count	Count	Count	Count	Count	Count
Time Interval						
0-52	.	3	3	3	3	12
53-78	5	10	8	5	4	32
79-91	10	6	4	5	3	28
92-104	12	10	8	7	5	42
105-106	23	21	27	30	35	136
Total	50	50	50	50	50	250

Table 10: This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald Thomas, National Cancer Institute

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	6.43	0.0112
	Depart from Trend	2.45	0.4845
	Homogeneity	8.88	0.0642
Kruskal-Wallis	Dose-Mortality Trend	5.31	0.0212
	Depart from Trend	2.36	0.5011
	Homogeneity	7.67	0.1045

Species: mouse
Sex:
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
2	Adrenal	173	B-ADENOMA, SUBCAPSULAR CE	0.7350	0.7986	0.7991
2	Adrenal	311	B-CORTICAL ADENOMA	0.1227	0.1631	0.1635
2	Adrenal	523	B-PHEOCHROMOCYTOMA	1.0000	0.7531	0.7541
8	Colon	296	M-ADENOCARCINOMA	0.1946	0.0238	0.0240
9	Duodenum	315	B-ADENOMA	0.6820	0.7372	0.7378
10	Epididymis	219	B-INTERSTITIAL CELL ADENO	1.0000	0.7541	0.7552
10	Epididymis	629	M-HAEMANGIOSARCOMA	0.7272	0.6904	0.6921
12	Gall bladder	656	B-PAPILLOMA	1.0000	0.7548	0.7558
13	Harderian gland	238	B-ADENOMA	0.0348	0.0277	0.0278
14	Heart	244	B-HAEMANGIOMA	0.1946	0.0238	0.0240
14	Heart	256	B-MESOTHELIOMA, BENIGN	0.1946	0.0238	0.0240
17	Kidney	152	B-RENAL TUBULE ADENOMA	0.7205	0.7785	0.7791
17	Kidney	318	M-RENAL TUBULE CARCINOMA	1.0000	0.7531	0.7541
18	Liver	136	B-HEPATOCELLULAR ADENOMA	0.0017	0.0009	0.0009
18	Liver	269	M-HAEMANGIOSARCOMA	0.7773	0.7787	0.7790
18	Liver	167	M-HEPATOCELLULAR CARCINOM	0.3851	0.3997	0.3997
19	Lungs	108	B-BRONCHIOLAR-ALVEOLAR AD	0.4822	0.4914	0.4918
19	Lungs	143	M-BRONCHIOLAR-ALVEOLAR CA	0.8615	0.8604	0.8606
21	Lymphoreticular	25	M-GRANULOCYTIC LEUKAEMIA	1.0000	0.8828	0.8831
21	Lymphoreticular	355	M-HISTIOCYTIC SARCOMA	0.4314	0.5506	0.5518
21	Lymphoreticular	199	M-LYMPHOMA	0.6713	0.6843	0.6843
21	Lymphoreticular	242	M-MAST CELL TUMOUR	1.0000	0.7531	0.7541
29	Pituitary	310	B-ADENOMA, PARS DISTALIS	0.1959	0.0242	0.0244
29	Pituitary	395	B-ADENOMA, PARS INTERMEDI	1.0000	0.7525	0.7536
31	Salivary gland	638	M-FIBROUS HISTIOCYTOMA, M	0.6419	0.7104	0.7115
33	Skin and adnexa	337	M-FIBROUS HISTIOCYTOMA, M	0.7834	0.7883	0.7888
35	Spleen	260	M-HAEMANGIOSARCOMA	0.4273	0.2376	0.2383
36	Stomach	312	B-ADENOMA	0.5806	0.6900	0.6908
36	Stomach	655	M-ADENOCARCINOMA	0.6376	0.7092	0.7103
37	Testes	635	B-HAEMANGIOMA	0.6376	0.7092	0.7103
37	Testes	216	B-INTERSTITIAL CELL ADENO	0.8766	0.8724	0.8723
37	Testes	251	M-INTERSTITIAL CELL CARCI	0.3170	0.3159	0.3166

Species: se
Sex:
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
40	Thyroid	215	B-FOLLICULAR CELL ADENOMA	1.0000	0.8342	0.8347
40	Thyroid	382	M-FOLLICULAR CELL CARCINO	0.4228	0.5337	0.5350
42	Urinary bladder	353	M-LEIOMYOSARCOMA	0.5719	0.6835	0.6841

Species: Mouse
 Sex: Fr
 Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
1	Abdomen	433	M-SARCOMA, NOS	1.0000	0.7799	0.7809
2	Adrenal	523	B-PHEOCHROMOCYTOMA	0.9244	0.9189	0.9190
13	Harderian gland	238	B-ADENOMA	0.0510	0.0503	0.0504
18	Liver	136	B-HEPATOCELLULAR ADENOMA	0.3357	0.3160	0.3163
18	Liver	269	M-HAEMANGIOSARCOMA	1.0000	0.9083	0.9085
18	Liver	167	M-HEPATOCELLULAR CARCINOM	0.4780	0.5886	0.5899
19	Lungs	108	B-BRONCHIOLAR-ALVEOLAR AD	0.4276	0.4763	0.4769
19	Lungs	143	M-BRONCHIOLÄR-ALVEOLAR CA	0.9049	0.9018	0.9018
21	Lymphoreticular	25	M-GRANULOCYTIC LEUKAEMIA	0.4999	0.3729	0.3736
21	Lymphoreticular	355	M-HISTIOCYTIC SARCOMA	0.9644	0.9559	0.9559
21	Lymphoreticular	199	M-LYMPHOMA	0.9701	0.9648	0.9648
22	Mesenteric node	194	B-HAEMANGIOMA	0.3148	0.1739	0.1745
25	Ovaries	530	B-CYSTADENOMA	0.9460	0.8722	0.8727
25	Ovaries	444	B-SEX CORD/STROMAL TUMOUR	0.8193	0.8260	0.8261
25	Ovaries	403	M-FIBROUS HISTIOCYTOMA, M	1.0000	0.7525	0.7535
25	Ovaries	572	M-SEX CORD/STROMAL TUMOUR	0.1663	0.1387	0.1393
25	Ovaries	643	M-TUBULOSTROMAL CARCINOMA	0.6764	0.7422	0.7433
26	Pancreas	617	B-ISLET CELL ADENOMA	0.4762	0.6430	0.6445
29	Pituitary	310	B-ADENOMA, PARS DISTALIS	0.8381	0.8200	0.8203
29	Pituitary	395	B-ADENOMA, PARS INTERMEDI	0.7293	0.7601	0.7608
33	Skin and adnexa	585	B-HAIR FOLLICLE TUMOUR	0.4602	0.6574	0.6582
33	Skin and adnexa	537	B-SQUAMOUS CELL PAPILLOMA	1.0000	0.6808	0.6825
33	Skin and adnexa	565	M-ADENOCARCINOMA, MAMMARY	0.8024	0.8507	0.8509
33	Skin and adnexa	337	M-FIBROUS HISTIOCYTOMA, M	0.3927	0.3574	0.3578
33	Skin and adnexa	548	M-HAIR FOLLICLE TUMOUR, M	1.0000	0.7813	0.7821
33	Skin and adnexa	673	M-OSTEOSARCOMA	1.0000	0.7813	0.7821
35	Spleen	610	M-FIBROUS HISTIOCYTOMA, M	0.4762	0.6430	0.6445
35	Spleen	260	M-HAEMANGIOSARCOMA	1.0000	0.8081	0.8087
36	Stomach	312	B-ADENOMA	0.2574	0.0481	0.0484
36	Stomach	486	M-SQUAMOUS CELL CARCINOMA	0.4249	0.2423	0.2430
39	Thymus	398	B-THYMOMA, EPITHELIAL PRE	0.6742	0.7471	0.7482
40	Thyroid	215	B-FOLLICULAR CELL ADENOMA	0.2270	0.3007	0.3013

Source: A:\mou_tum.fil

Species: mouse
Sex: F ?
Sorted by: n Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
43	Uterus	429	B-ENDOMETRIAL STROMAL POL	0.9061	0.9024	0.9026
43	Uterus	534	B-GRANULAR CELL TUMOUR	0.7504	0.8066	0.8070
43	Uterus	619	B-HAEMANGIOMA	0.6764	0.7422	0.7433
43	Uterus	602	B-LEIOMYOMA	0.7110	0.6993	0.6998
43	Uterus	459	M-CARCINOMA	0.6010	0.6085	0.6087
43	Uterus	389	M-FIBROUS HISTIOCYTOMA, M	1.0000	0.6941	0.6955
43	Uterus	430	M-HAEMANGIOSARCOMA	0.1422	0.0544	0.0546
43	Uterus	436	M-LEIOMYOSARCOMA	0.9749	0.9660	0.9660
43	Uterus	669	M-OSTEOSARCOMA	1.0000	0.7574	0.7583
43	Uterus	427	M-STROMAL CELL SARCOMA	0.8464	0.8357	0.8359
44	Vagina	483	B-GRANULAR CELL TUMOUR	1.0000	0.7799	0.7809
44	Vagina	532	M-SQUAMOUS CELL CARCINOMA	1.0000	0.7471	0.7482

Figure 7

Mean Body Weight of Male Groups

Study Number: 94021

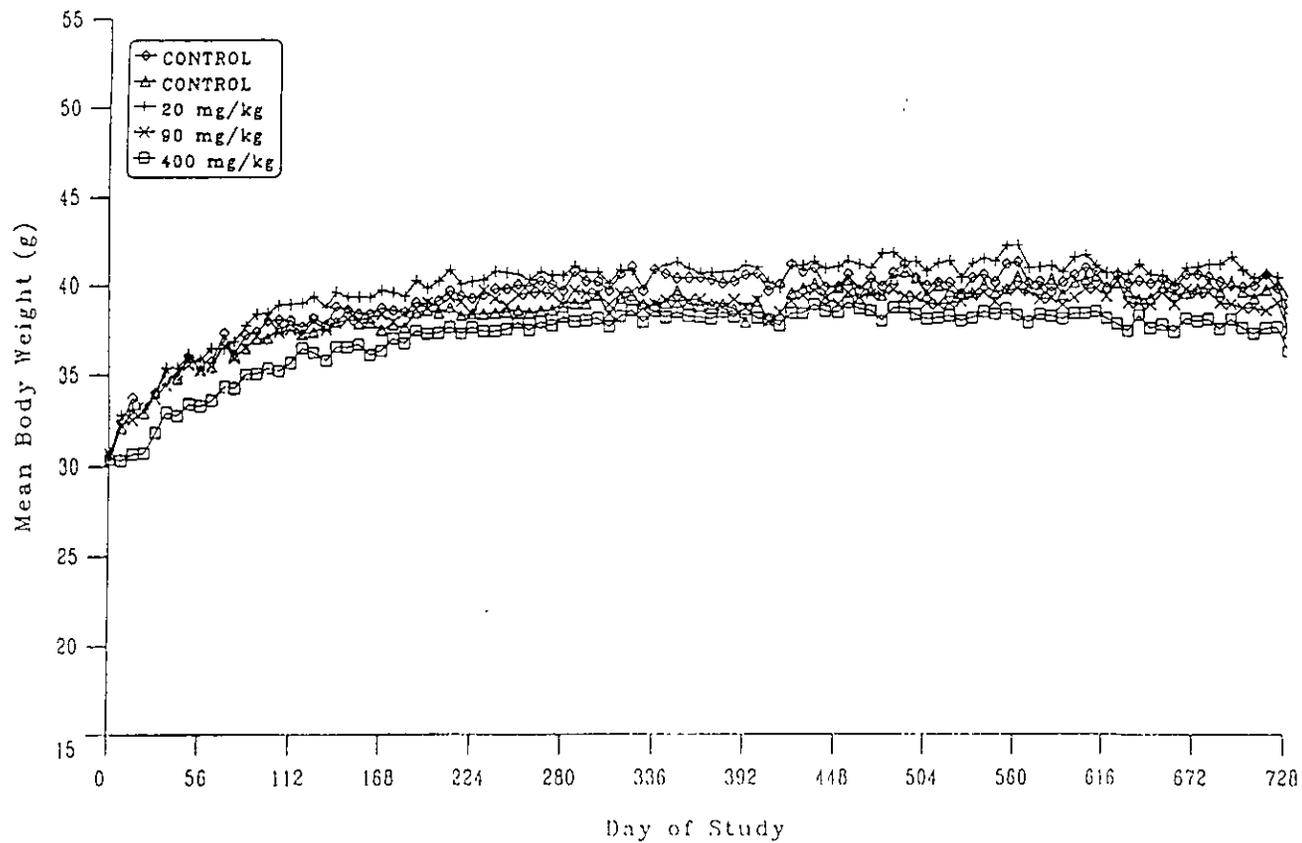


Figure 3 - Mean body weight of male groups

Figure 8
Mean Body Weight of Male Groups
Study Number: 94021

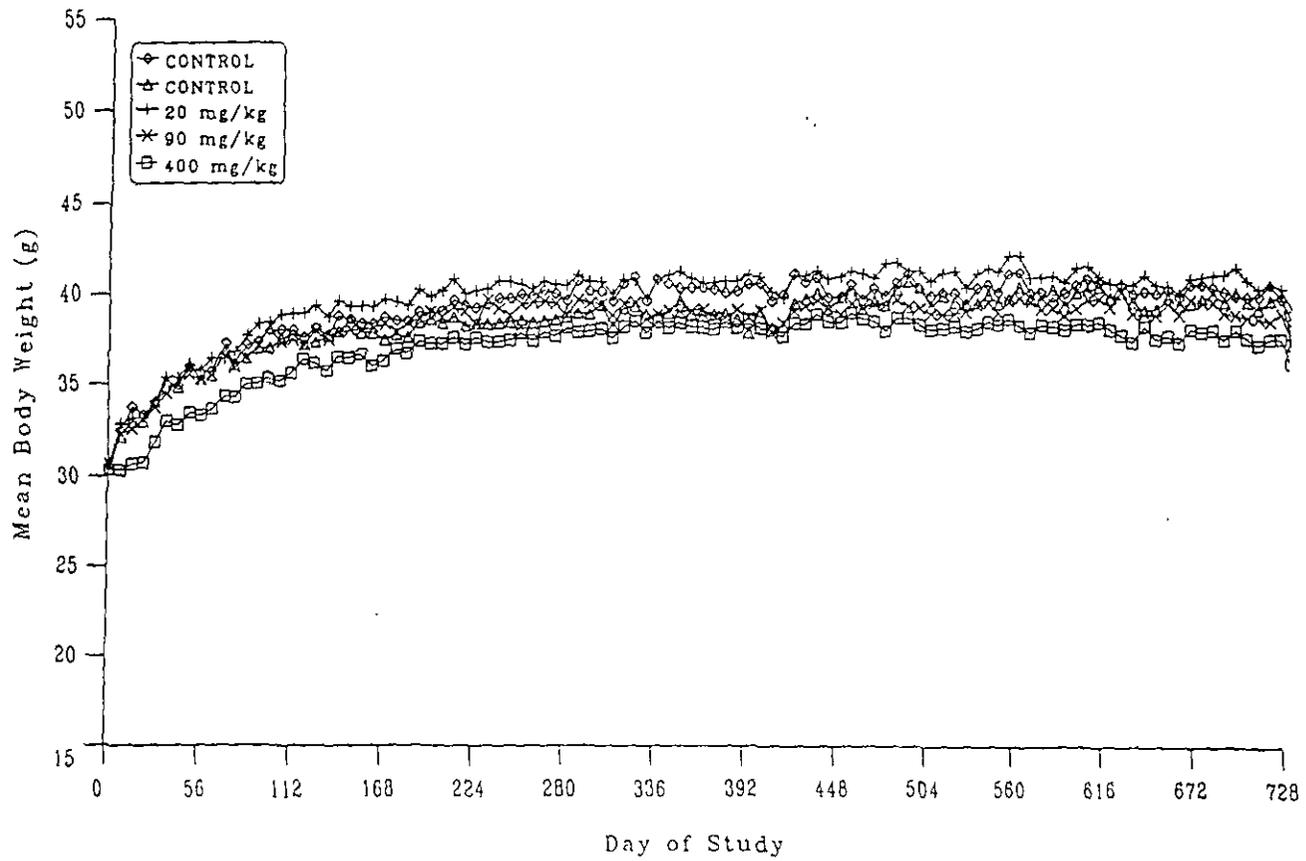


Figure 3 - Mean body weight of male groups

Figure 9. Cumulative Percentages of Death

Species: Mouse

Sex: Male

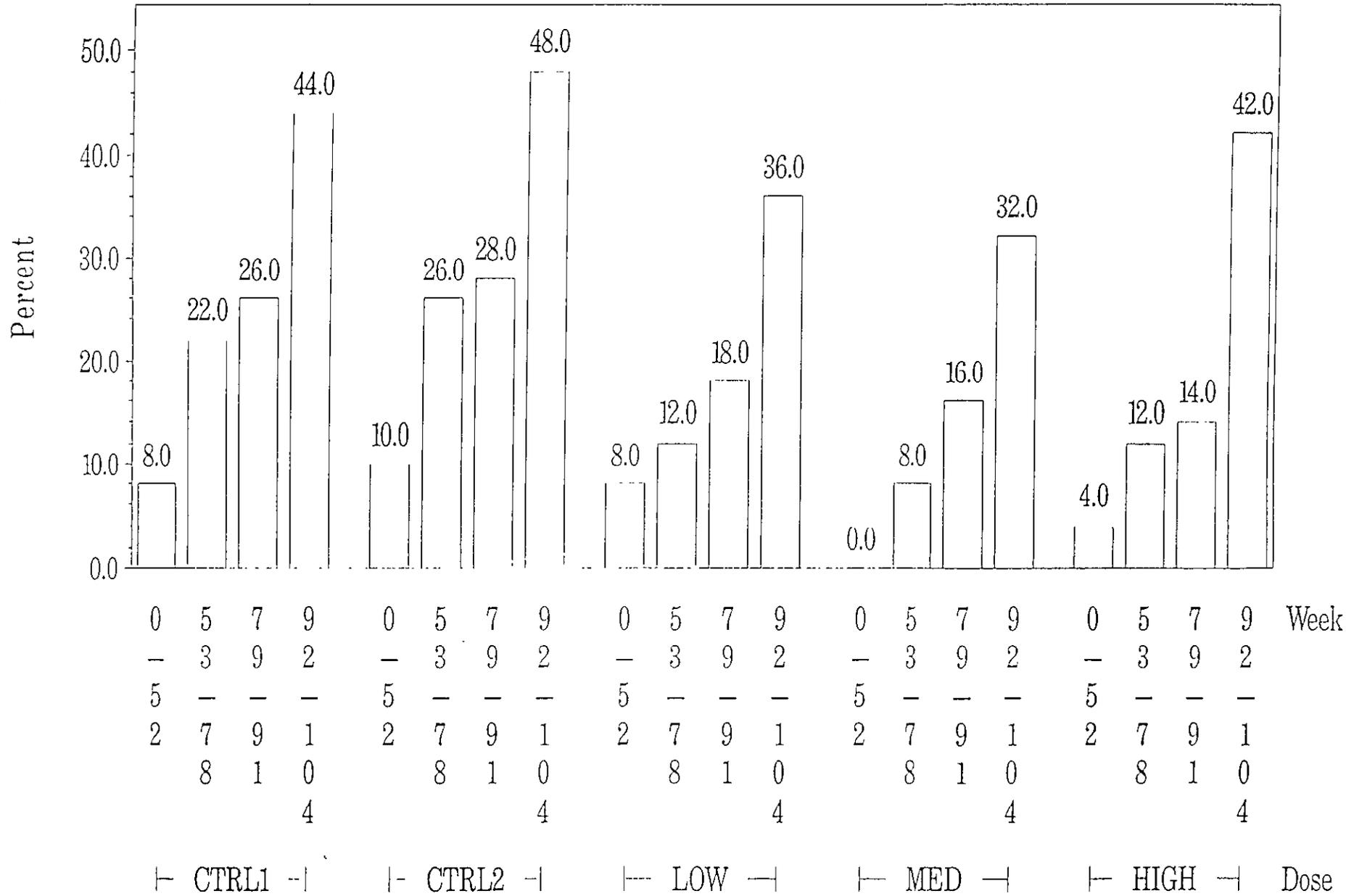


Figure 10. Kaplan-Meier Survival Function

Species: Mouse
Sex: Male

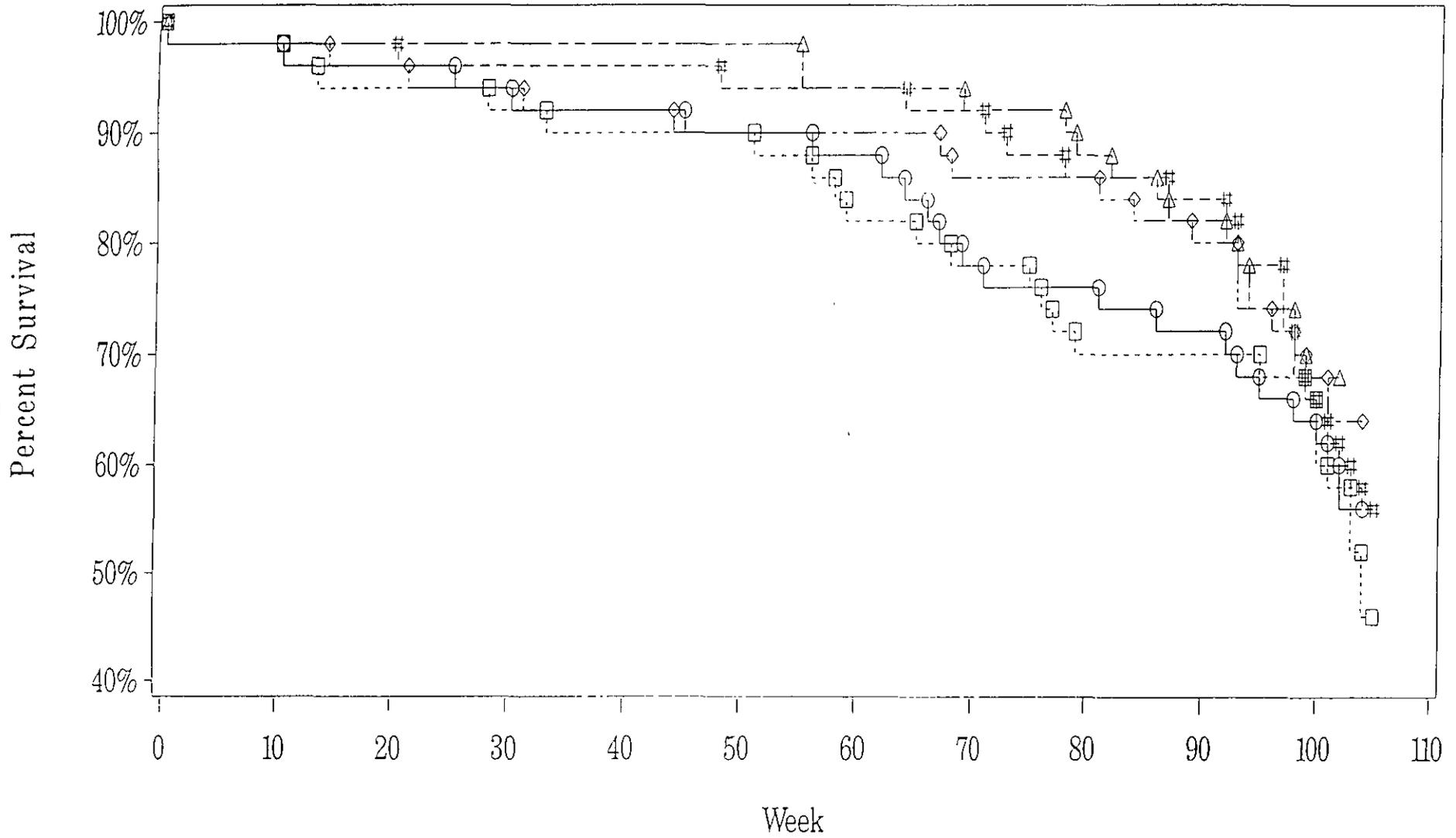
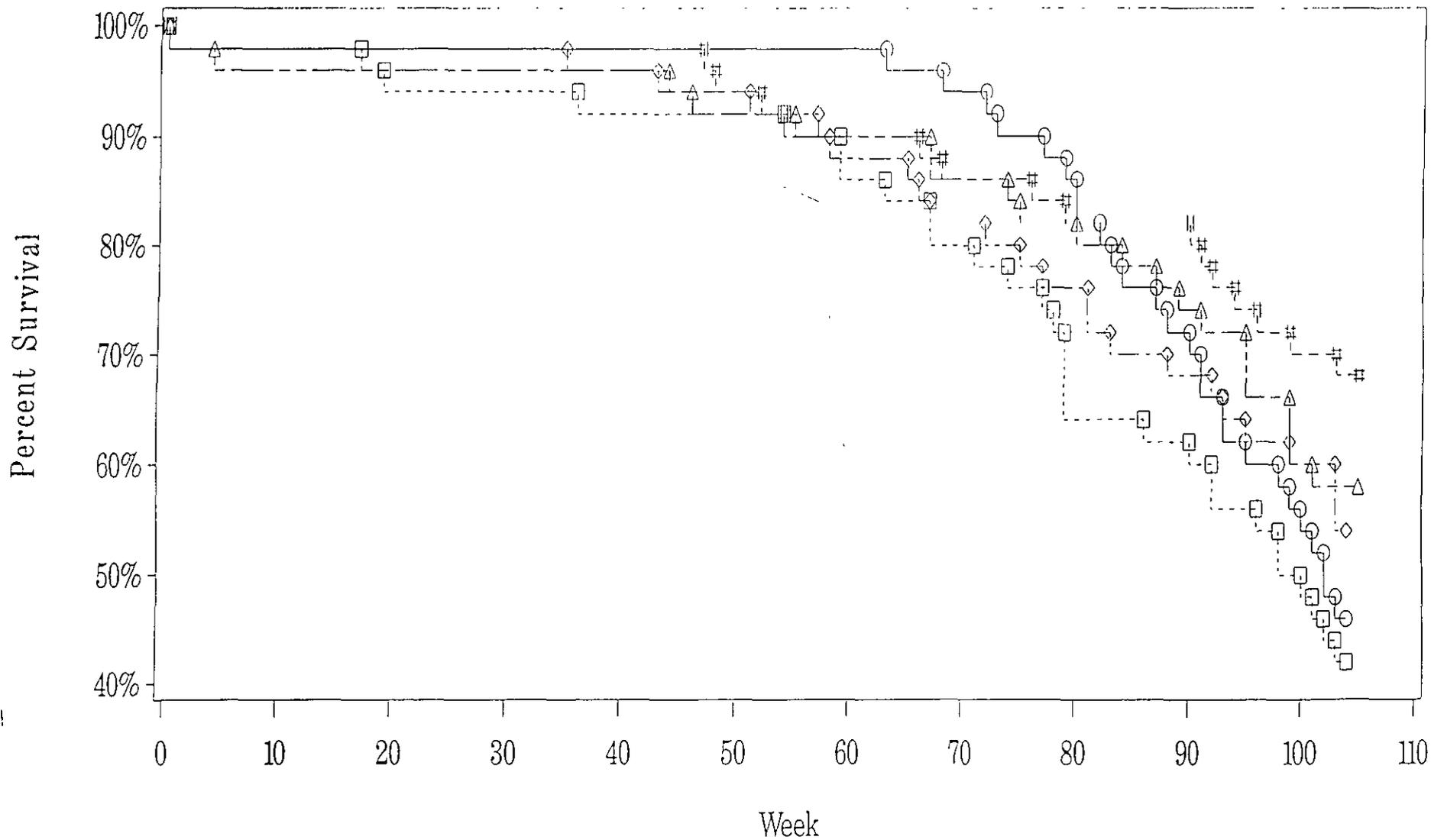


Figure 12: Kaplan-Meier Survival Function

Species: Mouse

Sex: Female



○-○-○ CTRL1 □-□-□ CTRL2 ◇-◇-◇ LOW △-△-△ MED #-#-# HIGH

Figure 11:

Cumulative Percentages of Death

Species: Mouse

Sex: Female

