CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-006

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Review for Carcinogenicity

NDA#:	21-006
APPLICANT:	Elan
NAME OF DRUG:	Frovatriptan (VHL 251)
DATE OF DOCUMENTS:	May 7, 2001
PHARMACOLOGY REVIEWER:	Aisar Atrakchi, Ph.D. (HFD-120)
STATISTICAL REVIEWER:	Yeh-Fong Chen, Ph.D. (HFD-710)

I. Introduction

The Approvable Letter as well as the Executive Carcinogenicity Assesment Committee (Exec CAC) meeting that addressed Frovatriptan on March 14, 2000, indicated that there was a deficiency in the carcinogenicity study in the mouse, so it was mutually agreed that the sponsor would complete an adequate study in p53(+/-) mice to supplement the data set and to complete the carcinogenic assessment.

Two separate 26-week bioassays of Frovatriptan have been conducted in the p53(+/-) mouse. The first study showed no effects of Frovatriptan on the development of any tumors. Due to an apparent misformulation of the positive control dose preparation, there was no thymic tumor response in the N-Methyl-N-nitrosourea (MNU) treated mice, and because of this, the Exec CAC considered the study to be invalid. Hence, a second study was conducted. The study was similar to the first, but included two positive control groups, MNU and p-cresidine, and was performed at a different location.

The purpose of this amendment was:

- To provide the final study report for the second "Twenty-six week gavage oncogenicity study with VML 251 in p53(+/-) C57BL/6 mice (Study No. 1165/238)."
- To provide an interpretation of the results of the study; and
- To demonstrate that this study, along with the previously submitted carcinogenicity and mutagenicity studies, provides an adequate assessment of potential for carcinogenic risk to patients.

Although the sponsor provides the previously submitted carcinogenicity and mutagenicity studies in this submission, this review will be focusing only on the evaluation of the sponsor's second 26 week study for p53(+/-) mice. In addition, due to the low mortality rate of this study, this review will be also focusing only on the evaluation of the tumor responses.

II. The Sponsor's Study Design and Results

Sponsor's Study Design:

The protocol for this study conducted at ———————— was based on the protocol for the first p53(+/-) study previously approved by the Exec CAC. Groups of 15 male and 15 female mice of confirmed genotype were dosed orally by gavage at 20, 62.5, 200 and 400 mg/kg/day with Frovatriptan for 26 weeks. Two additional groups of 15 males and 15 females were used as positive control groups and given either a single oral dose of 90 mg/kg MNU administered once only on Day 1 or 400 mg/kg p-cresidine administered orally daily for 26 weeks. An additional group of animals was given the aqueous vehicle (1% aqueous methyl cellulose) as a negative control.

All animals were identified by a subcutaneously implanted —— transponder and housed 3 to a cage. Observations for adverse effects of treatment on clinical health, morbidity or mortality were made daily. A detailed physical examination including palpation for tissue masses was conducted weekly. Any animal that died during the first two weeks of the study was replaced. During Week 1 additional three males and three females were added to the 400 mg/kg/day dose as a precaution to ensure adequate numbers of survivors in the high dose at the end of the study. Individual animal body weight and food consumption (per cage) were recorded weekly. Blood samples were taken from the main study animals on Day 11 and again terminally (3 animals/group/sex at 1, 2, 4, 8 or 24 h post dose) for toxicokinetic assessment. Additional blood samples were taken terminally at Week 26 for hematological analysis.

A necropsy examination was carried out on all animals that died during the study or were killed at the end of the 26-week dosing period. Sections of 42 tissues were examined microscopically from all animals in the vehicle control and 400 mg/kg/day Frovatriptan groups and from all decedents. In addition, gross lesions and tissue masses were examined for all animals. The thymus from all animals dosed with MNU and the bladder from all animals dosed with p-cresidine were examined. Following the observation of palpable subcutaneous masses associated with the transponder, a microscopic examination of the connective tissue adjacent to the final location of the transponder site was performed for all animals.

Sponsor's Results:

Overall, the sponsor stated that in Frovatriptan treated mice, the incidence of neoplasms, pre-neoplastic lesions and hyperplasia was similar to untreated control mice following histological evaluation of protocol designated tissues. However, two findings in the study were unusual and warranted some consideration.

First, transponder-related sarcomas were not detected in female control mice, but were present in the other treatment groups. The sponsor attributed this distribution to unexpected numerical imbalance across groups and noted historical control data providing incidences in females between 0% and 21%. Therefore, the incidence of transponder-related sarcoma in the female mice with the lower doses are considered equivalent to the historical control incidences, and those with the higher doses moderately, but not statistically significantly, increased.

Secondly, the microscopic evaluation of the transponder sites revealed the presence of pre-neoplastic lesions (mesenchymal dysplasia) in the subcutaneous connective tissue in all groups including the control group. The sponsor concluded that the process of sarcomagenesis had already commenced in a number of animals at the time that they were sacrificed.

The sponsor further found that Frovatriptan dosed at the MTD did not increase the incidence of neoplastic or pre-neoplastic lesions in any other tissue in p53(+/-) mice (detailed tables are not provided here).

Based on the sponsor's study reports, Table 1 shows the incidence of subcutaneous masses at the end of the study. Because of the apparent treatment-related effect on transponder-related lesions, all transponder implantation sites were then examined histologically. This resulted in a number of additional tumors being detected (see Table 2). The incidence of the pre-neoplastic findings at the transponder site are summarized in Table 3.

Table 1. Incidence of Transponder-Related Sarcoma-Like Masses Detected at Post-mortem in p53(+/-) (Study 1165/238)

	Control	Frovatriptan (mg/kg/day)				MNU 90mg/kg	p-Cresidine 400 mg/kg/day	Overall Incidence
		20	62.5	200	400			
Male	1	1	1	1	3	1	0	8/108 =7.4%
Female	0	3	1	6	6	1	0	17/108 =15.7%
Sexes Combined	1	4	2	7	9	2	0	25/216 =11.6%
No. Mice /sex/group (n)	15	15	15	15	18	15	15	

Table 2. Incidence of Transponder-related Sarcoma in p53(+/-) (Study 1165/238)

		Control	Frovatriptan (mg/kg/day) 20	62.5	200	400	MNU 90mg/kg	p-Cresidine 400 mg/kg/day	Overall Incidence[1]
Male		3	2	1	1	5	1	0	13/108 =12%
Female		0	4	3	6	6	1	0	20/108 =18.5%
Sexes Combined		3	6	4	7	11	2	0	33/216 =15.3%
p-values[2] by Cox	M	0.39	0.46	0.30	0.30	0.36			
	F	0.01	0.05	0.10	0.01	0.02			
p-values[3] by Gehan	M	0.36	0.29	0.16	0.16	0.38			
	F	0.01	0.02	0.03	0.005	0.01			
No. of Mice/sex /group (n)		15	15	15	15	18	15	15	

[1] The denominators of the overall incidences were corrected by this reviewer.

[2&3] The probability noted under 'Control' is the probability of trend (dose response) for the negative control group and the four treated groups. The probabilities noted under the other Frovatriptan groups are the probabilities of comparing the respective groups versus the negative control group.

Table 3. Transponder Site Mesenchymal Dysplasia Incidence and Grade Score

Grade Score	Sex	Control 0	Frovatriptan (mg/kg/day) 20	62.5	200	400	MNU 90mg/kg	p-Cresidine (400 mg/kg/day)
0	M/F	11/10	13/12	11/12	6/12	12/14	10/8	13/14
1	M/F	0/2	2/2	0/1	4/1	1 /2	4/0	1/0
2	M/F	0/1	0/0	1/0	2/0	1/0	0/0	0/0
3	M/F	1/0	0/0	2/1	1/1	1/1	0/0	0/0
4	M/F	0/1	0/0	0/0	1/0	0/0	0/0	0/0
5	M/F	0/1	0/0	0/0	0/0	0/0	0/0	0/0
Incidence	M/F	1/5	2/2	3/2	8/2	3/3	4/0	1/0
Σgrade scores	M/F	3/13	2/2	8/4	11/4	6/5	4/0	1/0
No. Mice Examined/ Sex/group		12/15	15/14	14/14	14/14	15/17	14/8	14/14

Grade Score Key: 0 = not present, 1 = minimal, 2 = slight, 3 = moderate, 4 = moderately severe, 5 = severe

The thymic and bladder tumor responses in the concurrent positive control groups (See Table 4) confirmed that the experiment was capable of detecting chemical carcinogens. There was an absence of increased incidence of transponder-related sarcoma in the positive control groups.

Table 4. Thymic and Bladder Tumor Responses in the Concurrent Positive Control Groups

Tumor Type	p-Cresidine	
	Male	Female
URINARY BLADDER		
-TRANSITIONAL CELL PAPILLOMA	1	1
-TRANSITIONAL CELL CARCINOMA	8	4
-SQUAMOUS CELL CARCINOMA	2	1
-SARCOMA	1	
-SQUAMOUS CELL PAPILLOMA		2
NUMBER OF ANIMALS EXAMINED	15	15
Tumor Type	MNU	
	Male	Female
HAEM/LYMPH/RETIC		
-MALIGNANT LYMPHOMA-LYMPHOBLASTIC	12	13
NUMBER OF ANIMALS EXAMINED	12	14

The Sponsor's Conclusion:

Exposure to VML 251 for 26 weeks did not increase the incidence of tumors, pre-neoplastic or proliferative lesions in any tissue, except for transponder-related subcutaneous sarcoma. In VML 251 treated female mice there was a statistically significant increase in the incidence of fibrosarcomas of the skin/subcutis, a tumour type associated with subcutaneously implanted identification transponders ($p=0.01$ in Table 2). The incidence of these tumors was not dose-related. However, in this study, there were no implant-associated sarcomas in the control females, contrary to expectation and contrary to published historical control data for p53 +/- mice implanted with transponders. The incidence of subcutaneous sarcomas in the positive control groups was also not increased.

The positive control substances employed in this study, MNU and p-cresidine, both produced the expected responses, with induction of thymic lymphoblastic lymphomas for MNU, and transitional cell carcinomas and squamous cell carcinomas of the urinary bladder for p-cresidine.

III. The Reviewer's Findings and Comments

1. According to the FDA's draft guidance for industry on chronic rodent carcinogenicity study, this reviewer performed exact permutation trend tests and Fisher's Exact tests for testing trend with dose and performing the pair-wise comparisons between the control group and treated groups. The tests were only performed for the transponder-related sarcoma data (shown in Table 2) and mesenchymal dysplasia data (shown in Table 3), but separately by gender. Other tumor findings were few and clearly did not show any Frovatriptan effect.

   Table 5 shows the one-sided p-values by the exact permutation trend test for the two findings of concern. Since the p-value for the skin+subcutis/transponder site sarcoma (rare tumor) shows 0.04 for female mice, which is significant at 0.05 level, it can be concluded that there is a statistical significant positive linear trend associated with this tumor. For the transponder related sarcoma among male mice or the transponder site mesenchymal dysplasia among either male or female mice, none of the p-values were less than the required alpha level for statistical significance. These results are consistent with the sponsor's findings.

   Table 6 shows the p-values for the pair-wise comparisons (by Fisher's Exact test). For the incidences of skin+subcutis transponder site sarcoma the p-values for female mice are less than 0.05 except for the comparison between the negative control group and the 62.5 mg/kg/day dose group. These findings are statistical significant because the incidence in the negative control groups was zero, a value that the sponsor considers unrepresentative. Comparing these p-values with the sponsor's shown in Table 2, similar but not identical results were obtained.

Table 5. Positive Trend Test Results for the Second 26 Week P53(+/-) Mouse Study

Tumor Type		One Sided p-value
Skin+Subcutis/Transponder Site Sarcoma	Male	0.15
	Female	0.04
Transponder Site Mesenchymal Dysplasia	Male	0.14
	Female	0.31

Table 6. Test Results of Pair-wise Comparisons Between the Control Group and the Treated Groups

Tumor Type		One Sided p-value			
		C vs 20	C vs 62.5	C vs 200	C vs 400
Skin+Subcutis/Transponder Site Sarcoma	Male	0.5	0.33	0.33	0.46
	Female	0.04	0.10	0.01	0.02
Transponder Site Mesenchymal Dysplasia	Male	0.59	0.36	0.02	0.39
	Female	0.22	0.22	0.22	0.27

In addition to the different statistical methods used, it was noticed that the sponsor performed the tests based on the total number of animals in the study. However, not all animals in the study were examined and, therefore, the appropriate denominators were 'numbers of animals examined'. The effect of different denominators is minor, but did contribute to the numeric differences in results between the sponsor and this reviewer.

2. For the incidence of transponder site mesenchymal dysplasia, there was one p-value less than 0.05, namely from the comparison of the negative control and the 200 mg/kg/day male mouse groups. As the observed incidence in the negative control group is greater than 1%, these findings are, however, not considered statistically significant (use α=0.01).

3. In the appendix, this reviewer explored the skin+subcutis sarcoma findings as given in the ——— report. The major conclusions of this study are not effected.

Summary

This appears to be a valid study as both positive control groups showed evidence of tumorigenicity.

A statistically significant linear trend was found for female mice for the skin+subcutis/transponder site sarcoma data.

The trend for the skin+subcutis sarcoma data among the female mice when not all mid dose groups of mice were examined appears to follow a quadratic function. This is confirmed by the statistically significant pair-wise comparisons.

Among the animals treated with Frovatriptan, pair-wise comparisons between the negative control and the treated female mice reached statistical significance in skin/subcutis/transponder sarcomas. This finding is disputed by the sponsor based on historical evidence observed among controls.

Testing the incidence of transponder site mesenchymal dysplasia did not show statistical significance at the 0.01 level in either gender.

Other tumor findings were few and did not approach statistical significance.

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This review consists of 8 pages and 2 pages of appendix. MS Word:

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Appendix: The Analysis for Skin+Subcutis Sarcoma Data when not all Mid-Dose Animals Were Examined.

In the contract lab's report ——— the same numbers of skin+subcutis sarcoma were reported, but only all control and high dose mice were examined. For the mid doses relatively few animals were examined (see Table 7) which greatly influences the incidence rates of these groups. This reviewer performed the exact permutation trend test and Fisher's Exact tests for pair-wise comparisons on these incidence rates.

Table 8 and 9 show the test results. When few of the mid dose female mice were examined, the p-value for linear trend was 0.21, which compares to 0.04 when almost all animals were examined (Table 5). Although the data lack the linear trend component, they exhibit a roughly quadratic trend (Figure 1). This finding is supported by the fact that the pair-wise comparisons reached statistical significance although the linear trend test did not show statistical significance.

Table 7. Incidence of Skin+Subcutis Sarcoma in p53(+/-) (Study 1165/238)

	Control	Frovatriptan (mg/kg/day)			
		20	62.5	200	400
Male	3	2	1	1	5
Female	0	4	3	6	6
No. of Mice Examined	M: 15 F: 15	3 5	1 6	2 6	18 18

Table 8. Positive Trend Test for Skin+Subcutis Sarcoma Data

Tumor Type		One Sided p-value
Skin+Subcutis Sarcoma	Male	0.46
	Female	0.21

Table 9. Fisher's Exact Test for Skin+Subcutis Sarcoma Data

Tumor Type		One Sided p-value			
		C vs 20	C vs 62.5	C vs 200	C vs 400
Skin+Subcutis Site Sarcoma	Male	0.17	0.25	0.43	0.46
	Female	≈ 0	0.02	≈ 0	0.02

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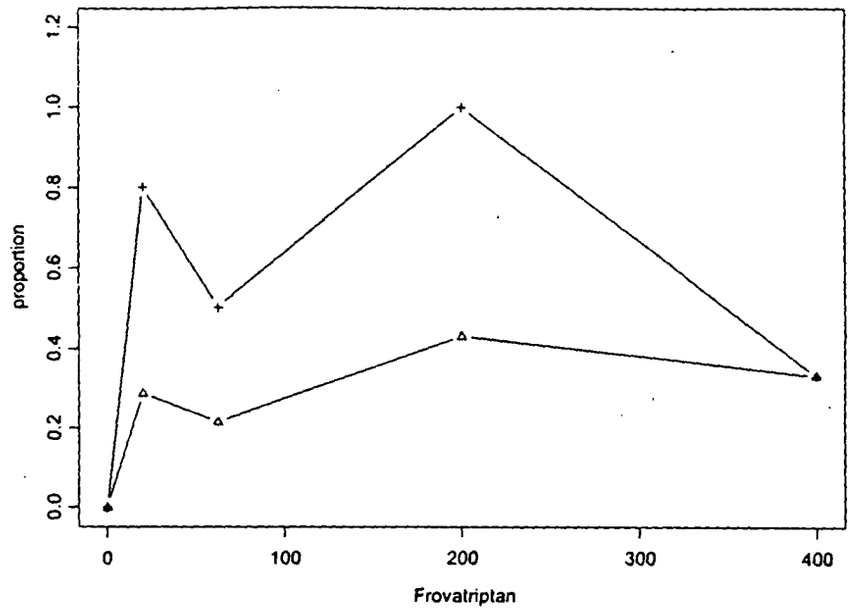
Figure 1. The graph for the proportions of tumor responses for the female mice based on different total numbers of animals.



Note: The line with + is based on the skin+subcutis sarcoma data when not all mid dose animals were examined and the line with Δ is based on the data when almost all mice in the study were examined.

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Executive CAC
October 2, 2001

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Frank Sistare, Ph.D., HFD-901, Member
Karen DavisBruno, Ph.D., HFD-510, Alternate Member
Barry Rosloff, Ph.D., HFD-120

Author of Draft: Aisar Atrakchi, Ph.D.

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

NDA # 21-006
Drug Name: Frovelan (Frovatriptan succinate)
Sponsor: Elan Pharmaceuticals
S. San Francisco, CA

Background:

Frovatriptan is proposed to treat acute migraine. The NDA was filed with the FDA on Jan 29th 1999. Additional preclinical studies were recommended, they were then conducted and completed final study reports were submitted as major amendment to the NDA on Jan 21st 2000. Approvable letter was issued to the sponsor on Apr 28th, 2000 with several CMC, clinical, and preclinical issues. The preclinical issues included the results for then, the ongoing p53, 26-week mouse carcinogenicity study. The study results were submitted to the Agency on Oct 3rd 2000 and the Executive CAC concluded that the study was invalid due to the failure of the positive control to produce the appropriate response (Exec CAC minutes Oct 31, 2000). Therefore, the carcinogenic risk assessment of frovatriptan was inadequate. The sponsor consequently initiated a 2nd p53 mouse, 26-week carcinogenicity study and withdrew the labeling text of the Complete Response on Feb 20th 2001.

P53 Mouse Carcinogenicity Study:

This 2nd p53 study was conducted using the same doses as those in the 1st study, 20, 62.5, 200, and 400mg/kg/d administered daily via oral gavage for 26wks to C57Bl/6TacfBR-[KO] N5 male and female mice. The study differed from the previous one by using ——— instead of Biomedic transponders implanted subcutaneously as identification devices. The study was done in ——————— instead of ——————— and therefore, mice were shipped from the ——————— and other differences included all technical aspects of different lab location (food, water, air, gavage syringe etc.). Note that ——— transponders have never been used previously in p53 mice, in traditional mice they have several fold higher incidence of skin sarcomas than Biomedics, especially in female mice. Results of this p53 showed 40&33% skin sarcoma incidence in 200&400mg/kg/d female groups compared to zero incidence in concurrent control. This incidence exceeded the negative control incidence in the previous p53 study of 4/7% using Biomedic transponders and the historical range of 5.5-21% of macroscopic sarcomas and 0-12% of microscopic sarcomas; all using Biomedic transponders (no historical data for ——— in p53 mice). These skin sarcomas were physically associated with the transponder sites.

Executive CAC Recommendations and Conclusions:

The Committee members agreed that this was a valid study and the results did not support a conclusion that frovatriptan is a genotoxic carcinogen. (Previous conventional rat and mouse bioassays indicated that frovatriptan was not an epigenetic carcinogen at acceptable margins of exposure.) The higher incidence of skin sarcomas in female mice administered the two highest doses compared to concurrent control and to data bases using Biomedic transponders may be related to an unknown drug effect. Frovatriptan may have potentiated the progression of non-neoplastic lesions (mesenchymal dysplasia), to malignant sarcomas via unidentified mechanism. In the positive control p-cresidine group there were no skin sarcomas (0/30 mice), and in the MNU treated group only 2/29 sarcomas were observed in both sexes. In absence of data bases for ——— transponders in p53 mice and the reported sensitivity of this strain of mice particularly females, to subcutaneous transponders in general, to make accurate and clear conclusions regarding the apparent increased incidence of skin sarcoma is difficult.

1) The study does not demonstrate genotoxic carcinogenic potential for frovatriptan.

2) Although the 2-year mouse assay was not considered a valid study given the genetox signal in the chromosome aberration assay and the dose selection criteria used, and the rat assay was considered to have been conducted at a marginal MTD, both studies achieved relatively high exposures and there was no evidence of enhanced carcinogenesis in these studies.

3) A repeat study is not necessary.

4) There was not agreement on the appropriateness of labeling regarding the potential effect on transponder site skin tumors.

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
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Statistical Evaluation & Review

NDA #	21-006
Sponsor	Vanguard Medica Limited
Drug	VML 251
Indication	Acute Migraine
Reviewer	Kallappa M. Koti
Medical officer	Armando Oliva, M.D.

Table of Contents

1. INTRODUCTION

Migraine is a chronic, recurrent headache disorder characterized by unilateral, pulsating headache that is usually localized in the temple or around or behind the eye, although any part of the head may be affected. It is a chronic paroxysmal disorder estimated to affect approximately 12% of the adult population. If typically affects patients for the major part of their lives, resulting in considerable socio-economic and personal expense. Although it has a varied symptomatology, migraine commonly presents as severe incapacitating unilateral headache lasting up to 72 hours, associated with nausea, vomiting, photo- and phonophobia. In about 10% of cases, the headache is associated with neurological symptoms known as aura, which is characterized by visual, sensory, speech, or motor dysfunction.

Many antimigraine drugs share the common characteristic of activity at 5HT receptors. Intravenous administration of 5HT itself can alleviate migraine attacks, though its use is limited by side effects. **Sumatriptan** (Imitrex ®) is an agonist at the $5HT_{1D}$ receptor subtype which *in vitro* causes both animal and human cerebral arterial vasoconstriction and also in animal models reduces the degree of neurogenic inflammation resulting from trigeminal nerve stimulation. Clinically, sumatriptan has proved to be effective in the acute treatment of migraine attacks with a response rate of about 80% for relief of the initial headache. However, sumatriptan has a short duration of action and recurrence of headache symptoms occurs within 24 hours in about 30% of patients. This high recurrence rate may be related to the fact that the plasma half life of sumatriptan is only 2 hours.

VML 251 (SB 209509) is a novel tetrahydrocarbazole derivative that has been characterized in vitro as a 5-hydroxytryptamine $(5HT)_{1D}$ agonist demonstrating five-fold greater affinity than sumatriptan in human $5HT_{1D}$ receptor binding assays. In human basilar and middle cerebral arterial preparations, VML 251 also demonstrated vasoconstrictive properties with an approximate 10-fold greater potency than sumatriptan. VML 251 is therefore a potent and specific $5HT_{1D}$ agonist with marked in vitro cerebral arterial vasoconstrictive properties.

A compound such as VML 251, which is both a more potent $5HT_{1D}$ agonist and which possesses a much longer terminal elimination half life than sumatriptan, may result in a superior efficacy profile in the acute treatment of a migraine attack.

The major efficacy studies discussed in this NDA are the 5 double-blind placebo-controlled short-term Phase 2 and Phase 3 studies, all of which included a fravatriptan 2.5 mg treatment group. The Phase 2 studies were 251/95/02 and 251/96/14 and the Phase 3 studies were 251/96/06, 251/96/07 and 251/96/09.

2. DESIGN, EFFICACY AND DEMOGRAPHICS

All five studies have identical definitions of efficacy and ITT population. They also have similar schedule of events. Male and female patients, 18 or over 18 years of age, with at least a 12-month history of migraine, with or without aura, according to HIS criteria and a frequency of between 1 and 8 moderate or severe attacks per month, over the previous 2 months and age at onset of migraine < 50 years were to be recruited. The studies consisted of 3 visits:

- Visit 1 (screening and enrollment)
- Visit 2 (within 5 working days of first treated attack)
- Visit 3 (termination within 5 working days of third treated attack or at Week 12)

The schedule of events is shown in Table 2.1 below.

Table 2.1: **Schedule of events**

	Day / Visit		
	Screening / Randomization (Visit 1)	Day of Dosing [1]	End-of-Study (Visit 2) [2]
Informed consent	X		
Medical history	X		
Physical examination	X		X
Vital signs	X		X
Height and weight	X		
ECG	X		X
Clinical laboratory tests [3]	X		X
Serum pregnancy test [4]	X		
Telephone contact with study site		X [5]	
Evaluation of headache severity [6]		X	
Evaluation of associated symptoms [6]		X	
Evaluation of functional impairment [6]		X	
Global evaluation of study medication			X
Review Patient Diary		X	X
Review concomitant medications		X	X
Adverse event monitoring	X [7]	X	X

1 At onset of moderate or severe migraine attack
2 Within 168 hours (5 working days) of the onset of the migraine attack
3 Hematology, serum chemistry, and urinalysis
4 For women of child-bearing potential
5 Within 72 hours after taking study medication
6 Evaluated prior to dosing and at 2, 4, 6, 12, and 24 hours postdose
7 The CRF stated that adverse events were to be collected from 24 hours prior to dosing until the end-of-study visit. See Section 3.5.2.1 of this report.

After dosing, at 2, 4, 6, 12, and 24 hours post-treatment, the patient was to record the following in the Patient Diary:

- Headache severity score
- Associated migraine symptoms
- Functional impairment score.

After dosing, for the period up to 24 hours post-treatment, the patient was also to record:

- Time to onset of meaningful relief
- Time of onset and severity of any recurrence of headache
- Consumption of rescue medication (time taken and type of medication)
- Nature, time of onset, and time to resolution of any unusual, untoward, or unexpected events.

In all these studies efficacy is based on headache severity. Headache severity is of 4 levels defined as follows.

Grade 0 = no headache
Grade 1 = mild headache
Grade 2 = moderate headache
Grade 3 = severe headache.

At the end of study the patient completed the following statement: Overall, I would rate the effectiveness of study medication in relieving my migraine symptoms as:

0 = Poor
1 = Fair
2 = Good
3 = Excellent.

RECURRENCE HEADACHE

A recurrence of headache was defined as the onset of a Grade 2 or Grade 3 headache (after reduction in severity to Grade 0 or Grade 1) within 24 hours of the initial administration of study medication.

EFFICACY ENDPOINTS

The primary efficacy endpoint was headache response at 2 hours after dosing (proportion of patients whose headache severity changed from severe or moderate [Grades 3 or 2, respectively] to mild or no headache [Grade 1 to 0, respectively] at 2 hours after dosing). Response at 4 hours after the first dose of study medication is a secondary efficacy parameter used in the 5 major studies.

ITT POPULATION

This was defined (by the sponsor) as all randomized patients, who received any study medication and who had any evaluable post-baseline efficacy data. Across the 5 major efficacy studies, the percentages of randomized patients who met the criteria for inclusion in the ITT population ranged from 80% to 92%. Within studies 251/96/06, 251/96/07 and 251/96/09, the percentages for each treatment group were similar.

The ITT-observed and ITT-worst case, are modifications of the ITT population. In the observed population, data for patients who were asleep or whose assessment was missing were excluded from the analysis. In these cases, such patients were to be excluded from the numerator and denominator when calculating the response and when comparing treatment groups. The ITT-worst case population is applied to analyses of response at 2 and 4 hours only. The ITT-worst case population is calculated as follows: If the 4 hour (nominal time) headache severity score is not *observed*, bring forward and substitute the *observed* 2 hour headache severity score, or set to worst case (non-response) if the 2 hour headache severity is not *observed*. If rescue medication is taken prior to or at the 4 hour assessment (actual time) then the 4 hour (nominal time) assessment is set to non-response. A per protocol (PP) population is the ITT population but excluding protocol violators and non-compliant patients.

Table 2.2 below presents the number of randomized patients, the number of patients excluded from the ITT population and the number of patients included in the ITT population, by study.

Table 2.2: **Short-term Efficacy- Population Membership**

	Study				
	251/96/06	251/96/07	251/96/09	251/95/02	251/96/14
Number of randomized patients	374	1274	1316	1013	695
Number who failed to treat a single attack	52 (14%)	126 (10%)	111 (8%)	114 (11%)	60 (9%)
Number who treated at least 1 attack, but had no post-baseline efficacy data	14 (4%)	37 (3%)	9 (<1%)	55 (5%)	37 (5%)
Number of patients in ITT population	308 (82%)	1111 (87%)	1196 (91%)	844 (83%)	598 (86%)

Percentages are based on the number of randomized patients.

A complete discussion of the major efficacy Phase 3 studies VML/96/06, VML/96/07, and VML/96/09 is presented below in sections 4-5. THE PROTOCOL DEFINED PRIMARY EFFICACY ENDPOINT IS THE PROPORTION OF PATIENTS WITH COMPLETE OR ALMOST COMPLETE RELIEF OF HEADACHE 2 HOURS AFTER TAKING THE STUDY MEDICATION. The proportion of patients with complete or almost complete relief of headache at 4 hours after study medication is a secondary endpoint. The binary response variable OBSRESP = 1 denotes the desired headache response. The response OBSRESP = 0 means the opposite. LOGISTIC REGRESSION IS THE PROTOCOL DEFINED PRIMARY METHOD OF ANALYSIS. For data analysis, placebo is set equal to 0 and VML 251 as 1.

The demographics of the ITT observed populations at 2 hours for Phase 3 studies are summarized in Table 2.3 below. As a very small percentage of patients are non-Caucasian, race-wise subgroup analysis is not done.

Table 2.3: **Demographics**

Study	Gender		Race		Age
251/96/06	Male	35 (12.2 %)	Caucasian	263 (92 %)	Mean = 41.8, SD = 9.1
	Female	251 (87.81%)	Black	12 (4.2 %)	Minimum = 18
			Other	11 (3.8 %)	Maximum = 65
251/96/07	Male	121 (11.9 %)	Caucasian	953 (93.4 %)	Mean = 41.6, SD = 10.
	Female	899 (88.1 %)	Black	38 (3.7 %)	Minimum = 18
			Other	29 (2.8 %)	Maximum = 69
251/96/09	Male	164 (14.8 %)	Caucasian	1069 (96.8%)	Mean = 40.6, SD = 10.4
	Female	941 (85.2 %)	Black	12 (1.1 %)	Minimum = 18
			Other	23 (2.1 %)	Maximum = 69

3. PHASE 2 STUDY VML/95/02

It was a Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-center, Single-Dose, Dose-Range-Finding Study to assess the efficacy and tolerability of VML in the Acute Treatment of Migraine. The purpose of this study were:

- to evaluate the safety of VML 251 when used in the acute treatment of migraine attacks
- to determine the dose-range characteristics of VML 251 (at doses of 2.5, 5, 10, 20, and 40 mg) when used in the acute treatment of migraine attacks.

It was typical of a dose-range-finding study. A total of 38 investigators enrolled patients at their sites. Patients with 1 to 6 migraine attacks/month during the past 1 year were included. A total of 899 were analyzed for safety and 844 for efficacy. Mantel-Haenszel and the extended Mantel-Haenszel statistics are used to analyze the data.

Overall, all doses of VML gave similar efficacy results. The proportion of patients responding to the VML 251 dose group was twice that of the placebo group. However, the 20-mg dose group had the earliest meaningful relief of all the VML 251 dose groups. No clinically significant changes in vital signs and physical findings were reported.

4. PHASE 3 STUDY VML/96/06

It was a Double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of a single dose of VML 251 (2.5mg) in the acute treatment of migraine. Study Objective was to compare the efficacy, safety and tolerability of a single oral dose of VML 251 with that of placebo in the acute treatment of up to three migraine attacks. The study included 16 centers and 42 males and 280 females aged between 18 and 65 years took study medication. Treatments were allocated according to a predetermined computer-generated randomization schedule, balanced in blocks of three, provided by [redacted] was to be in a 2:1 ratio of VML 251 to placebo.

The primary efficacy parameter, analyzed on the first attack, was the proportion of patients with complete (grade 0) or almost complete (grade 1) relief of headache 2 hours after taking study medication (headache response). The 16 individual study sites in the trial were pooled on a geographical basis into five new centers to allow the logistic regression model to be fitted.

4.1 Sponsor's efficacy results and conclusions:

The sponsor's efficacy results for the ITT observed and per protocol populations are presented in Table 4.1.1 below.

Table 4.1.1: **Attack 1- Response at 2 hours (ITT observed and Per protocol)**

	VML 251 n= 204	**Placebo** n = 104	p-value	**Odds ratio**
ITT observed	73/187 (39%)	21/99 (21%)	0.002	2.420
Per protocol	68/178 (38%)	21/96 (22%)	0.006	2.256

The following are the sponsor's conclusions.
Headache response with 2.5mg VML was significantly superior to placebo at 2, 4, 6 and 12 hours post dosing ($p<.002$). There was an approximate two-fold difference in headache response rate versus placebo at 2 and 4 hours post-dose (39% versus 21% and 56% versus 31%). The 2.5 mg dose of VML 251 was well tolerated for the acute treatment of up to three migraine attacks. The overall incidence of adverse events was only marginally higher than placebo and the adverse event profile was similar to placebo.

4.2 **Reviewer's analyses and comments**:

Baseline comparison: The ITT observed data do not indicate a significant association between treatment and baseline headache Severity. It is also noted that there is no association between treatment and baseline functional impairment severity. The treatment groups are comparable.

Protocol defined primary efficacy
The logistic regression model

$$\text{Logit}(p) = \alpha + \beta_1 \text{CENTER} + \beta_2 \text{BASEHEAD} + \beta_3 \text{TRT},$$

where p is the probability of response is the protocol specified analytic method. The parameter estimate for Treatment-Group is 0.8802 (p-value = 0.0023). The odds ratio is 2.411. The c-statistic is 0.628. The Hosmer and Lemeshow Goodness-of-Fit Test is not significant (p-value = 0.1494). That is, the model is not inadequate and the odds of responding to the test drug increased to 2.4-fold that of placebo. The model based estimates of proportions of responders for the two treatment groups are as follows.

Table 4.2.1: **Model base estimates of proportions of response**

	Baseline Severity = 2		Baseline Severity = 3	
Pooled center	Placebo	VML 251	Placebo	VML 251
1	0.2183	0.4024	0.1597	0.3143
2	0.2226	0.4085	0.1631	0.3197
3	0.2270	0.4146	0.1666	0.3252
4	0.2315	0.4207	0.1701	0.3308
5	0.2360	0.4269	0.1737	0.3364

The chi-square test for the ITT observed data of Study 06 show a significant difference between the proportions of observed response at 2 hours after the first attack under VML 251 and placebo (p-value = 0.002). Estimates of these proportions for VML 251 and placebo are 0.39 and 0.21, respectively.
Center-wise empirical comparison of treatment-groups in terms of percentage of responders at 2 hours is provided in Table 4.2.2 below.

Table 4.2.2: **ITT Observed Data**
Observed Percentages of Responders (Number)

Pooled Center	Total Number	Placebo	VML 251
1	10	33.33 (3)	28.57 (7)
2	101	24.32 (37)	40.63 (64)
3	61	24.32 (20)	40.63 (41)
4	83	13.79 (29)	46.30 (54)
5	31	20.00(10)	47.62(21)

Gender-wise comparison of treatment-groups in terms of percentage of responders at 2 hours is shown in Table 4.2.3 below.

Table 4.2.3: **Observed Percentages of Responders (Number)**

Sex	Percentage of responders Placebo	VML 251	Sample size	Chi-square p-value
Female	20.93 (86)	39.39 (165)	251	0.003
Male	23.08 (13)	36.36 (22)	35	0.413
# of subjects	99	187	286	

Protocol defined Secondary efficacy (Study 06 continued)
Headache response rate at 4 hours post-dose:

The logistic regression model (that includes pooled-center, baseline severity and treatment) analysis of ITT data at 4 hours yields an odds ratio for treatment-group of 3.056 (p-value = 0.0002). That is, the odds of responding to VML 251 increased to 3-fold that of placebo.

The ITT observed data of Study 06 show a significant difference between VML 251 and placebo with respect to the proportion of patients experiencing observed response at 4 hours post-dose (p-value = 0.001). Estimates of these proportions for VML 251 and placebo are 0.56 and 0.31, respectively.

5. PHASE 3 STUDY VML/96/07

It was a double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of up to two doses of VML 251 in the acute treatment of migraine. Study objective was to compare the efficacy, safety and tolerability of 2.5 mg VML 251 with that of placebo in the acute treatment of up to three migraine attacks. Also, to assess the migraine recurrence rate following a first dose of VML 251. There were 48 centers that recruited patients and 131 males and 1017 females aged between 18 and 69 years took study medication.

5.1 Sponsor's efficacy results and conclusions

The sponsor's efficacy results for the ITT observed and per protocol populations are presented in Table 5.1.1 below.

Table 5.1.1: **Attack 1- Response at 2 hours (ITT observed and Per protocol)**

	VML 251 n= 733	**Placebo** n = 378	p-value	**Odds ratio**
ITT observed	308/672 (46%)	92/347 (27%)	<0.002	2.527
Per Protocol	300/638 (47%)	87/322 (27%)	<0.006	2.379

For the first primary efficacy parameter there was a statistically significant difference between VML 251 and placebo: The 2 hour response was 46% for the VML group and 27% for the

placebo group ($p<0.001$). There was also a statistically significant difference between VML 251 and placebo for response at 4, 6 and 12 hours post-dose.

Sponsor's Conclusions are as follows.
Treatment with VML also resulted in significantly more patients achieving complete relief at 2, 4 and 6 hours than treatment with placebo. The proportion of responses within 6 hours post-dose was consistent for each of the three attacks (ranging from 73% to 76% in the VML 251 group and from 53% to 60% in the placebo group). The majority of patients (72%) in the VML 251 group recorded that the treatment was fair, good or excellent compared to 44% in the placebo group. Twice as many placebo patients noted the treatment as poor (56%) compared to the VML 251 group (28%).

5.2 Reviewer's analyses and comments

Baseline comparison: The ITT observed data do not indicate a significant association between treatment and baseline headache severity. It is also noted that there is no association between treatment and baseline functional impairment severity. The treatment groups were comparable.

Protocol defined primary efficacy
The logistic regression model

$$\text{Logit}(p) = \alpha + \beta_1 \text{CENTER} + \beta_2 \text{BASEHEAD} + \beta_3 \text{TRT},$$

where p is the probability of response is the protocol specified analytic method. The parameter estimate for Treatment-Group is 0.9219 (p-value = 0.0001). The odds ratio is 2.514. The c-statistic is 0.646. The Hosmer and Lemeshow Goodness-of-Fit Test is not significant (p-value = 0.9532). That is, the model is not inadequate and the odds of responding to the test drug increased to 2.5-fold that of placebo. The model based estimates of proportions of responders for the two treatment groups are as follows.

Table 5.2.1: **Model base estimates of proportions of response**

	Baseline Severity = 2		Baseline Severity = 3	
Pooled center	Placebo	VML 251	Placebo	VML 251
1	0.3091	0.5293	0.1444	0.2978
2	0.3064	0.5262	0.1428	0.2952
3	0.3036	0.5230	0.1412	0.2925
4	0.3009	0.5200	0.1397	0.2899
5	0.2983	0.5166	0.1382	0.2873

The chi-square test for the ITT observed data of Study 07 show a significant difference between the proportions of observed response at 2 hours after the first attack under VML 251 and placebo (p-value = 0.001). Estimates of these proportions for VML 251 and placebo are 0.467 and 0.265, respectively.

Center-wise empirical comparison of treatment-groups in terms of percentage of responders is provided in Table 5.2.2 below.

Table 5.2.2: **ITT Observed Data**
Observed Percentages of Responders (Number)

Pooled Center	Total Number	Placebo	VML 251
1	248	23.46 (81)	47.31 (167)
2	253	24.18 (91)	48.77 (162)
3	118	27.50 (40)	42.31 (78)
4	198	29.41 (68)	44.62 (130)
5	203	29.85 (67)	43.38 (136)

Gender-wise comparison of treatment-groups in terms of percentage of responders at 2 hours is shown in Table 5.2.3 below.

Table 5.2.3: **Observed Percentages of Responders (Number)**

Sex	Percentage of responders Placebo	VML 251	Sample size	Chi-square p-value
Female	26.33 (300)	47.25 (599)	899	0.001
Male	27.66 (47)	33.78 (74)	121	0.479
# of subjects	347	673	1020	

Protocol defined Secondary efficacy (Study 07 continued)
Headache response rate at 4 hours post-dose

The logistic regression model (that includes pooled-center, baseline severity, and treatment) analysis of ITT data at 4 hours yields an odds ratio for treatment is 3.138 (p-value = 0.0001). That is, the odds of responding to VML 251 increased to 3.1-fold that of placebo.
The ITT observed data of Study 07 show a significant difference between VML 251 and placebo with respect to the proportion of patients experiencing the headache response at 4 hours post-dose (p-value = 0.001). Estimates of these proportions for VML 251 and placebo are 0.646 and 0.377, respectively.

6. PHASE 3 STUDY VML/96/09

It was a double-blind, placebo-controlled, parallel-group comparison of the efficacy and safety of VML 251 (2.5 mg) with that of sumatriptan (100 mg) in the acute treatment of one migraine attack; followed by open-label treatment with VML 251 for up to two further attacks. Objective was to compare the efficacy of a single dose of VML 251 with that of sumatriptan in the acute treatment of migraine – for the first attack. Also, to assess the recurrence rate following the first dose of VML 251, or sumatriptan. To describe the safety and tolerability of 2.5 mg VML and 100 mg sumatriptan for the first attack and to collect information on the efficacy, safety and tolerability of VML 251 for the second and third attacks. There were 127 study centers in 14 countries. Medication was administered to 174 males and 1032 females aged 18 to 69 years.

6.1 Sponsor's efficacy results and conclusions

The sponsor's efficacy results for the ITT observed and per protocol populations are presented in Table 6.1.1 below.

Table 6.1.1: **Headache response at 2 hours (ITT observed and per protocol)**

Attack 1 Treatment	VML 251 n=475	Sumatriptan n= 479	Placebo n = 242	VML 251 vs Sumatriptan {odds ratio}	VML 251 vs. Placebo {odds ratio}
ITT observed	160/438 (37%)	206/441 (47%)	51/225 (23%)	p < 0.001 { 0.622 }	p < 0.001 {3.074}
Per protocol	156/420 (37%)	206/435 (47%)	49/211 (23%)	p = 0.001 { 0.626 }	Not tested
Odds ratio > 1 shows superiority of VML 251					

Sponsor's conclusions are as follows.
Response rates at 2 hours and 4 hours were higher for sumatriptan than for VML 251 (47% versus 37%, respectively at 2 hours and 70% versus 62%, respectively at 4 hours). VML 251 was statistically significantly superior to placebo for response rates at 2 and 4 hours post-dose. VML 251 had higher response rates than placebo at 6, 12, and 24 hours but these timepoints were not statistically analyzed.

6.2 Reviewer's analyses and comments

Baseline comparison: The ITT observed data do not indicate a significant association between treatment and baseline headache severity. It is also noted that there is no association between treatment and baseline functional impairment severity. The treatment groups were comparable.

We present here the results of the analyses of the subset of data that excludes sumatriptan. The results of the logistic regression model $\text{Logit}(p) = \alpha + \beta_1 \text{BASEHEAD} + \beta_2 \text{TRT}$ are as follows. The odd ratio for treatment is 2.029 (p-value = 0.0002). That is odds of responding to VML 251 is 2-fold that of placebo. The model based estimates of probabilities of response are as follws.

Table 6.2.1: Model based proportions of response

Treatment	Baseline Severity=2	Baseline Severity =3
Placebo	0.2613	0.1472
VML 251	0.4178	0.2593

The chi-square test also indicates that the proportion of responders under VML 251 is higher than that of placebo (p-value = 0.001). The estimates of the proportions of response under VML 251 and placebo are 0.36 and 0.22, respectively.

Table 6.2.2 shows the observed proportions of observed response for the three treatment-groups by center. The numbers in parentheses are the numbers of patients assigned to the treatments.

Table 6.2.2: **Center by treatment Observed Response Rates at 2 hours**

Pooled-Center	Placebo	VML 251, 2.5mg	Sumatriptan	Total
1	27.27 (22)	35.56 (45)	57.45 (47)	114
2	10.00 (20)	29.27 (41)	39.39 (33)	94
3	21.05 (19)	38.89 (36)	50.0 (34)	89
4	31.58 (19)	37.14 (35)	55.56 (36)	90
5	20.83 (24)	48.0 (50)	46.81 (47)	121
6	15.38 (13)	46.15 (26)	61.54 (26)	65
7	25.71 (35)	44.44 (63)	36.36 (66)	164
8	13.33 (15)	28.57 (35)	55.56 (36)	86
9	44.44 (18)	28.57 (35)	51.52 (33)	86
10	11.11 (27)	26.92 (52)	41.07 (56)	135
11	23.08 (13)	30.43 (23)	28.00 (25)	61
Total	225	441	439	1105

The following by-gender subgroup analysis excludes the subjects under the sumatriptan treatment group. This subset includes 564 females and 102 males. Table 6.2.3 contains the percentages of responders for VML 251 and placebo under the two subgroups- females and males.

Table 6.2.3: **Observed Percentages of Responders (Number)**

Sex	Percentage of responders		Sample size	Chi-square p-value
	Placebo	VML 251		
Female	21.05 (190)	35.83 (374)	564	0.001
Male	28.57 (35)	38.81 (67)	102	0.304
# of subjects	225	441	666	

Protocol defined secondary efficacy (Study 09)
Headache response rate at 4 hours post-dose

The logistic regression model (that includes baseline severity, and treatment) analysis of ITT data at 4 hours yields an odds ratio for treatment is 3.642 (p-value = 0.0001). That is, the odds of responding to VML 251 increased to 3.6-fold that of placebo.
The ITT observed data of Study 09 show a significant difference between VML 251 and placebo with respect to the proportion of patients experiencing the headache response at 4 hours post-dose (p-value = 0.001). Estimates of these proportions for VML 251 and placebo are 0.63 and 0.32, respectively.

7. PHASE 2 STUDY VML/96/14

It was a Randomized, Double-Blind, Placebo-Controlled, Parallel-group, Multi-center, Dose-Range-Finding Study to assess the efficacy, tolerability and safety of VML 251 (administered as a single dose of 0.5 mg, 1.0 mg, 2.5 mg, or 5.0 mg) in the acute treatment of migraine. Objectives were (i) to further determine the dose-range characteristics of VML 251, and (ii) to evaluate the safety and tolerability of VML 251 when used in the acute treatment of migraine attacks. Each patient was randomized to one of five treatment groups, receiving either a single oral placebo or VML 251 to treat a single migraine attack. When the patient became aware of a

moderate or severe migraine headache, the patient noted the time of onset in a patient diary and scored, on a four-point categorical scale, headache severity and functional impairment. The patient also noted the presence or absence of the associated symptoms: nausea, vomiting, photo- and phonophobia. After recording this information, the patient took the assigned dose of study medication. At 2, 4, 6, 12 and 24 hours after dosing, the patient recorded headache severity, functional impairment scores, and associated migraine symptoms. During the period up to 24 hours after dosing, the patient recorded the time at which meaningful relief was experienced, the time of onset and severity of any recurrence of headache, the consumption of rescue medication, and the occurrence of any adverse events. A total of 635 (542 females and 93 males) were analyzed for safety and 598 (508 females and 90 males) for efficacy.

Overall, VML 251 was most effective at doses of 2.5 and 5.0 mg, specially in eliciting complete migraine headache relief. For the majority of statistically analyzed response measures, the 2.5 and 5.0 mg dose groups were significantly superior to placebo in producing effective headache relief.

8. REVIEWER'S OVERALL CONCLUSIONS

The sponsor's overall conclusions are:

" In the ITT observed populations for the 3 major Phase 3 efficacy studies, there was statistically significant difference between the frovatriptan 2.5 mg and placebo treatment groups with respect to response at 2 hours: 251/96/06 $p = 0.001$, 251/96/07 $p < 0.001$, 251/96/09 $p < 0.001$ (logistic regression models with terms for pooled center, initial headache severity and treatment)."

These conclusions are consistent with the reviewer's overall conclusions stated below.

The ITT data at 2 hours post-dose after the first attack of Study 06 provided sufficient evidence in support of the sponsor's claim that VML 251 is efficacious compared to placebo. The odds of responding to VML 251 increased to 2.4-fold that of placebo. The proportion of VML 251 patients whose headache severity changed from severe or moderate to mild or no headache at 2 hours post-dose is significantly higher than that of placebo (39% vs. 21%).

The ITT data at 2 hours post-dose after the first attack of Study 07 provided sufficient evidence in support of the sponsor's claim that VML 251 is efficacious compared to placebo. The odds of responding to VML 251 increased to 2.3-fold that of placebo. The proportion of VML 251 patients whose headache severity changed from severe or moderate to mild or no headache at 2 hours post-dose is significantly higher than that of placebo (47% vs. 27%).

The ITT data at 4 hours post-dose of Study 06 and Study 07 also support the superiority of VML 251 over placebo. The proportions of response at 4 hours (in both treatment groups) are numerically better than the proportions of response at 2 hours post-dose.

The subset of ITT data (excluding sumatriptam) at 2 hours post-dose after the first attack of Study 09 provided sufficient evidence in support of the sponsor's claim that VML 251 is efficacious compared to placebo. The odds of responding to VML 251 is 2-fold that of placebo. The proportions of response under VML 251 and placebo are 0.63 and 0.32, respectively.

The ITT data at 4 hours post-dose of Study 09 are supportive of these conclusions.

/S/

Kallappa M. Koti
Mathematical Statistician

Concur:

/S/

Dr. Kun Jin

/S/

Dr. George Chi

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APPEARS THIS WAY
ON ORIGINAL

Statistical Review and Evaluation

Review of Stability Data

NOV 5 1999

NDA #: 21-006

APPLICANT: Vanguard Medica Limited

NAME OF DRUG: Miguard (frovatriptan succinate monohydrate)

DOCUMENTS REVIEWED: Pages 40-41 and 275-299 of Sponsor's 09/29/99 Chemistry Amendment

CHEMISTRY REVIEWER: Martha Heimann, Ph.D., HFD-120

Background

The Division of Biometrics 1 was requested to evaluate the sponsor's analyses of the stability data of 'percent other related substances'.

Sponsor's Findings

The sponsor submitted 18 months stability data of five batches and 12 months stability data of an additional batch. Percent related substances other than OA90482C was analyzed when the tablets were stored in clear — blisters at 25°C/60% RH. The sponsor performed two sets of analyses which differed in the initial values. It was argued that the set of values obtained at the start of the stability study did not accurately reflect the true levels of impurities but that lot release values did. With either set of data the sponsor fit a common regression line and estimated the one-sided upper 95% confidence limit of the predicted level of degradation at 104 weeks. These estimates were 0.67% and 0.64% for the data with stability and with lot release initial values respective. The sponsor requests a 2-year expiry period.

Reviewer's Findings

As the sponsor did not test which model fit the data best, this reviewer re-analyzed the data first testing whether the slopes or intercepts of the individual regression lines could be pooled. The first data set as given in the sponsor's table 1 regressed to a model of common slope but separate intercepts (Table 1). The extrapolated estimated expiration dating periods are at least 72 months for each batch. When substituting the lot release values for the stability study initial values, as suggested by the sponsor as being more appropriate, the data again regressed to a model with common slope but different intercepts (Table 2). The extrapolated estimated expiration dating periods ranged from 58 months (batch 005) to 67 months (batch 006). From both findings it appears that 'other related' substances for VML 251 tablets stored in — blisters are not expected to reach the upper limit of —for a long time. It may be reasonable to consider lowering the upper limit to a more realistic requirement. It is also noted that the initial values of batch 007 were not replaced.

Summary and Conclusions

When estimating the expiration dating period based on 'other related' substances, the sponsor had not tested which regression model would fit the data best but fit a single common line to all the data. The initial time point observations were considered significantly higher than later data and the sponsor repeated the statistical analysis, replacing the initial stability time points with lot release results from the NDA. With either set of data the sponsor proposed a shelf life of 2 years.

This reviewer first tested whether the data would pool to a single regression line. The best model was that of a common slope and individual intercepts. When analyzing the data provided in the sponsor's Table 1, the extrapolated estimated expiry periods were at least 72 months. When substituting the lower initial values, the extrapolated estimated expiry periods ranged from 58 to 67 months. The two-year expiry period requested by the sponsor is well supported by these findings.

/S/

Roswitha Kelly, M.S.

Mathematical Statistician

/S/

Kun Jin, Ph.D.

Team Leader

/S/

George Chi, Ph.D.

Director, Division of Biometrics I

APPEARS THIS WAY
ON ORIGINAL

cc: Archival NDA #21-006, Miguard, Vanguard Medica Lim., STABILITY
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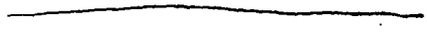
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Ms. Kelly
HFD-710/Chron.
This review consists of 2 pages and 2 tables. 11/05/99.

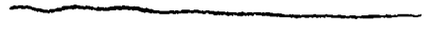
Table 1: Total Related Substances
NDA 21-006
MIGUARD

ANOVA TABLE

SOURCE	SS	DF	MS	F	P
A	0.30911	10	0.03091	3.09031	0.00261
B	0.28184	5	0.05637	5.63536	0.00020
C	0.02727	5	0.00545	0.54526	0.74134
D	0.70017	70	0.01000		
E	7.19443	12	0.59954		

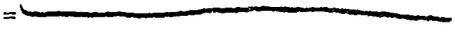
Fitted Line Batch 001: Y =  X

Fitted Line Batch 002: Y =  X

Fitted Line Batch 004: Y =  X

Fitted Line Batch 005: Y =  X

Fitted Line Batch 006: Y = X

Fitted Line Batch 007: Y =  X

95% One-Sided Upper Confidence Limit
Separate Intercepts and Common Slope

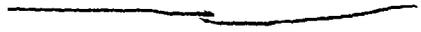
BATCH	EST. EXPIRY PERIOD (MONTHS)
001	72
002	72
004	72
005	72
006	72
007	72

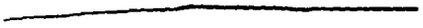
Table 2: Total Related Substances
Initial Values from Lot Release
NDA 21-006
MIGUARD

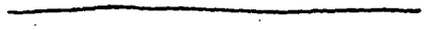
ANOVA TABLE

SOURCE	SS	DF	MS	F	P
A	0.21507	10	0.02151	2.23970	0.02485
B	0.19073	5	0.03815	3.97241	0.00314
C	0.02434	5	0.00487	0.50698	0.77003
D	0.67219	70	0.00960		
E	6.51471	12	0.54289		

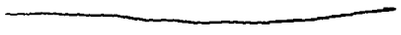
Fitted Line Batch 001: Y =  X

Fitted Line Batch 002: Y =  X

Fitted Line Batch 004: Y =  X

Fitted Line Batch 005: Y =  X

Fitted Line Batch 006: Y = X

Fitted Line Batch 007: Y =  X

95% One-Sided Upper Confidence Limit
Separate Intercepts and Common Slope

BATCH	EST. EXPIRY PERIOD (MONTHS)
001	65
002	64
004	63
005	58
006	67
007	66

COMPLETED JUL 2 8 1999

/S/ 7/28/99

JUL 27 1999

Statistical Review and Evaluation

Review of Carcinogenicity Data

Chen

NDA#: 21-006

Applicant: Vanguard Medica Limited

Name of Drug: Miguard (frovatriptan succinate monohydrate)

Documents Reviewed: Volumes 1.016 and 1.026 Containing the Mouse and Rat Study Reports. Data Were Submitted on Two CDROMs.

Pharmacology Reviewer: Sidney Stolzenberg, Ph.D. (HFD-120)

I. Background

The Division of Biometrics 1 was requested to review and the rat and mouse carcinogenicity studies. The results were discussed with the reviewing pharmacologist, Dr. Sidney Stolzenberg.

II. The Rat Study

II.1 Sponsor's Findings

In this study, sixty male and female Crl:CDBR Sprague Dawley rats were treated with Miguard via gavage at doses of 8.5, 27, and 85 mg/kg/day for 104 weeks. Each sex also had two control groups. Generally, tissues of all control and high dose animals as well as from decedents of the low and mid doses were microscopically examined. However, if there were possible treatment-related changes, hyperplastic, preneoplastic or neoplastic lesions seen in high dose groups, then the tissues from the low and intermediate dose groups were also examined. This was the case for the adrenals, kidneys, and pituitary of the males and the ovaries, uterus, mammary, adrenals, kidneys, and pituitary of the females. Gross lesions and tissue masses seen at necropsy were also followed by histopathology.

The sponsor observed increased mortality for the low and high dose males, as well as a dose response. Survival of the females was not affected by the treatment.

The mid and high dose males had greater average weight gains that the controls (Table 1, Figure 1). For the mid and high dose females the weight gain was greater than controls during the first 13 weeks of dosing. By the end of the study the difference in weight gain was inversely proportional to dose level, with the greatest difference being between control and low dose females (Table 2, Figure 2).

The sponsor observed a treatment related increase in the incidence of pituitary tumors in the high dose males as well as a dose response.

There was also a dose-related increase in adrenal medullary tumors in the intermediate and high dose females. No other tumor findings were statistically significant.

II.2 Reviewer's Findings

This reviewer could not find an explicit reference that the controls received the vehicle only, but it appears that the two control groups were identical and are treated as such in all analyses. This reviewer could reproduce the sponsor's number of animals living till terminal sacrifice and the tumor incidence rates. The significant tumor findings reported by the sponsor are for adenoma and carcinoma of the pituitary (males) and for adrenal medullary tumors for the females. However, there were only adenomas of the pituitary among the males and only adrenal phaeochromocytomas among the females. Therefore, this reviewer will address these tumors only.

There was a statistically significant increase in mortality with dose among the male rats ($p<0.05$), but not among the females (Tables 3-6, Figures 3-4).

The trend test for tumors is appropriate only for those tissues where all animals were examined, which were adrenals, kidneys, and pituitary for the males and ovaries, uterus, mammary gland, adrenals, kidneys, and pituitary for the females. From these tissues only adenoma of the pituitary reached statistical significance (p(asymptotic)=0.0018, Table 7) among the males. The pairwise comparison between the controls and high dose resulted in a p-value of 0.0012. Since this pairwise test was conditional on a significant tumor finding there is no defined α-level for it. However, the small p-value would indicate that this comparison is probably also statistically significant. Among the females, there were no statistically significant trends in tumor incidences (Table 8). The p-value for adrenal phaeochromocytoma was 0.0059, which only approaches the α-level of 0.0050 for common tumors. The p-value for the pairwise comparison of this tumor between the controls and high dose was 0.0174. The α-level of an unconditional pairwise comparison for common tumors is 0.01. As mentioned before, the α-level for pairwise comparions pursuant to a statistically significant finding has not been established but should be more stringent than the one for the unconditional test. Therefore, p=0.0174 is unlikely to be statistically significant. Tumors in the remaining tissues were be tested using pairwise comparisons between the combined controls and high dose animals. None of these comparisons reached statistical significance for either the males or the females. (Note: The p-values in Tables 7 and 8 are for trend tests, which are only appropriate for those tissues for which all animals were examined. For the remaining tissues pairwise comparisons were performed, whose p-values are not reported here but were all statistically non-significant).

II.3 Validity of the Rat Study

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

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

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

The following rules of thumb are suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol5, pp 66-78, 19985) had found that in his experience on the average approximately 50 % of the animals in the high dose group survived a two-year study. In a personal communication with Dr. Karl Lin (HFD-720), he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed that 'To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50 % survival at one year'. From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

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

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

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

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

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

The length of the study (104 weeks) and the number of animals surviving till terminal sacrifice (24 in HD) are adequate. Assessing whether the high dose is close to the MTD is more difficult. On the average the high dose females gained more bodyweight than the controls throughout the study. Similarly, survival was best among the high dose animals, again not an indication that the high dose was close to the MTD. The evaluation of clinical signs or severe histopathologic toxic effects is left to the expertise of the pharmacologist to assess whether the high dose was close to the MTD. The statistical criteria employed for this assessment do not suggest such a conclusion.

III. The Mouse Study

III.1 Sponsor's Findings

This study was performed in Crl:CD-1(JCR)BR mice. There were 51 animals in each treatment group and in each of the two control groups per sex. The drug was administered via gavage at doses of 0, 4, 13, 40, and 0

mg/kg/day for 84 weeks. Tissues were examined for all animals of the controls and high dose groups, and for the decedents of the low and mid dose groups, as well as for all gross lesions and tissue masses.

Among the male mice, there was no significant difference in the mortality of the treated groups with respect to the combined control groups. However, the second control group experienced significantly higher mortality than the first one. Among the females, there was no significant difference in mortality among any groups.

The sponsor did not observe any effect of treatment on body weight (Figures 5-6).

No tumors of an unusual nature or incidence were observed.

III.2 Reviewer's Findings

It is not clear to this reviewer why this study was conducted for only 84 weeks. Mortality was not statistically significantly different among the groups and survival was very high throughout. At week 84 the worst survival was 47 percent, which was observed for the second male control group. All other male or female groups enjoyed a better than 50 percent survival at the end of the study.

This reviewer could reproduce the sponsor's mortality and tumor incidence findings. For the males, the trend in mortality is not statistically significant, but departure from trend is (Tables 9-12, Figures 7-8). The latter reflects the fact that the survival curves of the treated groups are bracketed by the survival curves of the two control groups. For the female mice, neither trend nor departure from trend reaches statistical significance.

For certain organs, when masses were detected, the tissue of all animals were examined. This seems to have been the case for lung, gall bladder, blood vessel, liver, hem./lymph./reticular system, testes for the males and blood vessel, duodenum, hem./lymph/reticular system, lung, pituitary, ovary, and uterus for the females. Tables 13 and 14 contain the trend tests, none of which reaches statistical significance. Other tissues were microscopically examined only for the control and high dose animals and for the decedents of the low and medium dose groups. For these, pairwise comparisons between controls and high dose animals can be performed as well as trend tests with terminal sacrifice animals excluded. None of the pairwise comparisons between the combined controls and high dose animals reached statistical significance at the $\alpha=0.05$ level for rare tumors and the $\alpha=0.01$ level for common tumors. Though the trend tests based on decent animals only are not independent from these pairwise comparisons and their proper α-levels is not be established, it is reasonable to say that none of them reached statistical significance either(Tables 15-16).

There appear to be an unusual number of tissues labeled 'not usable'. These codes include autolyzed and 'insufficient' samples. For the males, 355 of the 595 data lines (60%) were coded as such. For the females, 221 of the 478 data lines (46%) were coded as such. If these findings imply that these tissues could have had tumors but they could not be detected due to the condition of the tissue, then there may be an underestimation of any tumorgenic effect of the product. Dr. Stolzenberg pointed out that there were some 55 tissues examined for each animal and it appears that only some tissues, not total animals, were lost.

As there were no statistically significant tumor findings, **the validity of both study portions** (male and female) **needs to be investigated.** Following the criteria above, it is obvious that there were sufficient numbers of animals surviving to the end of the study, as mortality barely surpassed 50 percent. However, it is not clear whether the length of the study, 84 weeks, presented a sufficient length of exposure, especially as there seemed no reasons for a short study. Whether the high dose represented a sufficient tumor challenge is assessed by the effects of treatment on body weights, mortality, and clinical signs. As could be seen from the sponsor's figures (Figures 5-6), the treatment had no effect on body weight gain. Mortality was not affected by treatment either. The evaluation of clinical signs and severe histopathologic toxic effects is left to the expertise of the reviewing pharmacologist. From a statistical point of view it is questionable whether the study lasted long enough and there are no indications that the high dose was close to the MTD.

IV. Summary

In the rat study, 60 animals per group per sex were treated with Miguard for 104 weeks at doses of 0, 8.5, 27, 85, and 0 mg/kg/day via gavage. There was a statistically significant effect on mortality with dose for the males, but not for the female rats. When analyzing tumor incidence rates, the trend test for adenoma of the pituitary reached statistical significance for the males. This finding was also reflected in a small p-value of the pairwise comparison between the controls and high dose animals. There were no other statistically significant findings for either the males or the females. Evaluating the validity of the female study portion, it is apparent that there were sufficient numbers of animals exposed to the drug for a sufficient length of time. However, based on statistical criteria, the high dose does not appear to be close to the MTD.

In this mouse study there were 51 animals per treatment group per sex. The drug was administered via gavage at doses of 0, 4, 13, 40, and 0 mg/kg/day. It is not clear why the study lasted only 84 weeks, as survival was about 50 percent at that time. There was no treatment associated increase in mortality for either sex and the drug did not appear to have any effect on the average body weight gains. Tissues were microscopically examined for all control and high dose animals and all decedents of the low and mid doses. Neither pairwise comparisons between controls and high dose animals nor trend tests (where appropriate) revealed any statistically significant increases in tumor findings. The evaluation of the validity of the study showed a sufficient number of animals being exposed, but the length of the exposure and the level of exposure are in question. The study lasted for only 84 weeks and based on statistical considerations the high dose does not appear to be close

to the MTD. In addition, a fair number of tissues were coded as 'not usable'. If this code implies that these tissues were of such poor quality that any tumors present would not have been detected, then the carcinogenic potential of the drug may be underreported.

/S/

Roswitha Kelly, M.S.
Mathematical Statistician

/S/

Kun Jin, Ph.D.
Team Leader

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

Cc: Archival NDA 21-006, Miguard (frovatriptan succinate monohydrate),Vanguard Medica,
CARCINOGENICITY

HFD-120/Ms. Chen, CSO
HFD-120/Dr. Stolzenberg
HFD-120/Dr. Fitzgeral
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Ms. Kelly
HFD-710/Chron.
This review consists of 6 pages, 16 tables, 8 figures.
MSWord:

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TABLE 1 (from Sponsor)

Group mean body weight gains

Test Article	Control	VML 251			Control
Group	1	2	3	4	5
Level (mg/kg/day)	0	8.5	27	85	0

Week of study		Mean body weight gains (g) for Group and Sex 1M	2M	3M	4M	5M	Statistics	
0 to 13	Mean	289.0	301.0	299.2	300.2	285.5	DR*	A
	SD	36.34	40.56	42.97	43.01	37.51		
0 to 104	Mean	517.3	501.7	572.4	613.4*	532.6		A
	SD	100.82	116.78	147.46	120.43	120.95		
13 to 24	Mean	74.9	79.7	79.8	76.8	74.5		A
	SD	17.49	21.07	22.25	22.54	19.06		
24 to 52	Mean	103.7	115.7	121.5	119.3	112.7	DR*	A
	SD	28.52	34.56	48.93	35.27	30.38		
52 to 76	Mean	49.1	45.0	48.3	48.0	52.0		A
	SD	43.55	37.30	44.95	47.78	44.12		
76 to 104	Mean	7.2	0.5	15.5	60.7	25.3		A
	SD	56.98	54.34	79.21	63.38	66.74		

* P<0.05
** P<0.01
*** P<0.001
DR = significant dose response test

A = ANOVA, regression and Dunnett's

TABLE 2 (from sponsor)

Group mean body weight gains

Test Article	Control	VML 251			Control
Group	1	2	3	4	5
Level (mg/kg/day)	0	8.5	27	85	0

Week of study		Mean body weight gains (g) for Group and Sex 1F	2F	3F	4F	5F	Statistics	
0 to 13	Mean	117.1	119.5	125.4*	130.2***	119.7		A
	SD	16.86	18.10	18.88	18.36	14.31		
0 to 104	Mean	310.0	375.4	362.9	335.2	329.8		A
	SD	84.17	89.37	108.18	50.15	104.79		
13 to 24	Mean	31.1	32.7	34.5	34.3	28.0	DR*	A
	SD	12.64	11.30	18.82	12.98	10.83		
24 to 52	Mean	80.8	87.0	88.7	88.8	75.1	DR*	A
	SD	35.01	42.13	35.85	39.62	39.38		
52 to 76	Mean	66.8	82.7*	68.5	75.2	66.3		A
	SD	34.21	34.35	29.46	25.84	38.89		
76 to 104	Mean	34.3	51.9	59.6	39.4	45.7		A
	SD	40.12	51.91	41.09	43.26	47.57		

* P<0.05
** P<0.01
*** P<0.001
DR = significant dose response test

A = ANOVA, regression and Dunnett's

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Table 3: Number of Animals
Species: Rat
Sex: Male

	Treatment Group					
	CTRL1	LOW	MED	HIGH	CTRL2	Total
	N	N	N	N	N	N
Week						
0-52	5	4	1	5	1	16
53-78	8	10	9	10	8	45
79-91	11	8	6	13	9	47
92-104	7	20	15	16	13	71
105-106	29	18	29	16	29	121
Total	60	60	60	60	60	300

Source: _____

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Table 4: Dose-Mortality Trend Tests

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

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	5.93	0.0149
	Depart from Trend	5.99	0.1122
	Homogeneity	11.92	0.0180
Kruskal-Wallis	Dose-Mortality Trend	5.19	0.0227
	Depart from Trend	5.06	0.1675
	Homogeneity	10.25	0.0364

Source: ———————

Table 5: Number of Animals
Species: Rat
Sex: Female

	Treatment Group					
	CTRL1	LOW	MED	HIGH	CTRL2	Total
	N	N	N	N	N	N
Week						
0-52	1	3	4	1	3	12
53-78	13	14	10	11	15	63
79-91	11	12	10	14	10	57
92-104	17	19	18	10	13	77
105-106	18	12	18	24	19	91
Total	60	60	60	60	60	300

Source: _____

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ON ORIGINAL

Table 6: Dose-Mortality Trend Tests

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

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	2.07	0.1500
	Depart from Trend	2.97	0.3956
	Homogeneity	5.05	0.2826
Kruskal-Wallis	Dose-Mortality Trend	1.44	0.2296
	Depart from Trend	2.33	0.5060
	Homogeneity	3.78	0.4370

Source: _____

Table7: Test for Positive Dose-Response (Tumor) Linear Trend
Species: Rat
Sex: Male
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
AB	ABDOMINAL CAVITY	562	B-LIPOMA	1.0000	0.7515	0.7572
AB	ABDOMINAL CAVITY	286	M-SARCOMA	0.5748	0.6651	0.6713
AD	ADRENAL	271	B-BENIGN PHAEOCHROMOCYTOM	0.7069	0.7109	0.7109
AD	ADRENAL	450	B-CORTICAL ADENOMA	0.5745	0.7098	0.7145
AD	ADRENAL	508	B-GANGLIONEUROMA	0.7183	0.7177	0.7229
AD	ADRENAL	379	M-CORTICAL CARCINOMA	0.3719	0.3870	0.3939
AD	ADRENAL	342	M-MALIGNANT PHAEO.	0.2350	0.2236	0.2260
BR	BRAIN	268	B-GRANULAR CELL MENINGIOM	1.0000	0.9349	0.9359
BR	BRAIN	415	M-ASTROCYTIC GLIOMA	1.0000	0.7515	0.7572
BR	BRAIN	439	M-MENINGEAL SARCOMA	1.0000	0.7692	0.7742
BR	BRAIN	349	M-OLIGODENDROCYTIC GLIOMA	0.6444	0.7045	0.7097
CA	CAECUM	614	M-LEIOMYOSARCOMA	0.5167	0.6447	0.6513
CT	CONNECTIVE TISS	578	M-SARCOMA	1.0000	0.7515	0.7572
EA	EAR	572	B-NEURFIBROMA	1.0000	0.7515	0.7572
HE	HAEM/LYMPH/RETIC	376	M-GRANULOCYTIC LEUKEMIA	0.5968	0.6813	0.6869
HE	HAEM/LYMPH/RETIC	70	M-LYMPHOCYTIC LEUKAEMIA	0.5669	0.5707	0.5734
HT	HEART	608	B-BENIGN SCHWANNOMA	0.7183	0.7177	0.7229
K	KIDNEY	351	B-LIPOMA	0.6511	0.7475	0.7510
K	KIDNEY	332	B-TUBULAR CELL ADENOMA	0.6444	0.7045	0.7097
LI	LIVER	517	B-HEPATOCELLULAR ADENOMA	0.7487	0.7785	0.7810
LI	LIVER	358	M-HEPATOCELLULAR CARCINOM	1.0000	0.7849	0.7889
LU	LUNG	405	B-BRONCHIOLO-ALVEOLAR ADE	0.2736	0.1968	0.1999
LU	LUNG	579	M-BRONCIOLO-ALVEOLAR CARC	1.0000	0.7515	0.7572
MA	MAMMARY GLAND	125	B-FIBROADENOMA	0.2933	0.3332	0.3361
MA	MAMMARY GLAND	87	M-CARCINOMA	1.0000	0.7515	0.7572
MS	MESENTERIC LN	259	B-HAEMANGIOMA	0.9358	0.8666	0.8686
MS	MESENTERIC LN	456	B-LYMPHANGIOMA	0.0787	0.0415	0.0423
MS	MESENTERIC LN	501	M-HEMANGIOSARCOMA	0.7183	0.7177	0.7229
MU	MUSCLE	564	M-HISTIOCYTIC SARCOM	1.0000	0.7515	0.7572
PA	PANCREAS	374	B-ACINAR CELL ADENOMA	1.0000	0.7849	0.7886
PA	PANCREAS	373	B-ISLET CELL ADENOMA	0.5497	0.5707	0.5726
PA	PANCREAS	557	B-MIXED ACINAR ISLET ADEN	1.0000	0.7515	0.7572
PA	PANCREAS	541	M-ACINAR CELL CARCINOMA	0.1429	0.0116	0.0122
PA	PANCREAS	442	M-ISLET CELL CARCINOMA	0.4594	0.4931	0.4966
PT	PARATHYROID	431	B-ADENOMA	0.9989	0.9692	0.9699
PI	PITUITARY	33	B-ADENOMA	0.0023	0.0018	0.0019
PR	PROSTATE	402	M-CARCINOMA	1.0000	0.7657	0.7706
SK	SKIN + SUBCUTIS	377	B-BASAL CELL ADENOMA	0.7895	0.7973	0.8006
SK	SKIN + SUBCUTIS	312	B-DERMAL FIBROMA	0.2648	0.2673	0.2686
	SKIN + SUBCUTIS	554	B-FIBROLIPOMA	0.7723	0.7729	0.7766
	SKIN + SUBCUTIS	114	B-FIBROMA	0.0940	0.0868	0.0873
SK	SKIN + SUBCUTIS	218	B-KERATOACANTHOMA	0.3290	0.3370	0.3386
SK	SKIN + SUBCUTIS	231	B-LIPOMA	0.1196	0.1117	0.1123
SK	SKIN + SUBCUTIS	605	B-NEUROFIBROMA	0.7183	0.7177	0.7229
SK	SKIN + SUBCUTIS	503	B-SEBACEOUS CELL ADENOMA	0.7183	0.7177	0.7229

Table 7 con'd: Test for Positive Dose-Response (Tumor) Linear Trend
Species: Rat
Sex: Male
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor
SK	SKIN + SUBCUTIS	138	M-FIBROSARCOMA	0.6520	0.6610	0.663
SK	SKIN + SUBCUTIS	466	M-HAEMANGIOSARCOMA	1.0000	0.7726	0.777
SK	SKIN + SUBCUTIS	426	M-HISTIOCYTIC SARCOMA	0.4352	0.4372	0.440
SK	SKIN + SUBCUTIS	159	M-MALIGNANT SCHWANNOMA	0.8595	0.8560	0.857
SK	SKIN + SUBCUTIS	170	M-SARCOMA	0.9630	0.9237	0.924
SK	SKIN + SUBCUTIS	206	M-SQUAMOUS CELL CARCINOMA	0.2333	0.1816	0.184
SP	SPLEEN	422	M-SARCOMA	0.2766	0.0581	0.059
ST	STOMACH	386	M-LEIOMYSOSARCOMA	0.3884	0.4335	0.439
TA	TAIL	474	B-KERATOACANTHOMA	0.8649	0.8104	0.813
TA	TAIL	307	B-SQUAMOUS CELL PAPILLOMA	0.3473	0.3717	0.374
TE	TESTIS	577	B-BENIGN MESOTHELIOMA	1.0000	0.7515	0.757
TE	TESTIS	502	B-INTERSTITIAL CELL ADENO	0.9534	0.9107	0.912
TC	THORACIC CAVITY	367	M-HISTIOCYTIC SARCOMA	1.0000	0.7654	0.770
TH	THYMUS	303	B-BENIGN THYMOMA	0.6591	0.7100	0.715
TH	THYMUS	470	M-MALIGNANT THYMOMA	0.5860	0.6705	0.676
TY	THYROID	117	B-C-CELL ADENOMA	0.5722	0.5838	0.585
TY	THYROID	476	B-FOLLICULAR CELL ADENOMA	0.6931	0.7069	0.709
T	THYROID	473	M-C-CELL CARCINOMA	0.7469	0.7738	0.776

Table 8: Test for Positive Dose-Response (Tumor) Linear Trend

Species: Rat

Sex: Female

Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
AB	ABDOMINAL CAVITY	562	B-LIPOMA	0.3636	0.3913	0.3983
AB	ABDOMINAL CAVITY	329	M-OSTEOSARCOMA	0.6022	0.6879	0.6934
AB	ABDOMINAL CAVITY	286	M-SARCOMA	0.2637	0.0545	0.0560
AD	ADRENAL	271	B-BENIGN PHAEOCHROMOCYTOM	0.0059	0.0033	0.0033
AD	ADRENAL	450	B-CORTICAL ADENOMA	1.0000	0.7954	0.7994
AD	ADRENAL	379	M-CORTICAL CARCINOMA	0.8309	0.8259	0.8281
BR	BRAIN	415	M-ASTROCYTIC GLIOMA	1.0000	0.8751	0.8772
EY	EYE	590	B-BENIGN MELANOMA	1.0000	0.7954	0.7994
FO	FOOT/LEG	449	B-HISTIOCYTOMA	0.4210	0.5047	0.5105
HE	HAEM/LYMPH/RETIC	376	M-GRANULOCYTIC LEUKEMIA	0.6178	0.6960	0.7014
HE	HAEM/LYMPH/RETIC	70	M-LYMPHOCYTIC LEUKAEMIA	0.5282	0.6554	0.6592
HE	HAEM/LYMPH/RETIC	137	M-MIXED LYMPHOMA	1.0000	0.8680	0.8702
KI	KIDNEY	351	B-LIPOMA	1.0000	0.7888	0.7930
LI	LIVER	517	B-HEPATOCELLULAR ADENOMA	0.6573	0.6844	0.6884
LI	LIVER	358	M-HEPATOCELLULAR CARCINOM	0.2456	0.0459	0.0473
MA	MAMMARY GLAND	618	B-ADENOLIPOMA	0.5934	0.7198	0.7246
MA	MAMMARY GLAND	320	B-ADENOMA	0.8807	0.8768	0.8775
M	MAMMARY GLAND	125	B-FIBROADENOMA	0.9554	0.9536	0.9537
M	MAMMARY GLAND	87	M-CARCINOMA	0.4808	0.4905	0.4911
MA	MAMMARY GLAND	506	M-SARCOMA	0.5906	0.6994	0.704
MS	MESENTERIC LN	259	B-HAEMANGIOMA	0.1746	0.0191	0.019
MS	MESENTERIC LN	456	B-LYMPHANGIOMA	0.3636	0.3913	0.398
NC	NASAL CAVITY	323	M-SARCOMA	0.6056	0.6898	0.695
NC	NASAL CAVITY	454	M-SQUAMOUS CELL CARCINOMA	1.0000	0.7789	0.783
OC	ORAL CAVITY	603	M-SARCOMA	1.0000	0.7781	0.782
OV	OVARY	524	B-SEX CORD/STROMAL ADENOM	1.0000	0.8797	0.881
OV	OVARY	507	M-MALIGNANT THECOMA	0.6104	0.6555	0.662
PA	PANCREAS	374	B-ACINAR CELL ADENOMA	1.0000	0.7954	0.799
PA	PANCREAS	373	B-ISLET CELL ADENOMA	0.1408	0.1295	0.131
PT	PARATHYROID	431	B-ADENOMA	0.9759	0.9206	0.921
PI	PITUITARY	33	B-ADENOMA	0.7837	0.7847	0.784
PI	PITUITARY	413	M-CARCINOMA	0.4330	0.4084	0.411
SK	SKIN + SUBCUTIS	377	B-BASAL CELL ADENOMA	0.4100	0.5479	0.552
SK	SKIN + SUBCUTIS	114	B-FIBROMA	0.7239	0.7281	0.729
SK	SKIN + SUBCUTIS	218	B-KERATOACANTHOMA	0.5302	0.4450	0.448
SK	SKIN + SUBCUTIS	231	B-LIPOMA	0.1719	0.1601	0.161
SK	SKIN + SUBCUTIS	138	M-FIBROSARCOMA	0.1337	0.0884	0.090
SK	SKIN + SUBCUTIS	426	M-HISTIOCYTIC SARCOMA	0.6929	0.7171	0.720
SK	SKIN + SUBCUTIS	159	M-MALIGNANT SCHWANNOMA	0.5305	0.4490	0.452
	SKIN + SUBCUTIS	170	M-SARCOMA	0.7908	0.8195	0.821
S	SKIN + SUBCUTIS	206	M-SQUAMOUS CELL CARCINOMA	1.0000	0.7863	0.790
SC	SPINAL CORD	570	M-ASTROCYTIC GLIOMA	0.4519	0.4959	0.50
ST	STOMACH	596	B-SQUAMOUS CELL PAPILLOMA	0.2637	0.0545	0.05
TA	TAIL	307	B-SQUAMOUS CELL PAPILLOMA	1.0000	0.7615	0.76
TH	THYMUS	303	B-BENIGN THYMOMA	0.4158	0.4039	0.40

Table 8 cont'd: Test for Positive Dose-Response (Tumor) Linear Trend
Species: Rat
Sex: Female
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-
TY	THYROID	473	M-C-CELL CARCINOMA	0.4136	0.5352	0.5404
UB	URINARY BLADDER	592	B-LEIOMYOMA	1.0000	0.7954	0.7994
UT	UTERUS	523	B-BENIGN GRANULAR CELL TU	0.9751	0.9307	0.9317
UT	UTERUS	514	B-FIBROMA	0.4246	0.3862	0.3896
UT	UTERUS	156	B-POLYP	0.6020	0.6135	0.614
UT	UTERUS	522	M-CARCINOMA	1.0000	0.7615	0.7671
UT	UTERUS	226	M-MALIGNANT SCHWANNOMA	0.2063	0.0308	0.031
UT	UTERUS	255	M-SARCOMA	0.4007	0.4629	0.469
UT	UTERUS	411	M-STROMAL SARCOMA	0.6316	0.7100	0.715

Table 9: Number of Animals
Species: Mouse
Sex: Male

	Treatment Group					
	CTRL1	LOW	MED	HIGH	CTRL2	Total
	N	N	N	N	N	N
Week						
0-52	2	10	8	6	17	43
53-78	9	7	8	10	4	38
79-84	3	2	9	5	6	25
85-85	37	32	26	30	24	149
Total	51	51	51	51	51	255

Source: [redacted].

Table 10: Dose-Mortality Trend Tests

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

Species: Mouse
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.01	0.9072
	Depart from Trend	9.83	0.0200
	Homogeneity	9.85	0.0431
Kruskal-Wallis	Dose-Mortality Trend	0.00	0.9521
	Depart from Trend	11.70	0.0085
	Homogeneity	11.71	0.0197

Source: _____

Table II

Number of Animals
Species: Mouse
Sex: Female

	Treatment Group					
	CTRL1	LOW	MED	HIGH	CTRL2	Total
	N	N	N	N	N	N
Week						
0-52	3	5	4	6	8	26
53-78	10	12	9	9	13	53
79-84	5	4	2	3	2	16
85-87	33	30	36	33	28	160
Total	51	51	51	51	51	255

Source: _____

Table 12: Dose-Mortality Trend Tests

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

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.54	0.4635
	Depart from Trend	3.09	0.3785
	Homogeneity	3.62	0.4593
Kruskal-Wallis	Dose-Mortality Trend	0.51	0.4741
	Depart from Trend	3.37	0.3384
	Homogeneity	3.88	0.4225

Source: ~~~~~~~~~~~~~~~~~~~~

Table 13 Test for Positive Dose-Response (Tumor) Linear Trend
Species: Mouse
Sex: Male
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-I
AD	ADRENAL	637	B-CORTICAL ADENOMA	1.0000	0.7695	0.7793
BV	BLOOD VESSEL	389	M-HAEMANGIOSARCOMA - TEST	0.2067	0.0315	0.0339
BV	BLOOD VESSEL	323	M-HAEMANGIOSARCOMA - BONE	0.6216	0.6952	0.7067
BV	BLOOD VESSEL	601	B-HAEMANGIOMA - LIVER	0.8527	0.8312	0.8371
BV	BLOOD VESSEL	711	B-HAEMANGIOMA - MES. LN	1.0000	0.7695	0.7793
BV	BLOOD VESSEL	631	B-HAEMANGIOMA - SPLEEN	1.0000	0.8523	0.8575
BO	BONE	234	B-CHONDROMA	1.0000	0.7803	0.7899
BO	BONE	478	M-OSTEOSARCOMA	1.0000	0.7695	0.7793
CO	COLON	661	M-CARCINOMA	1.0000	0.7695	0.7793
GB	GALL BLADDER	617	B-PAPILLOMA	0.5878	0.6790	0.690
HE	HAEM/LYMPH/RETIC	135	M-LYMPHOCYTIC LYMPHOMA	0.0588	0.0309	0.032
HE	HAEM/LYMPH/RETIC	170	M-LYMPHOCYTIC LEUKAEMIA	0.6244	0.6964	0.707
HE	HAEM/LYMPH/RETIC	169	M-MIXED LYMPHOMA	0.7285	0.7854	0.790
HE	HAEM/LYMPH/RETIC	429	M-LEUKAEMIA	0.8349	0.8092	0.815
HE	HAEM/LYMPH/RETIC	360	M-HISTIOCYTIC SARCOMA-LIV	1.0000	0.7770	0.786
KI	KIDNEY	658	B-TUBULAR CELL ADENOMA	1.0000	0.7695	0.779
LI	LIVER	157	B-HEPATOCELLULAR ADENOMA	0.0758	0.0708	0.071
I	LIVER	158	M-HEPATOCELLULAR CARCINOM	0.3405	0.3528	0.359
L	LUNG	129	B-BRONCHIOLO-ALVEOLAR ADE	0.1824	0.1799	0.181
LU	LUNG	130	M-BRONCHIOLO-ALVEOLAR CAR	0.4037	0.4158	0.419
PA	PANCREAS	638	B-ISLET CELL ADENOMA	1.0000	0.7695	0.779
SK	SKIN + SUBCUTIS	328	M-SARCOMA	0.8307	0.8371	0.841
TE	TESTIS	570	B-RETE TUBULAR ADENOMA	0.2000	0.0322	0.034
TE	TESTIS	632	B-INTERSTITIAL CELL ADENO	0.4785	0.4870	0.493

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ON ORIGINAL

Table 14: Test for Positive Dose-Response (Tumor) Linear Trend
Species: Mouse
Sex: Female
Sorted by: Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
AD	ADRENAL	637	B-CORTICAL ADENOMA	1.0000	0.7848	0.7943
BV	BLOOD VESSEL	631	B-HAEMANGIOMA - SPLEEN	0.2977	0.2782	0.2828
BV	BLOOD VESSEL	601	B-HAEMANGIOMA - LIVER	0.8332	0.8022	0.8087
BV	BLOOD VESSEL	579	B-HAEMANGIOMA - UTERUS	1.0000	0.9429	0.9447
BO	BONE	478	M-OSTEOSARCOMA	0.6097	0.6971	0.7085
BO	BONE	699	B-OSTEOMA	1.0000	0.7848	0.7943
BR	BRAIN	562	B-MENINGIOMA	1.0000	0.7826	0.7922
DU	DUODENUM	553	B-ADENOMA	0.4153	0.4647	0.4780
HE	HAEM/LYMPH/RETIC	135	M-LYMPHOCYTIC LYMPHOMA	0.0935	0.0557	0.0576
HE	HAEM/LYMPH/RETIC	171	M-GRANULOCYTIC LEUKAEMIA	0.2103	0.0329	0.0353
HE	HAEM/LYMPH/RETIC	612	M-MAST CELL SARCOMA	0.2147	0.0350	0.0376
HE	HAEM/LYMPH/RETIC	584	M-LYMPHOMA	0.3017	0.2603	0.2666
HE	HAEM/LYMPH/RETIC	169	M-MIXED LYMPHOMA	0.3250	0.3285	0.3330
HE	HAEM/LYMPH/RETIC	170	M-LYMPHOCYTIC LEUKAEMIA	0.4714	0.4943	0.4997
HE	HAEM/LYMPH/RETIC	360	M-HISTIOCYTIC SARCOMA-LIV	0.9208	0.9003	0.9028
HE	HAEM/LYMPH/RETIC	361	M-HISTIOCYTIC SARCOMA-UTE	0.9463	0.8888	0.8923
HG	HARDERIAN GLAND	482	B-ADENOMA	0.2123	0.1737	0.1796
KI	KIDNEY	658	B-TUBULAR CELL ADENOMA	1.0000	0.7848	0.7943
LL	LUNG	130	M-BRONCHIOLO-ALVEOLAR CAR	0.2882	0.2728	0.2777
LU	LUNG	129	B-BRONCHIOLO-ALVEOLAR ADE	0.6134	0.6304	0.6337
MA	MAMMARY GLAND	471	M-CARCINOMA	0.9772	0.9210	0.9234
OV	OVARY	559	B-CYSTADENOMA	0.3436	0.1948	0.2015
OV	OVARY	701	B-BENIGN GRANULOSA TUMOUR	0.6188	0.6999	0.7113
OV	OVARY	675	B-BENIGN LUTEOMA	1.0000	0.7848	0.7943
PI	PITUITARY	481	B-ADENOMA	0.9322	0.8998	0.9027
PG	PREPUT/CLIT GL	299	M-CARCINOMA	1.0000	0.7717	0.7816
SK	SKIN + SUBCUTIS	552	M-OSTEOSARCOMA	0.6209	0.6960	0.7075
SK	SKIN + SUBCUTIS	328	M-SARCOMA	0.8543	0.8208	0.8269
SK	SKIN + SUBCUTIS	688	B-SQUAMOUS CELL PAPILLOMA	1.0000	0.7848	0.7943
TH	THYMUS	513	B-BENIGN THYMOMA	1.0000	0.7820	0.7915
UT	UTERUS	615	B-ADENOMA	0.3551	0.1991	0.2058
UT	UTERUS	682	M-LEIOMYOSARCOMA	0.3665	0.2196	0.2266
UT	UTERUS	461	B-LEIOMYOMA	0.5043	0.5073	0.5133
UT	UTERUS	460	B-POLYP	0.8161	0.8166	0.8188

Table 15: Test for Positive Dose-Response (Tumor) Linear Trend Excluding TS
Species: Mouse
Sex: Male
Sorted by: Exact P

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
HE	HAEM/LYMPH/RETIC	135	M-LYMPHOCYTIC LYMPHOMA	0.0683	0.0411	0.0427
3V	BLOOD VESSEL	389	M-HAEMANGIOSARCOMA - TEST	0.2203	0.0386	0.0414
_I	LIVER	158	M-HEPATOCELLULAR CARCINOM	0.3668	0.2423	0.2499
_U	LUNG	130	M-BRONCHIOLO-ALVEOLAR CAR	0.3906	0.3021	0.3090
1E	HAEM/LYMPH/RETIC	169	M-MIXED LYMPHOMA	0.6154	0.4746	0.4895
_I	LIVER	157	B-HEPATOCELLULAR ADENOMA	0.6342	0.7176	0.7289
3V	BLOOD VESSEL	323	M-HAEMANGIOSARCOMA - BONE	0.6850	0.7225	0.7338
1E	HAEM/LYMPH/RETIC	170	M-LYMPHOCYTIC LEUKAEMIA	0.6875	0.7235	0.7347
1E	HAEM/LYMPH/RETIC	429	M-LEUKAEMIA	0.8449	0.8344	0.8406
SK	SKIN + SUBCUTIS	328	M-SARCOMA	0.8999	0.8889	0.8919
3O	BONE	234	B-CHONDROMA	1.0000	0.7987	0.8079
1E	HAEM/LYMPH/RETIC	360	M-HISTIOCYTIC SARCOMA-LIV	1.0000	0.7969	0.8060

Table16, Test for Positive Dose-Response (Tumor) Linear Trend Excluding TS
Species: Mouse
Sex: Female
Sorted by: Exact P

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
HE	HAEM/LYMPH/RETIC	169	M-MIXED LYMPHOMA	0.1076	0.1119	0.1147
HE	HAEM/LYMPH/RETIC	171	M-GRANULOCYTIC LEUKAEMIA	0.2286	0.0384	0.0410
DU	DUODENUM	553	B-ADENOMA	0.3043	0.4141	0.4276
HE	HAEM/LYMPH/RETIC	584	M-LYMPHOMA	0.3810	0.3953	0.4021
BO	BONE	478	M-OSTEOSARCOMA	0.5778	0.6879	0.6990
HG	HARDERIAN GLAND	482	B-ADENOMA	0.5778	0.6879	0.6990
SK	SKIN + SUBCUTIS	328	M-SARCOMA	0.6111	0.6493	0.6622
SK	SKIN + SUBCUTIS	552	M-OSTEOSARCOMA	0.6364	0.6676	0.6800
HE	HAEM/LYMPH/RETIC	612	M-MAST CELL SARCOMA	0.6667	0.2398	0.2522
HE	HAEM/LYMPH/RETIC	170	M-LYMPHOCYTIC LEUKAEMIA	0.7173	0.7510	0.7558
MA	MAMMARY GLAND	471	M-CARCINOMA	0.8181	0.7883	0.7951
LU	LUNG	130	M-BRONCHIOLO-ALVEOLAR CAR	0.8510	0.8084	0.8130
SV	BLOOD VESSEL	579	B-HAEMANGIOMA - UTERUS	1.0000	0.7513	0.7619
BR	BRAIN	562	B-MENINGIOMA	1.0000	0.7722	0.7819
HE	HAEM/LYMPH/RETIC	360	M-HISTIOCYTIC SARCOMA-LIV	1.0000	0.9856	0.9862
PG	PREPUT/CLIT GL	299	M-CARCINOMA	1.0000	0.7468	0.7578
TH	THYMUS	513	B-BENIGN THYMOMA	1.0000	0.7512	0.7611
UT	UTERUS	682	M-LEIOMYOSARCOMA	1.0000	0.7590	0.7694

FIGURE 1 (from Spencer)

Group mean body weight - males

Test Article	Control	VML 251			Control
Group	1	2	3	4	5
Level (mg/kg/day)	0	8.5	27	85	0

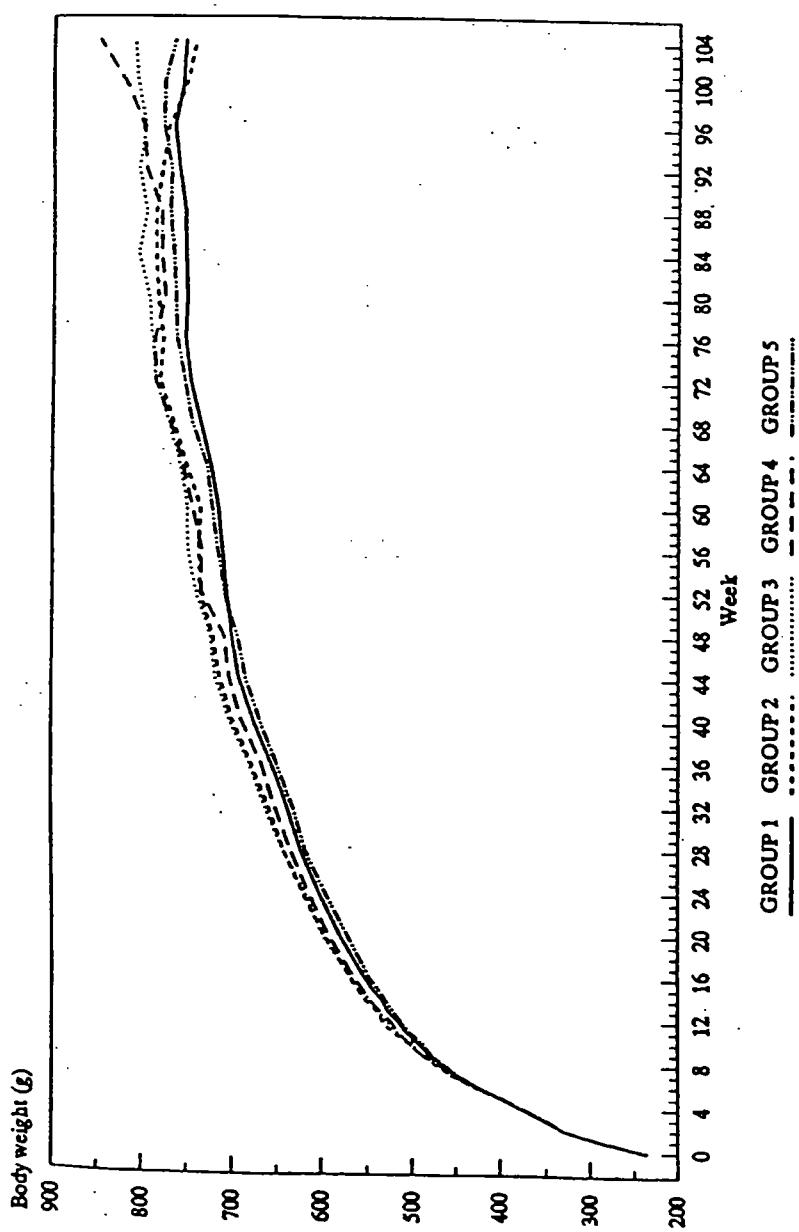


FIGURE 2 (from sponsor)

Group mean body weight - females

Test Article	Control	VML 251			Control
Group	1	2	3	4	5
Level (mg/kg/day)	0	8.5	27	85	0

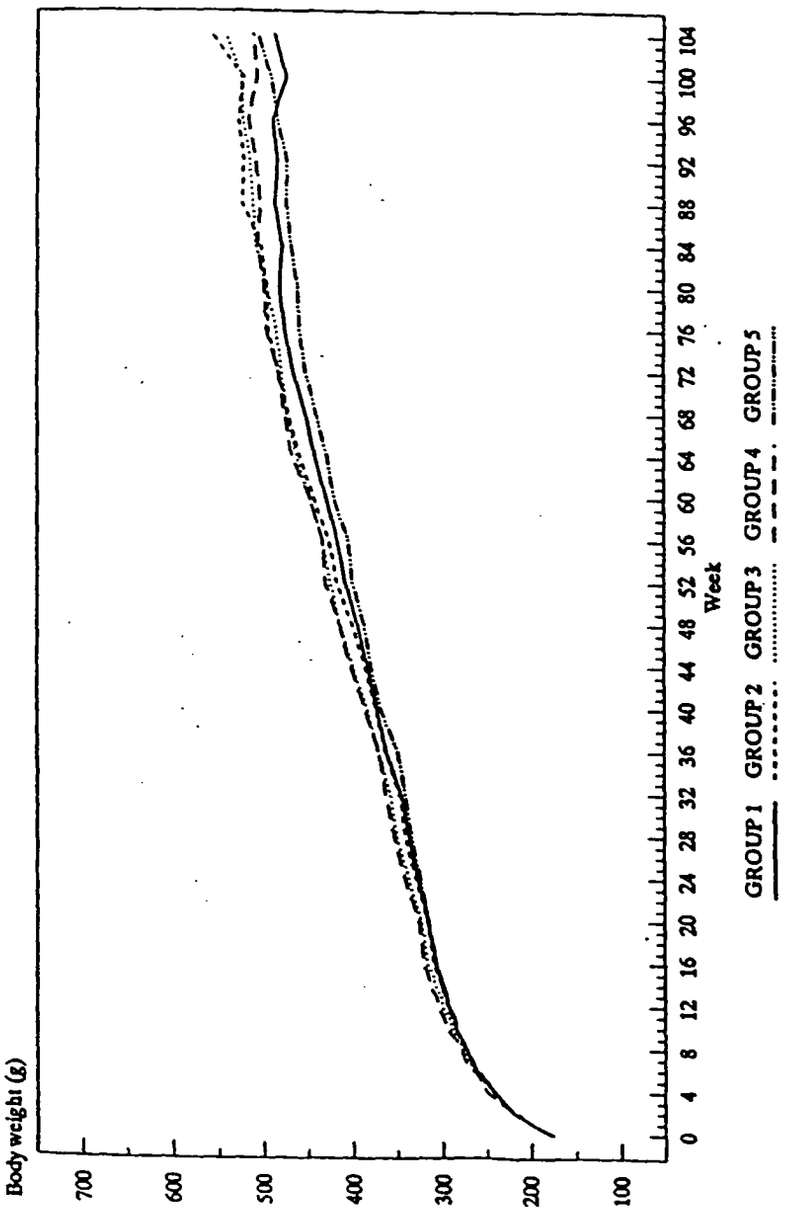


Figure 3

Kaplan–Meier Survival Function

Species: Rat

Sex: Male

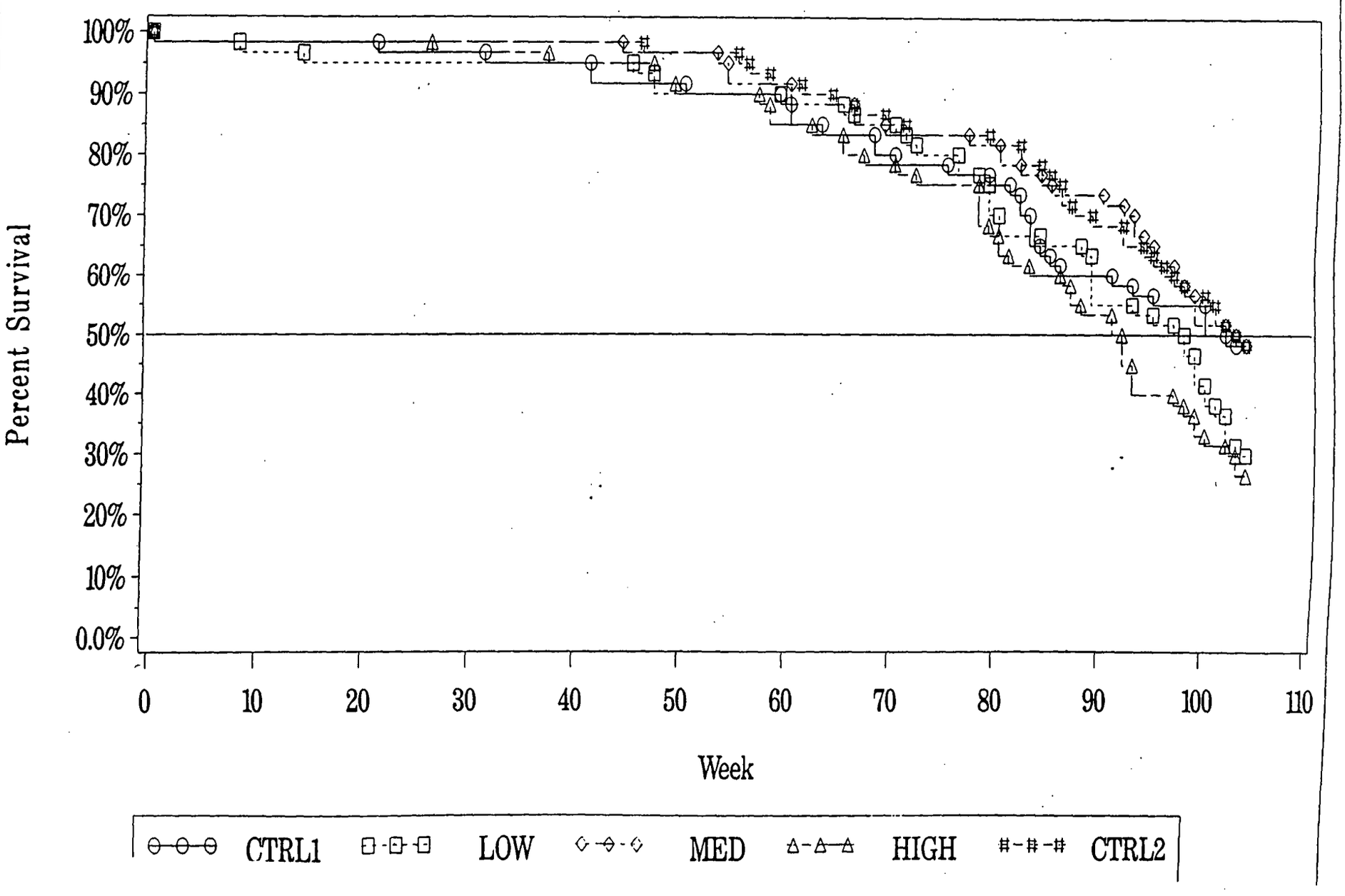


Figure 4: Kaplan–Meier S ival Function

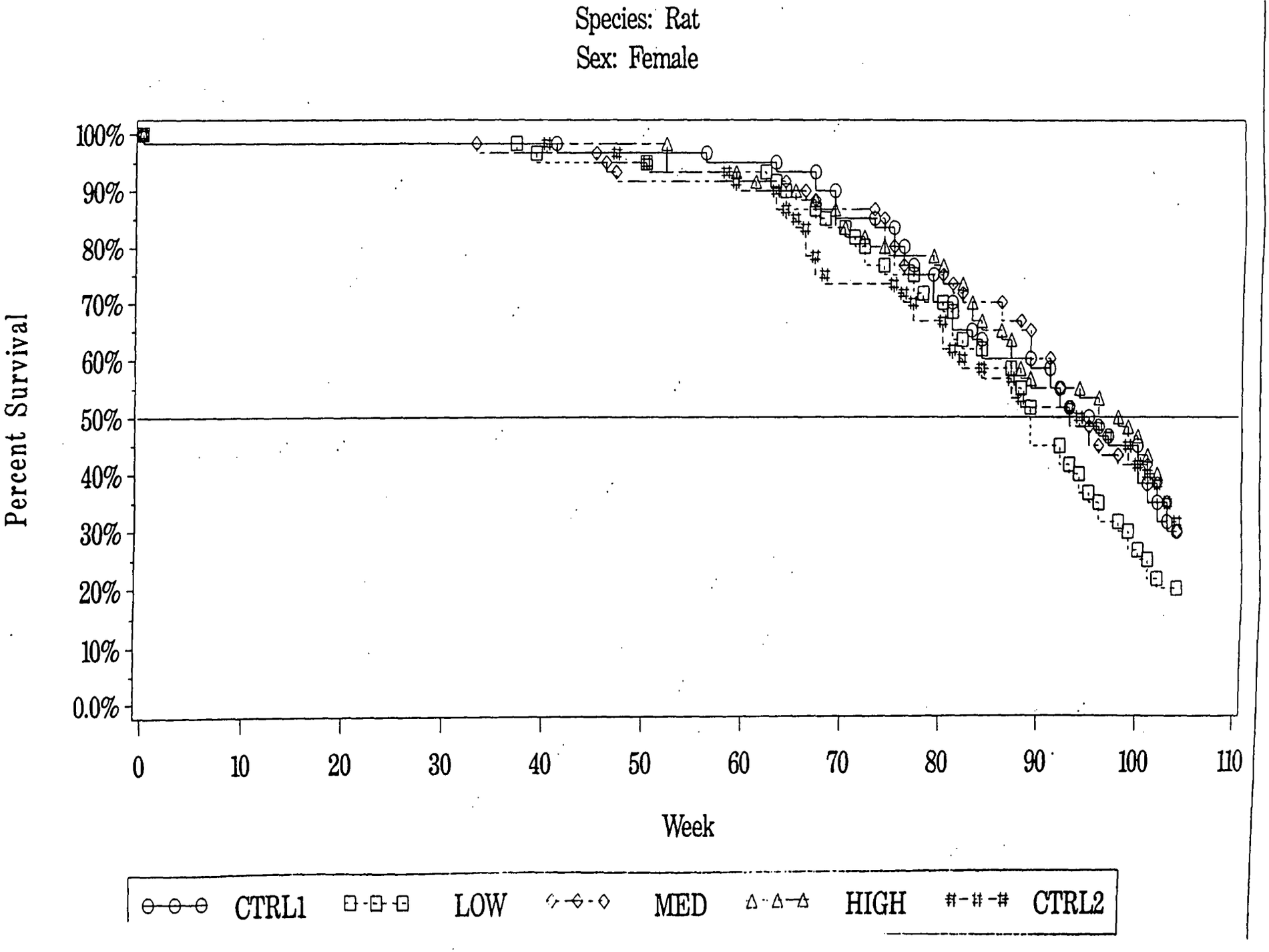


Figure 5 (from sponsor)

Group mean body weight - males

Test article	Control I	VML 251			Control II
Group	1	2	3	4	5
Level (mg/kg/day)	0	4	13	40	0

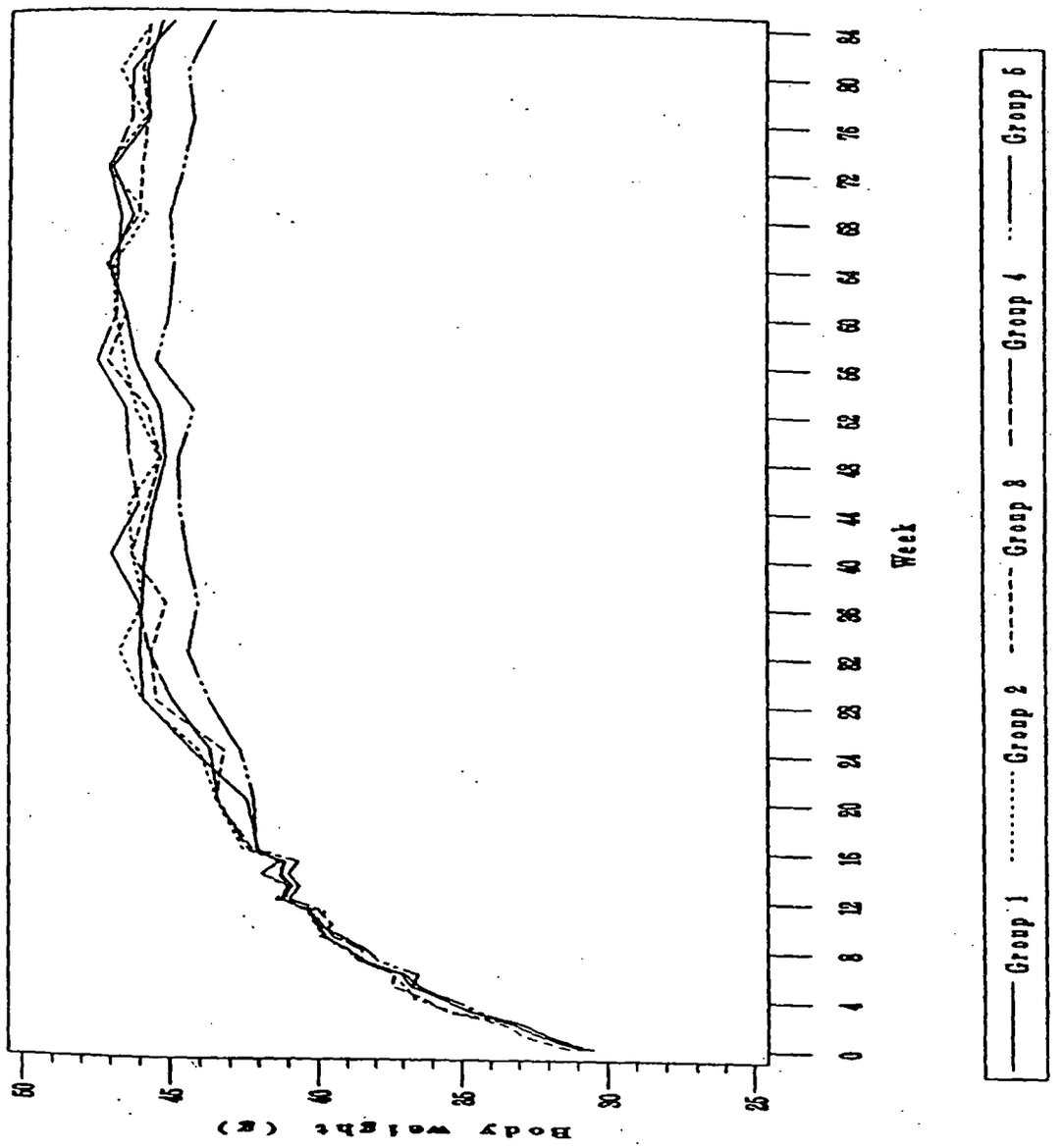
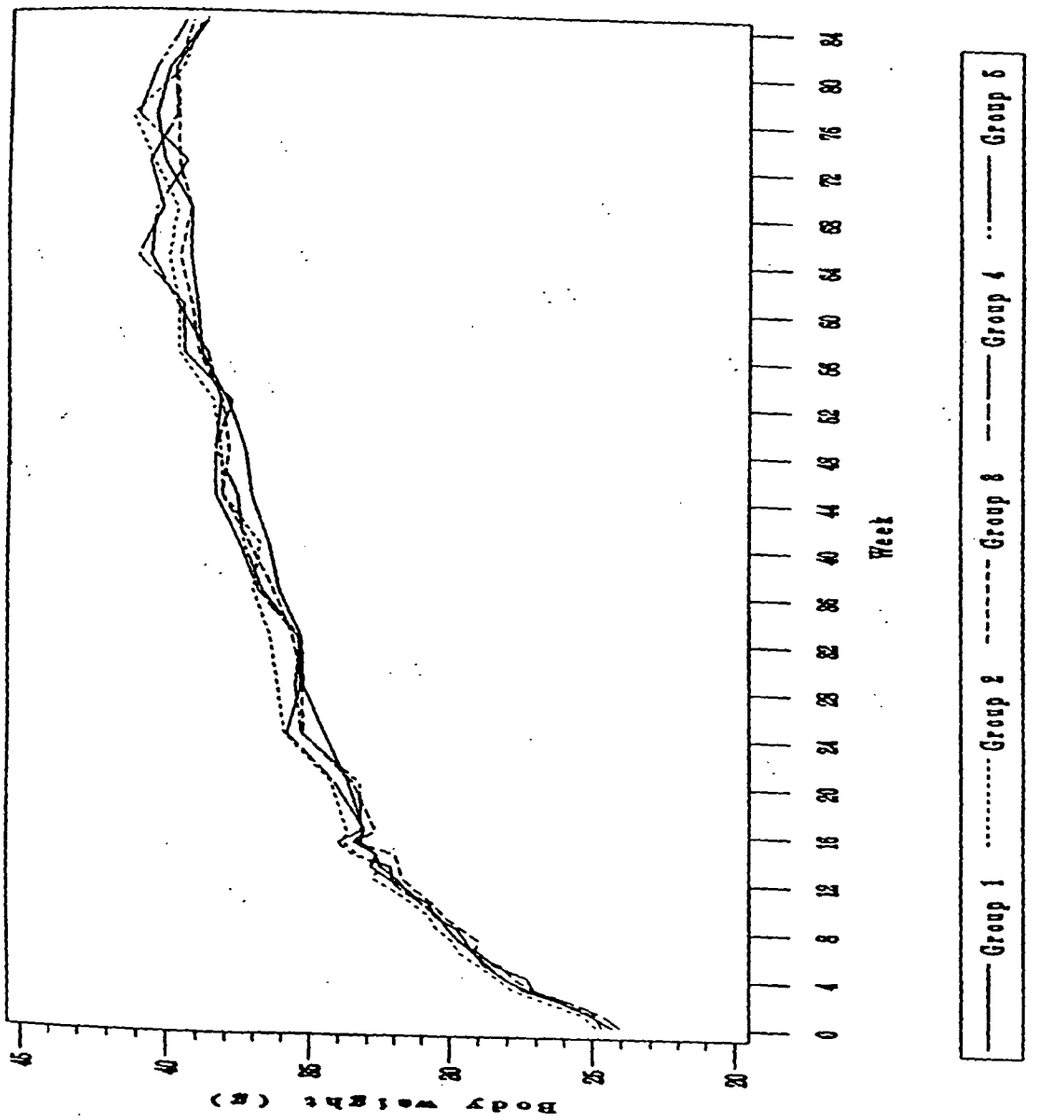


Figure 6 (from sponsor)

Group mean body weight - females

Test article	Control I		VML 251		Control II
Group	1	2	3	4	5
Level (mg/kg/day)	0	4	13	40	0



[redacted]

Figure 7: Kaplan–Meier Survival Function

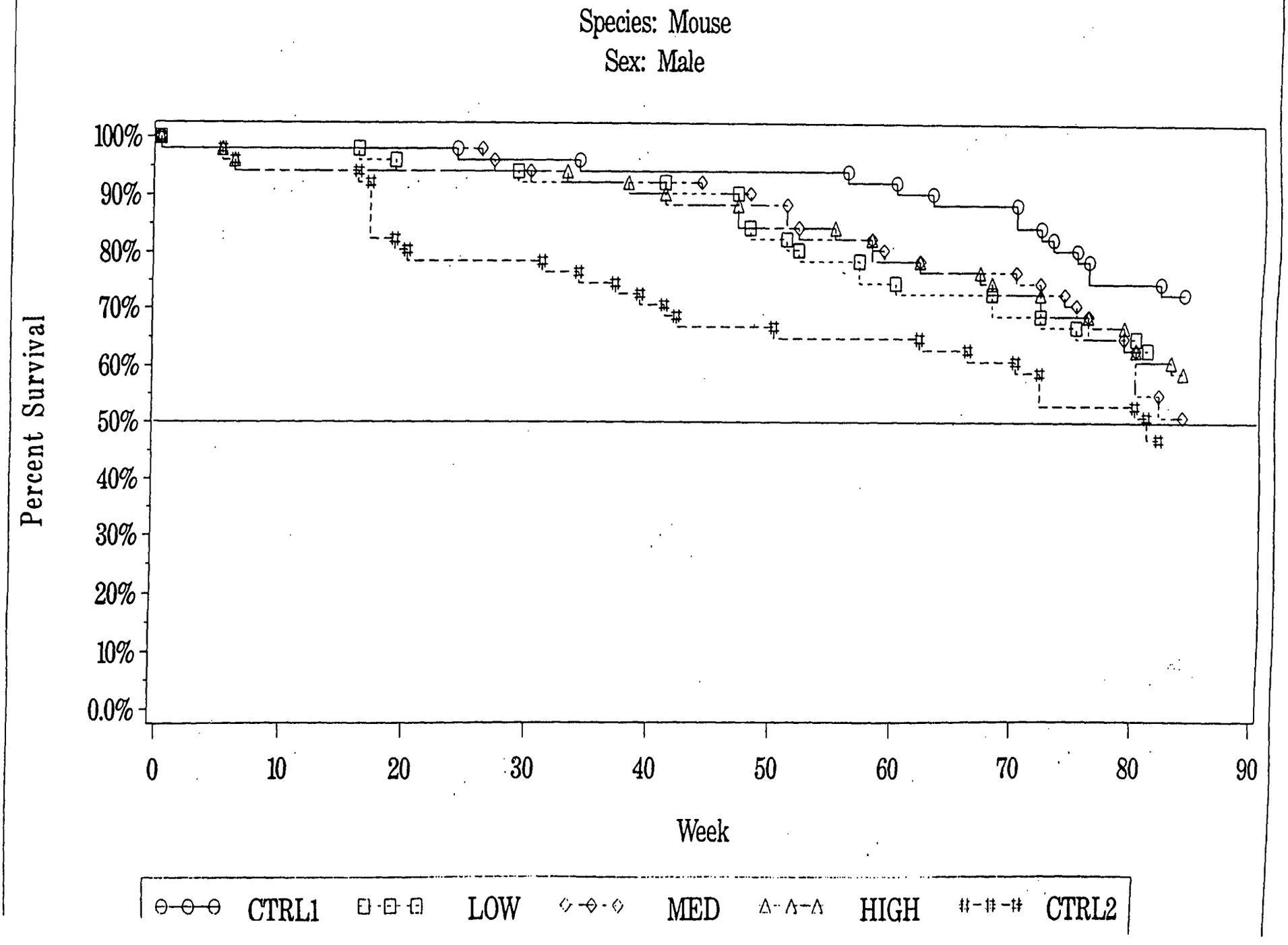


Figure 8: Kaplan–Meier Survival Function