Statistical Review and Evaluation

Review of Carcinogenicity Studies

NDA#:	21,468
APPLICANT:	Shire Pharmaceutical Development
NAME OF DRUG:	Fosrenol (Lanthanum carbonate)
STUDIES REVIEWED:	Two-Year Study in Rats and 99-Week Study in Mice
PHARMACOLOGY REVIEWER:	Xavier Joseph, Ph.D. (HFD-110)
STATISTICAL REVIEWER:	Jasmine Choi, M.S. (HFD-710)

Jasmine Choi, MS
Mathematical Statistician

Concur : Roswitha Kelly, MS

George Chi, Ph.D.

CC:
HFD-110/Dr. Joseph
HFD-110/Dr. Resnick
HFD-110/Ms. Hinton
HFD-710/Dr. Chi
HFD-710/Dr. Hung
HFD-710/Ms. Kelly
HFD-710/Ms. Choi
HFD-700/Dr. Anello

This review consists of 10 pages of text and another 20 pages of graphs and tables.

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1. Introduction

This NDA was submitted for assessing the influence of lanthanum carbonate on tumor formation. A statistical review was done for two carcinogenicity studies: a two-year rat study (Study SPD/87/C) and a 99-week mouse study (Study SPD/88/C).

2. Two-Year Study in Rat (SPD/87/C)

2.1 Study Design

A total of 300 — CD (SD) BR VAF PLUS rats per gender (60 rats/sex/group) were assigned to one of the two control groups, or to the 100 mg/kg/day, the 500 mg/kg/day, or the 1,500 mg/kg/day dose groups. The dose levels were approximately 0.9, 4.3 and 13 times the human dose of 5.77g lanthanum carbonate, assuming a 50kg human. The high dose level was considered to be the maximum tolerated dose based on findings of a 6-month toxicity study in rats. The animals were dosed once daily, via gavage, for up to 104 weeks. The rats in the control groups received the vehicle alone (0.5% w/v aqueous carboxymethylcellulose). At the end of the treatment period all surviving animals were sacrificed.

2.2 Sponsor's Analysis Methods and Results

Survival probability functions for each gender were estimated by the Kaplan-Meier method, and comparisons of the survival curves were performed by the log-rank procedure. The sponsor stated that there were no effects upon survival. However, the p-values were not included in the study report.

Trend tests on tumor incidences were performed, and each treated group was compared to the control groups. The tests were two-sided and significance was declared at the 5% level. Analysis was performed for all tumor findings that had at least 3 occurrences. If there were between 3 and 9 occurrences inclusive, the data were analyzed using an exact permutation test. If the number of observed tumors exceeded 9, the tumor incidences were analyzed using a chi-squared test. An exception was made for tumors in skin and subcutaneous tissues, which were analyzed, in each case, using the exact permutation test provided the number of animals with tumors was three or more. All analyses were adjusted for mortality, and fatal and incidental tumors were combined. The two vehicle control groups were combined for the statistical analyses.

Without giving the actual p-values, the sponsor considered the following tumor findings statistically significant at the 0.05 level:

Table 1: Sponsor's Statistically Significant Tumor Findings in Rats

Gender	Organ	Tumor	Test
Male	Haemopoietic System	Histiocytic Sarcoma	Trend
Male	Liver	Histiocytic Sarcoma	Control v. high/Trend
Female	Skin and Subcutaneous Tissue	Adenocarcinoma	Control v. low
Female	Skin and Subcutaneous Tissue	Fibroma	Control v. high/Trend
Female	Skin and Subcutaneous Tissue	Lipoma	Trend
Combined	Liver	Histiocytic Sarcoma	Control v. high/Trend
Combined	Skin and Subcutaneous Tissue	Lipoma	Trend

2.3 Reviewer's Analysis Methods and Results

This reviewer performed dose-mortality trend tests and homogeneity tests as survival analysis. The survival of the male rats in the high dose group was slightly decreased compared to the control groups, but the difference was not significant. The survival of the female rats was similar across all groups (Appendices 1-4). The test results are summarized in the following Table 2.

Table 2: Survival Analysis of Rats

Gender	Tests	P-values	
		Cox	Kruskal-Wallis
Male	Dose-Mortality Trend	0.5366	0.3288
	Homogeneity	0.4067	0.3143
Female	Dose-Mortality Trend	0.5065	0.6968
	Homogeneity	0.5693	0.6040

Tumor findings were analyzed by an exact permutation trend test. The following standard approach was used in the analyses: for rare tumors (defined as incidence rate ≤1% usually based on concurrent controls) the significance level was 0.025 while for common tumors, the significance level was 0.005. Fatal and incidental tumors were analyzed separately using the death rate and the prevalence method, respectively. When tumors were observed in both incidental and fatal contexts, the findings from the different methods were combined to yield an overall result. When fatal and incidental tumors occurred in the same time interval, the asymptotic test was used since the exact test is not accurate in those circumstances, and the asymptotic test may give a better approximation unless the number of tumors was small. This rule was different from the sponsor's. As noted above, fatal and incidental tumors were combined, and the use of exact or asymptotic test results depended in most cases on whether there were at most nine or more than nine animals with tumors. Furthermore, the level of significance was set at 0.05 for all situations. These differences resulted in different conclusions regarding significance.

Among the male rats, histiocytic sarcoma in the haemopoietic system occurred in 1, 1, 1, 0, and 4 animals of the control 1, the control 2, the low, the mid, and the high dose group, respectively. The exact test of this tumor finding produced a p-value=0.0237 which was larger than the 0.005 significance level for common tumors (1.67% occurrence rate in the

concurrent control group and 2.02% in historical controls, Table 3). Therefore, this tumor finding was not statistically significant. Other than histiocytic sarcoma in the haemopoietic system in the male rats, no tumor finding in either gender approached the appropriate significance levels. All results of trend tests for males and females are summarized in Appendices 5&6. The following table summarizes the test result in histiocytic sarcoma in males.

Table 3: Selected Tumor Findings and Test Results for Rats

Sex	Organ	Tumor	Control 1&2	100 mg/kg	500 mg/kg	1,500 mg/kg	Exact Trend Test
Male	Haemopoietic System	Histiocytic Sarcoma	2	1	0	4	0.0237*

* not statistically significant compared to the 0.005 significance level.

This reviewer examined more closely the tumors that were declared statistically significant by the sponsor. The following table summarizes the number of tumors in each group and the p-values associated with the trend test.

Table 4: Sponsor's Statistically Significant Tumor Findings and Reviewer's Results in Mice

Sex	Organ	Tumor	Control (group 1/ group 2)	100 mg/kg	500 mg/kg	1,500 mg/kg	p-value for trend
M	Haemopoietic System	Histiocytic Sarcoma	2 (1/1)	1	0	4	0.0237*
M	Liver	Histiocytic Sarcoma	0 (0/0)	0	0	1	0.1885*
F	Skin and Subcutaneous Tissue	Adeno-carcinoma	15 (7/8)	16	8	6	0.8943*#
F	Skin and Subcutaneous Tissue	Fibroma	6 (4/2)	2	3	4	0.1866*#
F	Skin and Subcutaneous Tissue	Lipoma	2 (2/0)	0	2	3	0.0512*

* not statistically significant
# p-value from the asymptotic test

The number of histiocytic sarcomas in the liver among the male rats was not consistent between the sponsor and this reviewer. According to the sponsor's table, 0, 0, 1, 0, and 4 animals manifested this tumor in the control 1, the control 2, the low, the mid, and the high dose group, respectively. The sponsor's tumor occurrence rate may show a statistically significant trend, but the tumor rates based on the sponsor's electronic data file resulted in a non-significant trend. The occurrence rates of the other tumors in Table 4 were the same as the ones in the sponsor's report. It seems that the sponsor performed tests using the two control groups separately and combined. Fibroma and lipoma of the skin and subcutaneous tissue in females had significant trends when using control 2 only.

However, as the sponsor stated in 3.10.3 of the study report, the two control groups needed to be combined, as the control groups were identical and did not show any evidence of differences in mortality or in tumor rate. Therefore, the finding based on control group 2 alone was not considered relevant by this reviewer. Also, if all possible comparisons were done with each control group separately and combined, a further multiplicity adjustment would be required. The trend test for adenocarcinoma in the skin and the subcutaneous tissue in females was insignificant. The sponsor had found statistical significance from the pairwise comparison between the control and the low dose group. This result is not considered reasonable in view of comparisons with the mid and the high dose groups being clearly non-significant. This reviewer considers this a spurious finding. As shown in Table 4, none of the sponsor's findings reached statistical significance by this reviewer's trend tests.

2.4 Validity of Rat Study

Since there were no statistically significant dose related tumor trends in rats, the validity of the rat study was evaluated. The following two questions need to be answered:

1) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?
2) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

To answer the first question, the proportion surviving at weeks 80-90 was examined in determining the adequacy of the number of animals at risk. If more than 50% of the usual 50 initial animals in the high dose group were alive between weeks 80-90, it would be considered a sufficient number and adequate length of exposure.

The survival rates for all groups of male and female rats at weeks 80-90 were over 50% (Appendices 3 & 4), therefore, it could be concluded that a sufficient number of animals were at risk for a sufficient length of time.

In determining the appropriateness of the chosen dose level, it is generally accepted that the high dose should be close to the MTD (Maximum Tolerated Dose). The following criteria were adopted:

1) A dose is considered adequate if there is a detectable reduction in body weight of up to 10% in a dosed group relative to the controls.
2) The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical.
3) Doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls.

The sponsor's body weight graphs for the male and female rats (Appendices 7-10) showed very similar body weights for the high dose and the control groups, giving insufficient support for criterion 1. The mortality of the high dose males was slightly

increased early in the study compared to the controls, possibly meeting criterion 3. However, among the female rats, there was no real difference in mortality between the high dose group and the controls. By these analyses, it may be concluded that the high dose in the male rats possibly reached the MTD. However, the determination of the adequacy of the high dose level in the female rats needs to rely on clinical signs or histopathologic toxic effects (criterion 2), which will be evaluated by the reviewing pharmacologist. Based on this reviewer's assessment, the high dose did not reach the MTD for the female rats.

3. 99-Week Study in Mouse (SPD/88/C)

3.1 Study Design

A total of 200 — CD-1(ICR)BR strain (VAF plus) mice per gender (50 mice/sex/group) were assigned to the control, the 100 mg/kg/day, the 500 mg/kg/day, and the 1,500 mg/kg/day dose groups. The dose levels were approximately 0.9, 4.3 and 13 times a human dose of 5.77g lanthanum carbonate, assuming a 50kg human. The high dose level was considered to be the maximum tolerated dose based on a 3-month study in the some strain of mouse. The animals were dosed once daily, via gavage, for up to 99 weeks. The mice in the control group received the vehicle only (0.5% w/v aqueous carboxymethylcellulose). At the end of the treatment period all surviving animals were sacrificed.

3.2 Sponsor's Analysis Methods and Results

The number of early deaths out of the total in each group was analyzed using the Peto method (chi-squared analysis with time adjustment). A test for difference in survival across all groups was performed at the 5% significance level, and pairwise tests of the control group against each lanthanum carbonate treated group were also performed at the same level of α. The sponsor stated that the tests showed no statistically significant difference in survival for either gender. The p-values were not included in the study report.

Statistical analysis was performed for all neoplastic findings that had an incidence greater than 3. If the number of occurrences was between 3 and 9, an exact test was used while an asymptotic chi-squared test was used if the number of occurrences was 10 or more over all groups. The tests were mortality-adjusted, and fatal and incidentals tumors were combined. The analysis included a one-sided test for increasing trend and pairwise comparisons for increasing incidence against the control group. Statistical tests were declared significant if the p-value for the one-sided test was smaller than 5%.

The trend test showed that bronchioalveolar adenoma in the lung had a statistically significant increase among the males. The sponsor also stated that adenoma in the stomach and hemangiosarcoma in the liver had statistically significant positive trends

when males and females were combined. The p-values from the trend tests were not reported.

3.3 Reviewer's Analysis Methods and Results

For the survival analysis, dose-mortality trend tests and homogeneity tests were performed. As shown in Appendices 11-14, the survival of male mice was similar across all groups. The survival in the high dose female was slightly increased as compared to the controls. However, the dose-mortality trend test and homogeneity test of the females did not reach the statistical significance (Table 5).

Table 5: Survival Analysis of Mice

Gender	Tests	P-values	
		Cox	Kruskal-Wallis
Male	Dose-Mortality Trend	0.4070	0.7505
	Homogeneity	0.7217	0.9000
Female	Dose-Mortality Trend	0.0866	0.0877
	Homogeneity	0.1859	0.2170

The exact permutation trend test was performed to analyze the positive linear trend of any tumor occurrences. The asymptotic test was used when fatal and incidental tumors occurred in the same time interval if the number of tumors was not small. Levels of significance for rare and common tumors were used as described in section 2.3. These cut-off points for p-values were different from that the 5% level used by the sponsor. These differences in analysis methods resulted in different conclusions regarding significance.

Bronchioalveolar carcinoma in the lung occurred in 5, 1. 7, and 9 animals of the control, the low, the mid, and high dose male groups, respectively. The asymptotic test was performed for this common tumor and the p-value did not reach the significance level. (p-value=0.0151, >0.005). Adenoma in the stomach occurred in 0, 0, 0, and 4 male mice of the control, the low, the mid, and the high dose group, respectively. The p-value from the exact trend test was 0.0041 (≤0.025), showing a statistically significant positive trend. In addition to adenoma in the stomach, hemangiosarcoma in the liver showed a statistically significant positive trend among the male mice (Table 6). This tumor occurred in 0, 0, 1, and 3 animals of the control, the low, the mid, and the high dose group, respectively, and the p-value from the exact trend test was 0.0149 (≤0.025). These two tumors were considered rare since none was found in the concurrent control group. These tumor findings are summarized in the table below. No other tumor findings reached statistical significance among the male mice.

Table 6: Significant Tumor Findings and Test Results for Male Mice

Organ	Tumor	Control	100 mg/kg	500 mg/kg	1,500 mg/kg	Exact Trend Test
Stomach	Adenoma	0	0	0	4	0.0041
Liver	Hemangiosarcoma	0	0	1	3	0.0149

Among the female mice, no tumor findings showed a significant positive trend. The results of the trend tests are listed in Appendices 15&16.

At the request of Dr. Charles Resnick, a supervisory pharmacologist from the Division of Cardio-Renal Drug Products, incidences of hemangiomas and hemangiosarcomas in the liver of male mice were combined as well as incidences of hemangiomas and hemangiosarcomas in all organs. The hemangioma and hemangiosarcoma in the liver had a statistically significant trend with p-value=0.0182 (<0.025). However, the combined tumors across all organs had a different result. Both fatal and incidental tumors occurred in the same time interval, and the tumors were common based on both concurrent and historical control. Therefore, the asymptotic test was performed using the significance level of 0.005 for these tumors. The asymptotic test showed that the combined tumors across all organs were not statistically significant with p-value = 0.022 (>0.005). Dr. Resnick had also requested to combine adenomas and carcinomas of the stomach in males. Since no carcinoma was found in the male stomach, an analysis for the combined incidences was not performed. The results are shown in the table below.

Table 7: Combined Tumor Findings and Test Results for Male Mice

Organ	Tumor	Control	100 mg/kg	500 mg/kg	1,500 mg/kg	Exact Test	Asymp. Test
Liver	Hemangioma & Hemangiosarcoma	0	0	2	3	0.0182*	0.0099
All Organs	Hemangioma & Hemangiosarcoma	1	0	3	4	0.0338	0.0220*

* Appropriate p-value from tumor trend analysis.

At the request of Dr. Xavier Joseph, the reviewing pharmacologist, pairwise comparisons between the high dose males and the control group males were performed for adenoma in the stomach and hemangiosarcoma in the liver. The comparisons did not reach statistical significance, which is a reflection of insufficient power for this test. The results are summarized in the following table.

Table 8: Pairwise Comparisons for Selected Tumors in Male Mice

Sex	Organ	Tumor	Control	1,500 mg/kg	P-value
Male	Stomach	Adenoma	0	4	0.0672
Male	Liver	Hemangiosarcoma	0	3	0.0819

3.4 Validity of the Female Mouse Study

The validity of the female mouse study was evaluated because no statistically significant tumor trend was found. The criteria used were as stated in section 2.4. The survival rate at weeks 80-90 was over 50% (Appendix 14), therefore, it was concluded that sufficient numbers of animals were at risk for a sufficient length of time. The mean body weight graph and the mortality across the groups were examined to determine whether the high dose was close to MTD. Based on the sponsor's graph for female body weights (Appendices 19&20), the mean body weight of the high dose group over the course of the

study was very similar to that of the control group. The mean body weight of the high dose group at the end of the study was even slightly higher than the control group. Furthermore, the high dose female mice showed slightly increased survival compared to the controls. Based on this reviewer's evaluation, the high dose in female mice did not reach the MTD. However, the determination of the MTD should rely on the evaluation of clinical signs or histopathologic toxic effect, which will be done by the reviewing pharmacologist.

4. Summary

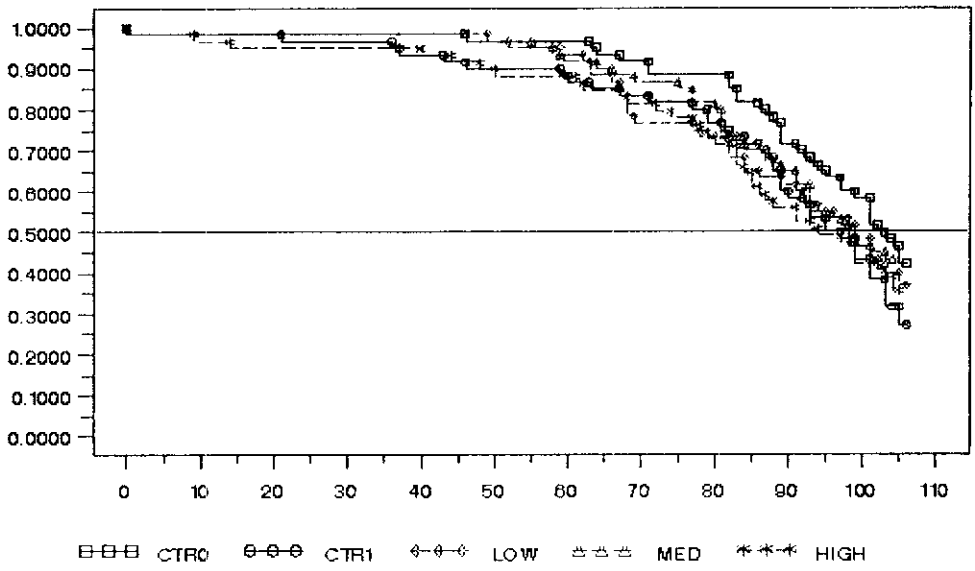
4.1 Rat Study

Sixty rats per group/sex received the drug at levels of 0, 0, 100, 500, and 1,500 mg/kg/day via gavage. This treatment did not affect the survival of either gender to a statistically significant degree; the adjusted dose-mortality trend tests and homogeneity tests for both genders produced p-values > 0.05. There were discrepancies between the sponsor and this reviewer regarding the significant tumor findings. According to the sponsor, there were four tumor findings that were statistically significant using a significance level of 0.05. However, this reviewer's analysis showed that none of the tumors reached statistical significance in either gender. The discrepancies were due to different analysis methods, levels of significance employed, and differences in tumor occurrence rates. In the sponsor's report, tumor occurrence rates of histiocytic sarcoma in the liver of the male rats (one of the four significant tumors) were higher in the low and the high dose groups than those recorded in the electronic data set submitted to the Agency. This reviewer evaluated the validity of the study. Based on the statistical criteria, there were a sufficient number of rats living long enough to present late developing tumors. It is this reviewer's conclusion that the high dose may have reached the MTD for the male rats but not for the female rats.

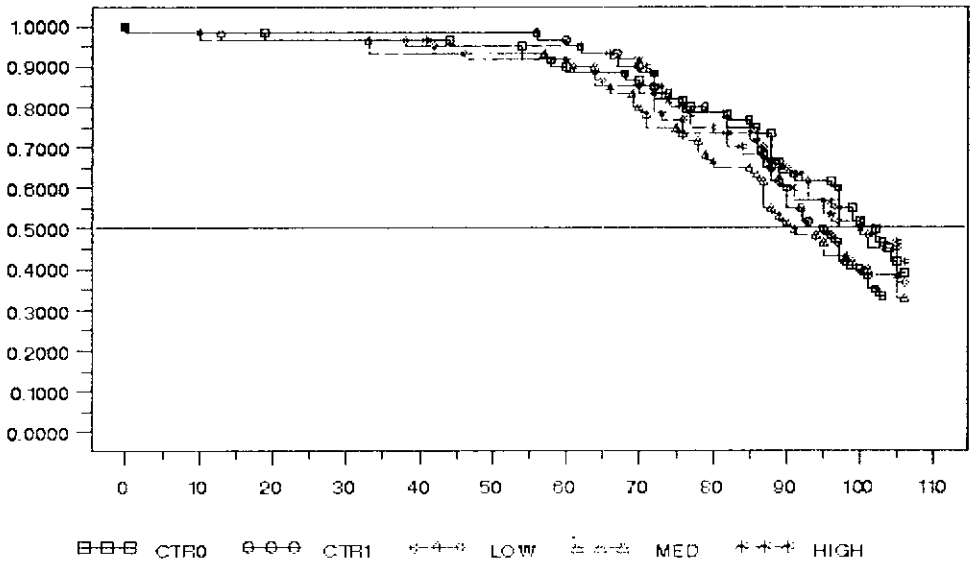
4.2 Mouse Study

Fifty mice per group/sex received lanthanum carbonate at levels of 0, 100, 500, and 1,500 mg/kg/day via gavage. The dose mortality trend tests and homogeneity tests showed that there was no statistically significant treatment effect on survival. Adenoma in the stomach and hemangiosarcoma in the liver showed a statistically significant trend in males. The corresponding pairwise comparisons between the control and the high dose group were not statistically significant. The sponsor stated in the report that an increase in bronchioalveolar carcinoma in the lung among treated males was statistically significant using a significance level of 0.05. However, the p-value did not reach FDA's adopted significance level of 0.005 for common tumors. Since there was no statistically significant tumor finding in the females, the validity of the study was evaluated. The evaluation suggested that sufficient numbers of animals were exposed for a sufficient length of time, but for female mice, the high dose did not reached the MTD.

Appendix 1: Survival Graph of Male Rats



Appendix 2: Survival Graph of Female Rats



Appendix 3: Mortality of Male Rats

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0	0-52	60	1	59	98.3	1.7
	53-78	59	4	55	91.7	8.3
	79-91	55	12	43	71.7	28.3
	92-104	43	14	29	48.3	51.7
	FINALKILL10 5-107	29	29	0		
CTR1	0-52	60	5	55	91.7	8.3
	53-78	55	6	49	81.7	18.3
	79-91	49	13	36	60	40
	92-104	36	17	19	31.7	68.3
	FINALKILL10 5-107	19	19	0		
LOW	0-52	60	2	58	96.7	3.3
	53-78	58	13	45	75	25
	79-91	45	8	37	61.7	38.3
	92-104	37	12	25	41.7	58.3
	FINALKILL10 5-107	25	25	0		
MED	0-52	60	1	59	98.3	1.7
	53-78	59	8	51	85	15
	79-91	51	12	39	65	35
	92-104	39	13	26	43.3	56.7
	FINALKILL10 5-107	26	26	0		
HIGH	0-52	60	6	54	90	10
	53-78	54	8	46	76.7	23.3
	79-91	46	12	34	56.7	43.3
	92-104	34	10	24	40	60
	FINALKILL10 5-107	24	23	1		
	INTERIM KILL		1			

Appendix 4: Mortality of Female Rats

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0	0-52	60	2	58	96.7	3.3
	53-78	58	10	48	80	20
	79-91	48	10	38	63.3	36.7
	92-104	38	11	27	45	55
	FINALKILL10 5-107	27	27	0		
CTR1	53-78	60	11	49	81.7	18.3
	79-91	49	13	36	60	40
	92-104	36	16	20	33.3	66.7
	FINALKILL10 5-107	20	20	0		
LOW	0-52	60	4	56	93.3	6.7
	53-78	56	10	46	76.7	23.3
	79-91	46	7	39	65	35
	92-104	39	12	27	45	55
	FINALKILL10 5-107	27	27	0		
MED	0-52	60	2	58	96.7	3.3
	53-78	58	15	43	71.7	28.3
	79-91	43	13	30	50	50
	92-104	30	6	24	40	60
	FINALKILL10 5-107	24	24	0		
HIGH	0-52	60	2	58	96.7	3.3
	53-78	58	11	47	78.3	21.7
	79-91	47	11	36	60	40
	92-104	36	7	29	48.3	51.7
	FINALKILL10 5-107	29	29	0		

Appendix 5: Tumor Trend Test of Male Rats

Organ code	Organ name				
1	Heart	69103	SCHWANNOMA - MALIGNANT	1	0.7565
10	Thyroid gland	53401	FOLLICULAR CELL ADENOMA - BENI	0.2282	0.185
10	Thyroid gland	55801	C CELL ADENOMA - BENIGN	0.341	0.3431
10	Thyroid gland	74103	C-CELL CARCINOMA - MALIGNANT	0.8048	0.7987
10	Thyroid gland	80703	FOLLICULAR CELL CARCINOMA -	0.4016	0.4362
100	pancreatic fat	92811	LEIOMYOSARCOMA	0.4016	0.4362
11	Parathyroid glands	64101	ADENOMA - BENIGN	0.644	0.6581
12	Testes	67201	INTERSTITIAL CELL ADENOMA -	0.3974	0 395
12	Testes	75603	INTERSTITIAL CELL CARCINOMA -	1	0.7689
14	Prostate gland	69701	ADENOMA - BENIGN	0.9189	0.8715
15	Seminal vesicles	80903	ADENOCARCINOMA - MALIGNANT	0.4016	0.4362
2	Thymus	62503	MALIGNANT SCHWANNOMA – MALIGNA	0.5789	0.7056
2	Thymus	76301	THYMOMA - BENIGN	0.6066	0.7109
2	Thymus	78203	THYMIC LYMPHOMA - MALIGNANT	0.1885	0.0255
23	Urinary bladder	80201	PAPILLOMA - BENIGN	1	0.7689
24	Stomach	56501	PAPILLOMA - BENIGN	1	0.773
24	Stomach	75701	BASAL CELL ADENOMA - BENIGN	1	0.7689
26	Jejunum	70003	LEIOMYOSARCOMA - MALIGNANT	0.6066	0.7109
3	Mesenteric lymph node	65301	HEMANGIOMA - BENIGN	0.9298	0.9172
30	Rectum	77601	ADENOMA - BENIGN	0.1885	0.0255
33	Site of mammary gland	78901	BASAL CELL ADENOMA - BENIGN	0.1885	0.0255
37	Brain	50703	OLIGODENDROGLIOMA - MALIGNANT	0.1906	0.0259
37	Brain	65403	ANAPLASTIC GLIOMA - MALIGNANT	0.5622	0 696
37	Brain	65501	PINEAL GLAND TUMOR - BENIGN	1	0.784
37	Brain	69203	GRANULAR CELL TUMOR - MALIGNAN	0.6053	0.625
37	Brain	69503	MENINGEAL SARCOMA - MALIGNANT	1	0 7625
38	Pituitary gland	39801	ADENOMA PARS DISTALIS - BENIGN	0.6121	0 6145
38	Pituitary gland	57703	ADENOCARCINOMA - MALIGNANT	1	0 7638
38	Pituitary gland	67801	ADENOMA PARS INTERMEDIA - BENI	0.6102	0 6302
4	Lungs	4801	PULMONARY ADENOMA - BENIGN	0 2296	0 2176
42	Harderian glands	75801	ADENOMA - BENIGN	0 8472	0 8202

47	Hemopoietic System	46103	LARGE GRANULAR LYMPHOCYTE	0.8152	0.8038
47	Hemopoietic System	46203	LYMPHOMA - MALIGNANT	0.497	0.5466
47	Hemopoietic System	58703	HISTIOCYTIC SARCOMA - MALIGNAN	0.0237	0.0119
48	Skin and Subcutaneous tissue	54003	SARCOMA - MALIGNANT	0.2247	0.229
48	Skin and Subcutaneous tissue	54301	FIBROADENOMA - BENIGN	0.4081	0.3721
48	Skin and Subcutaneous tissue	54801	LIPOMA - BENIGN	0.3145	0.3217
48	Skin and Subcutaneous tissue	56001<	DERMAL FIBROMA - BENIGN	0.5796	0.5837
48	Skin and Subcutaneous tissue	5660	BASAL CELL TUMOR - BENIGN	0.8446	0.8449
48	Skin and Subcutaneous tissue	56901	KERATOACANTHOMA - BENIGN	0.6405	0.6457
48	Skin and Subcutaneous tissue	58201	FIBROMA - BENIGN	0.7407	0.7444
48	Skin and Subcutaneous tissue		HISTIOCYTIC SARCOMA - MALIGNAN	0.6066	0.7109
48	Skin and Subcutaneous tissue	6040	ZYMBALS GLAND CARCINOMA -	0.9254	0.8692
48	Skin and Subcutaneous tissue	63203	FIBROSARCOMA - MALIGNANT	0.2237	0.1886
48	Skin and Subcutaneous tissue		MALIGNANT SCHWANNOMA – MALIGNA	0.4382	0.5853
48	Skin and Subcutaneous tissue	68301	PAPILLOMA - BENIGN	0.4524	0.4656
48	Skin and Subcutaneous tissue	6	MAMMARY ADENOLIPOMA - BENIGN	1	0.7638
48	Skin and Subcutaneous tissue	74	HEMANGIOSARCOMA - MALIGNANT	0.5802	0.6994
48	Skin and Subcutaneous tissue	75001	FIBROMYXOMA - BENIGN	0.4016	0.4362
48	Skin and Subcutaneous tissue	7740	SQUAMOUS CELL CARCINOMA -	0.4236	0.5756
48	Skin and Subcutaneous tissue	78701	MAMMARY ADENOMA - BENIGN	0.9414	0.8807
48	Skin and Subcutaneous tissue		SEBACEOUS GLAND ADENOMA - BENI	0.644	0.6581
48	Skin and Subcutaneous tissue	8	FIBROMYXOSARCOMA - MALIGNANT	1	0.773
5	Liver	59103	HISTIOCYTIC SARCOMA - MALIGNAN	0.1885	0.0255
5	Liver	60801	ADENOMA - BENIGN	0.5473	0.5716
5	Liver	69603	ADENOCARCINOMA - MALIGNANT	0.9189	0.8715
7	Pancreas	55501	ISLET CELL ADENOMA - BENIGN	0.9352	0.9231
7	Pancreas	69403	ISLET CELL CARCINOMA - MALIGNA	0.8281	0.811
7	Pancreas	75301	EXOCRINE CELL ADENOMA - BENIGN	1	0.7689
7	Pancreas	77203	EXOCRINE CELL CARCINOMA -	0.5303	0.6798
70	Lymph nodes	89830	HAEMANGIOMA	1	0.7689
70	Lymph nodes	89832	CHROMAFFIN CELL ADENOMA	1	0.7689

74	Abdominal fat	90211	LIPOSARCOMA	1	0.7659
74	Abdominal fat	90213	LIPOMA	0.0319	0.0023
74	Abdominal fat	90214	HISTIOCYTIC SARCOMA	0.2105	0.0336
75	Abdominal cavity	90311	SARCOMA	1	0.7659
76	Forelimbs	90414	PAPILLOMA	0.4326	0.5799
77	Tail	90522	PAPILLOMA	0.5473	0.5716
77	Tail	90525	BASAL CELL TUMOUR	0.2051	0.0309
78	Pinnae	90619	BENIGN PAPILLOMA	1	0.7689
8	Kidneys	81503	MESENCHYMAL TUMOR - MALIGNANT	0.6066	0.7109
81	Epididymal fat	90915	LIPOMA	1	0.773
83	Cranium	91113	BENIGN OSTEOMA	0.5303	0 6798
85	Subcutaneous fat	91316	LIPOMA	0.0286	0.0017
9	Adrenals	55701	CORTICAL ADENOMA - BENIGN	0.6972	0.6742
9	Adrenals	66001	PHAEOCHROMOCYTOMA - BENIGN	0.8622	0.8574
9	Adrenals	66003	PHAEOCHROMOCYTOMA – MALIGNANT	0.7589	0.7519
92	ileo-caecal junction	92011	MALIGNANT LEIOMYOSARCOMA	1	0.7629
93	subcutaneous tissue	92114	SQUAMOUS CELL CARCINOMA	1	0.7449
93	subcutaneous tissue	92115	LIPOMA	1	0.7449

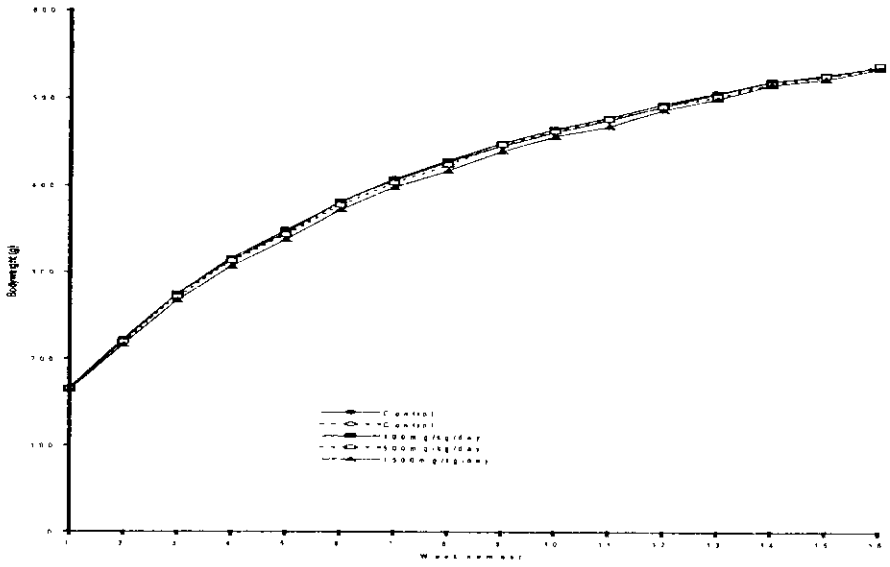
Appendix 6: Tumor Trend Test of Female Rats

Organ code	Organ name	Finding code	Finding		
10	Thyroid gland	53401	FOLLICULAR CELL ADENOMA - BENI	0.9514	0.8942
10	Thyroid gland	55801	C CELL ADENOMA - BENIGN	0.8831	0.8776
10	Thyroid gland	74103	C-CELL CARCINOMA - MALIGNANT	0.7063	0.8042
11	Parathyroid glands	64101	ADENOMA – BENIGN	0.0441	0.0049
16	Ovaries	74401	LUTEOMA – BENIGN	1	0.7129
16	Ovaries	75201	GRANULOSA CELL TUMOR - BENIGN	1	0.7799
16	Ovaries	79701	LEIOMYOMA – BENIGN	0.2283	0.0399
17	Uterus	67901	POLYP – BENIGN	0.4666	0.4729
17	Uterus	80501	LEIOMYOMA – BENIGN	1	0.7799
17	Uterus	81803	LEIOMYOSARCOMA - MALIGNANT	1	0.7799
18	Uterine cervix	70801	POLYP – BENIGN	0.1094	0.0941
18	Uterine cervix	71103	SARCOMA – MALIGNANT	1	0.7695
18	Uterine cervix	74601	BASAL CELL ADENOMA - BENIGN	0 4808	0.6418
18	Uterine cervix	78401	LEIOMYOMA – BENIGN	0.2356	0.2073
18	Uterine cervix	82001	MESENCHYMAL TUMOR - BENIGN	0.4173	0.4723
19	Vagina	74801	LIPOMA – BENIGN	1	0.7799
19	Vagina	81301	FIBROMA – BENIGN	0.6299	0.727
2	Thymus	78201	THYMIC LYMPHOMA - BENIGN	0.8649	0.8355
25	Duodenum	77801	LEIOMYOMA – BENIGN	0.6299	0.727
26	Jejunum	68203	ADENOCARCINOMA - MALIGNANT	1	0.7788
26	Jejunum	70003	LEIOMYOSARCOMA - MALIGNANT	0.4808	0.6418
3	Mesenteric lymph node	65301	HEMANGIOMA – BENIGN	0.4059	0.2431
33	Site of mammary gland	60601	FIBROADENOMA - BENIGN	0 7027	0.6764
34	Tongue	70103	SQUAMOUS CELL CARCINOMA -	0.4444	0 4578
37	Brain	50703	OLIGODENDROGLIOMA - MALIGNANT	0.5966	0.7117
37	Brain	68503	ASTROCYTOMA – MALIGNANT	0.9701	0.9129
37	Brain	69203	GRANULAR CELL TUMOR - MALIGNAN	0.1346	0.0079
38	Pituitary gland	39801	ADENOMA PARS DISTALIS - BENIGN	0.3061	0.306
38	Pituitary gland	57703	ADENOCARCINOMA - MALIGNANT	0 9712	0 9564
38	Pituitary gland	67801	ADENOMA PARS INTERMEDIA - BENI	1	0.8618

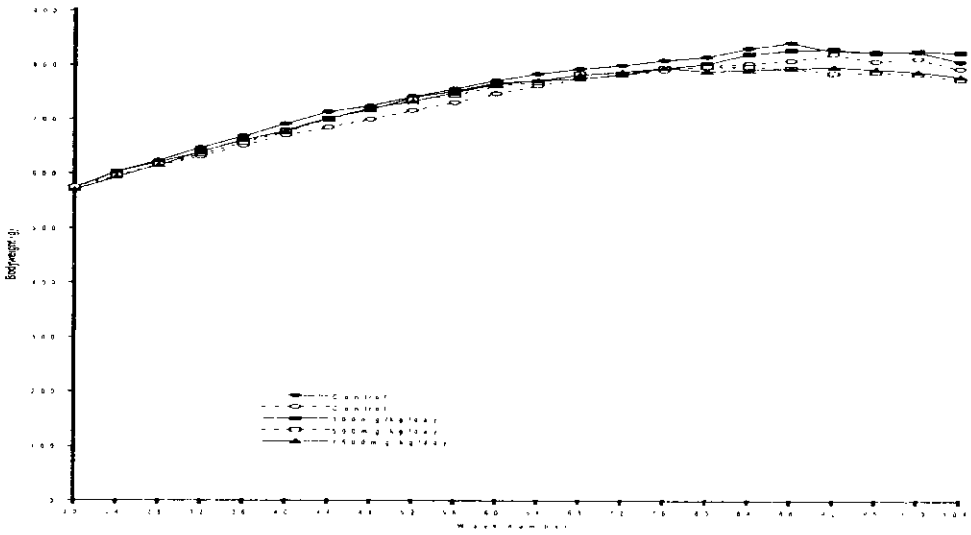
47	Hemopoietic System	46103	LARGE GRANULAR LYMPHOCYTE	1	0.7683
47	Hemopoietic System	46203	LYMPHOMA – MALIGNANT	0.5939	0.7107
47	Hemopoietic System	58703	HISTIOCYTIC SARCOMA - MALIGNAN	1	0.7723
48	Skin and Subcutaneous tissue	54003	SARCOMA – MALIGNANT	1	0.7799
48	Skin and Subcutaneous tissue	54301	FIBROADENOMA - BENIGN	0.7606	0.7594
48	Skin and Subcutaneous tissue	54303	FIBROADENOMA - MALIGNANT	0.6316	0.7289
48	Skin and Subcutaneous tissue	54801	LIPOMA – BENIGN	0.0512	0.0348
48	Skin and Subcutaneous tissue	56001<	DERMAL FIBROMA - BENIGN	0.0322	0.0216
48	Skin and Subcutaneous tissue	5660	BASAL CELL TUMOR - BENIGN	1	0.7799
48	Skin and Subcutaneous tissue	56901	KERATOACANTHOMA - BENIGN	0.2283	0.0399
48	Skin and Subcutaneous tissue	58201	FIBROMA – BENIGN	0.1953	0.1866
48	Skin and Subcutaneous tissue	6040	ZYMBALS GLAND CARCINOMA -	1	0.7662
48	Skin and Subcutaneous tissue	63101	MAMMARY ADENOMA - BENIGN	0.4309	0.4379
48	Skin and Subcutaneous tissue	63203	FIBROSARCOMA - MALIGNANT	0.9134	0.8959
48	Skin and Subcutaneous tissue	6	MAMMARY ADENOLIPOMA - BENIGN	1	0.8528
48	Skin and Subcutaneous tissue	70903	OSTEOSARCOMA - MALIGNANT	0.2108	0.0324
48	Skin and Subcutaneous tissue	749	TRICHOEPITHELIOMA - BENIGN	1	0.7799
48	Skin and Subcutaneous tissue	75001	FIBROMYXOMA – BENIGN	1	0.7799
48	Skin and Subcutaneous tissue	92118	[N]ADENOCARCINOMA	0.899	0.8943
5	Liver	60801	ADENOMA – BENIGN	0.9888	0.9559
7	Pancreas	55501	ISLET CELL ADENOMA - BENIGN	0.2363	0.2147
72	Hindlimbs	90019	PAPILLOMA	0.2283	0.0399
74	Abdominal fat	90213	LIPOMA	1	0.8634
77	Tail	90522	PAPILLOMA	1	0.7129
78	Pinnae	90615	NEURAL CREST TUMOUR	1	0.8542
8	Kidneys	49403	NEPHROBLASTOMA - MALIGNANT	1	0.768
85	Subcutaneous fat	91315	ADENOLIPOMA	0.6299	0.727
85	Subcutaneous fat	91316	LIPOMA	0.5592	0.5996
85	Subcutaneous fat	91319	MAMMARY ADENOCARCINOMA	0.6299	0.727
9	Adrenals	55701	CORTICAL ADENOMA - BENIGN	0.8461	0.8389
9	Adrenals	66001	PHAEOCHROMOCYTOMA - BENIGN	0.2947	0.2446
93	subcutaneous tissue	92111	FIBROADENOMA	1	0.7129

93	subcutaneous tissue	92115	LIPOMA	0.7063	0.8042
93	subcutaneous tissue	92118	[N]ADENOCARCINOMA	1	0.7788
96	stomach fat	92412	MESOTHELIOMA	0.6299	0.727

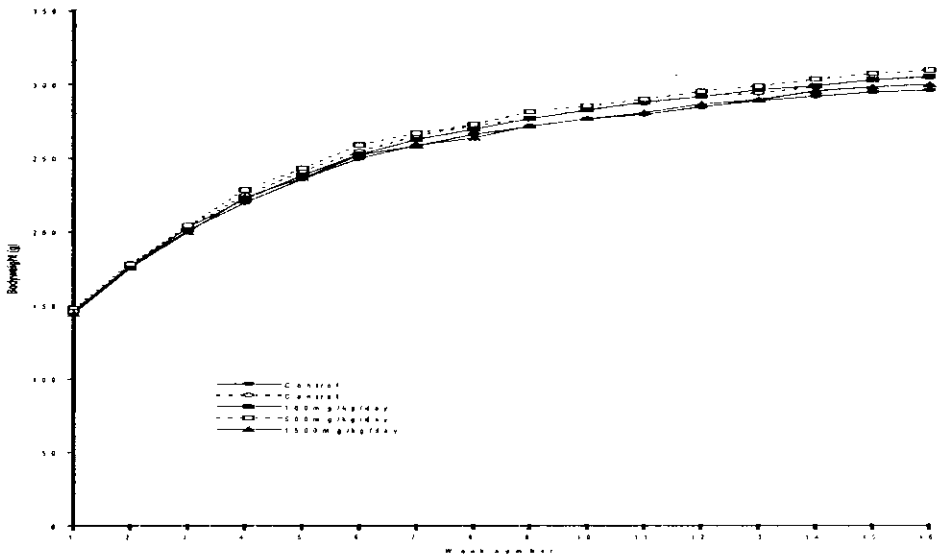
Appendix 7: Graph of Mean Body Weight of Male Rats (week 1-16)



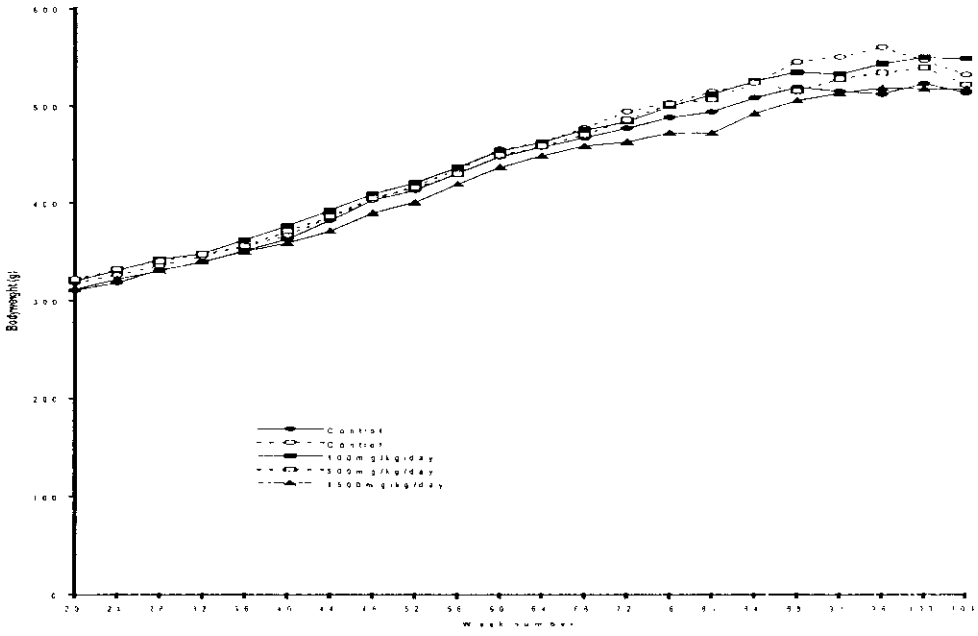
Appendix 8: Graph of Mean Body Weight of Male Rats (week 16-104)



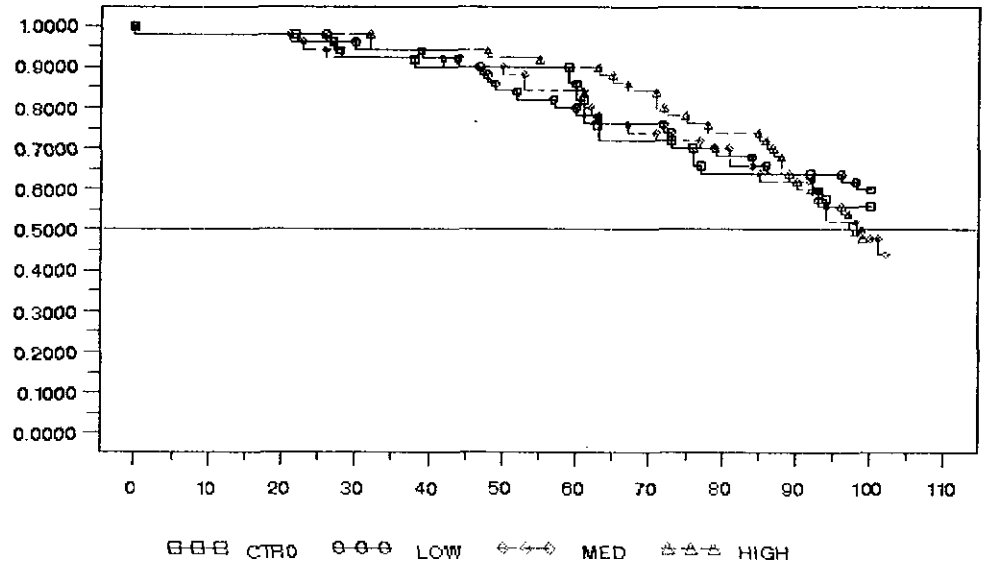
Appendix 9: Graph of Mean Body Weight of Female Rats (week 1-16)



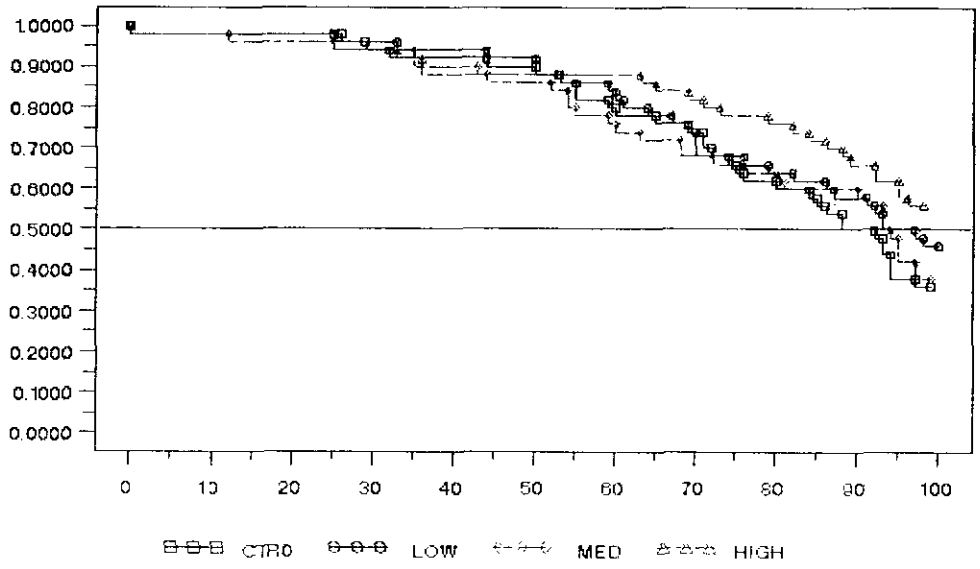
Appendix 10: Graph of Mean Body Weight of Female Rats (week 16-104)



Appendix 11: Survival Graph of Male Mice



Appendix 12: Survival Graph of Female Mice



Appendix 13: Mortality of Male Mice

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0	0-50	50	4	46	92	8
	51-80	46	13	33	66	34
	81-99	33	4	29	58	42
	FINALKILL10 0-102	29	29	0		
LOW	0-50	50	7	43	86	14
	51-80	43	8	35	70	30
	81-99	35	4	31	62	38
	FINALKILL10 0-102	31	31	0		
MED	0-50	50	5	45	90	10
	51-80	45	9	36	72	28
	81-99	36	11	25	50	50
	FINALKILL10 0-102	25	25	0		
HIGH	0-50	50	3	47	94	6
	51-80	47	9	38	76	24
	81-99	38	14	24	48	52
	FINALKILL10 0-102	24	24	0		

Appendix 14: Mortality of Female Mice

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0	0-50	50	5	45	90	10
	51-80	45	14	31	62	38
	81-99	31	13	18	36	64
	FINALKILL10 0-100	18	18	0		
LOW	0-50	50	4	46	92	8
	51-80	46	13	33	66	34
	81-99	33	9	24	48	52
	FINALKILL10 0-100	24	24	0		
MED	0-50	50	6	44	88	12
	51-80	44	12	32	64	36
	81-99	32	13	19	38	62
	FINALKILL10 0-100	19	19	0		
HIGH	0-50	50	4	46	92	8
	51-80	46	7	39	78	22
	81-99	39	11	28	56	44
	FINALKILL10 0-100	28	28	0		

Appendix 15: Tumor Trend Test of Male Mice

1	Adrenals	101301	PHAEOCHROMOCYTOMA BENIGN	0.0469	0.0057
1	Adrenals	55001	CORTICAL ADENOMA BENIGN	0.7203	0.7199
1	Adrenals	63501	SUBCAPSULAR CELL ADENOMA BENIG	0.799	0.7973
10	Lungs	44001	BRONCHIOALVEOLAR ADENOMA BENIG	0.6329	0.6337
10	Lungs	55603	ADENOCARCINOMA MALIGNANT	0.6008	0.6043
10	Lungs	76503	BRONCHIOALVEOLAR CARCINOMA	0.0188	0.0151
11	Testes	111901	HAEMANGIOMA BENIGN	0 2202	0.0374
11	Testes	74801	INTERSTITIAL CELL ADENOMA BENI	0.489	0.4382
12	Epididymides	112603	SARCOMA MALIGNANT	0.2202	0.0374
14	Seminal vesicles	53601	ADENOMA BENIGN	0.2754	0.0611
22	Stomach	59501	ADENOMA BENIGN	0.0041	0.0006
23	Duodenum	111501	ADENOMA BENIGN	0.0469	0.0057
27	Colon	102903	ADENOCARCINOMA MALIGNANT	1	0.7948
36	Tongue	54101	PAPILLOMA BENIGN	0.1579	0.016
38	Brain	41403	SARCOMA, MENINGEAL MALIGNANT	0.7459	0.7674
39	Pituitary gland	41503	SARCOMA, MENINGEAL MALIGNANT	0.7459	0.7674
39	Pituitary gland	68601	ADENOMA - PARS ANTERIOR BENIGN	0.5405	0.468
39	Pituitary gland	68803	ADENOCARCINOMA MALIGNANT	0.275	0.061
43	Femur (including bone marrow)		MAST CELL SARCOMA MALIGNANT	0.2202	0.0374
44	Sternum with bone marrow	10410	MAST CELL SARCOMA MALIGNANT	0.2202	0.0374
45	Spinal cord	104203	MAST CELL SARCOMA MALIGNANT	0 2202	0.0374
46	Hematopoetic Tumour	23503	LYMPHOMA MALIGNANT	0.3915	0.3934
46	Hematopoetic Tumour	81203	HISTIOCYTIC SARCOMA MALIGNANT	0.6031	0.5375
49	Harderian glands	58901	ADENOMA BENIGN	0.9791	0.9661
5	Liver	103803	MAST CELL SARCOMA MALIGNANT	0.2202	0.0374
5	Liver	116501	HEMANGIOMA BENIGN	0.4615	0.4882
5	Liver	119303	SARCOMA MALIGNANT	0 4495	0.4819
5	Liver	51701	HEPATOCELLULAR ADENOMA BENIGN	0 3073	0.305
5	Liver	51903	HEMANGIOSARCOMA MALIGNANT	0.0149	0.0049

5	Liver	58403	HEPATOCELLULAR CARCINOMA	0.1332	0.1252
51	Lymph Nodes	30903	LYMPHOMA MALIGNANT	0.4211	0.4268
55	Skin (non-protocol)	111403<	SQUAMOUS CELL CARCINOMA MALIGN	0.2202	0.0374
55	Skin (non-protocol)	117101	HIBERNOMA BENIGN	0.4495	0.4819
55	Skin (non-protocol)	121103	HEMANGIOSARCOMA MALIGNANT	0.5187	0.5388
55	Skin (non-protocol)	121301	PAPILLOMA BENIGN	1	0.7948
55	Skin (non-protocol)	76203	LYMPHOMA MALIGNANT	0.4242	0.1318
8	Spleen	103903	MAST CELL SARCOMA MALIGNANT	0.2202	0.0374
8	Spleen	57703	HEMANGIOSARCOMA MALIGNANT	0.4538	0.3085
9	Kidneys	77001	TUBULAR ADENOMA BENIGN	0.5761	0.6659

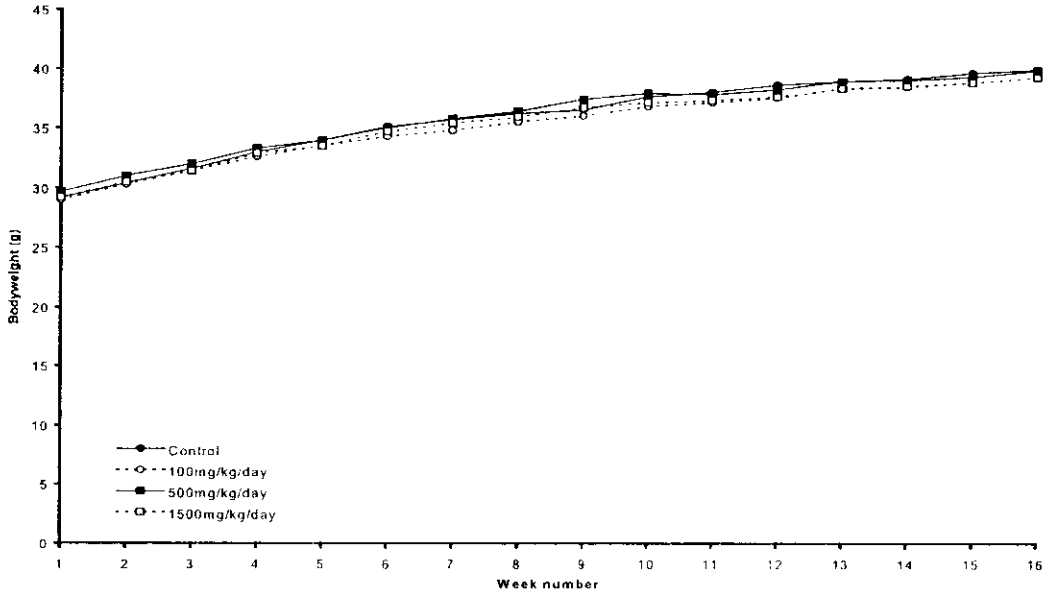
Appendix 16: Tumor Trend Test of Female Mice

Organ code	Organ	Tumor code	Tumor		
1	Adrenals	101303	PHAEOCHROMOCYTOMA MALIGNANT	0.7978	0.789
1	Adrenals	55001	CORTICAL ADENOMA BENIGN	0.9494	0.883
1	Adrenals	63501	SUBCAPSULAR CELL ADENOMA BENIG	0.6718	0.672
10	Lungs	44001	BRONCHIOALVEOLAR ADENOMA BENIG	0.8011	0.7988
10	Lungs	55603	ADENOCARCINOMA MALIGNANT	0.7531	0.7685
10	Lungs	76503	BRONCHIOALVEOLAR CARCINOMA	0.4508	0.4452
10	Lungs	94503	CARCINOMA - UNKNOWN ORIGIN	0.5259	0.5496
15	Uterus	54501	LEIOMYOMA BENIGN	0.2105	0.1213
15	Uterus	61601	ADENOMA BENIGN	1	0.8258
15	Uterus	62603	LEIOMYOSARCOMA MALIGNANT	0.8276	0.8332
15	Uterus	71801	POLYP BENIGN	0.6647	0.6644
15	Uterus	78403	ENDOMETRIAL ADENOCARCINOMA	0.5388	0.5582
15	Uterus	80801	HEMANGIOMA BENIGN	0.2237	0.2055
15	Uterus	81603	HEMANGIOSARCOMA MALIGNANT	0.462	0.4208
15	Uterus	84203	HISTIOCYTIC SARCOMA MALIGNANT	0.7978	0.789
16	Uterine cervix	109001	LEIOMYOMA BENIGN	0.7453	0.8102
16	Uterine cervix	115901	POLYP BENIGN	0.6928	0.755
16	Uterine cervix	62703	LEIOMYOSARCOMA MALIGNANT	0.8196	0.8264
17	Vagina	61203	SQUAMOUS CELL CARCINOMA MALIGN	1	0.821
17	Vagina	62803	LEIOMYOSARCOMA MALIGNANT	1	0.8179
17	Vagina	84601	POLYP BENIGN	1	0.8243
18	Ovaries	104801	LUTEOMA BENIGN	0.7801	0.7891
18	Ovaries	115501	TUBULOSTROMAL ADENOMA BENIGN	0.4533	0.4605
18	Ovaries	81701	PAPILLARY CYSTADENOMA BENIGN	0 3412	0.2904
2	Mesenteric lymph node	116001	HEMANGIOMA BENIGN	0.6928	0.755
22	Stomach	125903	ANAPLASTIC TUMOR, UNKNOWN ORIG	0.1522	0.0147
22	Stomach	48703	SQUAMOUS CELL CARCINOMA MALIGN	0 2539	0.0518
22	Stomach	59501	ADENOMA BENIGN	0 2324	0.1869
24	Jejunum	108503	ADENOCARCINOMA MALIGNANT	0.3146	0 078

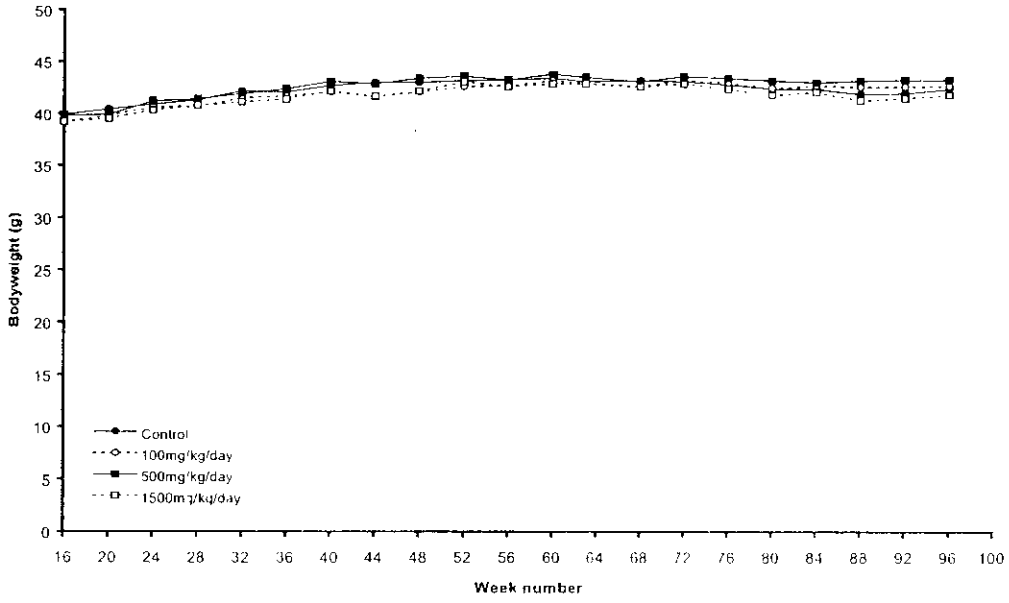
29	Thyroid gland	92401	FOLLICULAR CELL ADENOMA BENIGN	0.9501	0.886
39	Pituitary gland	115301	ADENOMA - PARS INTERMEDIA BENI	0.222	0.1304
39	Pituitary gland	68601	ADENOMA - PARS ANTERIOR BENIGN	0.863	0.8587
4	Thymus	76901	THYMOMA BENIGN	0.7978	0.789
4	Thymus	76903	THYMOMA MALIGNANT	1	0.8319
43	Femur (including bone marrow)		MAST CELL SARCOMA MALIGNANT	1	0.8319
43	Femur (including bone marrow)	54701	OSTEOMA BENIGN	1	0.8609
44	Sternum with bone marrow	10410	MAST CELL SARCOMA MALIGNANT	1	0.8319
44	Sternum with bone marrow	118301	OSTEOMA BENIGN	0.5281	0.5669
45	Spinal cord	104203	MAST CELL SARCOMA MALIGNANT	1	0.8319
46	Hematopoetic Tumour	23503	LYMPHOMA MALIGNANT	0.9738	0.9697
46	Hematopoetic Tumour	81203	HISTIOCYTIC SARCOMA MALIGNANT	0.8942	0.8791
49	Harderian glands	58901	ADENOMA BENIGN	0.3311	0.3323
49	Harderian glands	76803	ADENOCARCINOMA MALIGNANT	0.6105	0.5585
5	Liver	103803	MAST CELL SARCOMA MALIGNANT	1	0.8319
5	Liver	51701	HEPATOCELLULAR ADENOMA BENIGN	0.2269	0.2154
5	Liver	51903	HEMANGIOSARCOMA MALIGNANT	0.2197	0.1709
5	Liver	58403	HEPATOCELLULAR CARCINOMA	0.5327	0.3725
55	Skin (non-protocol)	110601	ADENOACANTHOMA BENIGN	0.7978	0.789
55	Skin (non-protocol)	110603	ADENOACANTHOMA MALIGNANT	1	0.8319
55	Skin (non-protocol)	116603	SARCOMA MALIGNANT	0.7731	0.7809
55	Skin (non-protocol)	116703<	MAMMARY ADENOCARCINOMA MALIGNA	0.2733	0.2438
55	Skin (non-protocol)	56003	ADENOCARCINOMA MALIGNANT	0.2391	0.0466
55	Skin (non-protocol)	77903	FIBROSARCOMA MALIGNANT	0.3146	0.078
55	Skin (non-protocol)	83403	OSTEOSARCOMA MALIGNANT	1	0.8243
55	Skin (non-protocol)	84801	MAMMARY ADENOMA BENIGN	1	0.8243
55	Skin (non-protocol)	88701	SEBACEOUS ADENOMA BENIGN	0.7174	0.7641
55	Skin (non-protocol)	91501	CHONDROMA BENIGN	0.5217	0.5137
55	Skin (non-protocol)	93003	RHABDOMYOSARCOMA MALIGNANT	0.7708	0.7749
62	Abdominal cavity	126003	ANAPLASTIC TUMOR, UNKNOWN ORIG	0.2745	0.0606
63	Clitoral glands	125701	HEMANGIOMA BENIGN	0.413	0.4128

64	Tail	64503	MALIGNANT FIBROUS HISTIOCYTOMA	0.6957	0.7133
66	Diaphragm	71703	LYMPHOMA MALIGNANT	1	0.776
8	Spleen	103903	MAST CELL SARCOMA MALIGNANT	1	0.8319
9	Kidneys	77001	TUBULAR ADENOMA BENIGN	0.7174	0.7641

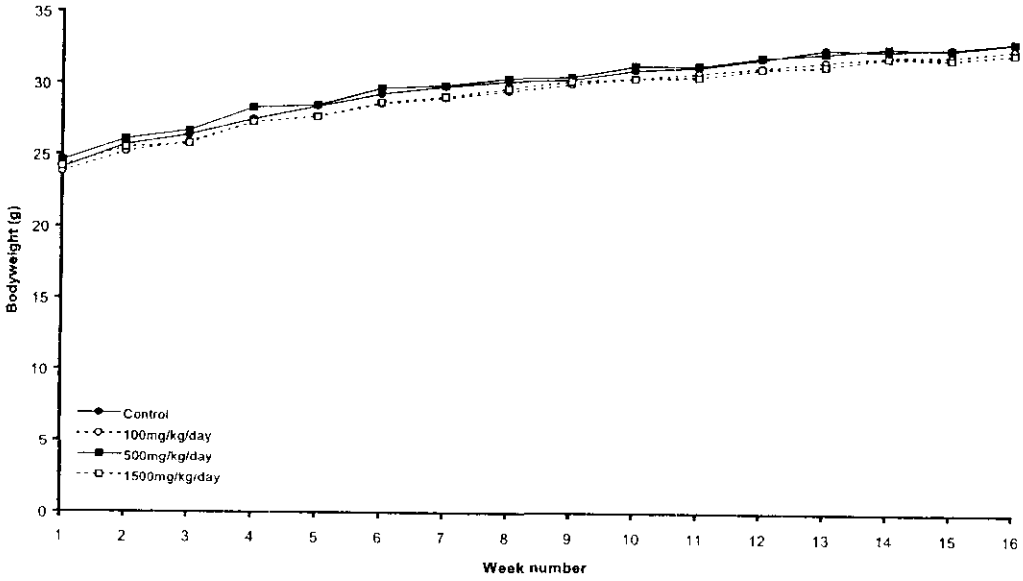
Appendix 17: Graph of Mean Body Weight of Male Mice (week 1-16)



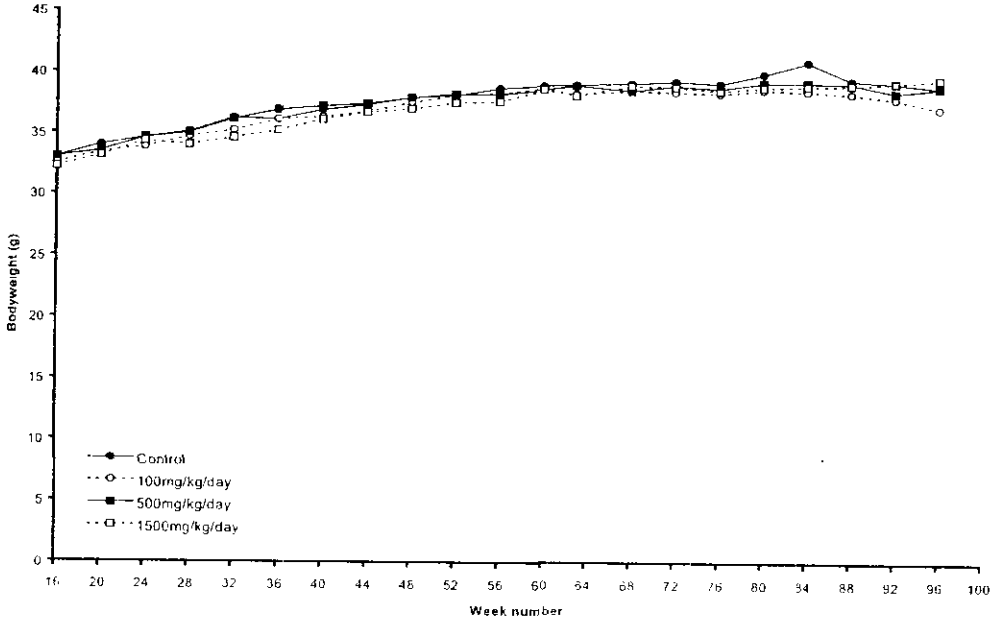
Appendix 18: Graph of Mean Body Weight of Male Mice (week 16-99)



Appendix 19: Graph of Mean Body Weight of Female Mice (week 1-16)



Appendix 20: Graph of Mean Body Weight of Female Mice (week 16-99)



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/s/

Jasmine Choi
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Roswitha Kelly
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George Chi
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Executive CAC
Date of Meeting: November 5, 2002

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Robin Huff, Ph.D., HFD-570, Alternate Member
Josie Yang, Ph.D., HFD-550, Alternate Member
Charles Resnick, Ph.D., Supervisory Pharmacologist, HFD-110

Presenting Reviewer and Author of Draft: Xavier Joseph, D.V.M., HFD-110

The following is a brief summary of the Division's presentation and the Committee's discussion and recommendations. Detailed study information can be found in Dr. Joseph's review.

NDA # 21-468
Drug Name: Fosrenol (Lanthanum carbonate hydrate)
Sponsor: Shire Pharmaceutical Inc.

Background: Fosrenol is a phosphate binding agent indicated for [ ] Fosrenol tested negative for genotoxicity in *in vitro* (bacterial reverse mutation assay, and mammalian cell gene mutation and cytogenetic assays in Chinese hamster ovary cells) and *in vivo* (mouse micronucleus assay) test systems.

Rat Carcinogenicity Study

A 104-week carcinogenicity study was conducted with lanthanum carbonate administered by oral gavage to [ ] Sprague-Dawley rats at 0 (vehicle control), 0 (vehicle control), 100, 500 and 1500 mg/kg/day. The top dose (MTD) was selected on the basis of the results of a twenty-six week oral toxicity study in rats (0, 100, 600 and 2000 mg/kg/day), in which dose-related increased incidences of stomach lesions were seen in mid and high dose animals (no prior FDA dose concurrence).

There were no significant treatment-related effects on male or female survival, body weight gain or food consumption. The only significant non-neoplastic findings were limited to the stomachs (epithelial hyperplasia of the glandular and non-glandular regions) of the mid and high dose males and females.

Sponsor's analysis of the rat tumor data showed statistically significant increasing trends for the histiocytic sarcomas of the hemopoietic system and the liver in males, and adeno-carcinoma, fibroma and lipoma of the skin and sc tissues in females. However, the FDA analyses of the data revealed that none of the above tumor findings reached statistical significance for either sex when α levels of 0.005 and 0.025 were used for the analysis of common and rare tumors, respectively. The sponsor used a significance level of 0.05 for all tumors. Furthermore, the sponsor had included metastatic as well as primary male liver tumors for their analysis, while the FDA analysis included only primary tumors.

Mouse Carcinogenicity study

A 99-week carcinogenicity study was performed with lanthanum carbonate administered by oral gavage to [redacted] CD-1 mice at 0 (vehicle control), 100, 500 and 1500 mg/kg/day. The high dose (MTD) was selected based on the results of a 13-week oral toxicity study in mice (0, 500, 1500 and 2000 mg/kg/day), in which dose-related increased incidences of stomach lesions were seen in mid and high dose animals (no prior FDA dose concurrence).

There were no significant treatment-related effects on male or female survival, body weight gain or food consumption. Significant non-neoplastic findings were limited to the stomachs (increased incidences of glandular hyperplasia, mucosal and/or submucosal inflammation of the glandular stomach and squamous epithelial hyperplasia of the limiting ridge) of the high dose males and females.

Sponsor's analysis showed a statistically significant trend for stomach adenoma in male mice. FDA analyses revealed significant positive trends, based on concurrent control incidence rate, for the following tumors (α level = 0.025)

- stomach adenoma – 0/50 (C), 0/50 (LD), 0/50 (MD) and 4/50 (HD) p = 0.0041
- liver hemangiosarcoma – 0/50 (C), 0/50 (LD), 1/50 (MD) and 3/50 (HD) p = 0.0149
- liver hemangiosarcoma + hemangioma – 0/50 (C), 0/50 (LD), 2/50 (MD) and 3/5(HD) p= 0.0182

The combined incidence rates for hemangiosarcoma and hemangioma for all organs did not attain statistical significance (based on concurrent control incidence rate); 1/50 (C), 0/50 (LD), 3/50 (MD) and 4/50 (HD) p = 0.022 (>0.005)

Historical control incidence rates from 46 studies ([redacted] showed that the liver hemangiosarcoma is a common tumor (incidence rate >1%; 29/2571) for the strain of mouse used in this study. When tested at an α level of 0.005, hemangiosarcoma of the liver and the combined incidence rates for hemangioma and hemangiosarcoma of the liver as well as for all organs, across groups, did not attain statistical significance. [Historical control data (12 studies) from the contract laboratory also showed that the liver hemangiosarcoma (incidence rates ranging from 0 to 6%) is a common tumor.]

The [redacted] historical control database showed that the stomach adenoma is a rare tumor (0/2571) for male CD-1 mice.

Executive CAC Conclusions and Recommendations

Rat Carcinogenicity Study

The committee agreed that the study was adequate.
The committee agreed that there were no treatment-related tumor findings.

Mouse Carcinogenicity Study

The committee agreed that the study was adequate.
The committee agreed that the stomach adenomas in male mice were drug related.

/S/

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, HFD-110
/ResnickC, HFD-110
/Joseph, HFD-110
/HintonD, HFD-110
/Ascifried, HFD-024

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Joe Contrera
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Ms. Roswitha Kelly 5S/DBI WOC 2 Rm 2032 HFD 710	Ms. Denise M. Hinton DCRDP WOC 2 Rm 5028 HFD 110

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 27, 2002		21-468	CD-Rom	June 20, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Fosrenol Lanthanum Carbonate Hydrate	S	3 New Formulation	July 29, 2002

NAME OF FIRM: Shire Pharmaceuticals Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
  ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ND OF PHASE II MEETING ONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS x OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	X PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
Preclinical data sets enclosed for the long-term carcinogenicity studies from study SPD/87/C rats and SPD/88/C in mice. Please complete review of statistical analysis for CAC.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Dr Joseph Xavier	☐ MAIL X Electronic
SIGNATURE OF RECEIVER Roswitha Kelly	SIGNATURE OF DELIVERER Denise M Hinton

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-468

Statistical Review(s)