CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020815

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
(Carcinogenicity Review)

Date: JUN 30 1997

NDA#: 20-815

Applicant: Eli Lilly and Company

Name of Drug: Evista (raloxifene hydrochloride)

Documents Reviewed: Pharmacology Section of the Submission, Vols. 29, and 39.

Reviewing Pharmacologist: Gemma Kuijpers, Ph.D.

Summary

The results of statistical tests show that there is statistical significance in survival distributions among the treatment groups in male rats but not in male mice, female mice, and female rats. The dose-mortality trend in mortality is significant in male mice and male rats, but not in female mice and female rats.

The dose-response relationships in incidence rates are statistically significant in the following tumors: (in male mice) liver malignant interstitial cell tumor ($p = 0.002$), prostate leiomyoblastoma ($p = 0.005$), testis benign interstitial cell tumor ($p < 0.0001$), and testis malignant interstitial cell tumor ($P = < 0.0001$), pooled maglinant and benign interstitial cell tumors ($p < 0.001$), pooled prostate adenoma and adenosarcoma ($p = 0.004$); (in female mice) ovary malignant granulosa cell tumor ($p = 0.002$), malignant ovarian tumors (pooled ovarian maglinant granulosa cell tumor and maglinant luteoma) ($p < 0.001$), benign ovarian tumors (pooled benign ovarian luteoma, papillary adenoma, benign granulosa cell tumor, adenoma, thecoma, and granulosa-theca tumor) ($p < 0.001$), and all malignant and benign ovarian tumors ($p < 0.001$); (male rats) kidney renal cell carcinoma ($p = 0.022$); (female rats) ovary benign granulosa-theca tumor ($p = 0.021$), and ovary benign granulosa cell tumor ($p = 0.004$).

I. Introduction

In this NDA submission, two animal carcinogenicity studies (one

in mice and one in rats) were included. The two studies were conducted to investigate the carcinogenic potential of raloxifene when administered in the diet at some selected dose levels for up to 24 months. Dr. Gemma Kuijpers of HFD-510, who is the reviewing pharmacologist of this NDA, has requested Division of Biometrics II to perform a statistical review and evaluation of the two studies. This statistical review report is based on the sponsor's pharmacology and toxicology reports included in the NDA submission, and outputs of computer runs produced by Ms. Moh-Jee Ng of Division of Biometrics II using the electronic data sets submitted by the sponsor. Results of this review have been discussed with Dr. Kuijpers.

II. The Study Designs

II.1. The Mouse Study

Two hundred and forty CD-1 male mice and two hundred and forty CD-1 female mice were used in this study. For each sex, the animals were randomly divided into four treatment groups of size 60. The animals were treated with 0%, 0.005%, 0.03%, and 0.15% raloxifene in the diet for 21 months. These dose levels provided daily doses of 0, 6.5, 38, and 195 mg/kg for males and 0, 8.7, 49, and 225 mg/kg for females.

All animals died during the study period and survived to the end of the study were microscopically examined for neoplastic lesions.

II.2. The Rat Study

Two hundred and forty F344 male rats and two hundred and forty F344 female rats were used in this study. For each sex, the animals were randomly divided into four treatment groups of size 60. The animals were treated with 0%, 0.005%, 0.02%, and 0.1% raloxifene in the diet for 24 months for males, and 0%, 0.02%, 0.1%, and 0.5% for 24 months for females. These dose levels provided daily doses of 0, 2.3, 9.3, and 48 mg/kg for males and 0, 10.4, 51, and 259 mg/kg for females.

All animals died during the study period and survived to the end of the study were microscopically examined for neoplastic lesions.

III. The Sponsor's Analyses and Results

In both the mouse and the rat studies, the sponsor used the methods of Tarone (1975) and of Cox (1972) in the PROC CHRONIC (Kodell et al. 1983) in SAS to test the heterogeneity of survival distributions and the dose-related increasing trend in mortality; and the survival-adjusted methods described in Peto et al. (1980) to test linear trends in tumor incidence rates. The Peto's trend tests using the ordinal scale 0, 1, 2, 3 were also implemented in the PROC CHRONIC. The randomization trend test (or exact permutation trend test) (Mehta and Patel, 1991) was used to test the linear trend for tumors with small numbers of tumor bearing animals. Further evaluations of dose-related tumor incidence were carried out using Peto's trend tests in a sequential fashion.

III.1. The Mouse Study

Based on the results of the above statistical tests of the mortality and tumor data, the sponsor reported the following statistically significant (at 0.05 level) findings:

Male mice

There was a significant increase in mortality in male mice receiving a raloxifene dose of 195 mg/kg ($p = 0.05$).

The positive trends were found statistically significant (at 0.05 level) in the following tumors in male mice: maglinant testicular interstitial cell tumor ($p < 0.001$), prostate adenocarcinoma ($p = 0.05$), benign testicular interstitial cell tumor ($p < 0.001$), prostate adenoma ($p = 0.025$), prostate leiomyoblastoma ($p = 0.003$), pooled maglinant and benign interstitial cell tumors ($p < 0.001$), pooled prostate adenoma and adenosarcoma ($p = 0.004$).

Female Mice

There was no dose-related increase in mortality in female mice.

The positive trends were found statistically significant (at 0.05 level) in the following tumors in female mice: malignant ovarian granulosa cell tumor ($p = 0.001$), benign ovarian luteoma ($p = 0.025$), benign ovarian granulosa cell tumor ($p = 0.017$), benign liver hepatocellular adenoma ($p = 0.036$), malignant ovarian tumors (pooled ovarian maglinant granulosa cell tumor and maglinant luteoma) ($p < 0.001$), benign ovarian tumors (pooled benign ovarian luteoma, papillary adenoma, benign granulosa cell tumor, adenoma, thecoma, and granulosa-theca tumor) ($p < 0.001$), and all malignant and benign ovarian tumors ($p < 0.001$).

III.2. The Rat Study

Based on the results of the above statistical tests of the mortality and tumor data, the sponsor reported the following statistically significant (at 0.05 level) findings:

Male Rats

The survival distributions were significantly heterogeneous ($p < 0.001$). There was a significant dose-related decreasing trend in mortality ($p < 0.001$).

The sponsor excluded the 2.3 mg/kg group in the tumor data analysis on the ground that the mortality of the group was significantly higher than that of the control group.

No statistically significant (at 0.05) positive linear trend was detected in the tumors tested in the sponsor's tumor data analyses excluding the 2.3 mg/kg group.

Female Rats

There was no statistical significance in either a dose-related increasing trend ($p = 0.923$) or any heterogeneity ($p = 0.184$) in mortality in female rats.

The sponsor's tumor data analyses showed statistically significant (at 0.05 level) positive linear trends in the following tumors: benign ovarian granulosa cell tumor ($p = 0.004$) and benign granulosa-theca tumor ($p = 0.020$), and benign ovarian tumors (pooled benign ovarian granulosa cell tumor, benign granulosa-theca tumor and benign thecoma tumor) ($p < 0.001$).

IV. The Review's Analyses, Results, and Comments

IV.1. Statistical Methods in Carcinogenicity Studies

The intercurrent mortality data should be tested first to see if the survival distributions of the treatment groups are significantly different and if the linear trend in mortality is significant. Since the effects of differences in intercurrent mortality on the number of tumor bearing animals can be very substantial, survival-adjusted methods should be used in the tests for positive linear trends or differences in tumor incidence rates. It is recommended in Peto et. al. (1980) that, whether or not survivals among treatment groups appear to be different, they should routinely be corrected for when presenting

experimental results. Therefore, before analyzing the tumor data, the intercurrent mortality data are tested first to see if the survival distributions of the treatment groups are significantly different or if there exists a significant dose-response relationship. The Cox's Test [Cox (1972), Thomas, Breslow, and Gart (1977), and Gart et al. (1986)], the generalized Wilcoxon or Kruskal-Wallis test [Breslow (1970), Gehan (1965), and Thomas, Breslow, and Gart (1977)], and the Tarone trend tests [Cox, (1959), Peto et al. (1980), and Tarone (1975)] are used to test the heterogeneity in survival distributions and significant dose-response relationship (linear trend) in mortality.

The choice of a survival-adjusted method to analyze tumor data depends on the role which a tumor plays in causing the animal's death. Tumors can be classified as "incidental", "fatal", and "mortality-independent (or observable)" according to the contexts of observation described in Peto et al. (1980). Tumors which are not directly or indirectly responsible for the animal's death, but are merely observed at the autopsy of the animal after it has died of some unrelated causes are said to have been observed in an incidental context. Tumors which kill the animal either directly or indirectly are said to have been observed in a fatal context. Tumors, such as skin tumors, whose times of criterion attainment (that is, detection of the tumor at a standard point of their development) other than the times or causes of death are of primary interest of analyses are said to have been observed in a mortality-independent (or observable) context. To apply a survival-adjusted method correctly, it is essential that the context of observation of a tumor be determined as accurately as possible.

The prevalence method, the death-rate method, and the onset-rate method should be used to analyze data of tumors observed in incidental, fatal, and mortality-independent contexts of observation, respectively. For tumors which are observed in more than one context, combinations of the above different methods should be used to obtain overall results.

When the numbers of tumor-bearing animals across treatment groups are small, the test results of the death-rate method, the onset-rate method, and the prevalence method which use the normal approximation are not stable and reliable. Under this circumstance, exact permutation methods should be used to replace the above methods in tests for positive linear trends or differences in tumor incidence rates.

Since linear trend tests were performed on all the tumor/tissue combinations, the overall false positive rate will be very large

if each tumor/tissue combination was tested at 0.05 level of significance. The decision rule described in Lin and Rahman (1996) should be used to adjust the effect of multiple testings and to control the overall false positive rate of a standard two-species-and-two-sex study to around 10%. The decision rule tests a common tumor at 0.005 level of significance and a rare tumor at 0.025 level of significance. A tumor is defined as rare if the spontaneous background rate, either based on concurrent control groups or combination of both concurrent control and reliable historical control data, is 1% or less.

In negative studies in which analyses did not detect any linear trend or difference in tumor rates, it is extremely important to perform a further evaluation of the validity of the design of the experiment to see if there are sufficient numbers of animals living long enough to get adequate exposure to the chemical and to be at risk of forming late-developing tumors; and if the doses used are high enough to present a reasonable tumor challenge to the tested animals.

IV.2. The Mouse Study

IV.2.1. Analysis of Intercurrent Mortality Data

The intercurrent mortality data for male, and female mice are summarized in Table 1a and Figure 1a for males, and Table 2a and Figure 2a for females. The statistical methods described in Section IV.1 were used to test the homogeneity of the survival distributions and the dose-related trends in mortality among the treatment groups. The results of those tests are presented in Tables 1b and 2b for males and females, respectively. The Kaplan-Meier survival distributions of the four treatment groups are given in Figure 1b and 2b for males and females, respectively.

The results of the Cox and the Kruskal-Wallis tests show that there is no statistical significance in survival distributions among the treatment groups for either males or females. The two tests also showed that there was a statistically significant (at 0.05 level) positive dose-mortality trend in male mice but not in female mice.

IV.2.2. Analysis of Tumor Data

The statistical methods described in Section IV.1 were used to analyze the pathology data. The average daily doses 0, 6.5, 38, and 195 mg/kg for males, and 0, 8.7, 49, and 225 mg/kg were used as weights in the above tests. The mortality-adjusted analyses

were based on the partition of the 21-month study period into the following intervals: 0-52, 53-78, 79-89, and 90-91 weeks. Detailed results of the tumor data analyses are presented in Tables 1c and 2c for males and females, respectively.

Based on the statistical decision rule which adjusts the effect of multiple testings, the positive linear trend in tumor incidences was found to be statistically significant in the following tumor types in male mice: liver malignant interstitial cell tumor ($p = 0.002$), prostate leiomyoblastoma ($p = 0.005$), testis benign interstitial cell tumor ($p < 0.0001$), and testis malignant interstitial cell tumor ($P = < 0.0001$).

For females, the positive linear trend in ovary malignant granulosa cell tumor is statistically significant ($p = 0.002$).

The overall incidence rates of the above tumors showing significant linear trends are as follows:

Sex	Tissue	Tumor	Incidence Rates				P-value
			C	L	M	H	
M	Liver	Malignant interstitial cell tumor	0	0	0	4	0.002
M	prostate	Leiomyoblastoma	0	0	0	4	0.005
M	Testis	Benign interstitial cell tumor	2	1	13	17	<0.0001
M	Testis	Malignant interstitial cell tumor	0	0	2	10	<0.0001
F	Ovary	Malignant granulosa cell tumor	0	2	4	8	0.002

IV.3. The Rat Study

IV.3.1. Analysis of Intercurrent Mortality

The intercurrent mortality data for male, and female rats are summarized in Table 3a and Figure 3a for males, and Table 4a and Figure 4a for females. The statistical methods described in

Section IV.1 were used to test the homogeneity of the survival distributions and the dose-related trends in mortality among the treatment groups. The results of those tests are presented in Tables 3b and 4b for males and females, respectively. The Kaplan-Meier survival distributions of the four treatment groups are given in Figure 3b and 4b for males and females, respectively.

The results of the Cox and the Kruskal-Wallis tests show that the survival distributions among the treatment groups are statistically significant ($p < 0.0001$) for male rats. The (negative) dose-mortality trend in male rats is also statistically significant ($p = 0.001$). The two tests showed that there was no statistically significant (at 0.05 level) positive dose-mortality trend in female rats. There were some differences in survival distributions among the treatment groups in female rats. However, the differences were not statistically significant ($p = 0.0601$ in Cox test and 0.0740 in Kruskal-Wallis test).

IV.3.2. Analysis of Tumor Data

The statistical methods described in Section IV.1 were used to analyze the pathology data. The average daily doses 0, 2.3, 9.3, and 48 mg/kg for males, and 0, 10.4, 51, and 259 mg/kg were used as weights in the above tests. The mortality-adjusted analyses were based on the partition of the 24-month study period into the following intervals: 0-84, 85-104, and 104-106 weeks. Detailed results of the tumor data analyses are presented in Tables 3c and 4c for males and females, respectively.

Based on the statistical decision rule which adjusts the effect of multiple testings, the positive linear trend in tumor incidences was found to be statistically significant in the following tumor types in male rats: kidney renal cell carcinoma ($p = 0.022$).

For female rats, the following statistically significant positive linear trends were detected: ovary benign granulosa-theca tumor ($p = 0.021$), and ovary benign granulosa cell tumor ($p = 0.004$).

The overall incidence rates of the above tumors showing significant linear trends are as follows:

Sex	Tissue	Tumor	Incidence Rates				P-value
			C	L	M	H	
M	Kidney	Renal cell carcinoma	0	0	0	3	0.022
F	Ovary	Benign granulosa-theca tumor	0	0	1	3	0.021
F	Ovary	Benign granulosa cell tumor	0	0	0	4	0.004

IV.3.3. Comments

1. The sponsor tested all positive linear trends at 0.05 significance level, and reported more significant results than the reviewer's results.

   As mentioned above, the overall false positive rate will be very large if each tumor/tissue combination was tested at 0.05 level of significance.

   The decision rule (testing common tumors at 0.005 and rare tumors at 0.025 levels) described in Lin and Rahman (1996) was used by this reviewer to adjust the effect of multiple testings and to control the overall false positive rate at an acceptable level about 10%.

2. After using the Lin-Rahman decision rule to adjust the effect of multiple testings, the reviewer's results are consistent with the sponsor's results except the results of the male rat study, in which the low dose was excluded in the sponsor's analysis due to high mortality of the group. It is not justified to do that since the survival adjusted test had taken the differences in mortality among treatment groups into consideration in the analysis.

3. In the male rat study, the significant dose related increase in kidney renal cell carcinoma ($p = 0.22$) was missed in the sponsor's analyses. The incidence rates were 0, 0, 0, 3 for the four treatment groups.

4. In the analyses of the mouse study data, the sponsor's included some tests on combination of data of different

tumors of the same site. The reviewer did not repeat those tests. The sponsor's results can be used if information about those tests is needed in the determination of the carcinogenic effect of raloxifene.

V. References

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Concur:
Concur: S. Edward Nevius, Ph.D.
Director
Division of Biometrics II

cc: Original: NDA 20-815
HFD-510/Division File
HFD-510/GKuijpers, RSteigerwalt
HFD-715/Chron, Division File
HFD-715/KLin, DMarticello, MNg

Attachments

The attachments to the report are listed on next pages.

Table or Figure — Page Number

Intercurrent Mortality Rates
Species: Mouse Sex: Male

	Dose											
	CTRL			LOW			MED			HIGH		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(-wks)												
0-52		.				1.7			1.7			1.7
53-78			11.7			8.5			13.3			13.3
79-89			20.0			15.3			18.3			31.7
90-91			80.0			84.7			81.7			68.3

TABLE 1a

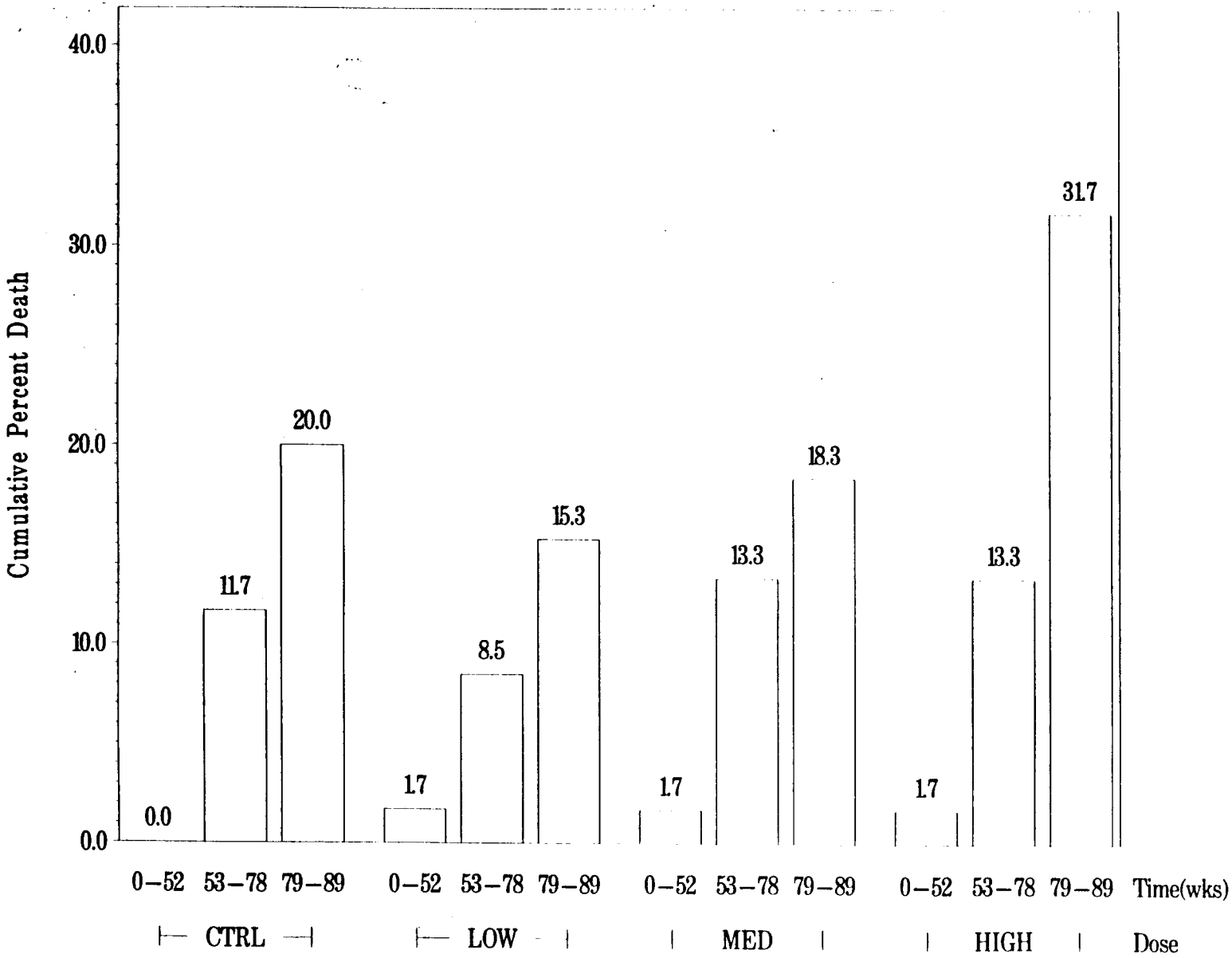
Dose-Mortality Trend Tests
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute
Species: Mouse
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	4.83	0.0279
	Depart from Trend	0.53	0.7661
	Homogeneity	5.37	0.1468
Kruskal-Wallis	Dose-Mortality Trend	4.55	0.0329
	Depart from Trend	0.50	0.7772
	Homogeneity	5.06	0.1678

TABLE 1b

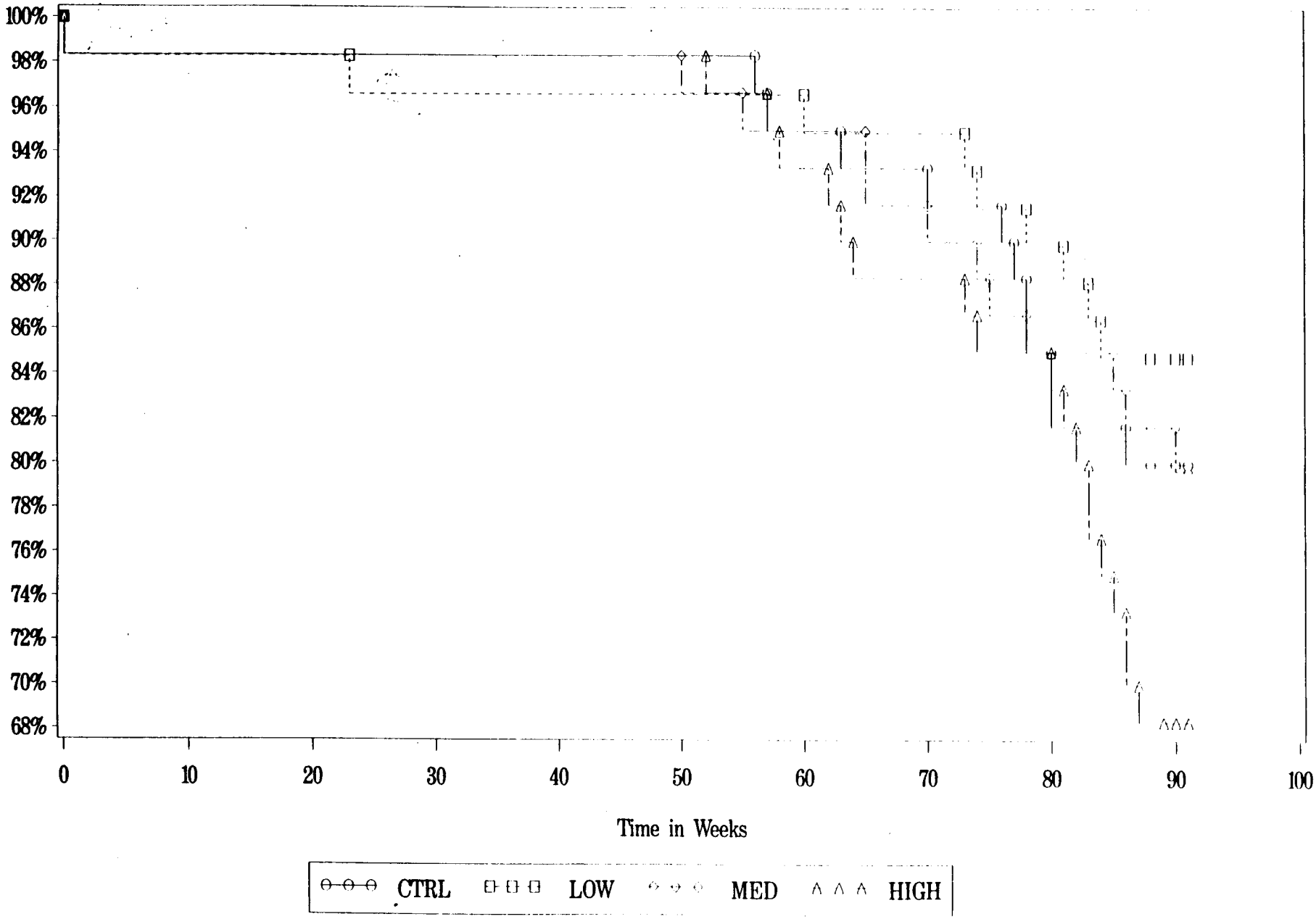
Cumulative Percent of Death

Species: Mouse
Sex: Male



Kaplan–Meier Survival Function

Species: Mouse
Sex: Male



Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: June 5, 1997 (10:18)
Source: c:_AA1\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 6.5 38 195)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
ADRENAL	(AD)	PHEOCHROMOCYT	(860)	IN	IN 90-91		0.479	0.584	0.587
					IN 90-91				
		Tumor rate: <1%		in CTL -	Total				
ADRENAL	(AD)	ADRENOCORTICA	(873)	IN	IN 90-91		0.620	0.626	0.627
					IN 90-91				
		Tumor rate: 7%		in CTL -	Total				
ADRENAL	(AD)	INTERSTITIAL	(935)	MX	IN 79-89		0.478	0.150	0.151
					IN 79-89				
		Tumor rate: <1%		in CTL -	Total				
BONE MARRO	(BM)	INTERSTITIAL	(935)	MX	IN 90-91		0.218	0.032	0.032
					IN 90-91				
		Tumor rate: <1%		in CTL -	Total				
BRAIN STEM	(BS)	ASTROCYTOMA,	(909)	MX	FA 65		0.496	0.601	0.603
					FA 65				
		Tumor rate: <1%		in CTL -	Total				
EPIDIDYMIS	(EP)	INTERSTITIAL	(935)	MX	IN 79-89		0.478	0.150	0.151
					IN 79-89				
		Tumor rate: <1%		in CTL -	Total				
EPIDIDYMIS	(EP)	SARCOMA, UNDI	(968)	IN	IN 90-91		0.218	0.032	0.032
					IN 90-91				
		Tumor rate: <1%		in CTL -	Total				
HARDERIAN	(HG)	ADENOMA	(876)	IN	IN 90-91		0.479	0.478	0.479
					IN 90-91				
		Tumor rate: 7%		in CTL -	Total				
KIDNEY	(KI)	RENAL CELL AD	(863)	IN	IN 90-91		0.647	0.746	0.747
					IN 90-91				
		Tumor rate: 2%		in CTL -	Total				
LIVER	(LI)	HEMANGIOMA	(805)	IN	IN 90-91		0.901	0.901	0.902
					IN 90-91				
		Tumor rate: 3%		in CTL -	Total				
LIVER	(LI)	HEPATOCELLULA	(831)	IN	IN 90-91		0.498	0.514	0.515
					IN 90-91				
		Tumor rate: 8%		in CTL -	Total				
LIVER	(LI)	HEMANGIOSARCO	(932)	MX	IN 53-78		0.283	0.312	0.312
					IN 53-78				
					IN 90-91				
					IN 90-91				
					FA 56				

TABLE 1c

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(Continued)

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:18)
Source: c:_AA1\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 6.5 38 195)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					FA 56				
					FA 84				
					FA 84				
					FA 88				
					FA 88				
					FA 91				
					FA 91				
		Tumor rate: 3%		in CTL	- Total				
LIVER	(LI	)HEPATOCELLULA	(934	) MX	IN 53-78		0.744	0.755	0.756
					IN 53-78				
					IN 90-91				
					IN 90-91				
					FA 52				
					FA 52				
					FA 70				
					FA 70				
					FA 78				
					FA 78				
					FA 81				
					FA 81				
					FA 84				
					FA 84				
					FA 85				
					FA 85				
					FA 86				
					FA 86				
					FA 87				
					FA 87				
		Tumor rate: 3%		in CTL	- Total				
LIVER	(LI	)INTERSTITIAL	(935	) MX	IN 90-91		0.002	0.000	0.000
					IN 90-91				
		Tumor rate: <1%		in CTL	- Total		(P<0.025)		
LYMPH NODE	(LN	)HEMANGIOMA	(805	) IN	IN 90-91		1.000	0.763	0.765
					IN 90-91				
		Tumor rate: 2%		in CTL	- Total				
LYMPH NODE	(LN	)INTERSTITIAL	(935	) MX	IN 90-91		0.218	0.032	0.032
					IN 90-91				
		Tumor rate: <1%		in CTL	- Total				
LUNG	(LU	)ALVEOLAR/BRON	(803	) IN	IN 53-78		0.326	0.328	0.329
					IN 53-78				
					IN 79-89				
					IN 79-89				
					IN 90-91				
					IN 90-91				

APPEARS THIS WAY
ON ORIGINAL

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:18)
Source: c:_AA1\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 6.5 38 195)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
		Tumor rate: 22%		in CTL -	Total					
LUNG	(LU	)ALVEOLAR/BRON	(904	) MX	IN 90-91			0.789	0.777	0.777
					IN 90-91					
					FA 57					
					FA 57					
		Tumor rate: 7%		in CTL -	Total					
LUNG	(LU	)HEMANGIOSARCO	(932	) MX	IN 79-89			0.478	0.150	0.151
					IN 79-89					
		Tumor rate: <1%		in CTL -	Total					
LUNG	(LU	)INTERSTITIAL	(935	) MX	IN 79-89			0.104	0.024	0.024
					IN 79-89					
					IN 90-91					
					IN 90-91					
		Tumor rate: <1%		in CTL -	Total					
MEDIASTINU	(MS	)ALVEOLAR/BRON	(904	) MX	IN 53-78			1.000	0.792	0.793
					IN 53-78					
		Tumor rate: 2%		in CTL -	Total					
PANCREAS	(PA	)ISLET CELL AD	(833	) IN	IN 90-91			1.000	0.763	0.765
					IN 90-91					
		Tumor rate: 2%		in CTL -	Total					
PERITONEUM	(PE	)INTERSTITIAL	(935	) MX	IN 90-91			0.218	0.032	0.032
					IN 90-91					
		Tumor rate: <1%		in CTL -	Total					
PITUITARY	(PI	)ASTROCYTOMA,	(909	) MX	IN 53-78			0.560	0.635	0.638
					IN 53-78					
		Tumor rate: <1%		in CTL -	Total					
PR ATE	(PR	)ADENOMA	(876	) IN	IN 90-91			0.052	0.049	0.049
					IN 90-91					
		Tumor rate: <1%		in CTL -	Total					
PROSTATE	(PR	)LEIOMYOBLASTO	(892	) IN	IN 79-89			0.005	0.001	0.001
					IN 79-89					
					IN 90-91					
					IN 90-91					
		Tumor rate: <1%		in CTL -	Total			(P<0.025)		
PROSTATE	(PR	)ADENOCARCINOM	(902	) MX	IN 53-78			0.104	0.117	0.118
					IN 53-78					
					IN 79-89					
					IN 79-89					
					IN 90-91					

(Continued)

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:18)
Source: c:_AA1\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 6.5 38 195)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					IN 90-91				
					FA 86				
					FA 86				
		Tumor rate: <1%		in CTL	- Total				
SKIN	(SK)	HEMANGIOMA	(805)	IN	IN 90-91		0.390	0.209	0.210
					IN 90-91				
		Tumor rate: 2%		in CTL	- Total				
SPLEEN	(SP)	HEMANGIOMA	(805)	IN	IN 90-91		1.000	0.763	0.765
					IN 90-91				
		Tumor rate: 2%		in CTL	- Total				
SPLEEN	(SP)	HEMANGIOSARCO	(932)	MX	IN 90-91		0.170	0.133	0.134
					IN 90-91				
					FA 65				
					FA 65				
		Tumor rate: <1%		in CTL	- Total				
SPLEEN	(SP)	INTERSTITIAL	(935)	MX	IN 90-91		0.218	0.032	0.032
					IN 90-91				
		Tumor rate: <1%		in CTL	- Total				
SEMINAL VE	(SV)	ADENOMA	(876)	IN	IN 90-91		0.745	0.735	0.737
					IN 90-91				
		Tumor rate: <1%		in CTL	- Total				
TESTIS	(TS)	INTERSTITIAL	(832)	MX	IN 0-52		0.000	0.000	0.000
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-89				
					IN 79-89				
					IN 90-91				
					IN 90-91				
					FA 85				
					FA 85				
		Tumor rate: 3%		in CTL	- Total				(P<0.005)
TESTIS	(TS)	INTERSTITIAL	(935)	MX	IN 90-91		0.000	0.000	0.000
					IN 90-91				
					FA 73				
					FA 73				
					FA 87				
					FA 87				
					FA 91				
					FA 91				
		Tumor rate: <1%		in CTL	- Total				(P<0.025)

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Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:18)
Source: c:_AA1\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 6.5 38 195)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
WHOLE ANIM	(WA)	FIBROUS HISTI	(925)	MX	FA 88		1.000	0.763	0.765
					FA 88				
		Tumor rate: 2%		in CTL	- Total				
WHOLE ANIM	(WA)	LYMPHOSARCOMA	(939)	MX	IN 90-91		0.207	0.213	0.214
					IN 90-91				
					FA 58				
					FA 58				
					FA 74				
					FA 74				
					FA 80				
					FA 80				
					FA 83				
					FA 83				
					FA 89				
					FA 89				
		Tumor rate: 7%		in CTL	- Total				
WHOLE ANIM	(WA)	SQUAMOUS CELL	(972)	FA	FA 73		0.243	0.041	0.042
					FA 73				
		Tumor rate: <1%		in CTL	- Total				
WHOLE ANIM	(WA)	PLASMA CELL M	(992)	IN	IN 90-91		0.218	0.032	0.032
					IN 90-91				
		Tumor rate: <1%		in CTL	- Total				

Intercurrent Mortality Rates
Species: Mouse Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(-wks)												
0-52			5.0			5.0			5.0			3.3
53-78			13.3			15.0			11.7			15.0
79-89			21.7			20.0			18.3			20.0
90-91			78.3			80.0			81.7			80.0

TABLE 2a

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	0.01	0.9312
	Depart from Trend	0.20	0.9066
	Homogeneity	0.20	0.9770
Kruskal-Wallis	Dose-Mortality Trend	0.01	0.9285
	Depart from Trend	0.19	0.9086
	Homogeneity	0.20	0.9776

TABLE 2b

Cumulative Percent of Death

Species: Mouse
Sex: Female

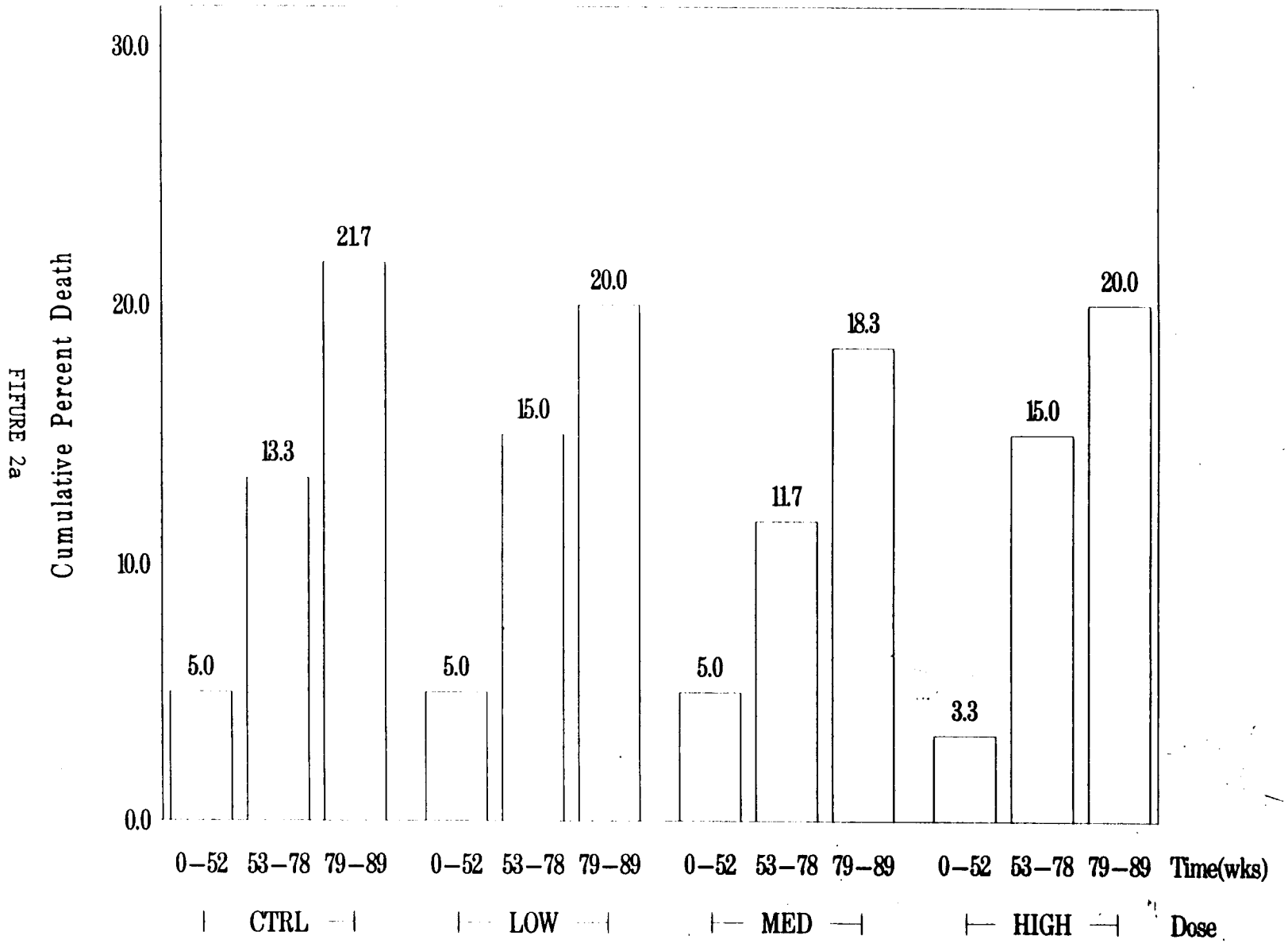

FIGURE 2a

Kaplan–Meier Survival Function

Species: Mouse
Sex: Female

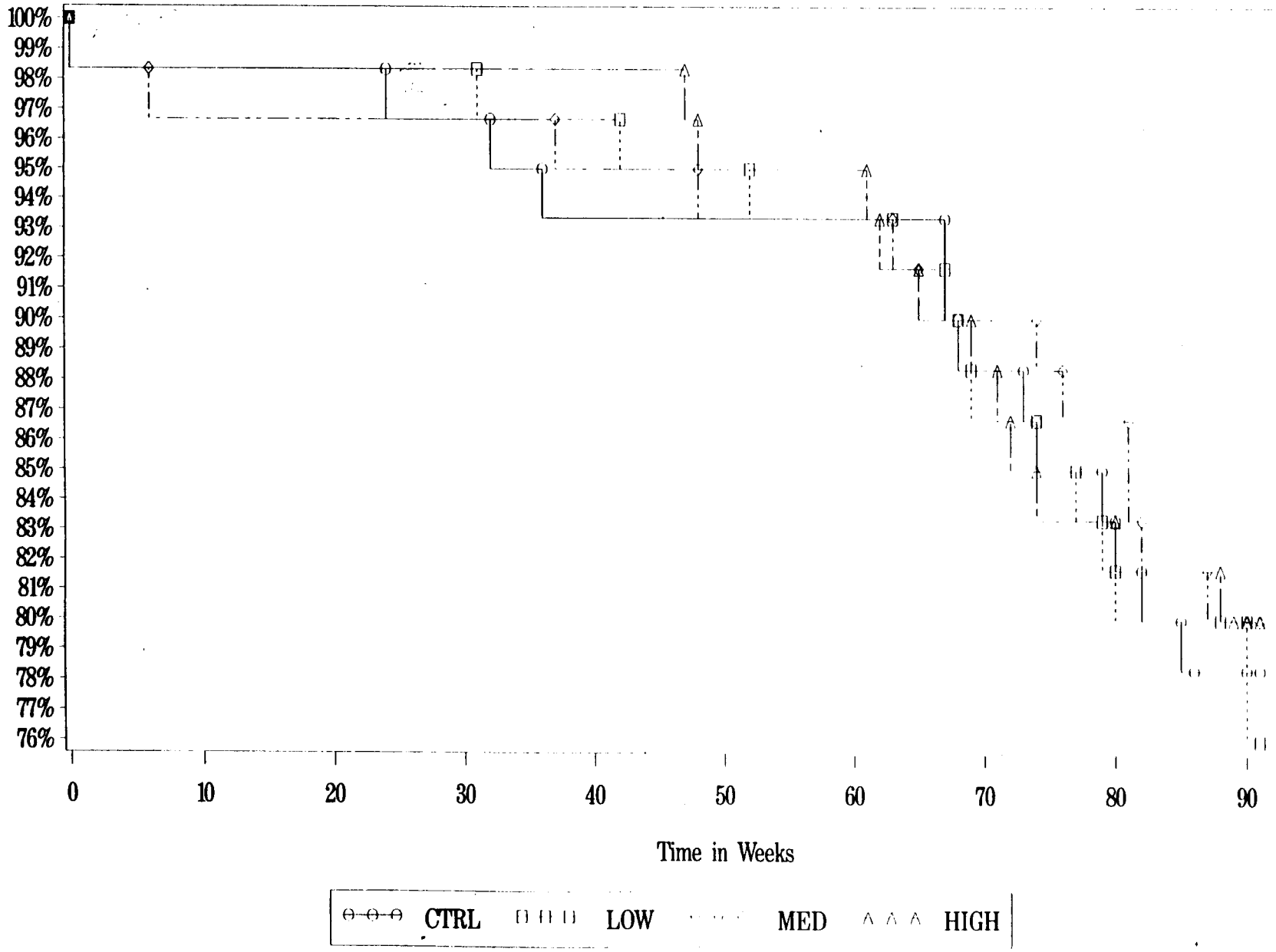

FIGURE 2b

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: June 5, 1997 (9:48)
Source: c:_AA\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 8.7 49 225)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
ADRENAL	(AD)	PHEOCHROMOCYT	(860)	IN	IN 90-91		0.190	0.151	0.152
					IN 90-91				
		Tumor rate: <1%		in CTL -	Total				
ADRENAL	(AD)	ADRENOCORTICA	(873)	IN	IN 90-91		0.413	0.466	0.467
					IN 90-91				
		Tumor rate: 2%		in CTL -	Total				
ADRENAL	(AD)	ADRENOCORTICA	(942)	IN	IN 90-91		0.503	0.634	0.635
					IN 90-91				
		Tumor rate: <1%		in CTL -	Total				
BLOOD	(BL)	SARCOMA, UNDI	(968)	MX	IN 79-89		0.467	0.551	0.553
					IN 79-89				
		Tumor rate: <1%		in CTL -	Total				
BONE	(BO)	OSTEOMA	(856)	IN	IN 90-91		0.505	0.595	0.597
					IN 90-91				
		Tumor rate: <1%		in CTL -	Total				
BONE	(BO)	OSTEOCHONDROS	(958)	FA	FA 91		0.755	0.753	0.755
					FA 91				
		Tumor rate: <1%		in CTL -	Total				
CECUM	(CC)	LEIOMYOMA	(835)	IN	IN 90-91		0.250	0.045	0.046
					IN 90-91				
		Tumor rate: <1%		in CTL -	Total				
GALLBLADDE	(GB)	ADENOMA	(876)	IN	IN 90-91		0.250	0.045	0.046
					IN 90-91				
		Tumor rate: <1%		in CTL -	Total				
HEART	(HE)	SARCOMA, UNDI	(968)	MX	IN 79-89		0.467	0.551	0.553
					IN 79-89				
		Tumor rate: <1%		in CTL -	Total				
HARDERIAN	(HG)	ADENOMA	(876)	IN	IN 53-78		0.112	0.109	0.110
					IN 53-78				
					IN 90-91				
					IN 90-91				
		Tumor rate: 3%		in CTL -	Total				
KIDNEY	(KI)	ALVEOLAR/BRON	(904)	MX	IN 53-78		0.318	0.074	0.075
					IN 53-78				
		Tumor rate: <1%		in CTL -	Total				
LIVER	(LI)	HEMANGIOMA	(805)	IN	IN 90-91		0.250	0.045	0.046
					IN 90-91				
		Tumor rate: <1%		in CTL -	Total				

~~TABLE 2c~~

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TABLE 2c

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (9:48)
Source: c:_AA\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 8.7 49 225)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	P VALUES ASYMP-TOTIC	P VALUES CONTINU CORRECT
LIVER	(LI	)HEPATOCELLULA	(831	) IN	IN 90-91		0.014	0.003	0.003
					IN 90-91				
		Tumor rate: 2%		in CTL -	Total				
LIVER	(LI	)HEMANGIOSARCO	(932	) MX	IN 53-78		1.000	0.800	0.801
					IN 53-78				
		Tumor rate: 2%		in CTL -	Total				
LIVER	(LI	)HEPATOCELLULA	(934	) IN	IN 90-91		0.186	0.206	0.207
					IN 90-91				
		Tumor rate: <1%		in CTL -	Total				
LIVER	(LI	)LEIOMYOSARCOM	(938	) MX	IN 79-89		1.000	0.759	0.761
					IN 79-89				
		Tumor rate: 2%		in CTL -	Total				
LIVER	(LI	)SARCOMA, UNDI	(968	) MX	IN 79-89		0.467	0.551	0.553
					IN 79-89				
		Tumor rate: <1%		in CTL -	Total				
LIVER	(LI	)OSTEOSARCOMA	(989	) MX	IN 0-52		0.182	0.020	0.020
					IN 0-52				
		Tumor rate: <1%		in CTL -	Total				
LIVER	(LI	)LUTEOMA, MALI	(994	) IN	IN 90-91		0.250	0.045	0.046
					IN 90-91				
		Tumor rate: <1%		in CTL -	Total				
LYMPH NODE	(LN	)HEMANGIOMA	(805	) IN	IN 90-91		1.000	0.782	0.784
					IN 90-91				
		Tumor rate: 2%		in CTL -	Total				
LYMPH NODE	(LN	)ALVEOLAR/BRON	(904	) MX	IN 53-78		0.318	0.074	0.075
					IN 53-78				
		Tumor rate: <1%		in CTL -	Total				
LYMPH NODE	(LN	)LUTEOMA, MALI	(994	) IN	IN 90-91		1.000	0.782	0.784
					IN 90-91				
		Tumor rate: 2%		in CTL -	Total				
LUNG	(LU	)ALVEOLAR/BRON	(803	) MX	IN 79-89		0.978	0.974	0.974
					IN 79-89				
					IN 90-91				
					IN 90-91				
					FA 76				
					FA 76				
		Tumor rate: 17%		in CTL -	Total				
LUNG	(LU	)ALVEOLAR/BRON	(904	) MX	IN 90-91		0.327	0.397	0.398

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Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (9:48)
Source: c:_AA\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 8.7 49 225)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					IN 90-91				
					FA 61				
					FA 61				
		Tumor rate: <1%		in CTL	- Total				
LUNG	(LU	)OSTEOSARCOMA	(989	) MX	IN 0-52		0.182	0.020	0.020
					IN 0-52				
		Tumor rate: <1%		in CTL	- Total				
MEDIASTINU	(MS	)SARCOMA, UNDI	(968	) MX	FA 82		0.507	0.595	0.597
					FA 82				
		Tumor rate: <1%		in CTL	- Total				
OVIDUCT	(OI	)ADENOMA	(876	) IN	IN 90-91		0.505	0.595	0.597
					IN 90-91				
		Tumor rate: <1%		in CTL	- Total				
OVARY	(OV	)GRANULOSA-THE	(827	) IN	IN 90-91		0.250	0.045	0.046
					IN 90-91				
		Tumor rate: <1%		in CTL	- Total				
OVARY	(OV	)LUTEOMA	(837	) IN	IN 0-52		0.036	0.031	0.031
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-89				
					IN 79-89				
					IN 90-91				
					IN 90-91				
		Tumor rate: 5%		in CTL	- Total				
OVARY	(OV	)PAPILLARY ADE	(857	) MX	IN 90-91		0.552	0.569	0.569
					IN 90-91				
					FA 90				
					FA 90				
		Tumor rate: 2%		in CTL	- Total				
OVARY	(OV	)THECOMA	(872	) IN	IN 90-91		0.301	0.328	0.329
					IN 90-91				
		Tumor rate: <1%		in CTL	- Total				
OVARY	(OV	)ADENOMA	(876	) IN	IN 90-91		0.645	0.751	0.752
					IN 90-91				
		Tumor rate: <1%		in CTL	- Total				
OVARY	(OV	)GRANULOSA CEL	(883	) MX	IN 0-52		0.028	0.025	0.025
					IN 0-52				
					IN 90-91				
					IN 90-91				

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (9:48)
Source: c:_AA\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 8.7 49 225)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					FA 81				
					FA 81				
		Tumor rate: <1%		in CTL -	Total				(P<0.025)
OVARY	(OV	)GRANULOSA CEL	(985	) MX	IN 90-91		0.002	0.001	0.001
					IN 90-91				
					FA 69				
					FA 69				
					FA 74				
					FA 74				
					FA 79				
					FA 79				
					FA 80				
					FA 80				
					FA 88				
					FA 88				
					FA 89				
					FA 89				
		Tumor rate: <1%		in CTL -	Total				(P<0.025)
OVARY	(OV	)LUTEOMA, MALI	(994	) IN	IN 90-91		0.172	0.168	0.169
					IN 90-91				
		Tumor rate: 2%		in CTL -	Total				
PERITONEUM	(PE	)GRANULOSA CEL	(985	) MX	IN 53-78		0.303	0.242	0.243
					IN 53-78				
					IN 79-89				
					IN 79-89				
		Tumor rate: <1%		in CTL -	Total				
PERITONEUM	(PE	)OSTEOSARCOMA	(989	) MX	FA 48		0.254	0.047	0.047
					FA 48				
		Tumor rate: <1%		in CTL -	Total				
SKIN	(SK	)HEMANGIOMA	(805	) IN	IN 90-91		1.000	0.782	0.784
					IN 90-91				
		Tumor rate: 2%		in CTL -	Total				
SKIN	(SK	)HISTIOCYTOMA	(885	) IN	IN 90-91		1.000	0.782	0.784
					IN 90-91				
		Tumor rate: 2%		in CTL -	Total				
SKIN	(SK	)HEMANGIOSARCO	(932	) MX	IN 53-78		1.000	0.800	0.801
					IN 53-78				
		Tumor rate: 2%		in CTL -	Total				
SPLEEN	(SP	)HEMANGIOMA	(805	) IN	IN 53-78		0.181	0.082	0.082
					IN 53-78				
					IN 90-91				

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (9:48)
Source: c:_AA\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 8.7 49 225)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					IN 90-91				
		Tumor rate: 2%		in CTL	- Total				
SPLEEN	(SP	)HEMANGIOSARCO	(932	) MX	IN 53-78		1.000	0.879	0.880
					IN 53-78				
					FA 68				
					FA 68				
		Tumor rate: 3%		in CTL	- Total				
STOMACH	(ST	)OSTEOCHONDROS	(958	) FA	FA 52		0.752	0.753	0.755
					FA 52				
		Tumor rate: <1%		in CTL	- Total				
THYROID	(TH	)FOLLICULAR CE	(823	) IN	IN 90-91		0.505	0.595	0.597
					IN 90-91				
		Tumor rate: <1%		in CTL	- Total				
THYMUS	(TY	)THYMOMA, MALI	(991	) IN	IN 79-89		1.000	0.759	0.761
					IN 79-89				
		Tumor rate: 2%		in CTL	- Total				
URINARY BL	(UB	)LEIOMYOSARCOM	(938	) MX	IN 79-89		1.000	0.759	0.761
					IN 79-89				
		Tumor rate: 2%		in CTL	- Total				
UTERUS	(UT	)LEIOMYOMA	(835	) IN	IN 90-91		0.631	0.744	0.746
					IN 90-91				
		Tumor rate: <1%		in CTL	- Total				
UTERUS	(UT	)PAPILLARY CYS	(858	) IN	IN 90-91		0.692	0.768	0.769
					IN 90-91				
		Tumor rate: 2%		in CTL	- Total				
UTERUS	(UT	)LEIOMYOSARCOM	(938	) MX	IN 90-91		1.000	0.912	0.912
					IN 90-91				
					FA 82				
					FA 82				
					FA 85				
					FA 85				
		Tumor rate: 5%		in CTL	- Total				
WHOLE ANIM	(WA	)LYMPHOSARCOMA	(939	) MX	IN 79-89		0.947	0.943	0.943
					IN 79-89				
					IN 90-91				
					IN 90-91				
					FA 36				
					FA 36				
					FA 47				
					FA 47				

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (9:48)
Source: c:_AA\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 8.7 49 225)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					FA 48				
					FA 48				
					FA 62				
					FA 62				
					FA 63				
					FA 63				
					FA 65				
					FA 65				
					FA 68				
					FA 68				
					FA 72				
					FA 72				
					FA 77				
					FA 77				
					FA 82				
					FA 82				
					FA 86				
					FA 86				
		Tumor rate: 25%		in CTL	- Total				
WHOLE ANIM	(WA)	HISTIOCYTIC S	(990)	FA	FA 37		0.506	0.599	0.601
					FA 37				
		Tumor rate: <1%		in CTL	- Total				

Page - 6 - (End of File)

Intercurrent Mortality Rates
Species: Rat Sex: Male

	Dose											
	CTRL			LOW			MED			HIGH		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(-wks)												
0-84			13.3			25.0			8.3			8.3
85-104			53.3			86.7			53.3			35.0
105-106			46.7			13.3			46.7			65.0

TABLE 3a

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: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	18.94	0.0000
	Depart from Trend	25.01	0.0000
	Homogeneity	43.95	0.0000
Kruskal-Wallis	Dose-Mortality Trend	15.89	0.0001
	Depart from Trend	21.09	0.0000
	Homogeneity	36.98	0.0000

TABLE 3b

Cumulative Percent of Death

Species: Rat
Sex: Male

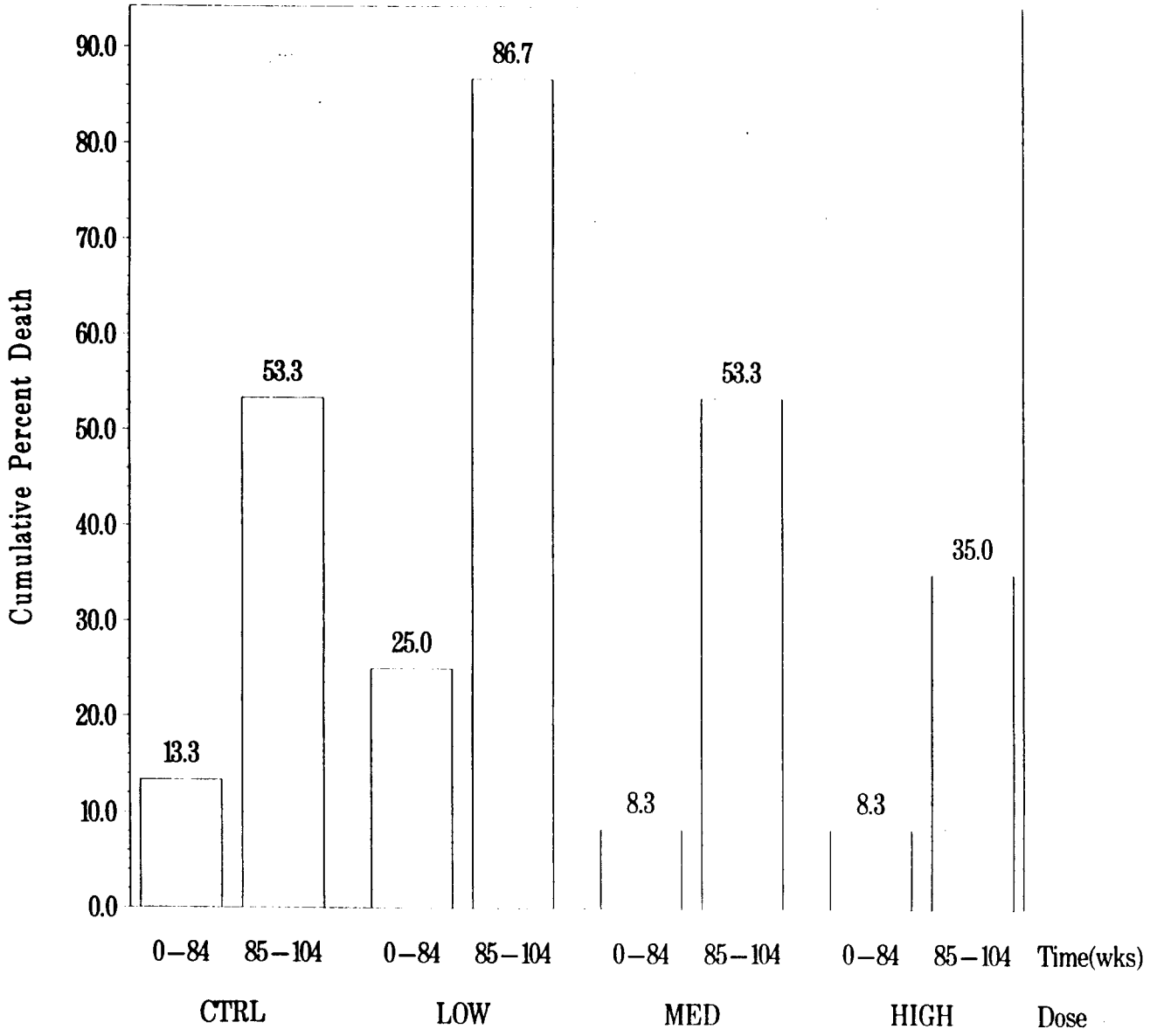
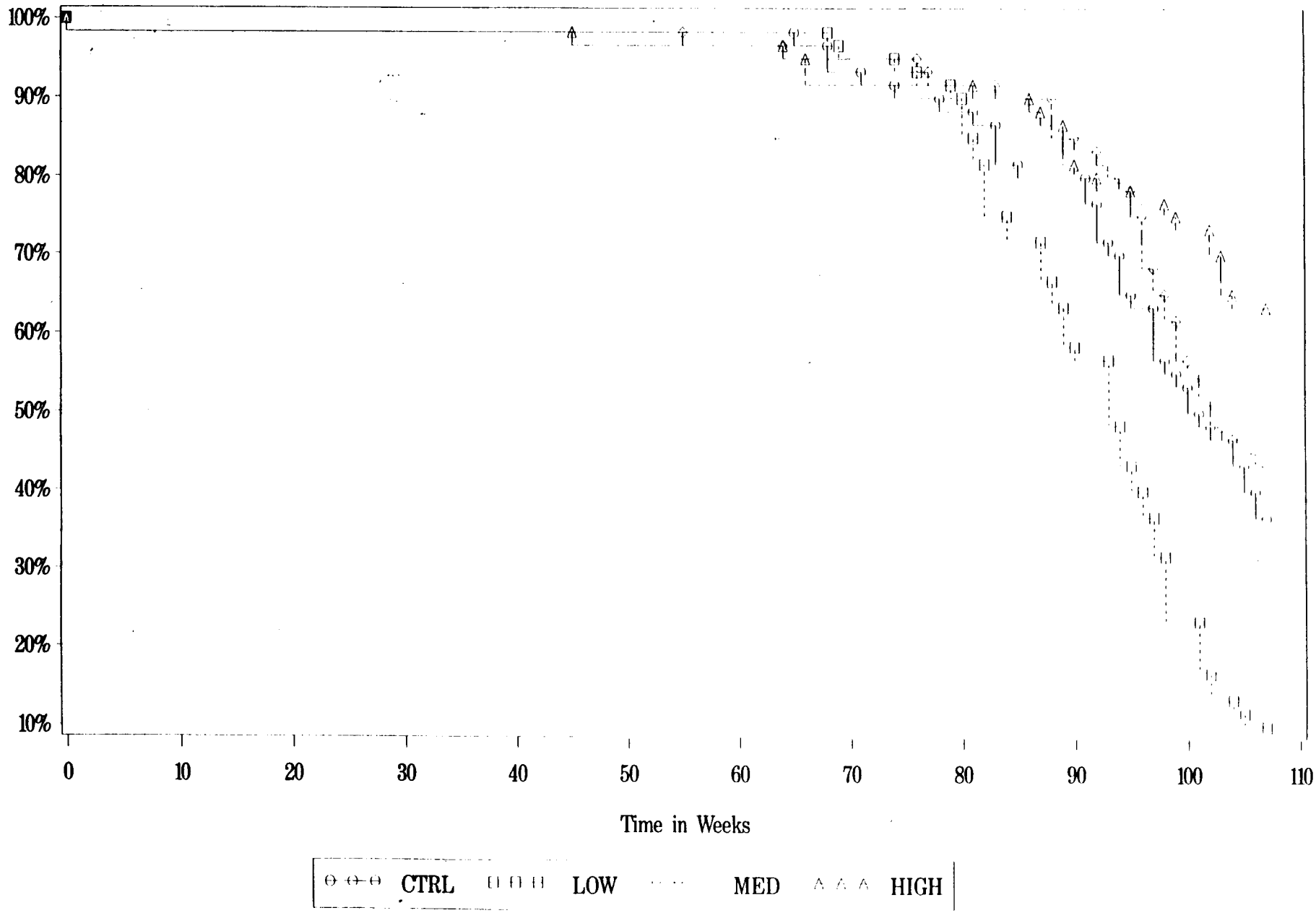


FIGURE 3a

Kaplan–Meier Survival Function

Species: Rat
Sex: Male



Analysis of Carcinogenic Potential in Male Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: June 5, 1997 (10:58)
Source: c:_AA4\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 2.3 9.3 48)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
ADRENAL	(AD	)FIBROMA	(821	) IN	IN 85-104		0.769	0.695	0.706
					IN 85-104				
		Tumor rate: <1%		in CTL -	Total				
ADRENAL	(AD	)PHEOCHROMOCYT	(860	) IN	IN 0-84		0.987	0.984	0.984
					IN 0-84				
					IN 85-104				
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: 10%		in CTL -	Total				
ADRENAL	(AD	)ADRENOCORTICA	(873	) IN	IN 85-104		0.795	0.795	0.800
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: 2%		in CTL -	Total				
ADRENAL	(AD	)ADRENOCORTICA	(942	) IN	IN 105-106		0.379	0.103	0.107
					IN 105-106				
		Tumor rate: <1%		in CTL -	Total				
ADRENAL	(AD	)PHEOCHROMOCYT	(963	) FA	FA 98		0.387	0.333	0.339
					FA 98				
					FA 101				
					FA 101				
		Tumor rate: <1%		in CTL -	Total				
CECUM	(CC	)MESOTHELIOMA,	(946	) MX	IN 85-104		1.000	0.742	0.752
					IN 85-104				
		Tumor rate: 2%		in CTL -	Total				
CEREBRUM	(CM	)MENINGIOMA, B	(841	) IN	IN 85-104		0.769	0.695	0.706
					IN 85-104				
		Tumor rate: <1%		in CTL -	Total				
CEREBRUM	(CM	)GLIOMA, MALIG	(929	) FA	FA 68		0.439	0.255	0.261
					FA 68				
					FA 81				
					FA 81				
		Tumor rate: 2%		in CTL -	Total				
COLON	(CO	)MESOTHELIOMA,	(946	) MX	IN 85-104		1.000	0.742	0.752
					IN 85-104				
		Tumor rate: 2%		in CTL -	Total				
CEREBELLUM	(CR	)GLIOMA, MALIG	(929	) FA	FA 68		1.000	0.776	0.783
					FA 68				
		Tumor rate: 2%		in CTL -	Total				

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TABLE 3c

(Continued)

Analysis of Carcinogenic Potential in Male Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:58)
Source: c:_AA4\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 2.3 9.3 48)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
EAR	(EA	)NEUROFIBROMA	(850	) IN	IN 0-84		1.000	0.723	0.733
					IN 0-84				
		Tumor rate: 2%		in CTL -	Total				
EPIDIDYMIS	(EP	)MESOTHELIOMA,	(946	) MX	IN 85-104		1.000	0.742	0.752
					IN 85-104				
		Tumor rate: 2%		in CTL -	Total				
HEART	(HE	)FIBROSARCOMA	(924	) MX	IN 0-84		0.303	0.510	0.523
					IN 0-84				
		Tumor rate: <1%		in CTL -	Total				
HARDERIAN	(HG	)ADENOMA	(876	) MX	IN 85-104		1.000	0.742	0.752
					IN 85-104				
		Tumor rate: 2%		in CTL -	Total				
JEJUNUM	(JE	)MUCINOUS ADEN	(948	) MX	IN 85-104		1.000	0.742	0.752
					IN 85-104				
		Tumor rate: 2%		in CTL -	Total				
KIDNEY	(KI	)RENAL CELL AD	(863	) IN	IN 105-106		0.379	0.103	0.107
					IN 105-106				
		Tumor rate: <1%		in CTL -	Total				
KIDNEY	(KI	)RENAL CELL CA	(965	) MX	IN 85-104		0.022	0.004	0.004
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: <1%		in CTL -	Total		(P<0.025)		
KIDNEY	(KI	)LIPOSARCOMA	(977	) IN	IN 85-104		0.413	0.532	0.544
					IN 85-104				
		Tumor rate: <1%		in CTL -	Total				
LIVER	(LI	)HEPATOCELLULA	(831	) IN	IN 105-106		0.141	0.036	0.038
					IN 105-106				
		Tumor rate: <1%		in CTL -	Total				
LIVER	(LI	)CHOLANGIOCARC	(915	) FA	FA 101		1.000	0.821	0.827
					FA 101				
		Tumor rate: 2%		in CTL -	Total				
LIVER	(LI	)HEPATOCELLULA	(934	) IN	IN 0-84		0.753	0.752	0.759
					IN 0-84				
					IN 85-104				
					IN 85-104				
		Tumor rate: <1%		in CTL -	Total				
LIVER	(LI	)ISLET CELL CA	(936	) MX	IN 105-106		0.650	0.705	0.713

Analysis of Carcinogenic Potential in Male Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:58)
Source: c:_AA4\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 2.3 9.3 48)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					IN 105-106				
		Tumor rate: <1%		in CTL	- Total				
LIVER	(LI	)MESOTHELIOMA,	(946	) MX	IN 85-104		1.000	0.742	0.752
					IN 85-104				
		Tumor rate: 2%		in CTL	- Total				
LYMPH NODE	(LN	)RENAL CELL CA	(965	) MX	IN 85-104		0.413	0.532	0.544
					IN 85-104				
		Tumor rate: <1%		in CTL	- Total				
LUNG	(LU	)ALVEOLAR/BRON	(803	) MX	IN 105-106		1.000	0.903	0.906
					IN 105-106				
					FA 97				
					FA 97				
		Tumor rate: 3%		in CTL	- Total				
LUNG	(LU	)FIBROSARCOMA	(924	) MX	IN 0-84		0.303	0.510	0.523
					IN 0-84				
		Tumor rate: <1%		in CTL	- Total				
LUNG	(LU	)NEUROFIBROSAR	(953	) MX	IN 85-104		0.413	0.532	0.544
					IN 85-104				
		Tumor rate: <1%		in CTL	- Total				
LUNG	(LU	)RENAL CELL CA	(965	) MX	IN 85-104		0.413	0.532	0.544
					IN 85-104				
		Tumor rate: <1%		in CTL	- Total				
MESENTERY	(ME	)LIPOMA	(836	) IN	IN 0-84		0.758	0.674	0.685
					IN 0-84				
		Tumor rate: <1%		in CTL	- Total				
MAMMARY GL	(MG	)FIBROADENOMA	(820	) MX	IN 85-104		0.024	0.020	0.021
					IN 85-104				
					IN 105-106				
					IN 105-106				
					FA 55				
					FA 55				
					FA 66				
					FA 66				
		Tumor rate: 2%		in CTL	- Total				
MAMMARY GL	(MG	)FIBROUS HISTI	(925	) IN	IN 105-106		0.650	0.705	0.713
					IN 105-106				
		Tumor rate: <1%		in CTL	- Total				
PANCREAS	(PA	)ACINAR CELL A	(801	) IN	IN 105-106		1.000	0.835	0.841
					IN 105-106				

Analysis of Carcinogenic Potential in Male Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:58)
Source: c:_AA4\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 2.3 9.3 48)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
		Tumor rate: 2%		in CTL -	Total				
PANCREAS	(PA	)ISLET CELL AD	(833	) MX	IN 85-104		0.988	0.962	0.963
					IN 85-104				
					IN 105-106				
					IN 105-106				
					FA 81				
					FA 81				
		Tumor rate: 7%		in CTL -	Total				
PANCREAS	(PA	)ISLET CELL CA	(936	) MX	IN 105-106		0.646	0.749	0.755
					IN 105-106				
					FA 97				
					FA 97				
		Tumor rate: <1%		in CTL -	Total				
PANCREAS	(PA	)MESOTHELIOMA,	(946	) MX	IN 85-104		1.000	0.742	0.752
					IN 85-104				
		Tumor rate: 2%		in CTL -	Total				
PERITONEUM	(PE	)MESOTHELIOMA,	(946	) MX	FA 102		1.000	0.832	0.838
					FA 102				
		Tumor rate: 2%		in CTL -	Total				
PITUITARY	(PI	)ADENOMA	(876	) MX	IN 0-84		0.999	0.999	0.999
					IN 0-84				
					IN 85-104				
					IN 85-104				
					IN 105-106				
					IN 105-106				
					FA 71				
					FA 71				
					FA 83				
					FA 83				
					FA 85				
					FA 85				
					FA 87				
					FA 87				
					FA 89				
					FA 89				
					FA 90				
					FA 90				
					FA 92				
					FA 92				
					FA 93				
					FA 93				
					FA 95				
					FA 95				
					FA 97				

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Analysis of Carcinogenic Potential in Male Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:58)
Source: c:_AA4\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 2.3 9.3 48)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					FA 97				
					FA 98				
					FA 98				
					FA 101				
					FA 101				
					FA 102				
					FA 102				
					FA 104				
					FA 104				
					FA 105				
					FA 105				
					FA 106				
					FA 106				
					FA 107				
					FA 107				
		Tumor rate: 60%		in CTL -	Total				
PITUITARY	(PI	)ADENOCARCINOM	(902	) FA	FA 74		1.000	0.779	0.787
					FA 74				
		Tumor rate: 2%		in CTL -	Total				
PROSTATE	(PR	)ADENOMA	(876	) MX	IN 85-104		0.834	0.834	0.838
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: 2%		in CTL -	Total				
PROSTATE	(PR	)MESOTHELIOMA,	(946	) MX	IN 85-104		1.000	0.742	0.752
					IN 85-104				
		Tumor rate: 2%		in CTL -	Total				
SUBCUTIS	(SB	)RHABDOMYOSARC	(967	) IN	IN 85-104		0.154	0.011	0.012
					IN 85-104				
		Tumor rate: <1%		in CTL -	Total				
SAI `RY G	(SG	)NEUROFIBROSAR	(953	) MX	IN 85-104		0.413	0.532	0.544
					IN 85-104				
		Tumor rate: <1%		in CTL -	Total				
SKIN	(SK	)PAPILLOMA	(806	) IN	IN 85-104		0.937	0.861	0.865
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: 2%		in CTL -	Total				
SKIN	(SK	)FIBROMA	(821	) IN	IN 105-106		0.987	0.960	0.961
					IN 105-106				
		Tumor rate: 5%		in CTL -	Total				

(Continued)

Analysis of Carcinogenic Potential in Male Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:58)
Source: c:_AA4\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 2.3 9.3 48)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	P VALUES ASYMP-TOTIC	P VALUES CONTINU CORRECT
SKIN	(SK	)KERATOACANTHO	(834	) IN	IN 105-106		0.981	0.950	0.951
					IN 105-106				
		Tumor rate: 3%		in CTL	- Total				
SKIN	(SK	)BASAL CELL CA	(910	) FA	FA 95		1.000	0.799	0.806
					FA 95				
		Tumor rate: 2%		in CTL	- Total				
SKIN	(SK	)FIBROSARCOMA	(924	) MX	FA 76		0.811	0.807	0.811
					FA 76				
					FA 99				
					FA 99				
		Tumor rate: 2%		in CTL	- Total				
SKELETAL M	(SM	)FIBROMA	(821	) IN	IN 85-104		0.154	0.011	0.012
					IN 85-104				
		Tumor rate: <1%		in CTL	- Total				
SKELETAL M	(SM	)FIBROUS HISTI	(925	) IN	IN 105-106		0.650	0.705	0.713
					IN 105-106				
		Tumor rate: <1%		in CTL	- Total				
SKELETAL M	(SM	)RHABDOMYOSARC	(967	) IN	IN 85-104		0.154	0.011	0.012
					IN 85-104				
		Tumor rate: <1%		in CTL	- Total				
SCIATIC NE	(SN	)RHABDOMYOSARC	(967	) IN	IN 105-106		0.650	0.705	0.713
					IN 105-106				
		Tumor rate: <1%		in CTL	- Total				
STOMACH	(ST	)MESOTHELIOMA,	(946	) MX	IN 85-104		1.000	0.742	0.752
					IN 85-104				
		Tumor rate: 2%		in CTL	- Total				
SEMINAL VE	(SV	)MESOTHELIOMA,	(946	) MX	IN 85-104		1.000	0.742	0.752
					IN 85-104				
		Tumor rate: 2%		in CTL	- Total				
THYROID	(TH	)C-CELL ADENOM	(810	) IN	IN 0-84		0.397	0.415	0.418
					IN 0-84				
					IN 85-104				
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: 5%		in CTL	- Total				
THYROID	(TH	)FOLLICULAR CE	(823	) IN	IN 85-104		0.937	0.861	0.865
					IN 85-104				
					IN 105-106				

Analysis of Carcinogenic Potential in Male Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:58)
Source: c:_AA4\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 2.3 9.3 48)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					IN 105-106				
		Tumor rate: 2%		in CTL	- Total				
THYROID	(TH	)PAPILLARY CYS	(858	) IN	IN 105-106		1.000	0.835	0.841
					IN 105-106				
		Tumor rate: 2%		in CTL	- Total				
THYROID	(TH	)C-CELL CARCIN	(908	) IN	IN 105-106		0.379	0.103	0.107
					IN 105-106				
		Tumor rate: <1%		in CTL	- Total				
THYROID	(TH	)FOLLICULAR CE	(926	) MX	IN 0-84		0.648	0.764	0.769
					IN 0-84				
					IN 85-104				
					IN 85-104				
					FA 79				
					FA 79				
		Tumor rate: <1%		in CTL	- Total				
TESTIS	(TS	)INTERSTITIAL	(832	) IN	IN 0-84		1.000	1.000	1.000
					IN 0-84				
					IN 85-104				
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: 50%		in CTL	- Total				
THYMUS	(TY	)THYMOMA, BENI	(851	) FA	FA 100		1.000	0.819	0.825
					FA 100				
		Tumor rate: 2%		in CTL	- Total				
THYMUS	(TY	)FIBROSARCOMA	(924	) MX	IN 0-84		0.303	0.510	0.523
					IN 0-84				
		Tumor rate: <1%		in CTL	- Total				
THYMUS	(TY	)NEUROFIBROSAR	(953	) MX	IN 85-104		0.413	0.532	0.544
					IN 85-104				
		Tumor rate: <1%		in CTL	- Total				
TH	(TY	)THYMOMA, MALI	(991	) IN	IN 0-84		0.152	0.010	0.011
					IN 0-84				
		Tumor rate: <1%		in CTL	- Total				
URINARY BL	(UB	)TRANSITIONAL	(815	) IN	IN 105-106		0.728	0.807	0.813
					IN 105-106				
		Tumor rate: <1%		in CTL	- Total				
URINARY BL	(UB	)MESOTHELIOMA,	(946	) MX	IN 85-104		1.000	0.742	0.752
					IN 85-104				

Analysis of Carcinogenic Potential in Male Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:58)
Source: c:_AA4\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 2.3 9.3 48)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
		Tumor rate: 2%		in CTL -	Total				
URINARY BL	(UB)	TRANSITIONAL	(976)	IN	IN 85-104		0.154	0.011	0.012
					IN 85-104				
		Tumor rate: <1%		in CTL -	Total				
WHOLE ANIM	(WA)	LYMPHOSARCOMA	(939)	MX	IN 105-106		0.769	0.762	0.764
					IN 105-106				
					FA 83				
					FA 83				
					FA 85				
					FA 85				
					FA 94				
					FA 94				
					FA 100				
					FA 100				
					FA 102				
					FA 102				
					FA 106				
					FA 106				
		Tumor rate: 10%		in CTL -	Total				
WHOLE ANIM	(WA)	MONONUCLEAR C	(941)	MX	IN 85-104		0.990	0.987	0.987
					IN 85-104				
					IN 105-106				
					IN 105-106				
					FA 45				
					FA 45				
					FA 64				
					FA 64				
					FA 65				
					FA 65				
					FA 71				
					FA 71				
					FA 78				
					FA 78				
					FA 81				
					FA 81				
					FA 85				
					FA 85				
					FA 86				
					FA 86				
					FA 88				
					FA 88				
					FA 90				
					FA 90				
					FA 91				
					FA 91				
					FA 92				

Analysis of Carcinogenic Potential in Male Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:58)
Source: c:_AA4\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 2.3 9.3 48)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					FA 92				
					FA 95				
					FA 95				
					FA 97				
					FA 97				
					FA 98				
					FA 98				
					FA 101				
					FA 101				
					FA 102				
					FA 102				
					FA 104				
					FA 104				
					FA 105				
					FA 105				
					FA 106				
					FA 106				
		Tumor rate: 40%	in CTL	-	Total				
WHOLE ANIM	(WA)	MUCINOUS ADEN	(948)	MX	FA 93		1.000	0.790	0.797
					FA 93				
		Tumor rate: 2%	in CTL	-	Total				
WHOLE ANIM	(WA)	NEUROFIBROSAR	(953)	MX	FA 99		0.616	0.678	0.687
					FA 99				
		Tumor rate: <1%	in CTL	-	Total				
WHOLE ANIM	(WA)	RENAL CELL CA	(965)	MX	FA 100		0.612	0.679	0.687
					FA 100				
		Tumor rate: <1%	in CTL	-	Total				
WHOLE ANIM	(WA)	HISTIOCYTIC S	(990)	FA	FA 81		0.756	0.747	0.755
					FA 81				
		Tumor rate: <1%	in CTL	-	Total				
ZY L'S G	(ZG)	NEUROFIBROSAR	(953)	MX	IN 85-104		0.413	0.532	0.544
					IN 85-104				
		Tumor rate: <1%	in CTL	-	Total				

 (End of File)

Intercurrent Mortality Rates
Species: Rat Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(-wks)												
0-84			10.0			5.0			8.3			6.7
85-104			35.0			15.0			20.0			20.0
105-106			65.0			85.0			80.0			80.0

TABLE 4a

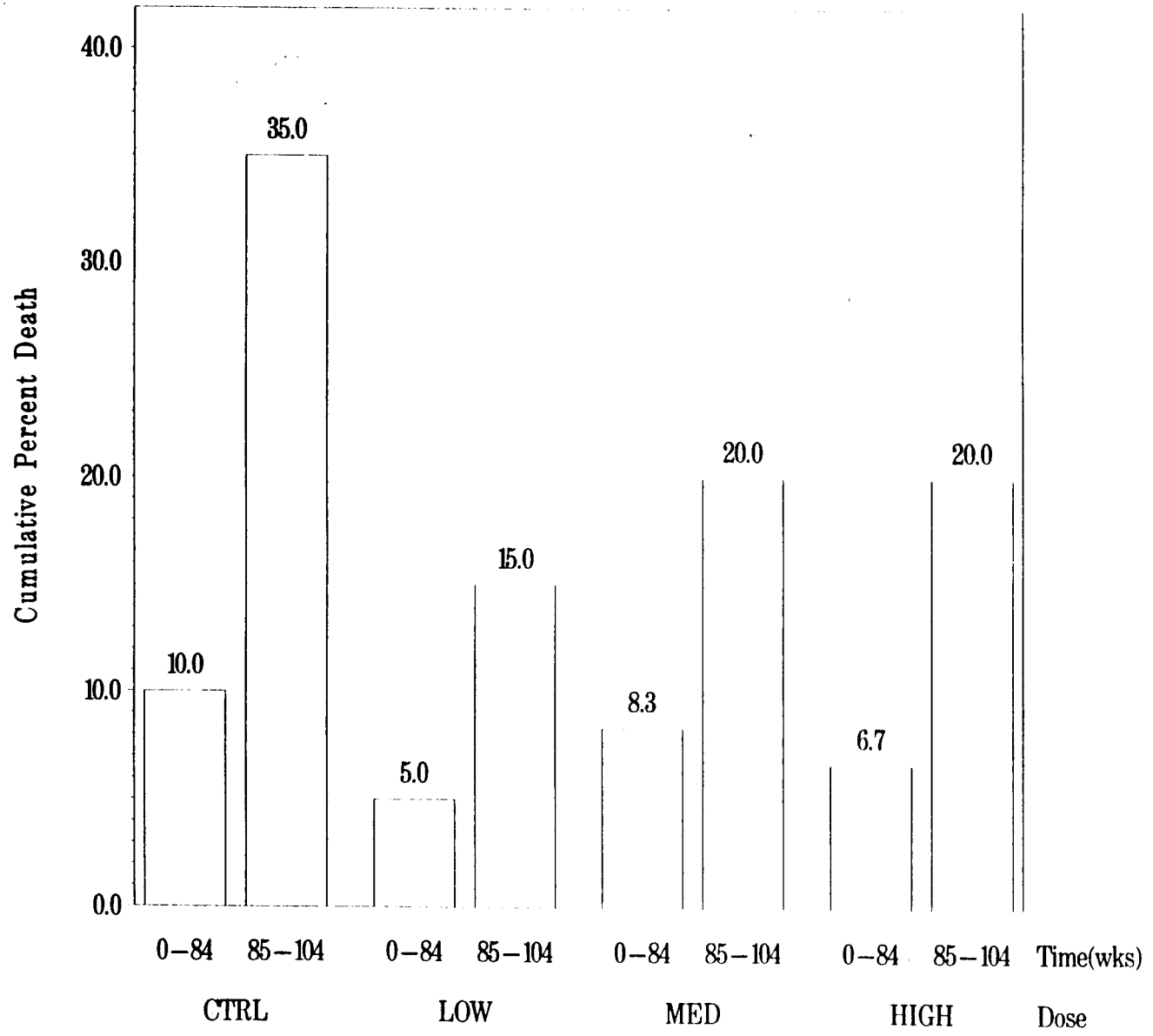
Dose-Mortality Trend Tests
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute
Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.39	0.5309
	Depart from Trend	7.01	0.0300
	Homogeneity	7.40	0.0601
Kruskal-Wallis	Dose-Mortality Trend	0.26	0.6118
	Depart from Trend	6.68	0.0355
	Homogeneity	6.93	0.0740

TABLE 4b

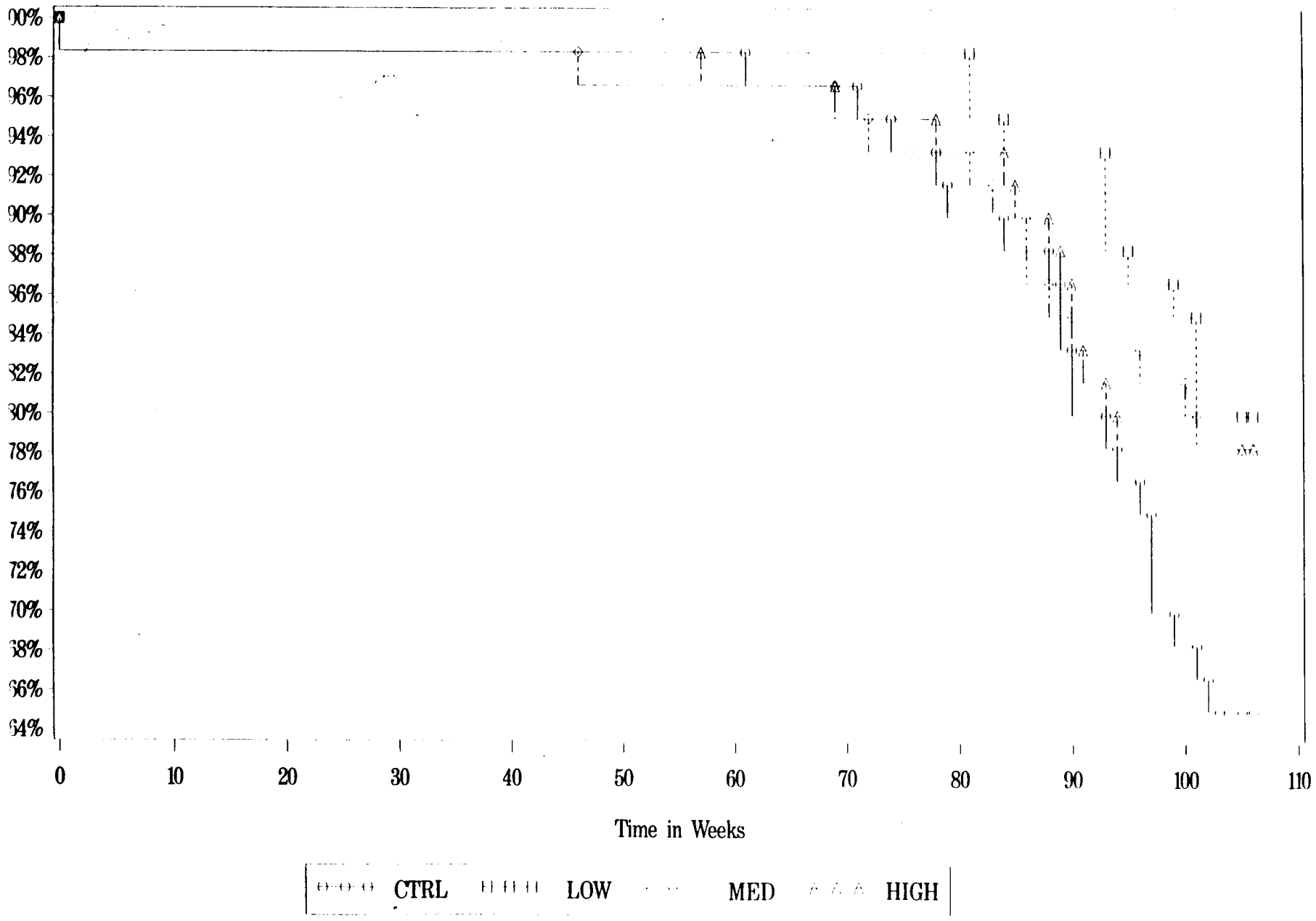
Cumulative Percent of Death

Species: Rat
Sex: Female



Kaplan–Meier Survival Function

Species: Rat
Sex: Female



Analysis of Carcinogenic Potential in Female Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: June 5, 1997 (10:38)
Source: c:_AA2\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 10.4 51 259)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
ADRENAL	(AD	)PHEOCHROMOCYT	(860	) IN	IN 0-84		0.291	0.296	0.297
					IN 0-84				
					IN 85-104				
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: 2%		in CTL -	Total				
ADRENAL	(AD	)ADRENOCORTICA	(873	) IN	IN 85-104		0.033	0.012	0.012
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: <1%		in CTL -	Total				
BRAIN STEM	(BS	)ASTROCYTOMA,	(808	) IN	IN 105-106		0.790	0.754	0.755
					IN 105-106				
		Tumor rate: <1%		in CTL -	Total				
CEREBRUM	(CM	)GLIOMA, MALIG	(929	) FA	FA 72		0.496	0.607	0.609
					FA 72				
		Tumor rate: <1%		in CTL -	Total				
LIVER	(LI	)HEPATOCELLULA	(831	) IN	IN 105-106		0.658	0.758	0.759
					IN 105-106				
		Tumor rate: <1%		in CTL -	Total				
LIVER	(LI	)HEPATOCELLULA	(934	) IN	IN 105-106		0.122	0.062	0.062
					IN 105-106				
		Tumor rate: <1%		in CTL -	Total				
LUNG	(LU	)ALVEOLAR/BRON	(803	) IN	IN 105-106		0.516	0.619	0.620
					IN 105-106				
		Tumor rate: <1%		in CTL -	Total				
MESENTERY	(ME	)LEIOMYOSARCOM	(938	) MX	IN 85-104		1.000	0.749	0.750
					IN 85-104				
		Tumor rate: 2%		in CTL -	Total				
MAMMARY GL	(MG	)FIBROADENOMA	(820	) MX	IN 85-104		0.472	0.489	0.490
					IN 85-104				
					IN 105-106				
					IN 105-106				
					FA 91				
					FA 91				
		Tumor rate: 20%		in CTL -	Total				
MAMMARY GL	(MG	)ADENOCARCINOM	(902	) IN	IN 0-84		1.000	0.908	0.908
					IN 0-84				
					IN 105-106				

Table 4c

TABLE 4c

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(Continued)

Analysis of Carcinogenic Potential in Female Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:38)
Source: c:_AA2\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 10.4 51 259)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					IN 105-106				
		Tumor rate: 5%		in CTL	- Total				
OVARY	(OV)	GRANULOSA-THE	(827)	IN	IN 105-106		0.021	0.009	0.009
					IN 105-106				
		Tumor rate: <1%		in CTL	- Total		(P<0.025)		
OVARY	(OV)	THECOMA	(872)	IN	IN 0-84		0.222	0.033	0.034
					IN 0-84				
		Tumor rate: <1%		in CTL	- Total				
OVARY	(OV)	GRANULOSA CEL	(883)	IN	IN 105-106		0.004	0.000	0.000
					IN 105-106				
		Tumor rate: <1%		in CTL	- Total		(P<0.025)		
OVARY	(OV)	GRANULOSA-THE	(930)	IN	IN 85-104		0.583	0.716	0.717
					IN 85-104				
		Tumor rate: <1%		in CTL	- Total				
PANCREAS	(PA)	LEIOMYOSARCOM	(938)	MX	IN 85-104		1.000	0.749	0.750
					IN 85-104				
		Tumor rate: 2%		in CTL	- Total				
PITUITARY	(PI)	ADENOMA	(876)	MX	IN 85-104		1.000	1.000	1.000
					IN 85-104				
					IN 105-106				
					IN 105-106				
					FA 71				
					FA 71				
					FA 78				
					FA 78				
					FA 79				
					FA 79				
					FA 90				
					FA 90				
					FA 93				
					FA 93				
					FA 97				
					FA 97				
					FA 99				
					FA 99				
					FA 101				
					FA 101				
					FA 103				
					FA 103				
		Tumor rate: 82%		in CTL	- Total				
SKIN	(SK)	KERATOACANTHO	(834)	IN	IN 105-106		0.594	0.477	0.478
					IN 105-106				

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Note: Dose Levels Included: CTRL LOW MED HIGH (0 10.4 51 259)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
		Tumor rate: 3%		in CTL -	Total				
SKIN	(SK	)SEBACEOUS ADE	(866	) IN	IN 85-104		0.553	0.515	0.516
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: 3%		in CTL -	Total				
SKIN	(SK	)FIBROSARCOMA	(924	) IN	IN 85-104		0.165	0.142	0.143
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: <1%		in CTL -	Total				
SKIN	(SK	)SQUAMOUS CELL	(972	) IN	IN 105-106		0.790	0.754	0.755
					IN 105-106				
		Tumor rate: <1%		in CTL -	Total				
STOMACH	(ST	)LEIOMYOSARCOM	(938	) MX	IN 85-104		1.000	0.749	0.750
					IN 85-104				
		Tumor rate: 2%		in CTL -	Total				
THYROID	(TH	)C-CELL ADENOM	(810	) IN	IN 85-104		0.282	0.287	0.288
					IN 85-104				
					IN 105-106				
					IN 105-106				
		Tumor rate: 8%		in CTL -	Total				
THYROID	(TH	)FOLLICULAR CE	(823	) IN	IN 85-104		0.583	0.716	0.717
					IN 85-104				
		Tumor rate: <1%		in CTL -	Total				
THYROID	(TH	)C-CELL CARCIN	(908	) MX	IN 105-106		1.000	0.863	0.864
					IN 105-106				
					FA 84				
					FA 84				
		Tumor rate: 3%		in CTL -	Total				
TC E	(TO	)PAPILLOMA	(806	) IN	IN 105-106		1.000	0.784	0.785
					IN 105-106				
		Tumor rate: 2%		in CTL -	Total				
THYMUS	(TY	)THYMOMA, MALI	(991	) FA	FA 46		0.500	0.609	0.611
					FA 46				
		Tumor rate: <1%		in CTL -	Total				
UTERUS	(UT	)PAPILLARY ADE	(857	) IN	IN 105-106		1.000	0.784	0.785
					IN 105-106				
		Tumor rate: 2%		in CTL -	Total				

Analysis of Carcinogenic Potential in Female Rat
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Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
UTERUS	(UT	)ENDOMETRIAL S	(880)	IN	IN 85-104			0.984	0.950	0.951
					IN 85-104					
					IN 105-106					
					IN 105-106					
		Tumor rate: 8%		in CTL -	Total					
VAGINA	(VA	)LEIOMYOSARCOM	(938)	MX	IN 85-104			1.000	0.749	0.750
					IN 85-104					
		Tumor rate: 2%		in CTL -	Total					
WHOLE ANIM	(WA	)LEIOMYOSARCOM	(938)	MX	FA 94			1.000	0.774	0.775
					FA 94					
		Tumor rate: 2%		in CTL -	Total					
WHOLE ANIM	(WA	)LYMPHOSARCOMA	(939)	IN	IN 105-106			0.258	0.048	0.048
					IN 105-106					
		Tumor rate: <1%		in CTL -	Total					
WHOLE ANIM	(WA	)MONONUCLEAR C	(941)	MX	IN 105-106			0.430	0.437	0.438
					IN 105-106					
					FA 57					
					FA 57					
					FA 61					
					FA 61					
					FA 69					
					FA 69					
					FA 74					
					FA 74					
					FA 78					
					FA 78					
					FA 81					
					FA 81					
					FA 83					
					FA 83					
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					FA 88					
					FA 88					
					FA 89					
					FA 89					
					FA 90					
					FA 90					
					FA 93					
					FA 93					
					FA 94					

Analysis of Carcinogenic Potential in Female Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: June 5, 1997 (10:38)
Source: c:_AA2\ANIMAL.STD

Note: Dose Levels Included: CTRL LOW MED HIGH (0 10.4 51 259)
For missing Tumor-Caused-Death set INCIDENTAL
IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols, ^ and + indicate that p-values are <0.005 and <0.025 respectively

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					FA 94				
					FA 95				
					FA 95				
					FA 96				
					FA 96				
					FA 99				
					FA 99				
					FA 100				
					FA 100				
					FA 101				
					FA 101				
					FA 102				
					FA 102				
					FA 105				
					FA 105				
		Tumor rate: 32%	in CTL	-	Total				
WHOLE ANIM	(WA	)HISTIOCYTIC S	(990	) IN	IN 105-106		0.516	0.619	0.620
					IN 105-106				
		Tumor rate: <1%	in CTL	-	Total				
ZYMBAL'S G	(ZG	)SQUAMOUS CELL	(972	) IN	IN 105-106		0.258	0.048	0.048
					IN 105-106				
		Tumor rate: <1%	in CTL	-	Total				

STATISTICAL REVIEW AND EVALUATION
(Carcinogenicity Review)

(An Addendum Report)

Date: OCT 2 1997

NDA#: 20-815

Applicant: Eli Lilly and Company

Name of Drug: Evista (raloxifene hydrochloride)

Reviewing Pharmacologist: Gemma Kuijpers, Ph.D.

I. Introduction

In this NDA submission, two animal carcinogenicity studies (one in mice and one in rats) were included. A statistical review was conducted by Division of Biometrics II and a statistical review and evaluation report was issued on June 30, 1997.

Dr. Gemma Kuijpers of HFD-510, who is the reviewing pharmacologist of this NDA, has requested Division of Biometrics II to perform some additional statistical analyses on the tumor data of female rats, male mice, and female mice. This addendum reports the results of the requested additional analyses.

This addendum report is based on the outputs of computer runs produced by Ms. Moh-Jee Ng of Division of Biometrics II using the electronic data sets submitted by the sponsor. Results of this review have been discussed with Dr. Kuijpers.

II. Results of Additional Analyses

The following additional statistical analyses were performed. To adjust of the effect of multiple testings, the levels of significance for the tests for positive trend are 0.025 for rare tumors, and 0.005 for common tumors. The levels of significance for pairwise comparison tests for difference are 0.05 for rare tumors and 0.01 for common tumors. A tumor is classified as rare if the background spontaneous tumor rate is 1% or less, and as common otherwise.

II.a. Female Rats

The test for positive trend in incidence in the combination of ovary benign granulosa-theca tumor, benign granulosa cell tumor, malignant granulosa-theca tumor, and thecoma was highly significant with a p-value less than 0.0001. The combined incidence rates were 0, 1, 1, and 8 for the control, low, medium, and high groups, respectively.

The control-high pairwise comparison test for difference in incidence in adrenal adrenocortical adenoma was not significant ($p = 0.163$). The incidence rates were 0, and 3 for the control and the high groups, respectively.

II.b. Male mice

The test for positive trend in incidence in combination of prostate malignant adenocarcinoma, benign adenoma, and benign leiomyoblastoma was significant ($p = 0.023$). The combined incidence rates were 0, 0, 4, and 4 for the control, low, medium, and high groups, respectively.

II.c. Female mice

The test for positive trend in incidence in combination of liver hepatocelluar adenoma and hepatocellular carcinoma was marginally significant ($p = 0.01$). The combined incidence rates were 1, 1, 3, and 6 for the control, low, medium, and high groups, respectively.

The test for positive trend in incidence in combination of ovary benign granulosa theca tumor, thecoma, benign granulosa cell tumor, malignant granulosa cell tumor, malignant luteoma, and benign luteoma was highly significant ($p < 0.0001$). The combined incidence rates were 4, 12, 17, and 27 for the control, low, medium, and high groups, respectively.

The test for positive trend in incidence in combination of ovary papillary adenoma and cystadenoma was not significant ($p = 0.667$). The combined incidence rates were 1, 9, 7, and 4 for the control, low, medium, and high groups, respectively.

The following pairwise comparisons of the combined incidence rates of the above tumor types were also performed. The results are summarized as follows:

(A). Combination of liver hepatocellular adenoma and hepatocellular carcinoma.

Comparison	P-value	Incidence Rates
Control VS Low	0.758	1, 1
Control VS Medium	0.324	1, 3
Control VS High	0.059	1, 6

(B). Combination of ovary benign granulosa theca tumor, thecoma, benign granulosa cell tumor, malignant granulosa cell tumor, malignant luteoma, and benign luteoma

Comparison	P-value	Incidence Rates
Control VS Low	0.021	4, 12
Control VS Medium	0.001	4, 17
Control VS High	<0.0001	4, 27

(C). Combination of ovary papillary adenoma and cystadenoma

Comparison	P-value	Incidence Rates
Control VS Low	0.008	1, 9
Control VS Medium	0.016	1, 7
Control VS High	0.187	1, 4

Based on the levels of significance adjusted for the effect of multiple testings described above, the following pairwise comparisons were significant: The control-vs-medium, and the control-vs-high comparisons of incidences of combination of ovary

benign granulosa theca tumor, thecoma, benign granulosa cell tumor, malignant granulosa cell tumor, malignant luteoma, and benign luteoma; and the control-vs-low comparison of incidence of combination of ovary papillary adenoma and cystadenoma.

Karl K. Lin, Ph.D.
Expert Mathematical Statistician
(Applications in Pharmacology
and Toxicology)

Moh-Jee Ng
Mathematical Statistician

Concur: S. Edward Nevius

S. Edward Nevius, Ph.D.
Director
Division of Biometrics II

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cc: Original: NDA 20-815
HFD-510/Division File
HFD-510/GKuijpers, Rsteigerwaalt
HFD-700/WFairweather
HFD-715/Chron, Division File
HFD-715/MNg. Dmarticello, KLin

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STATISTICAL REVIEW AND EVALUATION

OCT 2 1997

NDA#: 20-815

APPLICANT: Lilly Research Laboratories

NAME OF DRUG: Evista (raloxifene hydrochloride)

INDICATION: Prevention of osteoporosis in postmenopausal women

DOCUMENTS REVIEWED: Volumes 1:2.1, 2:2.1, 10:2.1, 10:2.16-10:2.38 dated June 8, 1997 and supplemental material (CANDA) in Adobe Portable Document Format (PDF).

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer, Eric C. Colman, M.D., HFD-510.

RELEVANT ISSUES DISCUSSED IN THIS REVIEW

1. Studies GGGF, GGGG, and GGGH have established a statistical association between each of the studied dosages (30 mg, 60 mg, and 150 mg) and an increase in lumber spine and total hip BMD.

2. The sponsor's justification for their proposed raloxifene 60 mg dosage regimen is a matter of clinical judgment as statistical evidence has not been provided which establishes an increased effect on lumbar spine and total hip BMD of raloxifene 60 mg over raloxifene 30 mg.

3. Patients who received Premarin .625 mg in study GGGH experienced a significantly greater increase in lumbar spine and total hip BMD than did patients who received raloxifene 60 mg or raloxifene 150 mg.

KEY WORDS: **bone mineral density, estrogen receptor, interim analysis, lumbar spine, osteoporosis, postmenopausal, Premarin, total hip**

BACKGROUND

The sponsor has submitted the results of 24-month interim analyses for their Phase 3 multicenter osteoporosis prevention trials in support of their proposed 60 mg tablet dosage given once daily.

Each of the Phase 3 studies was designed with a 36-month double-blind treatment duration. However, the sponsor presented data to the FDA which indicated that raloxifene acted via the estrogen receptor and that its action on the bone in animal and early clinical studies was very similar to that of estrogen.

Based on this data, the FDA agreed that as a new estrogen-like compound, raloxifene may be approved for the prevention of postmenopausal osteoporosis based on 24-month bone mineral density (BMD) data.

Consequently, the sponsor conducted 24-month interim analyses at the 2.9% significance level. It was agreed upon that failure to demonstrate significance at 24 months at the 2.9% significance level would result in 36-month analyses which would be conducted at a level of significance which would result in an overall Type 1 error rate of 5%.

The primary endpoints for each study were the treatment effects on BMD measured using dual-energy x-ray absorptiometry (DXA) in the lumbar (L-1 through L-4) spine and hip.

In addition to their double-blind randomized treatment, all patients in these three studies were provided oral calcium supplements throughout the study to assure adequate calcium intake.

A review of each of these studies follows.

STUDY GGGF

Study GGGF is an ongoing multicenter, double-blind, randomized, placebo-controlled trial which is being conducted in 11 sites in 8 European countries.

The primary objectives of Study GGGF are:

1) "To establish the effect of long-term therapy (at least 3 years) with raloxifene, compared with placebo, on lumbar spine and total hip bone mineral density in healthy, postmenopausal women".

2) "To establish the safety of chronic administration of raloxifene in healthy, postmenopausal women.

Postmenopausal women. of age who became menopausal 2 to 8 years before study commencement whose lumbar spine BMD measurements were between 2.0 standard deviations (SD) above and 2.5 SD below mean peak lumbar spine BMD for premenopausal women were randomized to receive 36 months of double-blind treatment.

Patients were randomized to receive a once daily dose of raloxifene 30 mg, raloxifene 60 mg (sponsor's proposed dose), raloxifene 150 mg or placebo. Subsequent to the 36-month double-blind treatment phase, patients are eligible to enter a 2-year double-blind extension phase. Raloxifene patients who so elect will continue to receive their randomized treatment. However, placebo patients will be randomized in a 2-to-1 ratio to receive daily doses of placebo or raloxifene 60 mg.

As mentioned above, all patients received daily oral calcium supplementation throughout the study.

REVIEWER'S COMMENTS ON STUDY GGGF

A total of 601 patients (150 placebo, 152 raloxifene 30 mg, 152 raloxifene 60 mg, 147 raloxifene 150mg) were randomized to receive double-blind treatment.

A total of 149 patients (31 placebo, 38 raloxifene 30mg, 33 raloxifene 60 mg, 47 raloxifene 150 mg) failed to complete 24 months of double-blind treatment. There was a significant trend (p=.026) with increasing doses of raloxifene with regard to the discontinuation rate. This trend was due primarily to the raloxifene 150 mg discontinuation rate (32.0%) which was significantly (p=.027) greater than the corresponding placebo rate (20.7%)). There was no significant difference in the discontinuation rate between placebo and raloxifene 60 mg (21.7%) which is the sponsor's proposed dose.

The most common reasons for discontinuation were adverse experiences (20 placebo, 24 raloxifene 30 mg, 18 raloxifene 60 mg, 26 raloxifene 150 mg) and personal conflict (6 placebo, 9 raloxifene 30 mg, 8 raloxifene 60 mg, 17 raloxifene 150 mg).

A significant treatment difference was not detected (p=.49) with respect to the adverse experience discontinuation rate or with regard to any specific adverse experience discontinuation reason the most common of which was vasodilatation (4 placebo, 5 raloxifene 30 mg, 3 raloxifene 60 mg, 7 raloxifene 150 mg, p=.56).

However, there was a significant trend (p=.007) with increasing doses of raloxifene

with regard to the personal conflict discontinuation reason. Once again, this was due primarily to the raloxifene 150 mg rate (11.6%) which was significantly (p=.015) greater than the corresponding placebo rate (4.0%) as there was no significant difference in the personal conflict discontinuation rate between placebo and raloxifene 60 mg (5.3%).

A total of 523 patients (132 placebo, 130 raloxifene 30mg, 132 raloxifene 60 mg, 129 raloxifene 150mg, p=.92) experienced at least one treatment-emergment adverse event during double-blind treatment.

Based on adverse event data submitted by the sponsor, this reviewer noted significant differences (p<.05) with regard to pharyngitis and pneumonia, and significant trends (p<.10) with regard to weight gain and depression. In examining these results (Table 1), it is apparent that the significant differences and trend with regard to pharyngitis, pneumonia, and weight gain were due to the higher raloxifene 60 mg rates. However, rates of this magnitude were not achieved by the raloxifene 150 mg patients.

In addition, significantly (p=.046) more patients randomized to any raloxifene dosage group experienced urinary tract infections than did placebo patients (13 raloxifene, 0 placebo). No other significant differences were detected in comparing patients who received any raloxifene treatment with patients who received placebo.

As mentioned above, the primary efficacy measures were lumbar spine (L-1 through L-4) and total hip BMD. The response measures for the primary efficacy variables were the change and percent change from baseline BMD as well as the slope of the regression of BMD versus time on study.

BMD measurements were conducted at baseline as well as subsequent to 6, 12, 18, and 24 months of double-blind treatment. The results of the sponsor's last observation carried forward (LOCF) analyses which included all patients with a baseline and at least one post-baseline BMD measurement are displayed in Tables 2 and 3.

In examining Tables 2 and 3, one notes that each raloxifene treatment group significantly (p<.001) outperformed the placebo treatment group with regard to the mean percent change in lumbar spine and total hip BMD as each raloxifene treatment group experienced a mean percent increase in BMD compared to a corresponding decrease in the placebo group. There were no significant differences between the raloxifene 150 mg and raloxifene 60 mg (sponsor's proposed dose) treatment groups. Similar results were obtained with regard to the absolute change from baseline.

Similar results were also obtained at each BMD timepoint (Tables 4 and 5) in which the LOCF procedure was not utilized.

As mentioned above, the sponsor also compared treatment groups with regard to the slopes of the BMD regression on time in which patients were stratified based on the number of post-randomization timepoints utilized to determine the slope.
In examining the results (Tables 6 and 7) of the slope analyses, one notes that they are consistent with the above mentioned percent change results in that each raloxifene treatment group significantly ($p<.001$) outperformed the placebo group and that there were no significant raloxifene 30 mg - raloxifene 60 mg, or raloxifene 60 mg - raloxifene 150 mg differences.

Consequently, it is apparent that study GGGF was successful in demonstrating a highly significant ($p<.001$) treatment effort in favor of each raloxifene dosage (30 mg, 60 mg, 150 mg) over placebo with regard to lumbar spine and total hip BMD.

As mentioned above, the sponsor's proposed dose is 60 mg once daily. Given the results of this study, it is a matter of clinical judgment as to the utility of the 30 mg dosage regimen in comparison to the 60 mg dosage regimen.

STUDY GGGG

Study GGGG is an ongoing multicenter (8 U.S., 1 Canada) double-blind, randomized, placebo-controlled trial which is being conducted under a protocol similar to that of Study GGGF.

REVIEWER'S COMMENTS ON STUDY GGGG

A total of 544 patients (136 placebo, 136 raloxifene 30 mg, 134 raloxifene 60 mg, 138 raloxifene 150 mg) were randomized to receive double-blind treatment.

A total of 178 patients (36 placebo, 41 raloxifene 30 mg, 44 raloxifene 60 mg, 57 raloxifene 150 mg) failed to complete 24 months of double-blind treatment. There was a significant trend ($p=.006$) with increasing doses of raloxifene with regard to the discontinuation rate. As in study GGGF, this trend was due primarily to the raloxifene 150 mg discontinuation rate (41.3%) which was significantly ($p=.01$) greater than the corresponding placebo rate (26.5%). There were no significant differences in the discontinuation rate between placebo and the remaining raloxifene treatment groups.

The most common reasons for discontinuation were adverse experiences (14 placebo, 11 raloxifene 30 mg, 12 raloxifene 60 mg, 17 raloxifene 150 mg, $p=.67$) and personal conflict (8 placebo, 10 raloxifene 30mg, 16 raloxifene 60 mg, 16 raloxifene 150 mg, p-.21). In addition a significant treatment difference was not detected with regard to the discontinuation rate for any specific adverse experience, the most common of which

was vasodilatation (3 placebo, 0 raloxifene 30 mg, 2 raloxifene 60 mg, 5 raloxifene 150 mg, p=.16).

A total of 468 patients (122 placebo, 113 raloxifene 30mg, 117 raloxifene 60 mg, 116 raloxifene 150 mg, p=.37) experienced at least one treatment-emergment adverse event during double-blind treatment.

Based on adverse event data submitted by the sponsor, this reviewer noted a significant difference (p=.03) with regard to vasodilatation which was experienced by a total of 86 (17 placebo, 14 raloxifene 30 mg, 30 raloxifene 60 mg, 25 raloxifene 150 mg) patients. This difference was due primarily to the raloxifene 60 mg rate (22.4%) which was significantly (p=.03) greater than the corresponding placebo rate (12.5%).

The results of the sponsor's LOCF lumbar spine and total hip analyses are displayed in Tables 8 and 9. In examining these tables, one notes that as in Study GGGF, each raloxifene treatment group significantly (p<.001) outperformed the placebo treatment group with regard to the mean percent change in lumbar spine and total hip BMD. Each raloxifene treatment group experienced a mean percent increase in lumbar spine and total hip BMD compared to corresponding decreases in the placebo treatment group. Furthermore, there were no significant differences detected between the raloxifene treatment groups. Similar results were obtained with regard to the absolute change from baseline.

Similar results were also obtained at each BMD timepoint (Tables 10 and 11) in which the LOCF procedure was not utilized.

The results of the slope analyses (Tables 12 and 13) were consistent with the percent change results in that each raloxifene treatment group significantly (p<.001) outperformed the placebo group and that there were no significant raloxifene 30 mg - raloxifene 60 mg, or raloxifene 60 mg - raloxifene 150 mg differences.

Consequently, as was Study GGGF, Study GGGG was successful in demonstrating a highly significant (p<.001) treatment effect in favor of each raloxifene dosage (30 mg, 60 mg, 150 mg) over placebo with regard to lumbar spine and total hip BMD.

Once again, it is a matter of clinical judgment as to the utility of the 30 mg dosage regimen in comparison to the 60mg dosage regimen.

STUDY GGGH

Study GGGH is an ongoing multicenter, double-blind randomized, placebo - and active - controlled trial which is being conducted by 38 investigators in four continents.

The primary objectives of Study GGGH are:

1. "To establish the effect of long-term therapy (at least 36 months) with raloxifene on lumbar spine and hip BMD in healthy, postmenopausal, hysterectomized women."

2. "To establish the safety of chronic administration of raloxifene in healthy, postmenopausal, hysterectomized women".

Postmenopausal women, who had undergone a hysterectomy no more than 15 years prior to commencing the study whose lumbar spine BMD measurements satisfied the Study GGGF and Study GGGG entrance criteria were randomized to receive 36 months of double-blind treatment.

Patients were randomized to receive a once daily dose of raloxifene 60 mg, raloxifene 150 mg, Premarin .625 mg, or placebo. Subsequent to the 36-month double-blind treatment phase, patients are eligible to enter a 24-month double-blind extension phase. Raloxifene and Premarin patients who so elect will continue to receive their randomized treatment. However, placebo patients will be randomized in a 2-to-1 ratio to receive daily doses of placebo or raloxifene 60 mg.

As in Studies GGGF and GGGG, all patients received daily oral calcium supplementation throughout the study.

REVIEWER'S COMMENTS ON STUDY GGGH

A total of 619 patients (152 placebo, 152 raloxifene 60 mg,, 157 raloxifene 150 mg, 158 Premarin .625 mg) were randomized to receive double-blind treatment.

A total of 179 patients (49 placebo, 46 raloxifene 60 mg, 44 raloxifene 150 mg, 40 Premarin .625 mg, p=.57) failed to complete 24 months of double-blind treatment.

The most common reasons for discontinuation were adverse experiences (21 placebo, 24 raloxifene 60 mg, 24 raloxifene 150 mg, 21 Premarin .625 mg, p=.91) and personal conflict (17 placebo, 8 raloxifene 60 mg, 11 raloxifene 150 mg, 6 Premarin .625 mg, p=.06).

In addition, a significant treatment difference was not detected with regard to the discontinuation rate for any specific adverse experience, the most common of which was vasodilatation (4 placebo, 4 raloxifene 60 mg, 5 raloxifene 150 mg, 0 Premarin, p=.20).

A total of 581 patients (140 placebo, 142 raloxifene 60 mg, 149 raloxifene 150 mg, 150

Premarin .625 mg, p=.69) experienced at least one treatment - emergment adverse event during double-blind treatment.

Based on adverse event data submitted by the sponsor, this reviewer noted significant differences ($p<.05$) with regard to vasodilatation, leg cramps, breast pain, and accidental injury (Table 14). In examining these results, this reviewer noted that patients randomized to receive the sponsor's proposed raloxifene 60 mg dose experienced a significantly ($p<.001$) greater leg cramp incidence rate than their placebo counterparts.

The results of the sponsor's LOCF lumbar spine and total hip analyses are displayed in Tables 15 and 16. In examining these tables, one notes that the raloxifene and Premarin treatment groups significantly ($p<.01$) out performed the placebo treatment groups with regard to the mean percent change in lumbar spine and total hip BMD. Each active treatment group experienced a mean percent increase in lumbar spine and total hip BMD compared to corresponding decreases in the placebo treatment group. Furthermore, there were no significant differences between the raloxifene 60 mg and 150 mg treatment groups. In addition, patients randomized to the Premarin .625 mg treatment group experienced a significantly ($p<.001$) greater mean percentage increase in lumbar spine and total hip BMD than patients randomized to either of the raloxifene treatment groups. Similar results were obtained with regard to the absolute change from baseline.

Results obtained at each BMD timepoint (Tables 17 and 18) in which the LOCF procedure was not utilized were consistent with the above mentioned LOCF results.

The results of the slope analyses (Tables 19 and 20) were consistent with the percent change results in that the raloxifene 60 mg treatment group significantly ($p<.01$) outperformed the placebo treatment group, but was in turn significantly ($p<.001$) outperformed by the Premarin treatment group.

Consequently, as were studies GGGF and GGGG, study GGGH was successful in demonstrating a highly significant treatment effect in favor of each raloxifene dosage (60 mg, 150 mg) over placebo with regard to lumbar spine and total hip BMD.

However, it should be noted that Premarin patients experienced a significantly ($p<.001$) greater increase in lumbar spine and total hip BMD than did patients in either of the raloxifene treatment groups.

REVIEWER'S CONCLUDING COMMENTS (may be conveyed to the sponsor)

Studies GGGF, GGGG and GGGH have established a statistical association between each of the studied raloxifene dosages (30 mg, 60 mg, and 150 mg) and an increase in lumbar spine and total hip BMD (Table 21).

However, statistical evidence has not been provided to support the sponsor's proposed raloxifene 60 mg regimen over that of raloxifene 30 mg with regard to the effect on lumbar spine and total hip BMD.

In addition, Study GGGH patients who were randomized to receive Premarin .625 mg experienced a significantly greater increase in lumbar spine and total hip BMD than did patients who received raloxifene 60 mg or raloxifene 150 mg.

Daniel N. Marticello
Mathematical Statistician

Concur: Dr. Nevius 10/2/97

Archival: NDA 20-815
HFD-510
HFD-510/SSobel,GTroendle, EColman, RHedin
HFD-715/Division File, DMarticello
Chron.

APPEARS THIS WAY
ON ORIGINAL

This review consists of 10 pages of text and 21 pages of tables

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Table 1

Study GGGF

Adverse Events+

Event	Placebo	*Raloxifene* 30 mg	*Raloxifene* 60 mg	*Raloxifene* 150 mg	P-value
Pharyngitis	4 (2.7%)	3 (2.0%)	10 (6.6%)	1 (0.7%)	.018
Pneumonia	3 (2.0%)	1 (0.7%)	9 (5.9%)	4 (2.7%)	.041
Weight Gain	10 (6.7%)	10 (6.6%)	22 (14.5%)	13 (8.8%)	.057
Depression	11 (7.3%)	2 (1.3%)	8 (5.3%)	10 (6.8%)	.077
Urinary Tract Infection	0	5 (3.3%)	3 (2.0%)	5 (3.6%)	.046#

\+ **Adverse events where p<.10**

\# **Raloxifene 30 mg, 60 mg, 150 mg versus placebo**

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Table 2

Study GGGF

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Lumbar Spine (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*30 mg*	*60 mg*	*150 mg*
Placebo	135	.935	-.795	<.001	<.001	<.001
Raloxifene 30 mg	139	.925	1.280		.35	.02
Raloxifene 60 mg	133	.934	1.639			.15
Raloxifene 150 mg	125	.937	2.211			
		P=.77	**P<.001**			

\+ **Analysis include all patients with a baseline and at least one post-randomization BMD measurement. Last (LOCF) post-randomization BMD values were carried forward.**

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ON ORIGINAL

Table 3

Study GGGF

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Total Hip (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*30 mg*	*60 mg*	*150 mg*
Placebo	135	.873	-.843	<.001	<.001	<.001
Raloxifene 30 mg	139	.870	1.037		.14	.30
Raloxifene 60 mg	132	.865	1.576			.69
Raloxifene 150 mg	125	.865	1.462			
		P=.95	**P<.001**			

\+ **See Table 1**

Table 4

Study GGGF

Mean Percentage Change
At Each Time Point (observed cases)

Lumbar Spine (g/cm^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	134	-.232	126	-.481	124	-.903	119	-.802
Raloxifene 30 mg	135	.623*	120	1.659**	116	1.095**	113	1.571**
Raloxifene 60 mg	133	1.333**	124	1.512**	124	1.641**	120	1.846**
Raloxifene 150 mg	120	1.250**	114	1.646**	104	1.793**	100	2.130**
	P<.001		**P<.001**		**P<.001**		**P<.001**	

* **p<.01 in favor of raloxifene over placebo**

** **p<.001 in favor of raloxifene over placebo**

APPEARS THIS WAY
ON ORIGINAL

Table 5

Study GGGF

Mean Percentage Change
At Each Time Point (observed cases)

Total Hip (g/cm^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	133	-.529	125	-.614	124	-.787	119	-.841
Raloxifene 30 mg	137	.025	120	1.126*	113	1.051*	113	1.364*
Raloxifene 60 mg	132	.606*	123	1.345*	122	1.661*	117	1.610*
Raloxifene 150 mg	121	.487*	112	.979*	105	1.293*	100	1.821*
	P<.001		**P<.001**		**P<.001**		**P<.001**	

* **p<.001 in favor of raloxifene over placebo**

Table 6

Study GGGF

Mean Analyzed Slope (g/cm^2)

Lumbar Spine

			Pairwise P-Values		
Treatment	***N***	***Slope***	***30 mg***	***60 mg***	***150 mg***
Placebo	135	-.0068	<.001	<.001	<.001
Raloxifene 30 mg	139	.0033		.134	.011
Raloxifene 60 mg	133	.0057			.294
Raloxifene 150 mg	125	.0074			
		P<.001			

Table 7

Study GGGF

Mean Analyzed Slope (g/cm^2)

Total Hip

			Pairwise P-Values		
Treatment	***N***	***Slope***	***30 mg***	***60 mg***	***150 mg***
Placebo	135	-.0056	<.001	<.001	<.001
Raloxifene 30 mg	139	.0022		.056	.180
Raloxifene 60 mg	133	.0047			.589
Raloxifene 150 mg	125	.0040			
		P<.001			

Table 8

Study GGGG

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Lumbar Spine (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*30 mg*	*60 mg*	*150 mg*
Placebo	124	.953	-1.165	<.001	<.001	<.001
Raloxifene 30 mg	119	.943	.397		.29	.35
Raloxifene 60 mg	118	.951	.782			.91
Raloxifene 150 mg	119	.955	.759			
		P=.86	**P<.001**			

\+ **See Table 1**

Table 9

Study GGGG

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Total Hip (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*30 mg*	*60 mg*	*150 mg*
Placebo	123	.841	- .762	<.001	<.001	<.001
Raloxifene 30 mg	119	.851	1.006		.34	.08
Raloxifene 60 mg	118	.855	1.197			.43
Raloxifene 150 mg	119	.848	1.595			
		P=.83	**P<.001**			

\+ **See Table 1**

Table 10

Study GGGG

Mean Percentage Change
At Each Time Point (observed cases)

Lumbar Spine (g/m^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	118	-.134	116	-.918	106	-.751	101	-1.025
Raloxifene 30 mg	112	.419	107	.403**	102	.845**	96	.289*
Raloxifene 60 mg	115	.363	104	.822**	96	1.247**	91	.950**
Raloxifene 150 mg	113	.405	103	.572**	90	.811*	81	.890**
	P=.35		**P<.001**		**P<.001**		**P<.001**	

* **p<.01 in favor of raloxifene over placebo**

** **p<.001 in favor of raloxifene over placebo**

Table 11

Study GGGG

Mean Percentage Change
At Each Time Point (observed cases)

Total Hip (g/m^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	118	-.588	115	-.786	105	-.357	100	-.643
Raloxifene 30 mg	112	.488*	107	.504*	102	1.135*	96	.938*
Raloxifene 60 mg	115	.627*	103	.898*	96	1.211*	90	1.571*
Raloxifene 150 mg	113	.958*	102	1.488*	90	2.163*	81	1.876*
	P<.001		**P<.001**		**P<.001**		**P<.001**	

* **p<.001 in favor of raloxifene over placebo**

Table 12

Study GGGG

Mean Analyzed Slope (g/cm^2)

Lumbar Spine

			Pairwise P-Values		
Treatment	***N***	***Slope***	***30 mg***	***60 mg***	***150 mg***
Placebo	124	-.0063	<.001	<.001	<.001
Raloxifene 30 mg	119	.0019		.129	.263
Raloxifene 60 mg	118	.0049			.687
Raloxifene 150 mg	119	.0041			
		P<.001			

Table 13

Study GGGG

Mean Analyzed Slope (g/cm^2)

Total Hip

			Pairwise P-Values		
Treatment	***N***	***Slope***	***30 mg***	***60 mg***	***150 mg***
Placebo	123	-.0044	<.001	<.001	<.001
Raloxifene 30 mg	119	.0022		.265	.016
Raloxifene 60 mg	118	.0040			.195
Raloxifene 150 mg	119	.0062			
		P<.001			

Table 14

Study GGGH

Adverse Events+

		Raloxifene			
Event	*Placebo*	*60 mg*	*150 mg*	*Premarin*	*P-Value*
Vasodilatation	40 (26.3%)	49 (32.2%)	69 (43.9%)	15 (9.5%)	<.001
Leg Cramps	2 (1.3%)	14 (9.2%)	13 (8.3%)	5 (3.2%)	.004
Breast Pain	9 (5.9%)	11 (7.2%)	8 (5.1%)	22 (13.9%)	.017
Accidental Injury	16 (10.5%)	17 (11.2%)	33 (21.0%)	23 (14.6%)	.033

\+ **Adverse events experienced by at least 5% of the patients in each raloxifene group where p<.10**

Table 15

Study GGGH

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Lumbar Spine (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*60 mg*	*150 mg*	*.625 mg*
Placebo	130	.974	-1.587	<.001	<.001	<.001
Raloxifene 60 mg	131	.967	.191		.50	<.001
Raloxifene 150 mg	136	.969	.450			<.001
Premarin .625 mg	137	.957	3.805			
		P=.67	**P<.001**			

\+ **See Table 1**

Table 16

Study GGGH

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Total Hip (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*60 mg*	*150 mg*	*.625 mg*
Placebo	125	.879	- .489	<.001	<.01	<.001
Raloxifene 60 mg	124	.892	.786		.37	<.001
Raloxifene 150 mg	128	.897	.516			<.001
Premarin .625 mg	131	.876	2.414			
		P=.36	**P<.001**			

\+ **See Table 1**

Table 17

Study GGGH

Mean Percentage Change
At Each Time Point (observed cases)

Lumbar Spine (g/cm^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	129	-.412	113	-.562	103	-1.314	103	-1.521
Raloxifene 60 mg	130	.761	116	.532	111	.792	107	.519
Raloxifene 150 mg	134	.580	124	.958	118	1.029	113	.649
Premarin .625 mg	136	2.177	129	3.316	124	3.739	118	3.917
	P<.001		**P<.001**		**P<.001**		**P<.001**	

	Pairwise P-Values			
Raloxifene 60 mg vs Placebo	<.001	.005	<.001	<.001
Raloxifene 150 mg vs Placebo	.002	<.001	<.001	<.001
Premarin .625 mg vs Placebo	<.001	<.001	<.001	<.001

	Pairwise P-Values			
Raloxifene 150 mg vs Raloxifene 60 mg	.620	.302	.641	.879
Premarin .625 mg vs Raloxifene 150 mg	<.001	<.001	<.001	<.001
Premarin .625 mg vs Raloxifene 60 mg	<.001	<.001	<.001	<.001

Table 18

Study GGGH

Mean Percentage Change
At Each Time Point (observed cases)

Total Hip (g/cm^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	124	-.035	108	-.057	98	.030	98	-.343
Raloxifene 60 mg	124	.668	108	.855	106	.893	101	.747
Raloxifene 150 mg	127	.529	116	.697	110	1.158	113	.696
Premarin .625 mg	131	1.409	122	1.774	119	2.280	112	2.237
	P<.001		**P<.001**		**P<.001**		**P<.001**	

	Pairwise P-Values			
Raloxifene 60 mg vs Placebo	.020	.016	.038	.004
Raloxifene 150 mg vs Placebo	.063	.039	.005	.007
Premarin .625 mg vs Placebo	<.001	<.001	<.001	<.001

	Pairwise P-Values			
Raloxifene 150 mg vs Raloxifene 60 mg	.621	.705	.474	.840
Premarin .625 mg vs Raloxifene 150 mg	.004	<.001	.004	<.001
Premarin .625 mg vs Raloxifene 60 mg	.018	.004	<.001	<.001

Table 19

Study GGGH

Mean Analyzed Slope (g/cm^2)

Lumbar Spine

			Pairwise P-Value		
Treatment	***N***	***Slope***	***60 mg***	***150 mg***	***Premarin***
Placebo	130	-.0108	<.001	<.001	<.001
Raloxifene 60 mg	131	- .0009		.276	<.001
Raloxifene 150 mg	136	.0012			<.001
Premarin .625 mg	137	.0172			
		P<.001			

Table 20

Study GGGH

Mean Analyzed Slope (g/cm^2)

Total Hip

			Pairwise P-Value		
Treatment	***N***	***Slope***	***60 mg***	***150 mg***	***Premarin***
Placebo	130	-.0030	.002	.017	<.001
Raloxifene 60 mg	130	.0024		.489	<.001
Raloxifene 150 mg	134	.0012			<.001
Premarin .625 mg	136	.0098			
		P<.001			

Table 21

Studies GGGF, GGGG, GGGH

Mean Percentage Change
From Baseline to Endpoint (LOCF[+])

	Lumbar Spine		
Treatment	***GGGF***	***GGGG***	***GGGH***
Placebo	-.795	-1.165	-1.587
Raloxifene 30 mg	1.280*	.397*	
Raloxifene 60 mg	1.639*	.782*	.191*
Raloxifene 150 mg	2.211*	.759*	.450*
Premarin .625 mg			3.805#

	Total Hip		
Treatment	***GGGF***	***GGGG***	***GGGH***
Placebo	-.843	-.762	-.489
Raloxifene 30 mg	1.037*	1.006*	
Raloxifene 60 mg	1.576*	1.197*	.786*
Raloxifene 150 mg	1.462*	1.595*	.516[a]
Premarin .625 mg			2.414#

a p<.01 in favor of raloxifene over placebo

*** p<.001 in favor of raloxifene over placebo**

 # p<.001 in favor of Premarin over raloxifene and placebo

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-815 OCT 2 1997

APPLICANT: Lilly Research Laboratories

NAME OF DRUG: Evista (raloxifene hydrochloride)

INDICATION: Prevention of osteoporosis in postmenopausal women

DOCUMENTS REVIEWED: Volumes 1:2.1, 2:2.1, 10:2.1, 10:2.16-10:2.38 dated June 8, 1997 and supplemental material (CANDA) in Adobe Portable Document Format (PDF).

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer, Eric C. Colman, M.D., HFD-510.

RELEVANT ISSUES DISCUSSED IN THIS REVIEW

1. Studies GGGF, GGGG, and GGGH have established a statistical association between each of the studied dosages (30 mg, 60 mg, and 150 mg) and an increase in lumber spine and total hip BMD.

2. The sponsor's justification for their proposed raloxifene 60 mg dosage regimen is a matter of clinical judgment as statistical evidence has not been provided which establishes an increased effect on lumbar spine and total hip BMD of raloxifene 60 mg over raloxifene 30 mg.

3. Patients who received Premarin .625 mg in study GGGH experienced a significantly greater increase in lumbar spine and total hip BMD than did patients who received raloxifene 60 mg or raloxifene 150 mg.

KEY WORDS: **bone mineral density, estrogen receptor, interim analysis, lumbar spine, osteoporosis, postmenopausal, Premarin, total hip**

BACKGROUND

The sponsor has submitted the results of 24-month interim analyses for their Phase 3 multicenter osteoporosis prevention trials in support of their proposed 60 mg tablet dosage given once daily.

Each of the Phase 3 studies was designed with a 36-month double-blind treatment duration. However, the sponsor presented data to the FDA which indicated that raloxifene acted via the estrogen receptor and that its action on the bone in animal and early clinical studies was very similar to that of estrogen.

Based on this data, the FDA agreed that as a new estrogen-like compound, raloxifene may be approved for the prevention of postmenopausal osteoporosis based on 24-month bone mineral density (BMD) data.

Consequently, the sponsor conducted 24-month interim analyses at the 2.9% significance level. It was agreed upon that failure to demonstrate significance at 24 months at the 2.9% significance level would result in 36-month analyses which would be conducted at a level of significance which would result in an overall Type 1 error rate of 5%.

The primary endpoints for each study were the treatment effects on BMD measured using dual-energy x-ray absorptiometry (DXA) in the lumbar (L-1 through L-4) spine and hip.

In addition to their double-blind randomized treatment, all patients in these three studies were provided oral calcium supplements throughout the study to assure adequate calcium intake.

A review of each of these studies follows.

STUDY GGGF

Study GGGF is an ongoing multicenter, double-blind, randomized, placebo-controlled trial which is being conducted in 11 sites in 8 European countries.

The primary objectives of Study GGGF are:

1) "To establish the effect of long-term therapy (at least 3 years) with raloxifene, compared with placebo, on lumbar spine and total hip bone mineral density in healthy, postmenopausal women".

2) "To establish the safety of chronic administration of raloxifene in healthy, postmenopausal women.

Postmenopausal women who became menopausal 2 to 8 years before study commencement whose lumbar spine BMD measurements were between 2.0 standard deviations (SD) above and 2.5 SD below mean peak lumbar spine BMD for premenopausal women were randomized to receive 36 months of double-blind treatment.

Patients were randomized to receive a once daily dose of raloxifene 30 mg, raloxifene 60 mg (sponsor's proposed dose), raloxifene 150 mg or placebo. Subsequent to the 36-month double-blind treatment phase, patients are eligible to enter a 2-year double-blind extension phase. Raloxifene patients who so elect will continue to receive their randomized treatment. However, placebo patients will be randomized in a 2-to-1 ratio to receive daily doses of placebo or raloxifene 60 mg.

As mentioned above, all patients received daily oral calcium supplementation throughout the study.

REVIEWER'S COMMENTS ON STUDY GGGF

A total of 601 patients (150 placebo, 152 raloxifene 30 mg, 152 raloxifene 60 mg, 147 raloxifene 150mg) were randomized to receive double-blind treatment.

A total of 149 patients (31 placebo, 38 raloxifene 30mg, 33 raloxifene 60 mg, 47 raloxifene 150 mg) failed to complete 24 months of double-blind treatment. There was a significant trend (p=.026) with increasing doses of raloxifene with regard to the discontinuation rate. This trend was due primarily to the raloxifene 150 mg discontinuation rate (32.0%) which was significantly (p=.027) greater than the corresponding placebo rate (20.7%)). There was no significant difference in the discontinuation rate between placebo and raloxifene 60 mg (21.7%) which is the sponsor's proposed dose.

The most common reasons for discontinuation were adverse experiences (20 placebo, 24 raloxifene 30 mg, 18 raloxifene 60 mg, 26 raloxifene 150 mg) and personal conflict (6 placebo, 9 raloxifene 30 mg, 8 raloxifene 60 mg, 17 raloxifene 150 mg).

A significant treatment difference was not detected (p=.49) with respect to the adverse experience discontinuation rate or with regard to any specific adverse experience discontinuation reason the most common of which was vasodilatation (4 placebo, 5 raloxifene 30 mg, 3 raloxifene 60 mg, 7 raloxifene 150 mg, p=.56).

However, there was a significant trend (p=.007) with increasing doses of raloxifene

with regard to the personal conflict discontinuation reason. Once again, this was due primarily to the raloxifene 150 mg rate (11.6%) which was significantly (p=.015) greater than the corresponding placebo rate (4.0%) as there was no significant difference in the personal conflict discontinuation rate between placebo and raloxifene 60 mg (5.3%).

A total of 523 patients (132 placebo, 130 raloxifene 30mg, 132 raloxifene 60 mg, 129 raloxifene 150mg, p=.92) experienced at least one treatment-emergment adverse event during double-blind treatment.

Based on adverse event data submitted by the sponsor, this reviewer noted significant differences ($p<.05$) with regard to pharyngitis and pneumonia, and significant trends ($p<.10$) with regard to weight gain and depression. In examining these results (Table 1), it is apparent that the significant differences and trend with regard to pharyngitis, pneumonia, and weight gain were due to the higher raloxifene 60 mg rates. However, rates of this magnitude were not achieved by the raloxifene 150 mg patients.

In addition, significantly (p=.046) more patients randomized to any raloxifene dosage group experienced urinary tract infections than did placebo patients (13 raloxifene, 0 placebo). No other significant differences were detected in comparing patients who received any raloxifene treatment with patients who received placebo.

As mentioned above, the primary efficacy measures were lumbar spine (L-1 through L-4) and total hip BMD. The response measures for the primary efficacy variables were the change and percent change from baseline BMD as well as the slope of the regression of BMD versus time on study.

BMD measurements were conducted at baseline as well as subsequent to 6, 12, 18, and 24 months of double-blind treatment. The results of the sponsor's last observation carried forward (LOCF) analyses which included all patients with a baseline and at least one post-baseline BMD measurement are displayed in Tables 2 and 3.

In examining Tables 2 and 3, one notes that each raloxifene treatment group significantly ($p<.001$) outperformed the placebo treatment group with regard to the mean percent change in lumbar spine and total hip BMD as each raloxifene treatment group experienced a mean percent increase in BMD compared to a corresponding decrease in the placebo group. There were no significant differences between the raloxifene 150 mg and raloxifene 60 mg (sponsor's proposed dose) treatment groups. Similar results were obtained with regard to the absolute change from baseline.

Similar results were also obtained at each BMD timepoint (Tables 4 and 5) in which the LOCF procedure was not utilized.

As mentioned above, the sponsor also compared treatment groups with regard to the slopes of the BMD regression on time in which patients were stratified based on the number of post-randomization timepoints utilized to determine the slope.
In examining the results (Tables 6 and 7) of the slope analyses, one notes that they are consistent with the above mentioned percent change results in that each raloxifene treatment group significantly ($p<.001$) outperformed the placebo group and that there were no significant raloxifene 30 mg - raloxifene 60 mg, or raloxifene 60 mg - raloxifene 150 mg differences.

Consequently, it is apparent that study GGGF was successful in demonstrating a highly significant ($p<.001$) treatment effort in favor of each raloxifene dosage (30 mg, 60 mg, 150 mg) over placebo with regard to lumbar spine and total hip BMD.

As mentioned above, the sponsor's proposed dose is 60 mg once daily. Given the results of this study, it is a matter of clinical judgment as to the utility of the 30 mg dosage regimen in comparison to the 60 mg dosage regimen.

STUDY GGGG

Study GGGG is an ongoing multicenter (8 U.S., 1 Canada) double-blind, randomized, placebo-controlled trial which is being conducted under a protocol similar to that of Study GGGF.

REVIEWER'S COMMENTS ON STUDY GGGG

A total of 544 patients (136 placebo, 136 raloxifene 30 mg, 134 raloxifene 60 mg, 138 raloxifene 150 mg) were randomized to receive double-blind treatment.

A total of 178 patients (36 placebo, 41 raloxifene 30 mg, 44 raloxifene 60 mg, 57 raloxifene 150 mg) failed to complete 24 months of double-blind treatment. There was a significant trend ($p=.006$) with increasing doses of raloxifene with regard to the discontinuation rate. As in study GGGF, this trend was due primarily to the raloxifene 150 mg discontinuation rate (41.3%) which was significantly ($p=.01$) greater than the corresponding placebo rate (26.5%). There were no significant differences in the discontinuation rate between placebo and the remaining raloxifene treatment groups.

The most common reasons for discontinuation were adverse experiences (14 placebo, 11 raloxifene 30 mg, 12 raloxifene 60 mg, 17 raloxifene 150 mg, $p=.67$) and personal conflict (8 placebo, 10 raloxifene 30mg, 16 raloxifene 60 mg, 16 raloxifene 150 mg, p-.21). In addition a significant treatment difference was not detected with regard to the discontinuation rate for any specific adverse experience, the most common of which

was vasodilatation (3 placebo, 0 raloxifene 30 mg, 2 raloxifene 60 mg, 5 raloxifene 150 mg, p=.16).

A total of 468 patients (122 placebo, 113 raloxifene 30mg, 117 raloxifene 60 mg, 116 raloxifene 150 mg, p=.37) experienced at least one treatment-emergment adverse event during double-blind treatment.

Based on adverse event data submitted by the sponsor, this reviewer noted a significant difference (p=.03) with regard to vasodilatation which was experienced by a total of 86 (17 placebo, 14 raloxifene 30 mg, 30 raloxifene 60 mg, 25 raloxifene 150 mg) patients. This difference was due primarily to the raloxifene 60 mg rate (22.4%) which was significantly (p=.03) greater than the corresponding placebo rate (12.5%).

The results of the sponsor's LOCF lumbar spine and total hip analyses are displayed in Tables 8 and 9. In examining these tables, one notes that as in Study GGGF, each raloxifene treatment group significantly (p<.001) outperformed the placebo treatment group with regard to the mean percent change in lumbar spine and total hip BMD. Each raloxifene treatment group experienced a mean percent increase in lumbar spine and total hip BMD compared to corresponding decreases in the placebo treatment group. Furthermore, there were no significant differences detected between the raloxifene treatment groups. Similar results were obtained with regard to the absolute change from baseline.

Similar results were also obtained at each BMD timepoint (Tables 10 and 11) in which the LOCF procedure was not utilized.

The results of the slope analyses (Tables 12 and 13) were consistent with the percent change results in that each raloxifene treatment group significantly (p<.001) outperformed the placebo group and that there were no significant raloxifene 30 mg - raloxifene 60 mg, or raloxifene 60 mg - raloxifene 150 mg differences.

Consequently, as was Study GGGF, Study GGGG was successful in demonstrating a highly significant (p<.001) treatment effect in favor of each raloxifene dosage (30 mg, 60 mg, 150 mg) over placebo with regard to lumbar spine and total hip BMD.

Once again, it is a matter of clinical judgment as to the utility of the 30 mg dosage regimen in comparison to the 60mg dosage regimen.

STUDY GGGH

Study GGGH is an ongoing multicenter, double-blind randomized, placebo - and active - controlled trial which is being conducted by 38 investigators in four continents.

The primary objectives of Study GGGH are:

1. "To establish the effect of long-term therapy (at least 36 months) with raloxifene on lumbar spine and hip BMD in healthy, postmenopausal, hysterectomized women."

2. "To establish the safety of chronic administration of raloxifene in healthy, postmenopausal, hysterectomized women".

Postmenopausal women who had undergone a hysterectomy no more than 15 years prior to commencing the study whose lumbar spine BMD measurements satisfied the Study GGGF and Study GGGG entrance criteria were randomized to receive 36 months of double-blind treatment.

Patients were randomized to receive a once daily dose of raloxifene 60 mg, raloxifene 150 mg, Premarin .625 mg, or placebo. Subsequent to the 36-month double-blind treatment phase, patients are eligible to enter a 24-month double-blind extension phase. Raloxifene and Premarin patients who so elect will continue to receive their randomized treatment. However, placebo patients will be randomized in a 2-to-1 ratio to receive daily doses of placebo or raloxifene 60 mg.

As in Studies GGGF and GGGG, all patients received daily oral calcium supplementation throughout the study.

REVIEWER'S COMMENTS ON STUDY GGGH

A total of 619 patients (152 placebo, 152 raloxifene 60 mg,, 157 raloxifene 150 mg, 158 Premarin .625 mg) were randomized to receive double-blind treatment.

A total of 179 patients (49 placebo, 46 raloxifene 60 mg, 44 raloxifene 150 mg, 40 Premarin .625 mg, p=.57) failed to complete 24 months of double-blind treatment.

The most common reasons for discontinuation were adverse experiences (21 placebo, 24 raloxifene 60 mg, 24 raloxifene 150 mg, 21 Premarin .625 mg, p=.91) and personal conflict (17 placebo, 8 raloxifene 60 mg, 11 raloxifene 150 mg, 6 Premarin .625 mg, p=.06).

In addition, a significant treatment difference was not detected with regard to the discontinuation rate for any specific adverse experience, the most common of which was vasodilatation (4 placebo, 4 raloxifene 60 mg, 5 raloxifene 150 mg, 0 Premarin, p=.20).

A total of 581 patients (140 placebo, 142 raloxifene 60 mg, 149 raloxifene 150 mg, 150

Premarin .625 mg, p=.69) experienced at least one treatment - emergment adverse event during double-blind treatment.

Based on adverse event data submitted by the sponsor, this reviewer noted significant differences ($p<.05$) with regard to vasodilatation, leg cramps, breast pain, and accidental injury (Table 14). In examining these results, this reviewer noted that patients randomized to receive the sponsor's proposed raloxifene 60 mg dose experienced a significantly ($p<.001$) greater leg cramp incidence rate than their placebo counterparts.

The results of the sponsor's LOCF lumbar spine and total hip analyses are displayed in Tables 15 and 16. In examining these tables, one notes that the raloxifene and Premarin treatment groups significantly ($p<.01$) out performed the placebo treatment groups with regard to the mean percent change in lumbar spine and total hip BMD. Each active treatment group experienced a mean percent increase in lumbar spine and total hip BMD compared to corresponding decreases in the placebo treatment group. Furthermore, there were no significant differences between the raloxifene 60 mg and 150 mg treatment groups. In addition, patients randomized to the Premarin .625 mg treatment group experienced a significantly ($p<.001$) greater mean percentage increase in lumbar spine and total hip BMD than patients randomized to either of the raloxifene treatment groups. Similar results were obtained with regard to the absolute change from baseline.

Results obtained at each BMD timepoint (Tables 17 and 18) in which the LOCF procedure was not utilized were consistent with the above mentioned LOCF results.

The results of the slope analyses (Tables 19 and 20) were consistent with the percent change results in that the raloxifene 60 mg treatment group significantly ($p<.01$) outperformed the placebo treatment group, but was in turn significantly ($p<.001$) outperformed by the Premarin treatment group.

Consequently, as were studies GGGF and GGGG, study GGGH was successful in demonstrating a highly significant treatment effect in favor of each raloxifene dosage (60 mg, 150 mg) over placebo with regard to lumbar spine and total hip BMD.

However, it should be noted that Premarin patients experienced a significantly ($p<.001$) greater increase in lumbar spine and total hip BMD than did patients in either of the raloxifene treatment groups.

REVIEWER'S CONCLUDING COMMENTS (may be conveyed to the sponsor)

Studies GGGF, GGGG and GGGH have established a statistical association between each of the studied raloxifene dosages (30 mg, 60 mg, and 150 mg) and an increase in lumbar spine and total hip BMD (Table 21).

However, statistical evidence has not been provided to support the sponsor's proposed raloxifene 60 mg regimen over that of raloxifene 30 mg with regard to the effect on lumbar spine and total hip BMD.

In addition, Study GGGH patients who were randomized to receive Premarin .625 mg experienced a significantly greater increase in lumbar spine and total hip BMD than did patients who received raloxifene 60 mg or raloxifene 150 mg.

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Concur: Dr. Nevius 10/2/97

Archival: NDA 20-815
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This review consists of 10 pages of text and 21 pages of tables

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Table 1

Study GGGF

Adverse Events[+]

Event	Placebo	*Raloxifene* 30 mg	*Raloxifene* 60 mg	*Raloxifene* 150 mg	P-value
Pharyngitis	4 (2.7%)	3 (2.0%)	10 (6.6%)	1 (0.7%)	.018
Pneumonia	3 (2.0%)	1 (0.7%)	9 (5.9%)	4 (2.7%)	.041
Weight Gain	10 (6.7%)	10 (6.6%)	22 (14.5%)	13 (8.8%)	.057
Depression	11 (7.3%)	2 (1.3%)	8 (5.3%)	10 (6.8%)	.077
Urinary Tract Infection	0	5 (3.3%)	3 (2.0%)	5 (3.6%)	.046[#]

\+ **Adverse events where p<.10**

\# **Raloxifene 30 mg, 60 mg, 150 mg versus placebo.**

Table 2

Study GGGF

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Lumbar Spine (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*30 mg*	*60 mg*	*150 mg*
Placebo	135	.935	-.795	<.001	<.001	<.001
Raloxifene 30 mg	139	.925	1.280		.35	.02
Raloxifene 60 mg	133	.934	1.639			.15
Raloxifene 150 mg	125	.937	2.211			
		P=.77	**P<.001**			

\+ **Analysis include all patients with a baseline and at least one post-randomization BMD measurement. Last (LOCF) post-randomization BMD values were carried forward.**

Table 3

Study GGGF

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Total Hip (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*30 mg*	*60 mg*	*150 mg*
Placebo	135	.873	-.843	<.001	<.001	<.001
Raloxifene 30 mg	139	.870	1.037		.14	.30
Raloxifene 60 mg	132	.865	1.576			.69
Raloxifene 150 mg	125	.865	1.462			
		P=.95	**P<.001**			

\+ **See Table 1**

sponsor has provided favorable interim data on the incidence of breast cancer in postmenopausal women participating in the ongoing phase 3 osteoporosis prevention and treatment trials.

Of the breast cancer data available at this time the most complete data base comes from the prevention studies, GGGF, GGGG, GGGH, and GGGY. Women in these studies had a "normal" mammogram that was done within one year of randomization and as of October 16, 1997 all patients who remained in the studies for two years have had their two-year mammogram performed, read, and the results reported to the sponsor. In this cohort of women, there have been nine breast cancer cases reported: 3/536 in placebo patients and 6/1364 in raloxifene-treated women; RR = 0.8 (0.20, 3.1). If one limits the cases to those diagnosed after 18 months of treatment (3/536 placebo and 3/1364), then the RR for breast cancer in the raloxifene- compared with placebo-treated women is 0.4 (0.08, 1.84).

While these preliminary data are encouraging, they are far from definitive. Limitations in study design aside, this Reviewer believes that responsible comments about raloxifene's effect on the risk for postmenopausal breast cancer cannot be made until the ongoing treatment and prevention trials are completed. Dialogue among the Division of Metabolic and Endocrine Drugs, the Division of Oncology Drugs, and the sponsor, continues to direct the review of the breast cancer data.

Uterine Cancer (see consult from the Division of Reproductive and Urological Drugs)

Data from the preclinical studies in mice and rats indicate that raloxifene has a weaker stimulatory effect on the endometrium than estradiol and tamoxifen. In randomized, placebo-controlled trials several parameters were used to evaluate raloxifene's effect on the endometrium. These included endometrial ultrasound, incidence of bleeding, and endometrial biopsy. Of these parameters the most useful from the standpoint of evaluating raloxifene's carcinogenic potential is endometrial biopsy, with an evaluation for hyperplasia. In study GGGZ, 67 subjects were randomized to 150mg once-daily of raloxifene and 69 to HRT. Twelve-month interim data are reported in this submission. None of the subjects that had evaluable biopsies at baseline and Month 12 developed hyperplasia. From these data one could conclude, with reasonable assurance, that raloxifene does not substantially increase ($\approx$ 20%) the incidence of hyperplasia.

While looking at the incidence of endometrial hyperplasia may be useful in the assessment of a drug's potential to initiate or promote the development of endometrial cancer, it remains a surrogate endpoint and therefore has inherent limitations. Therefore, the greatest effort should be placed in the analysis of the endometrial cancer data itself. Any analysis of raloxifene treatment and cancer incidence must be considered preliminary at this time given the relatively short exposure to drug.

With these caveats in mind, Dr. Bruce Stadel's (Medical Officer and Epidemiologist from HFD-510) analysis of the endometrial cancer data follows. "In total, eleven cases of endometrial cancer were diagnosed in the eight phase 3 trials through 22 September 1997, of which seven were found in the largest trial -- the GGGK study -- which enrolled 7704 women, or 78% of the 9853 women enrolled in the eight phase 3 trials as a whole. I will focus on the seven cases in the GGGK study, since the other four cases are dispersed across three of the remaining seven trials.

The GGGK study began in November 1994 and is scheduled for completion in August 1999. The treatment duration is scheduled for three years with a one year extension; the last patient to complete 2-years of treatment did so in August of 97. There are three arms -- placebo, raloxifene 60 mg per day, and raloxifene 120 mg per day. Of the 7704 women randomized to the three arms, 5957 had intact uteri at baseline, or 1986 per arm. Since the study has not been unblinded, this is the only denominator available for analyzing rates of endometrial cancer.

The rates of endometrial cancer are 4/1986 for placebo, 1/1986 for raloxifene 60 mg per day, and 2/1986 for raloxifene 120 mg per day. Combining the two raloxifene doses, the relative risk for raloxifene compared to placebo is 3/3972 / 4/1986 = 0.38, 95% confidence interval 0.08 - 1.67. The above finding is consistent with the finding on page 94 in volume 1 of the 14 October 1997 draft briefing document that Lilly sent in for the 19-20 November 1997 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. There, the relative risk for raloxifene compared to placebo is 0.64, 95% confidence interval 0.14 - 2.18, based on data obtained through 20 June 1997."

Therefore, based in large part on interim data from study GGGK, when compared with placebo, relatively short-term exposure to raloxifene does not appear to increase the risk for endometrial cancer.

Venous Thrombotic Events (VTE)

For the purposes of this discussion VTE is defined as follows: (1) any acute venous thrombosis (clot) involving a deep peripheral vein (commonly known as deep vein thrombosis (DVT); (2) acute pulmonary embolism (PE); (3) other acute serious vein thromboses, including mesenteric and intracerebral vein thromboses (of these, only retinal vein thrombosis (RVT) was actually reported). Excluded from this analysis are superficial vein thromboses and arterial thromboses. It is unlikely that a meaningful number of VTE went undetected by the sponsor. To identify the VTE cases, the sponsor searched their DEN database twice using a total of 63 event terms. A review of the event terms indicates that they were comprehensive and would pick-up most of the cases of VTE.

As of 6/20/97 the sponsor has identified 56 cases of VTE; the majority being DVTs.

For DVT, the majority of the cases were diagnosed by noninvasive methods - mostly duplex scanning and doppler flow studies. These two techniques, are for the most part, accurate in the diagnosis of proximal vein thromboses. Duplex scanning may lack sensitivity compared with doppler studies in the detection of isolated calf thromboses; yet, a very small percentage of clots originating below the knee will embolize to the lungs, and consequently, calf thromboses do not represent a serious health threat. Most of the cases of PE were diagnosed by the use of two noninvasive methods: duplex scanning of the lower extremities along with V/Q scanning. The use of two noninvasive techniques to diagnose PE is a commonly accepted approach that has a high positive predictive value when conducted in the presence of a high pre-test probability for disease. The clinical diagnosis of acute DVT can be complicated in a patient with a history of previous DVT as symptoms for acute thrombosis can mimic those of post-thrombotic syndrome. This is not a great concern when reviewing the raloxifene data because only seven patients diagnosed with an on-study DVT had a previous diagnosis of lower extremity thrombosis. Two of these seven patients had the on-study DVT diagnosed by venogram and the remaining five received a diagnosis by duplex scanning.

The majority of the VTE cases were identified in the ongoing, triple-blind study GGGK. Study GGGK is a large three-year treatment trial with reporting of interim data of serious adverse events. Because the study is still blinded (except for the serious adverse events) calculations of the incidence rates for VTE are based on the assumption of equal exposure distributions across treatment groups. This assumption may, or may not, be accurate, only time will tell.

The table below provides the relative risk estimates for VTE, VTE except retinal vein thrombosis (RVT), and PE. The risks are presented for the 60mg dose of raloxifene as well as for all doses of raloxifene combined. The results are also provided for all placebo-controlled studies combined, for the placebo-controlled prevention studies, for the placebo-controlled treatment studies, and for study GGGK alone.

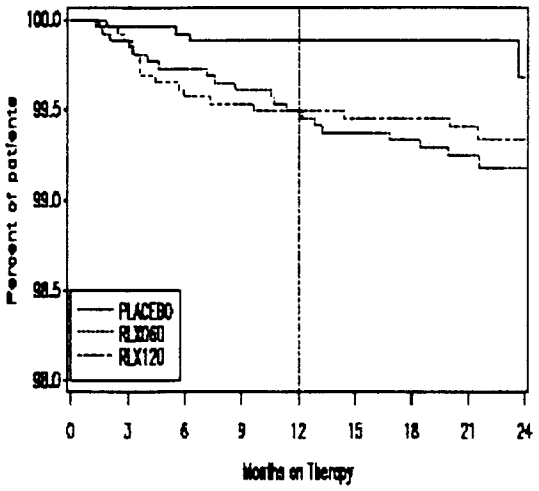
	PLACEBO		RLX 60 MG			RLX ALL DOSES		
	# Events	Estimated Exposure (years)	# Events	Estimated Exposure (years)	RR (95%CI)	# Events	Estimated Exposure (years)	RR (95%CI)
Overall[a]		N=3195		N=3192			N=6681	
All VTE	7	6150	24	6123	**3.4 (1.6,8)**	44	12879	**3.0 (1.4,6.4)**
VTE (-RVT)	5	6150	22	6123	**4.4(1.8,11)**	42	12879	**4.0 (1.7,9.4)**
PE	4	6150	9	6123	**2.3(0.7,7)**	15	12879	**1.8 (0.6,5.3)**
Prevention[b]		N=536		N=533			N=1364	
All VTE	1	1070	4	1045	**4.0(0.5,30)**	5	2723	**2.0 (0.2,16)**
VTE (-RVT)	0	1070	4	1045	**NE**	5	2723	**NE**
PE	0	1070	2	1045	**NE**	2	2723	**NE**
Treatment[c]		N=2659		N=2659			N=5317	
All VTE	6	5079	20	5078	**3.3(1.4,8)**	39	10156	**3.3 (1.5,7.3)**
VTE (-RVT)	5	5079	18	5078	**3.6(1.4,9)**	37	10156	**3.7 (1.6,8.8)**
PE	4	5079	7	5078	**1.8(0.5,6)**	13	10156	**1.6 (0.5,4.9)**
GGGK		N=2568		N=2568			N=5136	
All VTE	5	4962	20	4962	**4.0(1.7,10)**	38	9925	**3.8 (1.6,9.0)**
VTE (-RVT)	5	4962	18	4962	**3.6(1.4,9)**	36	9925	**3.6 (1.5,8.6)**
PE	4	4962	7	4962	**1.8(0.5,6)**	13	9925	**1.6 (0.5,4.9)**

a=GGGF,H,G,K,N,P,andY b=GGGF,H,G,andY c=GGGK,N,andP NE=inestimable -RVT=except retinal vein thrombosis

Four patients in Study GGGK had a previous history of VTE. When these patients are removed from the analyses — as is appropriate given that the drug will be contraindicated in women with a pre-existing history of VTE — the relative risk estimate are slightly reduced.

The sponsor claims that there is no evidence for a dose-related increase in the incidence of VTE. The data shown in table ISS.6.15 — estimated annual incidence rate per 1000 — support the sponsor's assertion.

The risk for VTE is greatest during the first three to four months of exposure, as shown in the below figure depicting the VTE incidence as a function of exposure to drug in study GGGK [relative risk for VTE during the first four months of treatment is 6.7 (1.2, 39) in raloxifene- vs. placebo-treated women].



It merits mention that the sponsor identified the incidence of idiopathic VTE (cases without identifiable risk factors). The major risk factors were considered antecedent major surgery, prolonged immobilization, or local or major trauma (all within 6 months prior to event), prior VTE, or known coagulopathy (including preexisting conditions not diagnosed until after the event). Minor risk factors were as follows: hypertension (HTN) requiring pharmacological treatment, BMI 30 kg/m^2, history of varicose veins or superficial thrombophlebitis, bilateral oophorectomy, or current tobacco smoking. Since risk factors for retinal vein thrombosis are not as well established as for DVT and PE, all cases of retinal vein thrombosis (RVT) were considered idiopathic. Cases were classified as idiopathic (no risk factors or RVT), nonidiopathic (major risk factor(s) present), or potentially idiopathic (minor risk factor(s) only). Of the 51 total reported VTE cases, seven (14%) were idiopathic (ie, had no known risk factors). Thus, excluding the four RVT cases, there were only three (6.3%) idiopathic cases of DVT or PE. If potentially idiopathic cases (ie, those with at least one known risk factor) were also considered as "idiopathic", then 16 (31%) of the 51 total cases or 12 (25%) of the 47 non-RVT cases were idiopathic. Thus, the majority of reported VTE cases had at least one major risk factor prior to the event.

While major surgery, prolonged immobilization, and local or major trauma certainly increase the immediate risk for VTE, it's questionable whether the risk is appreciably increased by one of these events if they predate the thrombotic episode by as much as four to six months. Nevertheless, the relative risk for idiopathic VTE (DVT and PE only) for all doses of raloxifene vs. placebo was 2.8 (0.6, 13). This estimate is not statistically significant and the magnitude of the estimated risk is not sizably greater than the risk for all (nonidiopathic and idiopathic) VTEs.

In an effort to identify risk factors for VTE in raloxifene-treated subjects the sponsor is conducting an ongoing nested case-control study in study GGGK. Although the results of this analysis will not be available for some time, the sponsor did perform a case-cohort analysis of baseline risk factors for VTE in study GGGK. A binomial regression model using a log-link function was used to determine which continuous baseline factors were statistically significantly associated with development of VTE. Similarly, a chi-square test was used to identify categorical factors associated with VTE risk. The following baseline factors were investigated:

- Age, weight, BMI, years postmenopause
- Systolic blood pressure, diastolic blood pressure, pulse
- LDL-C, HDL-C, hemoglobin A1C, apolipoprotein A1, apolipoprotein B
- Bone-specific alkaline phosphatase, osteocalcin, urine CrossLaps:creatinine ratio, random urine creatinine, random urine calcium, serum 25-hydroxyvitamin D, serum parathyroid hormone
- Current alcohol use (at least three drinks per week), current tobacco smoker (yes/no), hysterectomy (yes/no), family history of osteoporosis

(yes/no), family history of breast cancer (yes/no), prior HRT use (yes/no), prior thiazide diuretic use (yes/no), prior fluoride use (yes/no), prior bisphosphonate use (yes/no), prior myocardial infarction ([MI] yes/no), prior percutaneous transluminal coronary angioplasty ([PTCA] yes/no), prior stroke (yes/no), and prior coronary bypass graft (yes/no).

Following identification and categorization of potential VTE risk factors, a multivariate model incorporating treatment was used to determine the impact of these factors on treatment-associated VTE risk. Following a stepwise procedure, the most parsimonious model identified age, weight, prior MI, and treatment as independent VTE risk factors

The following baseline characteristics were significantly different between the cases randomized to 60mg and placebo vs the unaffected cohort.

BASELINE FACTOR	CASES (n=24)	UNAFFECTED COHORT (n=5085)
Age (yrs)	70.9	66.5
Weight (kg)	70.4	63.7
BMI (kg/m2)	27.1	25.2
Systolic BP (mmHg)	146	133
Diastolic BP (mmHg)	84.8	78.4
Prior use of thiazides (% yes)	39.1	12.0
Prior MI (% yes)	12.5	2.0

Information does not include data from four-month safety udpdate (10/8/97)

In a multivariate regression model, only age, weight, prior MI, and treatment with raloxifene were identified as independent risk factors for VTE. The magnitude of the risks associated with these variables are provided in the following table.

RISK FACTOR	ALL VTE CASES RELATIVE RISK (95%CI)
Treatment (raloxifene vs placebo)	4.0 (1.6, 10)
Prior MI (yes vs no)	5.0 (2, 12)
Age (above 71 yrs vs below)	2.1 (1.1, 3.8)
Weight (above 70 kg vs below)	3.1 (1.7, 5.5)

These interim data support the finding that raloxifene, at a daily dose of 60 mg, significantly increases the risk for VTE. Additional identifiable risk factors include previous MI, age above 71 years, and body weight above 70kg. If these risk factors are verified as independent predictors of VTE in the ongoing case-control study, this information will be valuable to prescribing physician when assessing the risk vs. benefit profile of raloxifene.

For obvious reasons, the identification of potential risk factors for VTE in the raloxifene-treated populations will be limited by the characteristics of the enrolled patients. In general, patients with concomitant illness and medication were excluded from the raloxifene trials. As an additional safety measure, those conditions that have been identified as risk factors for VTE from the published literature — e.g., heart failure, history of malignancy, lower-limb arteriopathy— should be mentioned in raloxifene's labeling.

The use of estrogen replacement therapy by postmenopausal women increases the risk for deep venous

thrombosis and pulmonary embolism by approximately 3 fold. Like raloxifene, the first six months or so of treatment are associated with the greatest risk.

Of note, there was only one VTE event in the placebo group and five in the raloxifene groups during the conduct of the prevention studies: relative risk = 2.0 (0.2, 17). This estimate — in a population of women with a mean age of approximately 55 years — must be viewed as very preliminary due to the low overall incidence rates for VTE events. At present the most reliable estimates for the risk for VTE come from study GGGK — a trial of women with a mean age of over 65 years.

Hepatic Function

Transaminase Levels

In general, patients were considered to have elevated levels of AST, ALT, or GGT if they had an increase 2x the upper limit of normal during the trial. In the primary placebo-controlled database, there were no significant differences between raloxifene- and placebo-treated patients in the percentage of patients with elevated levels of ALT, AST, and GGT, and the overall incidence rates were low. Fourteen subjects developed an elevated AST 1.5x the upper limit of normal during these trials: two receiving placebo and 12 receiving raloxifene (4 patients each in raloxifene low dose, 60mg, and the high-dose groups, p=0.3). The highest value observed was 311 U/L in a patient randomized to the 60 mg dose. In four raloxifene 60mg patients and one placebo patient, the elevated levels of AST did not return to within normal limits during the trial. In four raloxifene-treated patients the elevated AST levels spontaneously returned to within normal limits during the trial. In one placebo patient and four raloxifene patients the AST levels returned to within normal limits following a specific intervention, in most cases drug withdrawal.

The absolute risk for developing a mildly elevated AST level (1.5x ULN) was approximately 0.4% in the placebo group and 0.9% in the raloxifene group — relative risk 2.5 (0.6, 11) in raloxifene- vs. placebo-treated patients.

In the ongoing study GGGK, one patient out of 7704 has withdrawn because of abnormal liver function tests.

Hepatic and Biliary Abnormalities

In the primary placebo-controlled studies there were no significant differences among groups in the incidence of cholelithiasis, cholecystitis, fatty liver, or liver damage. Of note, one patient died as a result of acute liver failure. This patient was randomized to 30mg/day of raloxifene. She received a diagnosis of head and neck cancer after enrolling in the raloxifene trial, and the sponsor states that the patient admitted to heavy use of alcohol and acetaminophen, again after she was enrolled in the trial. The patient reportedly stopped taking the study medication two months prior to her death. Her workup at the time of admission to the hospital for liver failure revealed a positive hepatitis A IgM antibody and an acetaminophen blood level of 25 ug/ml. All things considered, it's reasonable to assume that alcohol, acetaminophen, and hepatitis A were the culprits in this case of acute liver failure (Schiodt).

In study GGGK one patient died as a result of hepatic cancer. This patient was randomized to the 120mg raloxifene arm. Study medication was started on June 15, 1995 at which time she had an elevated Alk Phos level . She died in November of 1995.

One patient in GGGK has discontinued because of hepatomegaly. This patient, who was reportedly obese and diabetic (NIDDM), was randomized to 60mg of raloxifene qd. She was diagnosed as having a tender enlarged liver and was discontinued from the study. No additional relevant information about this patient's condition (other than the fact that she has not had a liver biopsy) is available as of 10/15/97. The sponsor has committed to sending follow-up information as it becomes available.

Schiodt FV, Rochling FA, Casey DL, et al. Acetaminophen toxicity in an urban county hostpital. New Engl J Med. 1997; 337:1112

While the above data are not alarming, they do raise the possibility that raloxifene will be associated with some degree of hypertransaminasemia after introduction into the market place.

Central Nervous System

There is a growing body of literature on estrogens and cognitive function. There is evidence, although not universal, that estrogen enhances verbal memory and may be a useful preventive agent against Alzheimer's disease. The most prominent adverse event noted with raloxifene was vasodilatation, or flushing. That raloxifene increases this adverse event and estrogen decreases it suggests that raloxifene has estrogen antagonistic activity at the pituitary/hypothalmus. Does raloxifene act as an estrogen antagonist in other parts of the brain? If so, what consequences might this have?

In the one study in this NDA that specifically examined the cognitive effects —assessed from a computerized psychometric battery designed by the Memory Assessment Clinic — of raloxifene compared with placebo in women with established osteoporosis, no statistically significant differences were noted between groups for subjects that completed the 12-month study. Additionally, there were no obvious differences between raloxifene- and placebo-treated patients in the incidence of patient reported, cognitive-related adverse events (e.g., depression, anxiety, confusion). One may surmise, from these limited data, that raloxifene is probably not associated with large alterations in cognitive function. Yet, as with most drugs, experience in a larger, more heterogenous population is required to detect small or subtle drug-induced changes. If the drug is approved for the prevention of osteoporosis, tens of thousands of women, if not more, will be exposed to this compound for long periods of time. It would behoove the sponsor to continue to examine the impact, if any, that raloxifene has on cognitive function in postmenopausal women.

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8.0 Discussion

It's estimated that more than 30% of women between the ages of have osteoporosis —or low BMD. The incidence climbs to nearly 70% for women over the age of 80 years (Kanis and Melton). While low bone density is the hallmark of osteoporosis, fractures of the spine, hip, and wrist account for the morbidity and mortality of this disease. Therefore, effective interventions - be they the treatment or prevention of osteoporosis - should be defined by their ability to reduce the risk for fractures.

Raloxifene is the first selective estrogen receptor modulator to seek an indication for the prevention of osteoporosis. In support of this indication, the sponsor has provided two-year interim data from three trials involving over 1500 postmenopausal women, many of whom were osteopenic at baseline. In studies GGGF and GGGG, subjects were randomized to one of four arms: placebo, or raloxifene 30mg, 60mg or 150mg once daily, while in study GGGH patients were randomized to either placebo, raloxifene 60mg or 150mg, or Premarin 0.625mg once daily. All subjects were instructed to take 400-600mg/day of supplemental calcium.

After two years of treatment, the placebo-treated women in all three studies lost BMD at the lumbar spine and hip whereas the raloxifene-treated subjects had small but statistically significant increases in lumbar spine and hip BMD ($p<0.03$ all raloxifene doses vs. placebo). In study GGGH, women treated with Premarin had mean increases in lumbar spine and hip BMD of 3.8% and 2.4%, respectively ($p<0.03$ vs. placebo and raloxifene). The fact that total body BMD increased in raloxifene-treated women relative to placebo-treated subjects, indicates that the raloxifene-induced increases in lumbar spine and hip BMD did not occur at the expense of bone density at other skeletal sites.

The sponsor's proposal to market the 60mg dose of raloxifene seems reasonable since the dose-response curve relating dose to BMD is relatively flat between the 60 mg and 150mg doses. Moreover, the incidence of some adverse events is higher with the 150mg dose. And parenthetically, interim data from study GGGK, a large treatment trial, indicate that total mortality is significantly higher in the 120mg vs. 60mg raloxifene group [RR 2.28, (1.8, 3.45)]. Given that all data are interim at this time, the most appropriate dose for the prevention of postmenopausal osteoporosis should be re-evaluated after all studies have been completed and fracture data are available.

The phase 3 data provide evidence that, when compared with placebo, the 60mg dose of raloxifene produces modest reductions in the levels of TC, LDL-C, Apo B, and Lp(a) and has a neutral effect on the levels of HDL-C and TG. The notable difference between treatment with raloxifene and HRT was the ability of the latter to significantly increase the concentrations of HDL-C, TG, and Apo A1, and significantly lower the levels of Lp(a). Regarding parameters of coagulation, compared with placebo and HRT therapy, treatment with raloxifene was associated with a modest reduction in the levels of fibrinogen, a risk factor for coronary heart disease in women (Kannel WB). Plasminogen activator inhibitor-1, another fibrinolytic parameter that may increase the risk for cardiovascular disease (Cortellaro), decreased significantly in the HRT group when compared with the changes seen following treatment with placebo or raloxifene. Some observational data suggest that HRT reduces the risk for heart disease (Chae); it's reasonable to speculate, based on the changes in surrogate endpoints, that raloxifene will also impact favorably upon the risk for cardiovascular disease.

Kanis JA, Melton LJ, Christiansen C, et al. The diagnosis of osteoporosis. J Bone Miner Res. 1994;9:1137

Melton LJ. How many women have osteoporosis now? J Bone and Miner Res. 1995:10:175

Kannel WB, Wolf PA, Castelli WP, et al. Fibrinogen and risk for cardiovascular disease. The Framingham Study. JAMA. 1987;258:1186

Cortellaro M, Cofranscesco E, Boschelli C, et al. Increased fibrin turnover and high PAI-1 activity as predictors of ischemic events in atherosclerotic patients. A case-control study. The PLAT Group. Arteriscler Thromb. 1993;10:1412

Thus far, the most serious adverse event causally linked to raloxifene treatment is venous thromboembolism, principally DVT. The absolute risk for DVT and pulmonary embolism in placebo-treated women is approximately 1 case/1000 persons/year. Against this background rate, the relative risk for thromboembolic events during the first four months of treatment with raloxifene is 6.7 (1.2, 39). This risk declines substantially with longer-term exposure [relative risk during months 4-12 of treatment is 1.8 (0.6, 5.3)]. Unlike estrogen, the relationship between raloxifene and thromboembolism does not appear to be dose related.

Two major concerns with estrogen replacement therapy are breast and endometrial cancer. To date, the data indicate that raloxifene is not associated with an increased risk for either one of these diseases. However, precise estimates of raloxifene's effect on these risks must await longer-term study.

To conclude, raloxifene maintained BMD in relatively early postmenopausal women during two years of treatment. It's unknown, however, whether this preservation of BMD will persist with longer-term therapy and ultimately reduce the risk for osteoporotic fracture.

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Table 4

Study GGGF

Mean Percentage Change
At Each Time Point (observed cases)

Lumbar Spine (g/cm^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	134	-.232	126	-.481	124	-.903	119	-.802
Raloxifene 30 mg	135	.623*	120	1.659**	116	1.095**	113	1.571**
Raloxifene 60 mg	133	1.333**	124	1.512**	124	1.641**	120	1.846**
Raloxifene 150 mg	120	1.250**	114	1.646**	104	1.793**	100	2.130**
	P<.001		**P<.001**		**P<.001**		**P<.001**	

* **p<.01 in favor of raloxifene over placebo**

** **p<.001 in favor of raloxifene over placebo**

Table 5

Study GGGF

Mean Percentage Change
At Each Time Point (observed cases)

Total Hip (g/cm^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	133	-.529	125	-.614	124	-.787	119	-.841
Raloxifene 30 mg	137	.025	120	1.126*	113	1.051*	113	1.364*
Raloxifene 60 mg	132	.606*	123	1.345*	122	1.661*	117	1.610*
Raloxifene 150 mg	121	.487*	112	.979*	105	1.293*	100	1.821*
	P<.001		**P<.001**		**P<.001**		**P<.001**	

* **p<.001 in favor of raloxifene over placebo**

Table 6

Study GGGF

Mean Analyzed Slope (g/cm^2)

Lumbar Spine

			Pairwise P-Values		
Treatment	***N***	***Slope***	***30 mg***	***60 mg***	***150 mg***
Placebo	135	-.0068	<.001	<.001	<.001
Raloxifene 30 mg	139	.0033		.134	.011
Raloxifene 60 mg	133	.0057			.294
Raloxifene 150 mg	125	.0074			
		P<.001			

Table 7

Study GGGF

Mean Analyzed Slope (g/cm^2)

Total Hip

			Pairwise P-Values		
Treatment	***N***	***Slope***	***30 mg***	***60 mg***	***150 mg***
Placebo	135	-.0056	<.001	<.001	<.001
Raloxifene 30 mg	139	.0022		.056	.180
Raloxifene 60 mg	133	.0047			.589
Raloxifene 150 mg	125	.0040			
		P<.001			

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Table 8

Study GGGG

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Lumbar Spine (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*30 mg*	*60 mg*	*150 mg*
Placebo	124	.953	-1.165	<.001	<.001	<.001
Raloxifene 30 mg	119	.943	.397		.29	.35
Raloxifene 60 mg	118	.951	.782			.91
Raloxifene 150 mg	119	.955	.759			
		P=.86	**P<.001**			

\+ **See Table 1**

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Table 9

Study GGGG

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Total Hip (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*30 mg*	*60 mg*	*150 mg*
Placebo	123	.841	- .762	<.001	<.001	<.001
Raloxifene 30 mg	119	.851	1.006		.34	.08
Raloxifene 60 mg	118	.855	1.197			.43
Raloxifene 150 mg	119	.848	1.595			
		P=.83	**P<.001**			

\+ **See Table 1**

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Table 10

Study GGGG

Mean Percentage Change
At Each Time Point (observed cases)

Lumbar Spine (g/m^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	118	-.134	116	-.918	106	-.751	101	-1.025
Raloxifene 30 mg	112	.419	107	.403**	102	.845**	96	.289*
Raloxifene 60 mg	115	.363	104	.822**	96	1.247**	91	.950**
Raloxifene 150 mg	113	.405	103	.572**	90	.811*	81	.890**
	P=.35		**P<.001**		**P<.001**		**P<.001**	

* **p<.01 in favor of raloxifene over placebo**

** **p<.001 in favor of raloxifene over placebo**

Table 11

Study GGGG

Mean Percentage Change
At Each Time Point (observed cases)

Total Hip (g/m^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	118	-.588	115	-.786	105	-.357	100	-.643
Raloxifene 30 mg	112	.488*	107	.504*	102	1.135*	96	.938*
Raloxifene 60 mg	115	.627*	103	.898*	96	1.211*	90	1.571*
Raloxifene 150 mg	113	.958*	102	1.488*	90	2.163*	81	1.876*
	P<.001		**P<.001**		**P<.001**		**P<.001**	

* **p<.001 in favor of raloxifene over placebo**

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Table 12

Study GGGG

Mean Analyzed Slope (g/cm^2)

Lumbar Spine

			Pairwise P-Values		
Treatment	***N***	***Slope***	***30 mg***	***60 mg***	***150 mg***
Placebo	124	-.0063	<.001	<.001	<.001
Raloxifene 30 mg	119	.0019		.129	.263
Raloxifene 60 mg	118	.0049			.687
Raloxifene 150 mg	119	.0041			
		P<.001			

Table 13

Study GGGG

Mean Analyzed Slope (g/cm^2)

Total Hip

			Pairwise P-Values		
Treatment	***N***	***Slope***	***30 mg***	***60 mg***	***150 mg***
Placebo	123	-.0044	<.001	<.001	<.001
Raloxifene 30 mg	119	.0022		.265	.016
Raloxifene 60 mg	118	.0040			.195
Raloxifene 150 mg	119	.0062			
		P<.001			

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Table 14

Study GGGH

Adverse Events+

	Raloxifene				
Event	*Placebo*	*60 mg*	*150 mg*	*Premarin*	*P-Value*
Vasodilatation	40 (26.3%)	49 (32.2%)	69 (43.9%)	15 (9.5%)	<.001
Leg Cramps	2 (1.3%)	14 (9.2%)	13 (8.3%)	5 (3.2%)	.004
Breast Pain	9 (5.9%)	11 (7.2%)	8 (5.1%)	22 (13.9%)	.017
Accidental Injury	16 (10.5%)	17 (11.2%)	33 (21.0%)	23 (14.6%)	.033

+ **Adverse events experienced by at least 5% of the patients in each raloxifene group where p<.10**

Table 15

Study GGGH

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Lumbar Spine (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*60 mg*	*150 mg*	*.625 mg*
Placebo	130	.974	-1.587	<.001	<.001	<.001
Raloxifene 60 mg	131	.967	.191		.50	<.001
Raloxifene 150 mg	136	.969	.450			<.001
Premarin .625 mg	137	.957	3.805			
		P=.67	**P<.001**			

\+ **See Table 1**

Table 16

Study GGGH

Mean Percentage Change
From Baseline to Endpoint (LOCF+)

Total Hip (g/cm^2)

				P-Values Pairwise Comparisons		
Treatment	*N*	*Baseline*	*Percent Change*	*60 mg*	*150 mg*	*.625 mg*
Placebo	125	.879	- .489	<.001	<.01	<.001
Raloxifene 60 mg	124	.892	.786		.37	<.001
Raloxifene 150 mg	128	.897	.516			<.001
Premarin .625 mg	131	.876	2.414			
		P=.36	**P<.001**			

\+ **See Table 1**

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Table 17

Study GGGH

Mean Percentage Change
At Each Time Point (observed cases)

Lumbar Spine (g/cm^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	129	-.412	113	-.562	103	-1.314	103	-1.521
Raloxifene 60 mg	130	.761	116	.532	111	.792	107	.519
Raloxifene 150 mg	134	.580	124	.958	118	1.029	113	.649
Premarin .625 mg	136	2.177	129	3.316	124	3.739	118	3.917
	P<.001		**P<.001**		**P<.001**		**P<.001**	

	Pairwise P-Values			
Raloxifene 60 mg vs Placebo	<.001	.005	<.001	<.001
Raloxifene 150 mg vs Placebo	.002	<.001	<.001	<.001
Premarin .625 mg vs Placebo	<.001	<.001	<.001	<.001

	Pairwise P-Values			
Raloxifene 150 mg vs Raloxifene 60 mg	.620	.302	.641	.879
Premarin .625 mg vs Raloxifene 150 mg	<.001	<.001	<.001	<.001
Premarin .625 mg vs Raloxifene 60 mg	<.001	<.001	<.001	<.001

Table 18

Study GGGH

Mean Percentage Change
At Each Time Point (observed cases)

Total Hip (g/cm^2)

	6 Months		*12 Months*		*18 Months*		*24 Months*	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo	124	-.035	108	-.057	98	.030	98	-.343
Raloxifene 60 mg	124	.668	108	.855	106	.893	101	.747
Raloxifene 150 mg	127	.529	116	.697	110	1.158	113	.696
Premarin .625 mg	131	1.409	122	1.774	119	2.280	112	2.237
	P<.001		**P<.001**		**P<.001**		**P<.001**	

	Pairwise P-Values			
Raloxifene 60 mg vs Placebo	.020	.016	.038	.004
Raloxifene 150 mg vs Placebo	.063	.039	.005	.007
Premarin .625 mg vs Placebo	<.001	<.001	<.001	<.001

	Pairwise P-Values			
Raloxifene 150 mg vs Raloxifene 60 mg	.621	.705	.474	.840
Premarin .625 mg vs Raloxifene 150 mg	.004	<.001	.004	<.001
Premarin .625 mg vs Raloxifene 60 mg	.018	.004	<.001	<.001

Table 19

Study GGGH

Mean Analyzed Slope (g/cm^2)

Lumbar Spine

			Pairwise P-Value		
Treatment	***N***	***Slope***	***60 mg***	***150 mg***	***Premarin***
Placebo	130	-.0108	<.001	<.001	<.001
Raloxifene 60 mg	131	- .0009		.276	<.001
Raloxifene 150 mg	136	.0012			<.001
Premarin .625 mg	137	.0172			
		P<.001			

Table 20

Study GGGH

Mean Analyzed Slope (g/cm^2)

Total Hip

			Pairwise P-Value		
Treatment	***N***	***Slope***	***60 mg***	***150 mg***	***Premarin***
Placebo	130	-.0030	.002	.017	<.001
Raloxifene 60 mg	130	.0024		.489	<.001
Raloxifene 150 mg	134	.0012			<.001
Premarin .625 mg	136	.0098			
		P<.001			

Table 21

Studies GGGF, GGGG, GGGH

Mean Percentage Change From Baseline to Endpoint (LOCF*)

	Lumbar Spine		
Treatment	***GGGF***	***GGGG***	***GGGH***
Placebo	-.795	-1.165	-1.587
Raloxifene 30 mg	1.280*	.397*	
Raloxifene 60 mg	1.639*	.782*	.191*
Raloxifene 150 mg	2.211*	.759*	.450*
Premarin .625 mg			3.805#

	Total Hip		
Treatment	***GGGF***	***GGGG***	***GGGH***
Placebo	-.843	-.762	-.489
Raloxifene 30 mg	1.037*	1.006*	
Raloxifene 60 mg	1.576*	1.197*	.786*
Raloxifene 150 mg	1.462*	1.595*	.516a
Premarin .625 mg			2.414#

a **p<.01 in favor of raloxifene over placebo**

***** **p<.001 in favor of raloxifene over placebo**

# **p<.001 in favor of Premarin over raloxifene and placebo**

APPEARS THIS WAY
ON ORIGINAL