CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-318

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Carcinogenicity

(Addendum Report)

Date:

NDA No:	21-318
Applicant:	Eli Lilly and Company
Drug Name:	Forteo™
Pharmacologist:	Dr. Gemma Kuijpers (HFD-510)
Statistical Reviewer:	Moh-Jee Ng (HFD-715)

1. Introduction

In this NDA submission, an animal carcinogenicity study carried out in the rat was included. A statistical review was conducted by the Division of Biostatistics II and a statistical review and evaluation report was issued on March 19, 2001.

Dr Kuijpers of HFD-510, who is the reviewing pharmacologist of this NDA requested the Division of Biostatistics II to perform an additional statistical analysis of the following combined tumors.

- Combined skin tumors:
  1. Squamous cell papilloma, squamous cell carcinoma, and keratoacanthoma
  2. Squamous cell papilloma, squamous cell carcinoma, keratoacanthoma, sebaceous adenocarcinoma
- Thyroid C-cell adenoma and C-cell carcinoma combined
- Lung alveolar/bronchiolar adenoma and alveolar/bronchiolar carcinoma combined

2. Results of Additional Analysis

The incidence rates and the p-values of the tests of combined tumors are summarized in Table 1. In the table, the incidence rates of the combined tumors are equal to the sums of the incidence rates of the individual tumors in the combination. This means that there was no animal that developed two or more of the individual tumors in combination.

There is a statistically significant positive dose-response relationship (p=0.039) in the incidence rate of combined C-cell adenoma and C-cell carcinoma in the thyroid in males.

There are no statistically significant differences in any pairwise comparison of the above combined tumors.

Table 1
Combined Tumors Incidence for Female and Male

	Combined Tumors	Female (p-value) # of animal/per treatment group 60/60/60/60	Male (p-value) # of animal/per treatment group 60/60/60/60
Skin	Squamous cell papilloma (806)	0,2,1,1	1,2,1,3
	Squamous cell carcinoma (972)		0,0,2,1
	Keratoacanthoma (834)		0,1,1,0
	Combined		1,3,4,4 (p=0.082)
Skin	Squamous cell papilloma (806)	0,2,1,1	1,2,1,3
	Squamous cell carcinoma (972)		0,0,2,1
	Keratoacanthoma (834)		0,1,1,0
	Sebaceous adenocarcinoma (969)		0,1,0,1
	Combined		1,4,4,5 (p=0.055)
Thyroid	C-cell adenoma (810)	6,7,8,9	0,2,1,3
	C-cell carcinoma (908)	2,3,1,1	1,0,0,1
	Combined	8,10,9,10 (p=0.248)	1,2,1,4 **(p=0.039 *)**
Lung	Alveolar/bronchiolar adenoma (803)		0,1,1,1
	alveolar/bronchiolar carcinoma (904)		0,1,0,0
	Combined		0,2,1,1 (p=0.371)

* The trend is statistically significant at level 0.05

Moh-Jee Ng
Mathematical Statistician

Concur:

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

cc: NDA 21-318
HFD-510/Division File
HFD-510/Dr. Kuijpers
HFD-715/Division File, Chron
HFD-715/ENevius, TSahlroot, KLin, CAnello, MNg

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Moh-Jee Ng
5/14/01 02:14:13 PM
BIOMETRICS

Karl Lin
5/14/01 03:05:00 PM
BIOMETRICS
Concur with review

Statistical Review and Evaluation
Carcinogenicity

Date:

	21-318
Applicant:	Eli Lilly and Company
Drug Name:	Forteo™
Pharmacologist:	Dr. Gemma Kuijpers (HFD-510)
Statistical Reviewer:	Moh-Jee Ng (HFD-715)

1. Introduction

This reviewer evaluated the oncogenic potential of LY333334 given to rats by daily subcutaneous for 2 years. This report includes the results of the survival and tumor analyses.

2. Studies Designs

The study designs of male and female rats are summarized in the following table.

Table 1
Summary of Study Design

Species	**Rat**
Strain	**Fisher 344**
Route of Administration	**Subcutaneous injections**
Frequency of Drug Administration	**Daily**
Dose Unit	**µg/kg**
Dose Level (Control, Low, Medium, High)	**0, 5, 30, 75**
Number of Animals/sex/per treatment group	**60/males/dose; 60/females/dose**
Length of Study	**24-month**

In each of these experiments there were one control group and three treated groups known as low, medium, and high. The dose levels were 0, 5, 30, and 75 µg/kg/day in the rat study. There were 60 animals in each sex/group. All surviving males and females were necropsied following a minimum of 104 weeks of dosing. The terminal sacrifice started at and after weeks 104.

3. Sponsor's Tumor Analyses and Findings

The sponsor used the method of Tarone (1975) to evalate for a dose-related increasing trend of mortality data. The sponsor used Proc Chronic program to evaluate the tumor data.

The sponsor listed the following findings in its reports.

In survival analysis:

- There were no compound-related effects on survival in male rats.
- There was a decreasing trend in survival in females, due to increased body weight gain; and the sponsor claimed that it could not be attributed to fatal neoplasm.

In tumor analysis:

- Significantly positive trends were detected in incidence in osteosarcoma for both males and females.
- Significant increase in incidence in osteoblatoma in males was detected.

The sponsor concluded that the important finding was limited to bone and it was attributed to the bone anabolic effects of LY333334 in the 2-year rat study.

4. Reviewer's Evaluation

This reviewer performed independent analyses on the survival and tumor data submitted by the sponsor, using the programs written by Dr. Ted Guo of Division of Biostatistics II. The primary statistical methods used were described by Peto *et al.* (1980), and Lin and Ali (1994). These methods adjust differences in animal mortality and take the fatal or prevalence context of observation of the tumor into consideration. The intervals used for the adjustment of mortality were 0-52, 53-78, 79-91 and 92-104 weeks and terminal sacrifice for males and females.

The statistical analyses of carcinogenicity study data consisted of two parts, namely, the survival data analysis and the tumor data analysis. The survival data analysis was: 1) to examine the differences in survival distributions among the treatment groups (homogeneity test); and 2) to determine if there is a positive trend in the proportion of deaths with respect to the dose levels (Trend test). Two statistical tests were used in the survival data analysis: the Cox test and the generalized Kruskal-Wallis test. The theoretical background of these tests was described by Lin and Ali (1994) and Thomas *et al* (1977).

The tumor data analysis was: 1) to determine if there is a positive trend in the proportions of a selected tumor type in a selected organ/tissue with respect to the dose levels. The tumors were classified as either fatal (lethal) or non-fatal (non-lethal), according to Peto *et al* (1980). The reviewer applied the death-rate method to fatal tumors and the prevalence method to non-fatal tumors. For tumors that caused death for some, but not for all, animals, a combined test was performed.

A rule for adjusting the effect of multiple testings proposed by Haseman (1983) can be used to adjust for the effect of multiple testings in pairwise comparisons. A similar rule proposed by the Office of Biostatistics, CDER/FDA for trend tests was used in this

review. The rule states that in order to keep the overall false-positive rate at the nominal level of approximately 0.1, tumor types with spontaneous tumor rates of 1% or less (rare tumors) should be tested at 0.05 significance level, otherwise (common tumors) a 0.01 significance level should be used for studies using only one species. (Lin and Rahman, 1998).

4.1 Survival Data Analysis

The survival data analysis determines whether the dose-mortality trend in mortality is statistically significant. A positive result indicates that mortality increases as the dose level increases. Tables 3 and 4 present the cumulate percentages of deaths by dose group for female and male, respectively. The time interval "105-106" for female and "104-105" for males present the terminal-sacrifice interval.

Table 3
Cumulative Percentages of Deaths in Female Rat

Analysis of Mortality
Species: Rat
Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
Week	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	.	.	.	1	59	1.7	.	.	.	1	59	1.7
53-78	1	55	1.8	4	58	8.5	8	59	13.6	12	58	22.0
79-91	12	54	23.6	8	54	22.0	12	51	33.9	8	46	35.6
92-104	16	42	52.7	16	46	49.2	12	39	54.2	17	38	64.4
105-106	26	55	47.3	30	59	50.8	27	59	45.8	21	59	35.6

Table 4
Cumulative Percentages of Deaths in Male Rat

Analysis of Mortality
Species: Rat
Sex: Male

	Dose											
	CTRL			LOW			MED			HIGH		
Week	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	1	60	1.7	.	.	.	3	60	5.0	3	60	5.0
53-78	8	59	15.0	4	60	6.7	8	57	18.3	12	57	25.0
79-91	11	51	33.3	14	56	30.0	12	49	38.3	15	45	50.0
92-103	22	40	70.0	21	42	65.0	16	37	65.0	14	30	73.3
104-105	18	60	30.0	21	60	35.0	21	60	35.0	16	60	26.7

Figures 1 and 2 present plots of Kaplan-Meier estimates of the survival distributions of the treatment groups of female and male rats.

Figure 1
Kaplan-Meier Survival Functions for Female Rats

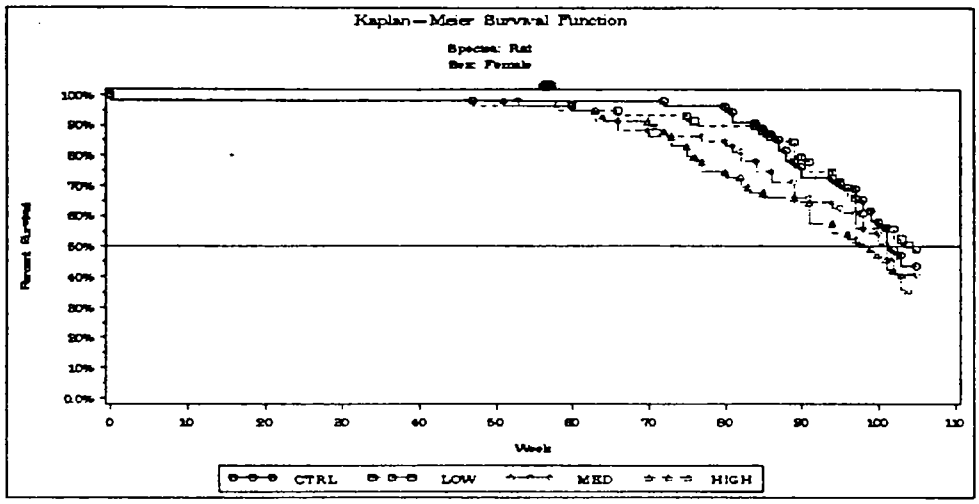
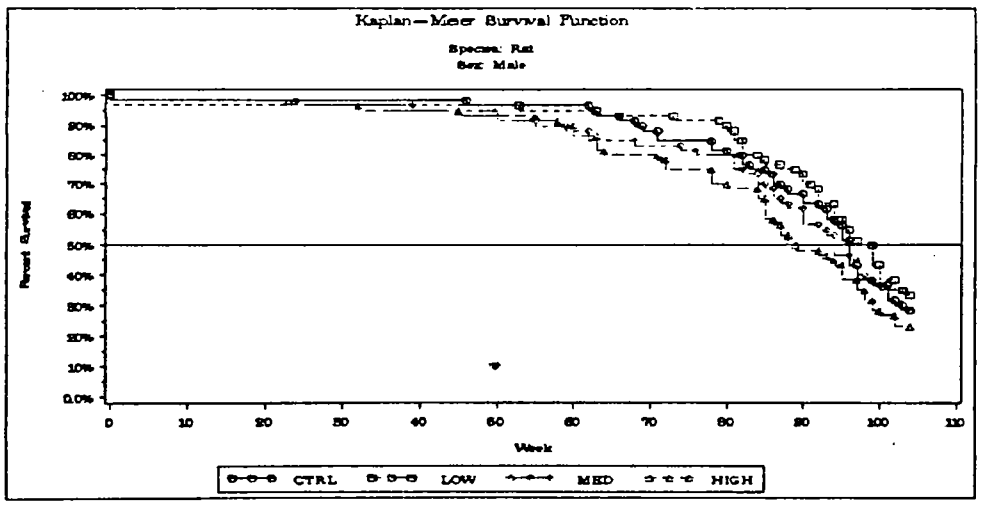


Figure 2
Kaplan-Meier Survival Functions for Male Rats



The dose-mortality trend for female rats (Table 5) is not significant using the Cox test (p=0.0602) but is significant using the Kruskal-Wallis test (p=0.0234).

Table 5

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	3.53	0.0602
	Depart from Trend	0.34	0.8429
	Homogeneity	3.88	0.2753
Kruskal-Wallis	Dose-Mortality Trend	5.14	0.0234
	Depart from Trend	0.28	0.8697
	Homogeneity	5.42	0.1435

Source: C:\NG\XAnimalX.txt

The dose-mortality trend test for male rats (Table 6) are not significant using the Cox test and the Kruskal-Wallis test .

Table 6

Dose-Mortality Trend Tests

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

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.83	0.1764
	Depart from Trend	0.63	0.7280
	Homogeneity	2.46	0.4820
Kruskal-Wallis	Dose-Mortality Trend	2.87	0.0904
	Depart from Trend	0.79	0.6730
	Homogeneity	3.66	0.3007

Source: C:\NG\XAnimalX.txt

Results of this reviewer's survival data analysis show that there is a positive increase in mortality in female but not in male rats.

4.2 Tumor Data Analysis

The statistical methods for testing tumor incidence rates described in this section were used to analyze the tumor data. The daily doeses 0, 5, 30, and 75 μg/kg were used as weights in those tests. The time intervals used for the adjustment of mortality were 0-52, 53-78. 79-91, 91-104, and terminal sacrifece weeks for female rats and 0-52, 53-78. 79-91, 92-103, and terminal sacrifice weeks for male rats. The results of the tumor data analyses are presented in Tables 8 and 9 for female and males, respectively at the end of this report.

The incidence rates and p-values of tumor types showing significant trends or differences are summarized in Table 7.

Table 7
Significant Trends in Tumor Incidence for Male and Female Rats

Organ	Tumor	Tumor-Bearing Animal	P-Value
Rat/Female			
Rib (BB)	Osteosarcoma (989)	0,1,2,4	0.011
Bone (BO)	Osteosarcoma (989)	0,0,3,2	0.041
Femur (BE)	Osteosarcoma (989)	0,0,2,7	<0.001
Tibia (BQ)	Osteosarcoma (989)	0,0,0,5	<0.001
Vertebra (BV)	Osteosarcoma (989)	0,2,5,5	0.02
Whole Animal (WA)	Osteosarcoma (989)	0,4,12,23	< 0.001
	Osteoblastoma (895)	0,1,1,3	0.023
Rat/Male			
Rib (BB)	Osteosarcoma (989)	0,1,3,4	0.004
Femur (BE)	Osteoblastoma (895)	0,0,1,4	0.005
	Osteosarcoma (989)	0,1,3,5	0.004
Bone (BO)	Osteosarcoma (989)	0,0,5,8	<0.001
Tibia (BQ)	Osteoblastoma (895)	0,0,1,3	0.026
Tibia (BQ)	Osteosarcoma (989)	0,2,12,14	<0.001
Vertebra (BV)	Osteosarcoma (989)	0,0,3,6	<0.001
Kidney (KI)	Osteosarcoma (989)	0,0,1,2	0.049
Liver (LI)	Osteosarcoma (989)	0,0,2,7	<0.001
Lung (LU)	Osteosarcoma (989)	0,0,10,18	<0.001
Spleen (SP)	Osteosarcoma (989)	0,0,4,3	0.019
Thyroid (TH)	C-Cell Adenoma	0,2,1,3	0.047
Whole Animal (WA)	Osteoblastoma (895)	0,0,2,7	<0.001
	Osteosarcoma (989)	0,3,21,31	<0.001

Note: The trends are statistically significant at level 0.05.

The results of this reviewer's tumor analysis are as follows:

- A statistically positive dose-response relationship in incidence rate of osteblastoma in whole animal was detected in females.
- Statistically positive dose-response relationships in incidence rate of osteosarcoma in rib, bone, femur, tibia, vertebra and whole animal were detected in females.
- Statistically positive dose-response relationships in incidence rate of osteblastoma in femur and whole animal were detected in males.
- Statistically positive dose-response relationships in incidence rate of ostesarcoma in rib, femur, bone, tibia, vertebra, kidney, liver, lung, spleen, and whole animal were deteched in males.
- A statistically positive dose-response relationship in incidence rate of c-cell adenoma in thyroid was detected in males.

5. References

1) Bart, Chi, and Tarone (1979). "Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity." Journal of the National Cancer Institute. Vol. 62, pp.957-974.
2) Chu, Cueto and Ward (1981). "Factors in the evaluation of 200 national cancer institute carcinogen bioassay." Journal of Toxicology and environmental Health. Vol. 8, pp.251-80.
3) Haseman, J. K. (1983). "A re-examination of false-positive rates for carcinogenesis studies." Fundamental and Applied Toxicology, 3, pp.334-9
4) Haseman, J. K. (1985). "Issues in carcinogenicity testing: Dose selection." Fundamental and Applied Toxicology. Vol. 5. Pp. 66-78.
5) Lang, P. L. (1992). "Spontaneous neoplastic lesions and selected non-neoplastics lesions in the Crl:CD BR rat." _____ Table 5b. neoplasms 24 Month Studies Female CD®Rats. pp.23
6) Lin, K. K. and M. Ali (1994), " Statistical Review and Evaluation of Animal Tumorigenicity Studies." Statistical in the Pharmaceutical Industry, Second Edition, Revised and Expanded, edited by C.R.Buncher and J.Y. Tsay, Marcel Dekker, Inc., New York. pp. 19-57.
7) Lin, K. K. and M. A. Rahman (1998). "Overall False Positive Rates in Tests for Linear Trend in Tumor Incidence in Animal Carcinogenicity Studies of New Drug." Journal of Biopharmaceutical Statistcs, 8(1), 1-15 (1998)
8) Peto *et al* (1980). "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Ling-Term Animal Experiments," In Long-Term and Short-Term Screening Assays for Carcinogens: An Critical Appraisal, International Agency for Research on Cancer, Lyon, France." IARC monographs supplement, 2, pp.311-426
9) Thomas *et al* (1977). "Trend and Homogeneity Analyses of Proportions and Life Table Data," Computer and Biomedical Research, 10, pp.373-381.

Moh-Jee Ng
Mathematical Statistician

Concur:

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

cc: Original NDA 21-318
HFD-510/Division File
HFD-510/Dr. Kuijpers

HFD-715/Division File, Chron
HFD-715/ENevius, TSahlroot, KLin, MNg

APPEARS THIS WAY
ON ORIGINAL

Table 8

Statistical Interpretation of Significance in Evaluation of Tumor -Data Analyses Currently Adopted by CDER Office of Biostatistics
Test of Dose-Tumor Positive Linear Trend
* Exact Test - The statistical interpretation of significance is based on the exact test, if one of the two following situation applies. 1. The tumor is found either fatal to all the animals or non-fatal to all the animals. 2. The tumor is fatal only to some but not to all animals, and time-intervals for both situations of lethality do not overlap. The exact test is done using the Permutation test with general scores, which are the actual dose values. When the scores are set to be equally spaced, the above test is known as the Cochran-Armitage test.
* Asymptotic test - The statistical interpretation of significance is based on the asymptotic test, if none of the above situations applies. The asymptotic test uses the Z-statistic, following the standard normal distribution.
* Cutoff Point for P-Value - To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 10%, this rule states: 1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level. 2. Otherwise, the 0.005 significance level may be used.
Test using pairwise comparisons 1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.05 significance level. 2. Otherwise, the 0.01 significance level may be used.

Analysis of Carcinogenic Potential in Female Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. R00497
Run Date & Time: March 12, 2001 (13:35)
Source: C:\NG\XAnimalX.txt

Note: Dose Levels Included: CTRL LOW MED HIGH (0 5 30 75)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT .GE. OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
ADRENAL	(AD)	IN	79-91	1	1 0 0 0	0.954	0.921	0.922
PHEOCHROMOCYTOMA	(860)	IN	79-91	2	11 8 12 8			
		IN	105-106	1	2 1 1 0			
		IN	105-106	2	24 29 26 21			
Spontaneous tumor pct: 5%	in ctrl.	-	Total	-	3 1 1 0			
ADRENAL	(AD)	IN	92-104	1	0 1 0 0	0.851	0.858	0.860

ADRENOCORTICAL ADENOMA	(873)	IN 92-104	2	16	15	12	17				
		IN 105-106	1	1	1	1	0				
		IN 105-106	2	25	29	26	21				
Spontaneous tumor pct: 2% in ctrl. - Total	-			1	2	1	0				
ADRENAL	(AD)	IN 79-91	1	0	0	1	0	0.500	0.428	0.435	
ADRENOCORTICAL ADENOCARCI	(942)	IN 79-91	2	12	8	11	8				
Spontaneous tumor pct: <= 1% in ctrl. - Total	-			0	0	1	0				
ADRENAL	(AD)	IN 105-106	1	1	1	1	0	0.799	0.786	0.789	
PHEOCHROMOCYTOMA, MALIGNA	(963)	IN 105-106	2	25	29	26	21				
Spontaneous tumor pct: 2% in ctrl. - Total	-			1	1	1	0				
ADIPOSE TISSUE	(AP)	IN 105-106	1	1	0	0	0	1.000	0.808	0.813	
HEMANGIOSARCOMA	(932)	IN 105-106	2	25	30	27	21				
Spontaneous tumor pct: 2% in ctrl. - Total	-			1	0	0	0				
RIB	(BB)	IN 105-106	1	0	0	1	2	0.011	0.005	0.005	
OSTEOSARCOMA	(989)	IN 105-106	2	26	30	26	19				
		FA 91	1	0	0	0	1				
		FA 91	2	42	47	42	38				
		FA 94	1	0	1	0	0				
		FA 94	2	42	45	39	38				
		FA 100	1	0	0	0	1				
		FA 100	2	34	36	33	28				
		FA 101	1	0	0	1	0				
		FA 101	2	32	36	31	28				
Spontaneous tumor pct: <= 1% in ctrl. - Total	-			0	1	2	4	(Exact		P<0.050)	
FEMUR	(BE)	IN 92-104	1	0	0	0	1	0.000	0.000	0.000	
OSTEOSARCOMA	(989)	IN 92-104	2	16	16	12	15				
		IN 105-106	1	0	0	2	4				
		IN 105-106	2	26	30	25	17				
		FA 83	1	0	0	0	1				
		FA 83	2	52	54	48	42				
		FA 104	1	0	0	0	1				
		FA 104	2	26	31	27	23				
Spontaneous tumor pct: <= 1% in ctrl. - Total	-			0	0	2	7	(Asymptotic		P<0.050)	
BONE	(BO)	IN 79-91	1	0	0	0	1	0.251	0.218	0.222	
OSTEOBLASTOMA	(895)	IN 79-91	2	12	8	12	7				
		IN 105-106	1	0	1	0	0				
		IN 105-106	2	26	29	27	21				
Spontaneous tumor pct: <= 1% in ctrl. - Total	-			0	1	0	1				
BONE	(BO)	IN 79-91	1	0	0	1	0	0.041	0.028	0.029	
OSTEOSARCOMA	(989)	IN 79-91	2	12	8	11	8				
		IN 105-106	1	0	0	2	2				
		IN 105-106	2	26	30	25	19				
Spontaneous tumor pct: <= 1% in ctrl. - Total	-			0	0	3	2	(Exact		P<0.050)	
PELVIS	(BP)	FA 91	1	0	0	1	0	0.591	0.586	0.590	
OSTEOSARCOMA	(989)	FA 91	2	42	47	41	39				
		FA 103	1	0	1	0	0				
		FA 103	2	27	32	27	25				
		FA 105	1	0	0	1	0				
		FA 105	2	26	30	26	21				
Spontaneous tumor pct: <= 1% in ctrl. - Total	-			0	1	2	0				
TIBIA	(BQ)	IN 79-91	1	0	0	0	1	0.040	0.013	0.014	
OSTEOBLASTOMA	(895)	IN 79-91	2	12	8	12	7				
		IN 105-106	1	0	0	1	1				
		IN 105-106	2	26	30	26	20				
Spontaneous tumor pct: <= 1% in ctrl. - Total	-			0	0	1	2	(Exact		P<0.050)	
TIBIA	(BQ)	IN 79-91	1	0	0	0	1	0.000	0.000	0.000	
OSTEOSARCOMA	(989)	IN 79-91	2	12	8	12	7				
		IN 92-104	1	0	0	0	2				
		IN 92-104	2	16	16	12	15				
		IN 105-106	1	0	0	0	2				
		IN 105-106	2	26	30	27	19				
Spontaneous tumor pct: <= 1% in ctrl. - Total	-			0	0	0	5	(Exact		P<0.050)	
VERTEBRA	(BV)	FA 85	1	0	0	0	1	0.215	0.040	0.041	
OSTEOMA	(856)	FA 85	2	50	53	46	40				
Spontaneous tumor pct: <= 1% in ctrl. - Total	-			0	0	0	1				
VERTEBRA	(BV)	IN 53-78	1	0	0	0	1	0.020	0.015	0.015	
OSTEOSARCOMA	(989)	IN 53-78	2	1	4	8	10				
		IN 105-106	1	0	1	2	1				
		IN 105-106	2	26	29	25	20				

		FA 75	1	0	0	0	1		
		FA 75	2	54	56	52	50		
		FA 82	1	0	0	0	1		
		FA 82	2	52	54	49	43		
		FA 84	1	0	0	1	0		
		FA 84	2	52	54	47	41		
		FA 90	1	0	1	0	0		
		FA 90	2	43	49	42	39		
		FA 91	1	0	0	1	0		
		FA 91	2	42	47	41	39		
		FA 96	1	0	0	0	1		
		FA 96	2	39	42	37	33		
		FA 100	1	0	0	1	0		
		FA 100	2	34	36	32	29		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	2	5	5	(Exact	P<0.050)
CLITORAL GLAND	(CG)	IN 92-104	1	0	0	0	1	0.278	0.065 0.067
ADENOMA	(876)	IN 92-104	2	16	16	12	16		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		
CLITORAL GLAND	(CG)	FA 94	1	0	0	0	1	0.230	0.045 0.047
SQUAMOUS CELL CARCINOMA	(972)	FA 94	2	42	46	39	37		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		
CLITORAL GLAND	(CG)	IN 105-106	1	0	1	1	1	0.236	0.221 0.224
CARCINOMA	(995)	IN 105-106	2	26	29	26	20		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	1	1		
CEREBRUM	(CM)	IN 92-104	1	0	0	0	1	0.278	0.065 0.067
ASTROCYTOMA, MALIGNANT	(909)	IN 92-104	2	16	16	12	16		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		
CEREBRUM	(CM)	IN 92-104	1	1	0	0	0	0.984	0.924 0.925
CARCINOMA	(995)	IN 92-104	2	15	16	12	17		
		IN 105-106	1	1	1	0	0		
		IN 105-106	2	25	29	27	21		
Spontaneous tumor pct: 4% in ctrl. - Total			-	2	1	0	0		
CERVIX	(CX)	IN 53-78	1	0	0	1	1	0.540	0.380 0.385
NEUROFIBROSARCOMA	(953)	IN 53-78	2	1	4	7	11		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	1		
EAR	(EA)	FA 73	1	0	0	0	1	0.243	0.051 0.053
OSTEOSARCOMA	(989)	FA 73	2	54	56	52	51		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		
HEART	(HE)	IN 92-104	1	0	1	0	0	0.737	0.772 0.776
OSTEOSARCOMA	(989)	IN 92-104	2	16	15	12	17		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0		
JEJUNUM	(JE)	IN 105-106	1	0	0	0	1	0.201	0.035 0.036
ADENOMA	(876)	IN 105-106	2	26	30	27	20		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		
LIVER	(LI)	IN 92-104	1	0	0	0	1	0.278	0.065 0.067
HEPATOCELLULAR ADENOMA	(831)	IN 92-104	2	16	16	12	16		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		
LYMPH NODE	(LN)	IN 53-78	1	0	0	0	1	0.480	0.161 0.166
NEUROFIBROSARCOMA	(953)	IN 53-78	2	1	4	8	11		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		
LUNG	(LU)	IN 92-104	1	0	1	1	1	0.117	0.100 0.102
OSTEOSARCOMA	(989)	IN 92-104	2	16	15	11	16		
		IN 105-106	1	0	0	0	1		
		IN 105-106	2	26	30	27	20		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	1	2		
MESENTERY	(ME)	IN 53-78	1	0	0	0	1	0.480	0.161 0.166
NEUROFIBROSARCOMA	(953)	IN 53-78	2	1	4	8	11		
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1		
MAMMARY GLAND	(MG)	IN 53-78	1	0	0	0	2	0.272	0.269 0.270
FIBROADENOMA	(820)	IN 53-78	2	1	3	7	10		
		IN 79-91	1	1	1	2	1		
		IN 79-91	2	11	7	10	7		
		IN 92-104	1	3	3	1	3		
		IN 92-104	2	13	13	11	14		
		IN 105-106	1	6	15	6	9		
		IN 105-106	2	20	15	21	12		
		FA 66	1	0	0	1	0		

			FA	66	2	55	56	55	55	
Spontaneous tumor pct: 18% in ctrl. - Total					-	10	19	10	15	
MAMMARY GLAND	(MG	)	IN	92-104	1	0	1	0	0	0.737 0.772 0.776
FIBROMA	(821	)	IN	92-104	2	16	15	12	17	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	1	0	0	
MAMMARY GLAND	(MG	)	IN	105-106	1	0	1	0	0	0.750 0.755 0.761
LIPOMA	(836	)	IN	105-106	2	26	29	27	21	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	1	0	0	
MAMMARY GLAND	(MG	)	IN	92-104	1	2	0	0	1	0.372 0.349 0.352
ADENOMA	(876	)	IN	92-104	2	14	16	12	16	
			IN	105-106	1	0	1	1	1	
			IN	105-106	2	26	29	26	20	
Spontaneous tumor pct: 4% in ctrl. - Total					-	2	1	1	2	
MAMMARY GLAND	(MG	)	IN	79-91	1	1	0	0	0	0.744 0.741 0.744
ADENOCARCINOMA	(902	)	IN	79-91	2	11	8	12	8	
			IN	92-104	1	1	1	1	1	
			IN	92-104	2	15	15	11	16	
			IN	105-106	1	0	1	0	0	
			IN	105-106	2	26	29	27	21	
Spontaneous tumor pct: 4% in ctrl. - Total					-	2	2	1	1	
MAMMARY GLAND	(MG	)	IN	105-106	1	1	0	0	0	1.000 0.808 0.813
SQUAMOUS CELL CARCINOMA	(972	)	IN	105-106	2	25	30	27	21	
Spontaneous tumor pct: 2% in ctrl. - Total					-	1	0	0	0	
OVARY	(OV	)	IN	53-78	1	0	0	1	0	0.298 0.207 0.210
NEUROFIBROSARCOMA	(953	)	IN	53-78	2	1	4	7	11	
			FA	76	1	0	0	0	1	
			FA	76	2	54	55	52	48	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	1	
OVARY	(OV	)	IN	105-106	1	1	1	1	0	0.799 0.786 0.789
GRANULOSA CELL TUMOR, MAL	(985	)	IN	105-106	2	25	29	26	21	
Spontaneous tumor pct: 2% in ctrl. - Total					-	1	1	1	0	
PANCREAS	(PA	)	IN	79-91	1	0	0	1	0	0.764 0.754 0.756
ISLET CELL ADENOMA	(833	)	IN	79-91	2	12	8	11	8	
			IN	105-106	1	2	0	1	0	
			IN	105-106	2	24	30	26	21	
Spontaneous tumor pct: 4% in ctrl. - Total					-	2	0	2	0	
PANCREAS	(PA	)	IN	105-106	1	1	0	1	0	0.712 0.683 0.687
ISLET CELL CARCINOMA	(936	)	IN	105-106	2	25	30	26	21	
Spontaneous tumor pct: 2% in ctrl. - Total					-	1	0	1	0	
PANCREAS	(PA	)	IN	53-78	1	0	0	0	1	0.480 0.161 0.166
NEUROFIBROSARCOMA	(953	)	IN	53-78	2	1	4	8	11	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	0	1	
PERICARDIUM	(PC	)	IN	92-104	1	0	0	1	0	0.475 0.475 0.482
OSTEOSARCOMA	(989	)	IN	92-104	2	16	16	11	17	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	0	
PITUITARY	(PI	)	IN	53-78	1	0	1	0	1	0.976 0.974 0.974
ADENOMA	(876	)	IN	53-78	2	1	1	3	9	
			IN	79-91	1	2	2	2	2	
			IN	79-91	2	3	3	7	5	
			IN	92-104	1	4	5	2	4	
			IN	92-104	2	5	2	3	10	
			IN	105-106	1	19	23	22	16	
			IN	105-106	2	6	6	3	5	
			FA	53	1	0	0	1	0	
			FA	53	2	55	58	57	58	
			FA	60	1	0	1	0	0	
			FA	60	2	55	57	56	58	
			FA	63	1	0	0	1	0	
			FA	63	2	55	57	55	57	
			FA	64	1	0	0	0	1	
			FA	64	2	55	57	55	55	
			FA	66	1	0	1	0	0	
			FA	66	2	55	56	55	55	
			FA	70	1	0	0	2	0	
			FA	70	2	55	56	51	55	
			FA	75	1	0	0	0	1	
			FA	75	2	54	56	51	50	
			FA	77	1	0	0	1	0	
			FA	77	2	54	54	50	47	

			FA	80	1	0	0	0	1	
			FA	80	2	54	54	50	45	
			FA	84	1	2	1	0	0	
			FA	84	2	50	53	47	41	
			FA	85	1	1	0	0	0	
			FA	85	2	49	53	46	41	
			FA	86	1	1	0	2	0	
			FA	86	2	48	52	44	40	
			FA	88	1	1	0	0	0	
			FA	88	2	46	51	44	40	
			FA	89	1	1	1	0	0	
			FA	89	2	44	50	44	40	
			FA	90	1	1	1	0	0	
			FA	90	2	42	49	42	39	
			FA	94	1	1	1	1	1	
			FA	94	2	41	45	38	37	
			FA	95	1	0	2	1	0	
			FA	95	2	40	42	37	34	
			FA	97	1	0	1	0	0	
			FA	97	2	39	40	37	32	
			FA	98	1	0	1	1	0	
			FA	98	2	38	38	35	31	
			FA	99	1	2	0	0	0	
			FA	99	2	34	36	33	30	
			FA	100	1	1	0	0	0	
			FA	100	2	33	36	33	29	
			FA	101	1	0	0	1	1	
			FA	101	2	32	36	31	27	
			FA	102	1	2	3	3	1	
			FA	102	2	29	33	27	26	
			FA	103	1	1	1	0	0	
			FA	103	2	26	32	27	25	
			FA	105	1	1	1	2	0	
			FA	105	2	25	29	25	21	
Spontaneous tumor pct: 73% in ctrl. - Total					-	40	46	42	29	
PITUITARY	(PI	)	IN	105-106	1	1	1	0	0	0.984 0.921 0.922
CARCINOMA	(995	)	IN	105-106	2	25	29	27	21	
			FA	95	1	1	0	0	0	
			FA	95	2	39	44	38	34	
Spontaneous tumor pct: 4% in ctrl. - Total					-	2	1	0	0	
RECTUM	(RE	)	IN	53-78	1	0	0	0	1	0.458 0.151 0.155
OSTEOSARCOMA	(989	)	IN	53-78	2	1	4	8	10	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	0	1	
SUBCUTIS	(SB	)	IN	79-91	1	0	0	0	1	0.200 0.036 0.037
OSTEOSARCOMA	(989	)	IN	79-91	2	12	8	12	7	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	0	1	
SKIN	(SK	)	IN	92-104	1	0	0	1	0	0.365 0.404 0.408
PAPILLOMA	(806	)	IN	92-104	2	16	16	11	17	
			IN	105-106	1	0	2	0	1	
			IN	105-106	2	26	28	27	20	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	2	1	1	
SKIN	(SK	)	IN	105-106	1	0	1	0	0	0.750 0.755 0.761
BASAL CELL TUMOR, BENIGN	(809	)	IN	105-106	2	26	29	27	21	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	1	0	0	
SKIN	(SK	)	FA	80	1	0	0	0	1	0.224 0.043 0.045
BASAL CELL CARCINOMA	(910	)	FA	80	2	54	54	51	45	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	0	1	
SKIN	(SK	)	FA	83	1	0	0	0	1	0.150 0.085 0.087
NEUROFIBROSARCOMA	(953	)	FA	83	2	52	54	48	42	
			FA	84	1	0	0	1	0	
			FA	84	2	52	54	47	41	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	1	
STOMACH	(ST	)	IN	53-78	1	0	0	0	1	0.480 0.161 0.166
PAPILLOMA	(806	)	IN	53-78	2	1	4	8	11	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	0	1	
THYROID	(TH	)	IN	53-78	1	0	0	0	1	0.170 0.165 0.166
C-CELL ADENOMA	(810	)	IN	53-78	2	1	4	8	11	
			IN	79-91	1	2	0	0	2	
			IN	79-91	2	10	8	12	6	
			IN	92-104	1	2	4	3	3	
			IN	92-104	2	14	11	9	14	
			IN	105-106	1	2	3	5	3	

			IN	105-106	2	24	27	22	18		
Spontaneous tumor pct: 11%	in ctrl.	-	Total		-	6	7	8	9		
THYROID	(TH	)	IN	92-104	1	0	0	0	1	0.769	0.771 0.773
C-CELL CARCINOMA	(908	)	IN	92-104	2	16	15	12	16		
			IN	105-106	1	2	3	1	0		
			IN	105-106	2	24	27	26	21		
Spontaneous tumor pct: 4%	in ctrl.	-	Total		-	2	3	1	1		
TONGUE	(TO	)	IN	105-106	1	0	0	0	1	0.376	0.263 0.267
PAPILLOMA	(806	)	IN	105-106	2	26	30	27	20		
			FA	81	1	1	0	0	0		
			FA	81	2	52	54	50	44		
Spontaneous tumor pct: 2%	in ctrl.	-	Total		-	1	0	0	1		
URINARY BLADDER	(UB	)	IN	92-104	1	0	0	1	0	0.475	0.475 0.482
TRANSITIONAL CELL CARCINO	(976	)	IN	92-104	2	16	16	11	17		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	0	1	0		
UTERUS	(UT	)	IN	105-106	1	0	0	1	0	0.461	0.420 0.427
LEIOMYOMA	(835	)	IN	105-106	2	26	30	26	21		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	0	1	0		
UTERUS	(UT	)	IN	53-78	1	0	0	1	2	0.197	0.194 0.195
ENDOMETRIAL STROMAL POLYP	(880	)	IN	53-78	2	1	4	7	8		
			IN	79-91	1	1	0	0	3		
			IN	79-91	2	11	8	12	5		
			IN	92-104	1	2	4	3	3		
			IN	92-104	2	13	12	8	14		
			IN	105-106	1	13	7	3	7		
			IN	105-106	2	13	23	24	14		
			FA	71	1	0	0	0	1		
			FA	71	2	55	56	52	53		
			FA	77	1	0	0	0	1		
			FA	77	2	54	54	52	46		
			FA	97	1	0	0	1	0		
			FA	97	2	39	41	36	32		
			FA	101	1	1	0	0	0		
			FA	101	2	31	36	32	28		
Spontaneous tumor pct: 31%	in ctrl.	-	Total		-	17	11	8	17		
UTERUS	(UT	)	IN	105-106	1	3	0	0	0	1.000	0.936 0.937
ENDOMETRIAL STROMAL SARCO	(921	)	IN	105-106	2	23	30	27	21		
Spontaneous tumor pct: 5%	in ctrl.	-	Total		-	3	0	0	0		
UTERUS	(UT	)	IN	105-106	1	0	0	2	0	0.430	0.387 0.392
LEIOMYOSARCOMA	(938	)	IN	105-106	2	26	30	25	21		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	0	2	0		
UTERUS	(UT	)	FA	58	1	0	0	1	0	0.506	0.471 0.478
NEUROFIBROSARCOMA	(953	)	FA	58	2	55	58	57	58		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	0	1	0		
VAGINA	(VA	)	IN	53-78	1	0	0	1	0	0.800	0.714 0.720
NEUROFIBROSARCOMA	(953	)	IN	53-78	2	1	4	7	12		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	0	1	0		
VAGINA	(VA	)	IN	53-78	1	0	0	0	1	0.286	0.197 0.201
OSTEOSARCOMA	(989	)	IN	53-78	2	1	4	8	11		
			IN	105-106	1	0	0	1	0		
			IN	105-106	2	26	30	26	21		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	0	1	1		
WHOLE ANIMAL	(WA	)	IN	79-91	1	0	0	0	1	0.200	0.036 0.037
OSTEOMA	(856	)	IN	79-91	2	12	8	12	7		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	0	0	1		
WHOLE ANIMAL	(WA	)	IN	79-91	1	0	0	0	2	0.023	0.013 0.013
OSTEOBLASTOMA	(895	)	IN	79-91	2	12	8	12	6		
			IN	105-106	1	0	1	1	1		
			IN	105-106	2	26	29	26	20		
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	1	1	3	(Exact	P<0.050)
WHOLE ANIMAL	(WA	)	IN	53-78	1	0	0	0	3	0.000	0.000 0.000
OSTEOSARCOMA	(989	)	IN	53-78	2	1	4	8	9		
			IN	79-91	1	0	1	4	4		
			IN	79-91	2	12	7	8	4		
			IN	92-104	1	0	2	2	6		
			IN	92-104	2	16	14	10	11		
			IN	105-106	1	0	1	6	10		
			IN	105-106	2	26	29	21	11		

Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	4	12	23	(Exact		P<0.050)
WHOLE ANIMAL	(WA)	FA 103	1	0	0	0	1	0.223	0.042	0.044
HISTIOCYTIC SARCOMA	(990)	FA 103	2	27	33	27	24			
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	0	0	1				
WHOLE ANIMAL	(WA)	IN 79-91	1	1	1	0	0	0.961	0.958	0.958
LARGE GRANULAR LYMPHOCYTI	(993)	IN 79-91	2	7	4	7	8			
		IN 92-104	1	3	3	2	1			
		IN 92-104	2	6	8	8	10			
		IN 105-106	1	6	9	5	2			
		IN 105-106	2	19	21	22	19			
		FA 51	1	0	0	0	1			
		FA 51	2	55	58	59	58			
		FA 63	1	0	0	0	1			
		FA 63	2	55	57	57	56			
		FA 72	1	1	0	0	1			
		FA 72	2	54	56	52	52			
		FA 75	1	0	1	0	0			
		FA 75	2	54	55	52	51			
		FA 80	1	1	0	1	0			
		FA 80	2	53	54	50	46			
		FA 81	1	0	0	1	0			
		FA 81	2	53	54	49	44			
		FA 85	1	0	1	0	0			
		FA 85	2	50	52	46	41			
		FA 86	1	0	1	0	0			
		FA 86	2	49	51	46	40			
		FA 87	1	1	0	0	0			
		FA 87	2	47	51	44	40			
		FA 88	1	1	0	0	0			
		FA 88	2	46	51	44	40			
		FA 89	1	1	0	2	0			
		FA 89	2	44	51	42	40			
		FA 91	1	0	1	1	0			
		FA 91	2	42	46	41	39			
		FA 94	1	1	0	0	1			
		FA 94	2	41	46	39	37			
		FA 96	1	0	1	0	1			
		FA 96	2	39	41	37	33			
		FA 97	1	1	1	0	0			
		FA 97	2	38	40	37	32			
		FA 98	1	2	2	2	1			
		FA 98	2	36	37	34	30			
		FA 99	1	0	0	0	1			
		FA 99	2	36	36	33	29			
		FA 100	1	1	0	0	0			
		FA 100	2	33	36	33	29			
		FA 102	1	2	0	0	1			
		FA 102	2	29	36	30	26			
		FA 104	1	0	1	0	1			
		FA 104	2	26	30	27	23			
		FA 105	1	1	0	0	0			
		FA 105	2	25	30	27	21			
Spontaneous tumor pct: 42% in ctrl. - Total		-	23	22	14	12				

Table 9

Analysis of Carcinogenic Potential in Male Rat
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. R00397
Run Date & Time: March 13, 2001 (9:08)
Source: C:\NG\XAnimalx.txt

Note: Dose Levels Included: CTRL LOW MED HIGH (0 5 30 75)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT .GE. OBSERVED)
ADRENAL	(AD)	IN	53-78	1	0 0 1 0	0.588	0.589	0.591
PHEOCHROMOCYTOMA	(860)	IN	53-78	2	8 4 7 10			
		IN	79-91	1	1 1 1 1			
		IN	79-91	2	10 13 11 14			
		IN	92-103	1	3 4 2 3			
		IN	92-103	2	19 17 14 11			
		IN	104-105	1	4 3 2 2			
		IN	104-105	2	14 18 19 14			
Spontaneous tumor pct: 13%	in ctrl. -	Total		-	8 8 6 6			
ADRENAL	(AD)	IN	79-91	1	1 0 1 1	0.078	0.061	0.062
ADRENOCORTICAL ADENOMA	(873)	IN	79-91	2	10 14 11 14			
		IN	92-103	1	1 1 1 0			
		IN	92-103	2	21 20 15 14			
		IN	104-105	1	0 0 0 3			
		IN	104-105	2	18 21 21 13			
Spontaneous tumor pct: 3%	in ctrl. -	Total		-	2 1 2 4			
ADRENAL	(AD)	IN	79-91	1	0 0 1 0	0.519	0.498	0.505
PHEOCHROMOCYTOMA, MALIGNA	(963)	IN	79-91	2	11 14 11 15			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 0 1 0			
ADRENAL	(AD)	IN	53-78	1	0 0 0 1	0.177	0.130	0.132
OSTEOSARCOMA	(989)	IN	53-78	2	8 4 8 9			
		IN	92-103	1	0 0 2 0			
		IN	92-103	2	22 21 14 14			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 0 2 1			
ANUS	(AN)	IN	104-105	1	1 0 0 0	1.000	0.817	0.821
FIBROSARCOMA	(924)	IN	104-105	2	17 21 21 16			
Spontaneous tumor pct: 2%	in ctrl. -	Total		-	1 0 0 0			
AORTA	(AO)	IN	104-105	1	0 1 0 0	0.763	0.766	0.771
ALVEOLAR/BRONCHIOLAR CARC	(904)	IN	104-105	2	18 20 21 16			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 1 0 0			
AORTA	(AO)	IN	53-78	1	0 0 0 1	0.224	0.173	0.175
OSTEOSARCOMA	(989)	IN	53-78	2	8 4 8 9			
		IN	79-91	1	0 0 1 0			
		IN	79-91	2	11 14 11 15			
		IN	92-103	1	0 0 1 0			
		IN	92-103	2	22 21 15 14			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 0 2 1			
RIB	(BB)	IN	53-78	1	0 0 1 0	0.600	0.546	0.552
OSTEOMA	(856)	IN	53-78	2	8 4 7 10			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 0 1 0			
RIB	(BB)	IN	104-105	1	0 0 1 0	0.486	0.435	0.442
CHONDROSARCOMA	(916)	IN	104-105	2	18 21 20 16			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 0 1 0			
RIB	(BB)	IN	104-105	1	0 0 1 3	0.004	0.002	0.002
OSTEOSARCOMA	(989)	IN	104-105	2	18 21 20 13			
		FA	82	1	0 0 1 0			
		FA	82	2	49 53 47 42			
		FA	85	1	0 0 0 1			
		FA	85	2	46 48 44 40			
		FA	103	1	0 0 1 0			
		FA	103	2	19 23 21 16			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0 0 3 4	(Exact		P<0.050)
FEMUR	(BE)	IN	53-78	1	0 0 0 1	0.005	0.001	0.001
OSTEOBLASTOMA	(895)	IN	53-78	2	8 4 8 9			

		IN 79-91	1	0	0	1	1		
		IN 79-91	2	11	14	11	14		
		IN 92-103	1	0	0	0	2		
		IN 92-103	2	22	21	16	12		
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	1	4	(Exact	P<0.050)
FEMUR	(BE)	IN 79-91	1	0	0	1	0	0.004 0.002	0.002
OSTEOSARCOMA	(989)	IN 79-91	2	11	14	11	13		
		IN 92-103	1	0	0	1	0		
		IN 92-103	2	22	21	15	11		
		IN 104-105	1	0	1	1	0		
		IN 104-105	2	18	20	20	16		
		FA 80	1	0	0	0	1		
		FA 80	2	51	55	49	44		
		FA 86	1	0	0	0	1		
		FA 86	2	45	47	42	38		
		FA 94	1	0	0	0	1		
		FA 94	2	37	41	33	27		
		FA 97	1	0	0	0	1		
		FA 97	2	31	33	28	25		
		FA 98	1	0	0	0	1		
		FA 98	2	26	31	27	22		
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	1	3	5	(Asymptotic	P<0.050)
BONE	(BO)	IN 53-78	1	0	0	0	1	0.000 0.000	0.000
OSTEOSARCOMA	(989)	IN 53-78	2	8	4	8	9		
		IN 79-91	1	0	0	0	2		
		IN 79-91	2	11	14	11	9		
		IN 92-103	1	0	0	1	0		
		IN 92-103	2	22	21	14	13		
		IN 104-105	1	0	0	1	0		
		IN 104-105	2	18	21	19	16		
		FA 80	1	0	0	0	1		
		FA 80	2	51	55	49	44		
		FA 87	1	0	0	1	0		
		FA 87	2	44	47	40	35		
		FA 88	1	0	0	0	1		
		FA 88	2	42	46	39	33		
		FA 89	1	0	0	0	2		
		FA 89	2	41	46	38	30		
		FA 93	1	0	0	0	1		
		FA 93	2	38	41	34	28		
		FA 98	1	0	0	1	0		
		FA 98	2	26	31	26	23		
		FA 104	1	0	0	1	0		
		FA 104	2	18	21	20	16		
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	5	8	(Asymptotic	P<0.050)
PELVIS	(BP)	FA 86	1	0	0	0	1	0.225 0.044	0.045
OSTEOSARCOMA	(989)	FA 86	2	45	47	42	38		
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	0	1		
TIBIA	(BQ)	IN 53-78	1	0	0	0	1	0.026 0.011	0.012
OSTEOBLASTOMA	(895)	IN 53-78	2	8	4	8	9		
		IN 79-91	1	0	0	1	1		
		IN 79-91	2	11	14	11	14		
		IN 104-105	1	0	0	0	1		
		IN 104-105	2	18	21	21	15		
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	1	3	(Exact	P<0.050)
TIBIA	(BQ)	IN 53-78	1	0	0	0	1	0.000 0.000	0.000
OSTEOSARCOMA	(989)	IN 53-78	2	8	4	8	7		
		IN 79-91	1	0	0	1	1		
		IN 79-91	2	11	14	11	11		
		IN 92-103	1	0	0	3	1		
		IN 92-103	2	22	20	10	11		
		IN 104-105	1	0	1	5	4		
		IN 104-105	2	18	20	16	12		
		FA 58	1	0	0	0	1		
		FA 58	2	59	58	55	53		
		FA 72	1	0	0	0	1		
		FA 72	2	53	57	51	47		
		FA 88	1	0	0	0	1		
		FA 88	2	42	46	39	33		
		FA 89	1	0	0	0	2		
		FA 89	2	41	46	38	30		
		FA 92	1	0	0	0	1		
		FA 92	2	40	42	37	29		
		FA 95	1	0	0	0	1		
		FA 95	2	35	38	32	26		
		FA 96	1	0	0	2	0		

			FA 96	2	34	35	30	26	
			FA 98	1	0	0	1	0	
			FA 98	2	26	31	26	23	
			FA 100	1	0	1	0	0	
			FA 100	2	23	29	23	19	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	2	12	14	(Asymptotic P<0.050)
VERTEBRA	(BV	)	FA 86	1	0	0	0	1	0.148 0.083 0.085
OSTEOMA	(856	)	FA 86	2	45	47	42	38	
			FA 100	1	0	0	1	0	
			FA 100	2	23	30	22	19	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	1	
VERTEBRA	(BV	)	FA 97	1	1	0	0	0	0.387 0.270 0.274
LIPOSARCOMA	(977	)	FA 97	2	30	33	28	26	
			FA 98	1	0	0	0	1	
			FA 98	2	26	31	27	22	
Spontaneous tumor pct: 2% in ctrl. - Total				-	1	0	0	1	
VERTEBRA	(BV	)	IN 92-103	1	0	0	2	0	0.000 0.000 0.000
OSTEOSARCOMA	(989	)	IN 92-103	2	22	21	14	12	
			IN 104-105	1	0	0	0	1	
			IN 104-105	2	18	21	21	15	
			FA 55	1	0	0	0	1	
			FA 55	2	59	58	57	54	
			FA 71	1	0	0	0	1	
			FA 71	2	54	57	51	48	
			FA 85	1	0	0	1	0	
			FA 85	2	46	48	43	41	
			FA 86	1	0	0	0	1	
			FA 86	2	45	47	42	38	
			FA 98	1	0	0	0	1	
			FA 98	2	26	31	27	22	
			FA 99	1	0	0	0	1	
			FA 99	2	26	31	24	20	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	3	6	(Asymptotic P<0.050)
MISC TISSUE 1	(D1	)	IN 79-91	1	1	0	0	0	1.000 0.835 0.839
SARCOMA	(996	)	IN 79-91	2	10	14	12	15	
Spontaneous tumor pct: 2% in ctrl. - Total				-	1	0	0	0	
DIAPHRAGM	(DI	)	IN 104-105	1	0	1	0	0	0.763 0.766 0.771
ALVEOLAR/BRONCHIOLAR CARC	(904	)	IN 104-105	2	18	20	21	16	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	
DIAPHRAGM	(DI	)	IN 53-78	1	0	0	0	1	0.188 0.122 0.124
OSTEOSARCOMA	(989	)	IN 53-78	2	8	4	8	9	
			IN 92-103	1	0	0	1	0	
			IN 92-103	2	22	21	15	14	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	1	
EAR	(EA	)	IN 92-103	1	0	0	1	0	0.411 0.392 0.399
SEBACEOUS ADENOMA	(866	)	IN 92-103	2	22	21	15	14	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	
HEART	(HE	)	IN 79-91	1	0	0	0	1	0.162 0.102 0.104
OSTEOSARCOMA	(989	)	IN 79-91	2	11	14	12	14	
			IN 92-103	1	0	0	1	0	
			IN 92-103	2	22	21	15	14	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	1	
HEART	(HE	)	IN 104-105	1	0	0	0	1	0.210 0.039 0.040
ATRIOCAVAL MESOTHELIOMA	(997	)	IN 104-105	2	18	21	21	15	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	
HARDERIAN GLAND	(HG	)	FA 86	1	0	0	0	1	0.225 0.044 0.045
FIBROSARCOMA	(924	)	FA 86	2	45	47	42	38	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	
JEJUNUM	(JE	)	IN 92-103	1	1	0	0	0	0.347 0.236 0.240
LEIOMYOSARCOMA	(938	)	IN 92-103	2	20	20	16	12	
			IN 104-105	1	0	0	0	1	
			IN 104-105	2	18	21	21	15	
Spontaneous tumor pct: 2% in ctrl. - Total				-	1	0	0	1	
JEJUNUM	(JE	)	IN 104-105	1	1	0	0	0	1.000 0.817 0.821
MUCINOUS ADENOCARCINOMA	(948	)	IN 104-105	2	17	21	21	16	
Spontaneous tumor pct: 2% in ctrl. - Total				-	1	0	0	0	
KIDNEY	(KI	)	IN 92-103	1	1	0	0	0	0.928 0.860 0.862
RENAL CELL ADENOMA	(863	)	IN 92-103	2	21	21	16	14	

		IN	104-105	1	0	1	0	0		
		IN	104-105	2	18	20	21	16		
Spontaneous tumor pct: 2% in ctrl. - Total	-				1	1	0	0		
KIDNEY	(KI)	IN	79-91	1	0	0	0	1	0.049	0.020	0.021
OSTEOSARCOMA	(989)	IN	79-91	2	11	14	12	14		
		IN	92-103	1	0	0	0	1		
		IN	92-103	2	22	21	16	13		
		IN	104-105	1	0	0	1	0		
		IN	104-105	2	18	21	20	16		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-				0	0	1	2	(Exact	P<0.050)
LIVER	(LI)	IN	104-105	1	1	1	0	0	0.946	0.877	0.879
HEPATOCELLULAR ADENOMA	(831)	IN	104-105	2	17	20	21	16		
Spontaneous tumor pct: 2% in ctrl. - Total	-				1	1	0	0		
LIVER	(LI)	IN	92-103	1	1	0	0	1	0.348	0.220	0.224
HEPATOCELLULAR CARCINOMA	(934)	IN	92-103	2	21	21	16	13		
Spontaneous tumor pct: 2% in ctrl. - Total	-				1	0	0	1		
LIVER	(LI)	IN	79-91	1	0	0	0	3	0.000	0.000	0.000
OSTEOSARCOMA	(989)	IN	79-91	2	11	14	12	12		
		IN	92-103	1	0	0	1	3		
		IN	92-103	2	22	21	15	11		
		IN	104-105	1	0	0	1	1		
		IN	104-105	2	18	21	20	15		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-				0	0	2	7	(Exact	P<0.050)
LUNG	(LU)	IN	104-105	1	0	1	1	1	0.258	0.242	0.245
ALVEOLAR/BRONCHIOLAR ADEN	(803)	IN	104-105	2	18	20	20	15		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-				0	1	1	1		
LUNG	(LU)	IN	104-105	1	0	1	0	0	0.763	0.766	0.771
ALVEOLAR/BRONCHIOLAR CARC	(904)	IN	104-105	2	18	20	21	16		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-				0	1	0	0		
LUNG	(LU)	FA	53	1	0	1	0	0	0.744	0.768	0.773
SQUAMOUS CELL CARCINOMA	(972)	FA	53	2	59	59	57	55		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-				0	1	0	0		
LUNG	(LU)	IN	53-78	1	0	0	0	4	0.000	0.000	0.000
OSTEOSARCOMA	(989)	IN	53-78	2	8	4	8	5		
		IN	79-91	1	0	0	2	7		
		IN	79-91	2	11	14	8	7		
		IN	92-103	1	0	0	3	4		
		IN	92-103	2	22	21	13	10		
		IN	104-105	1	0	0	3	1		
		IN	104-105	2	18	21	18	15		
		FA	60	1	0	0	0	1		
		FA	60	2	59	58	54	52		
		FA	82	1	0	0	1	0		
		FA	82	2	49	53	47	42		
		FA	86	1	0	0	1	1		
		FA	86	2	45	47	41	38		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-				0	0	10	18	(Asymptotic	P<0.050)
MASS 1	(M1)	IN	53-78	1	0	0	0	1	0.067	0.014	0.014
OSTEOSARCOMA	(989)	IN	53-78	2	8	4	8	9		
		FA	89	1	0	0	0	1		
		FA	89	2	41	46	38	31		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-				0	0	0	2		
MASS 2	(M2)	FA	89	1	0	0	0	1	0.203	0.035	0.036
OSTEOSARCOMA	(989)	FA	89	2	41	46	38	31		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-				0	0	0	1		
MESENTERY	(ME)	IN	92-103	1	0	1	0	0	0.807	0.805	0.807
MESOTHELIOMA, MALIGNANT	(946)	IN	92-103	2	22	20	16	14		
		IN	104-105	1	0	1	1	0		
		IN	104-105	2	18	20	20	16		
		FA	62	1	0	0	1	0		
		FA	62	2	59	58	53	52		
		FA	82	1	1	0	0	0		
		FA	82	2	48	53	48	42		
Spontaneous tumor pct: 2% in ctrl. - Total	-				1	2	2	0		
MESENTERY	(ME)	IN	79-91	1	0	0	0	1	0.288	0.071	0.073
OSTEOSARCOMA	(989)	IN	79-91	2	11	14	12	14		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-				0	0	0	1		
MAMMARY GLAND	(MG)	IN	104-105	1	0	0	1	0	0.428	0.373	0.380

CYSTADENOMA	(817)	IN	104-105	2	16	20	16	10		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-			0	0	1	0		
MAMMARY GLAND	(MG)	IN	104-105	1	0	0	1	0	0.201	0.179	0.182
FIBROADENOMA	(820)	IN	104-105	2	16	20	16	10		
		FA	88	1	0	0	0	1		
		FA	88	2	34	43	34	25		
		FA	96	1	0	1	0	0		
		FA	96	2	28	32	28	19		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-			0	1	1	1		
MEDIASTINUM	(MS)	IN	104-105	1	0	1	0	0	0.763	0.766	0.771
ALVEOLAR/BRONCHIOLAR CARC	(904)	IN	104-105	2	18	20	21	16		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-			0	1	0	0		
MEDIASTINUM	(MS)	IN	53-78	1	0	0	0	1	0.092	0.052	0.053
OSTEOSARCOMA	(989)	IN	53-78	2	8	4	8	9		
		IN	79-91	1	0	0	1	1		
		IN	79-91	2	11	14	11	14		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-			0	0	1	2		
PANCREAS	(PA)	IN	53-78	1	0	0	1	0	0.489	0.490	0.492
ISLET CELL ADENOMA	(833)	IN	53-78	2	8	4	7	10		
		IN	79-91	1	0	3	0	2		
		IN	79-91	2	11	11	12	13		
		IN	92-103	1	3	2	1	1		
		IN	92-103	2	19	19	15	13		
		IN	104-105	1	1	2	0	2		
		IN	104-105	2	17	19	21	14		
Spontaneous tumor pct: 7% in ctrl. - Total		-			4	7	2	5		
PANCREAS	(PA)	IN	92-103	1	0	1	0	3	0.121	0.099	0.100
ISLET CELL CARCINOMA	(936)	IN	92-103	2	21	20	16	11		
		IN	104-105	1	1	0	1	0		
		IN	104-105	2	17	21	20	16		
		FA	99	1	1	0	0	0		
		FA	99	2	25	31	24	21		
Spontaneous tumor pct: 3% in ctrl. - Total		-			2	1	1	3		
PANCREAS	(PA)	IN	92-103	1	0	0	1	0	0.411	0.392	0.399
OSTEOSARCOMA	(989)	IN	92-103	2	22	21	15	14		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-			0	0	1	0		
PERICARDIUM	(PC)	IN	79-91	1	0	0	0	1	0.288	0.071	0.073
OSTEOSARCOMA	(989)	IN	79-91	2	11	14	12	14		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-			0	0	0	1		
PREPUTIAL GLAND	(PD)	IN	92-103	1	0	1	1	0	0.522	0.598	0.603
ADENOCARCINOMA	(902)	IN	92-103	2	22	20	15	14		
Spontaneous tumor pct: <= 1% in ctrl. - Total		-			0	1	1	0		
PERITONEUM	(PE)	IN	53-78	1	1	0	0	0	0.921	0.899	0.900
MESOTHELIOMA, MALIGNANT	(946)	IN	53-78	2	7	4	7	10		
		FA	62	1	0	0	1	0		
		FA	62	2	59	58	53	52		
		FA	82	1	1	0	0	0		
		FA	82	2	48	53	48	42		
		FA	85	1	0	1	0	0		
		FA	85	2	46	47	44	41		
Spontaneous tumor pct: 3% in ctrl. - Total		-			2	1	1	0		
PITUITARY	(PI)	IN	53-78	1	1	1	1	2	0.958	0.956	0.956
ADENOMA	(876)	IN	53-78	2	3	2	5	6		
		IN	79-91	1	4	3	3	4		
		IN	79-91	2	4	6	6	9		
		IN	92-103	1	9	6	3	3		
		IN	92-103	2	6	6	7	9		
		IN	104-105	1	11	17	12	11		
		IN	104-105	2	7	4	9	4		
		FA	55	1	0	0	1	0		
		FA	55	2	58	58	56	55		
		FA	62	1	1	0	0	0		
		FA	62	2	57	58	54	52		
		FA	63	1	0	1	0	0		
		FA	63	2	57	57	53	52		
		FA	64	1	0	0	0	1		
		FA	64	2	56	57	53	49		
		FA	66	1	1	0	0	0		
		FA	66	2	55	57	53	49		
		FA	68	1	0	0	1	0		
		FA	68	2	55	57	52	49		

			FA	71	1	1	0	0	0	
			FA	71	2	52	57	51	49	
			FA	78	1	1	0	0	1	
			FA	78	2	51	56	49	46	
			FA	81	1	0	1	1	0	
			FA	81	2	48	53	48	42	
			FA	84	1	0	1	0	1	
			FA	84	2	45	50	45	41	
			FA	85	1	1	0	2	0	
			FA	85	2	44	48	42	41	
			FA	86	1	0	0	0	1	
			FA	86	2	44	47	42	38	
			FA	87	1	1	1	0	0	
			FA	87	2	42	46	41	35	
			FA	89	1	0	1	0	0	
			FA	89	2	40	45	38	32	
			FA	90	1	1	1	0	0	
			FA	90	2	39	44	38	30	
			FA	92	1	1	1	1	0	
			FA	92	2	38	41	36	30	
			FA	94	1	0	0	1	0	
			FA	94	2	37	41	32	28	
			FA	95	1	1	1	0	0	
			FA	95	2	34	37	32	27	
			FA	96	1	0	1	2	0	
			FA	96	2	34	34	30	26	
			FA	97	1	1	0	1	0	
			FA	97	2	30	33	27	26	
			FA	98	1	0	0	1	0	
			FA	98	2	26	31	26	23	
			FA	99	1	2	0	0	1	
			FA	99	2	24	31	24	20	
			FA	100	1	0	2	0	1	
			FA	100	2	23	28	23	18	
			FA	102	1	1	3	0	0	
			FA	102	2	21	23	22	17	
			FA	103	1	0	1	0	0	
			FA	103	2	19	22	22	16	
			FA	104	1	0	0	0	1	
			FA	104	2	18	21	21	15	
Spontaneous tumor pct: 63%		in ctrl. - Total			-	38	42	30	27	
PITUITARY	(PI	)	IN	92-103	1	1	0	0	0	1.000 0.791 0.796
CARCINOMA	(995	)	IN	92-103	2	20	21	16	14	
Spontaneous tumor pct: 2%		in ctrl. - Total			-	1	0	0	0	
PARATHYROID	(PT	)	IN	79-91	1	0	1	0	1	0.453 0.478 0.482
ADENOMA	(876	)	IN	79-91	2	11	13	12	14	
			IN	92-103	1	0	1	0	0	
			IN	92-103	2	22	20	16	14	
Spontaneous tumor pct: <= 1%		in ctrl. - Total			-	0	2	0	1	
PLEURA	(PU	)	IN	79-91	1	0	0	0	1	0.288 0.071 0.073
OSTEOSARCOMA	(989	)	IN	79-91	2	11	14	12	14	
Spontaneous tumor pct: <= 1%		in ctrl. - Total			-	0	0	0	1	
SUBCUTIS	(SB	)	IN	92-103	1	0	1	0	0	0.698 0.733 0.739
FIBROMA	(821	)	IN	92-103	2	22	20	16	14	
Spontaneous tumor pct: <= 1%		in ctrl. - Total			-	0	1	0	0	
SUBCUTIS	(SB	)	IN	104-105	1	0	0	1	0	0.486 0.435 0.442
LIPOMA	(836	)	IN	104-105	2	18	21	20	16	
Spontaneous tumor pct: <= 1%		in ctrl. - Total			-	0	0	1	0	
SALIVARY GLAND	(SG	)	FA	86	1	0	0	0	1	0.225 0.044 0.045
FIBROSARCOMA	(924	)	FA	86	2	45	47	42	38	
Spontaneous tumor pct: <= 1%		in ctrl. - Total			-	0	0	0	1	
SKIN	(SK	)	IN	92-103	1	0	1	1	0	0.116 0.100 0.101
PAPILLOMA	(806	)	IN	92-103	2	22	20	15	14	
			IN	104-105	1	1	1	0	3	
			IN	104-105	2	17	20	21	13	
Spontaneous tumor pct: 2%		in ctrl. - Total			-	1	2	1	3	
SKIN	(SK	)	IN	104-105	1	2	0	1	2	0.340 0.336 0.339
BASAL CELL TUMOR, BENIGN	(809	)	IN	104-105	2	16	21	20	14	
			FA	96	1	1	0	0	0	
			FA	96	2	33	35	32	26	
Spontaneous tumor pct: 5%		in ctrl. - Total			-	3	0	1	2	
SKIN	(SK	)	IN	92-103	1	2	0	0	2	0.513 0.522 0.524

FIBROMA	(821)	IN 92-103	2	20	20	15	12			
		IN 104-105	1	1	0	0	0			
		IN 104-105	2	17	21	21	16			
		FA 68	1	1	0	0	0			
		FA 68	2	55	57	53	49			
		FA 93	1	0	0	1	0			
		FA 93	2	38	41	33	29			
		FA 99	1	0	1	0	0			
		FA 99	2	26	30	24	21			
Spontaneous tumor pct: 7% in ctrl. - Total			-	4	1	1	2			
SKIN	(SK)	IN 79-91	1	0	1	0	0	0.600	0.661	0.665
KERATOACANTHOMA	(834)	IN 79-91	2	11	13	12	15			
		IN 92-103	1	0	0	1	0			
		IN 92-103	2	22	21	15	14			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	1	0			
SKIN	(SK)	IN 92-103	1	0	1	0	0	0.256	0.213	0.216
SEBACEOUS ADENOCARCINOMA	(969)	IN 92-103	2	22	20	16	14			
		FA 86	1	0	0	0	1			
		FA 86	2	45	47	42	38			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	1			
SKIN	(SK)	IN 104-105	1	0	0	2	0	0.152	0.105	0.107
SQUAMOUS CELL CARCINOMA	(972)	IN 104-105	2	18	21	19	16			
		FA 102	1	0	0	0	1			
		FA 102	2	22	26	22	16			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	2	1			
SKIN	(SK)	IN 79-91	1	0	0	0	1	0.288	0.071	0.073
OSTEOSARCOMA	(989)	IN 79-91	2	11	14	12	14			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1			
SKIN	(SK)	FA 95	1	1	0	0	0	1.000	0.802	0.807
SARCOMA	(996)	FA 95	2	34	38	32	27			
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0			
SKELETAL MUSCLE	(SM)	FA 82	1	0	1	0	0	0.744	0.760	0.765
FIBROSARCOMA	(924)	FA 82	2	49	52	48	42			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0			
SKELETAL MUSCLE	(SM)	IN 92-103	1	1	0	0	0	1.000	0.788	0.793
LIPOSARCOMA	(977)	IN 92-103	2	21	21	16	14			
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0			
SKELETAL MUSCLE	(SM)	IN 53-78	1	0	0	0	1	0.096	0.024	0.025
OSTEOSARCOMA	(989)	IN 53-78	2	8	4	8	9			
		IN 79-91	1	0	0	0	1			
		IN 79-91	2	11	14	12	14			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	2			
SPLEEN	(SP)	IN 53-78	1	0	0	0	1	0.019	0.016	0.016
OSTEOSARCOMA	(989)	IN 53-78	2	8	4	8	9			
		IN 79-91	1	0	0	0	1			
		IN 79-91	2	11	14	11	14			
		IN 92-103	1	0	0	2	1			
		IN 92-103	2	22	21	14	13			
		IN 104-105	1	0	0	1	0			
		IN 104-105	2	18	21	20	16			
		FA 86	1	0	0	1	0			
		FA 86	2	45	47	41	39			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	4	3	(Asymptotic		P<0.050)
THYROID	(TH)	IN 92-103	1	0	1	1	1	0.047	0.039	0.039
C-CELL ADENOMA	(810)	IN 92-103	2	21	19	15	13			
		IN 104-105	1	0	1	0	2			
		IN 104-105	2	18	20	21	14			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	2	1	3	(Exact		P<0.050)
THYROID	(TH)	IN 79-91	1	0	1	0	0	0.478	0.456	0.460
FOLLICULAR CELL ADENOMA	(823)	IN 79-91	2	11	13	12	15			
		IN 92-103	1	0	0	0	1			
		IN 92-103	2	21	20	16	13			
		IN 104-105	1	1	0	1	0			
		IN 104-105	2	17	21	20	16			
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	1	1	1			
THYROID	(TH)	IN 92-103	1	1	0	0	0	1.000	0.792	0.797
ADENOMA	(876)	IN 92-103	2	20	20	16	14			
Spontaneous tumor pct: 2% in ctrl. - Total			-	1	0	0	0			

THYROID	(TH |)	IN	92-103	1	0	0	0	1	0.366	0.252	0.256
C-CELL CARCINOMA	(908	)	IN	92-103	2	21	20	16	13			
			IN	104-105	1	1	0	0	0			
			IN	104-105	2	17	21	21	16			
Spontaneous tumor pct: 2%	in ctrl.	-	Total		-	1	0	0	1			
TONGUE	(TO |)	IN	92-103	1	1	0	0	0	0.361	0.246	0.250
PAPILLOMA	(806	)	IN	92-103	2	21	21	16	14			
			IN	104-105	1	0	0	0	1			
			IN	104-105	2	18	21	21	15			
Spontaneous tumor pct: 2%	in ctrl.	-	Total		-	1	0	0	1			
TESTIS	(TS |)	IN	53-78	1	3	0	1	1	0.341	0.333	0.334
INTERSTITIAL CELL TUMOR	(832	)	IN	53-78	2	5	4	7	9			
			IN	79-91	1	7	6	7	11			
			IN	79-91	2	4	8	5	4			
			IN	92-103	1	16	14	8	11			
			IN	92-103	2	6	7	8	3			
			IN	104-105	1	16	17	8	13			
			IN	104-105	2	2	4	3	3			
Spontaneous tumor pct: 70%	in ctrl.	-	Total		-	42	37	34	36			
TESTIS	(TS |)	IN	92-103	1	0	0	1	0	0.411	0.392	0.399
OSTEOSARCOMA	(989	)	IN	92-103	2	22	21	15	14			
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	0	1	0			
THYMUS	(TY |)	IN	53-78	1	0	0	0	1	0.171	0.168	0.170
OSTEOSARCOMA	(989	)	IN	53-78	2	8	4	8	9			
			IN	79-91	1	0	0	1	0			
			IN	79-91	2	11	14	11	15			
			IN	92-103	1	0	0	2	0			
			IN	92-103	2	22	21	14	14			
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	0	3	1			
WHOLE ANIMAL	(WA |)	IN	53-78	1	0	0	1	0	0.224	0.173	0.175
OSTEOMA	(856	)	IN	53-78	2	8	4	7	10			
			IN	79-91	1	0	0	0	1			
			IN	79-91	2	11	14	12	14			
			IN	92-103	1	0	0	1	0			
			IN	92-103	2	22	21	15	14			
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	0	2	1			
WHOLE ANIMAL	(WA |)	IN	53-78	1	0	0	0	2	0.000	0.000	0.000
OSTEOBLASTOMA	(895	)	IN	53-78	2	8	4	8	8			
			IN	79-91	1	0	0	2	2			
			IN	79-91	2	11	14	10	13			
			IN	92-103	1	0	0	0	2			
			IN	92-103	2	22	21	16	12			
			IN	104-105	1	0	0	0	1			
			IN	104-105	2	18	21	21	15			
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	0	2	7	(Exact		P<0.050)
WHOLE ANIMAL	(WA |)	FA	82	1	1	0	0	0	1.000	0.889	0.891
LYMPHOMA	(939	)	FA	82	2	48	53	48	42			
			FA	99	1	1	0	0	0			
			FA	99	2	25	31	24	21			
Spontaneous tumor pct: 3%	in ctrl.	-	Total		-	2	0	0	0			
WHOLE ANIMAL	(WA |)	IN	53-78	1	0	0	0	6	0.000	0.000	0.000
OSTEOSARCOMA	(989	)	IN	53-78	2	8	4	8	4			
			IN	79-91	1	0	0	7	11			
			IN	79-91	2	11	14	5	4			
			IN	92-103	1	0	1	6	8			
			IN	92-103	2	22	20	10	6			
			IN	104-105	1	0	2	8	6			
			IN	104-105	2	18	19	13	10			
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total		-	0	3	21	31	(Exact		P<0.050)
WHOLE ANIMAL	(WA |)	IN	53-78	1	0	0	0	1	0.999	0.999	0.999
LARGE GRANULAR LYMPHOCYTI	(993	)	IN	53-78	2	7	4	6	9			
			IN	79-91	1	1	1	0	0			
			IN	79-91	2	4	6	10	15			
			IN	92-103	1	0	2	0	0			
			IN	92-103	2	14	13	16	12			
			IN	104-105	1	7	2	1	2			
			IN	104-105	2	10	19	20	14			
			FA	39	1	0	0	1	0			
			FA	39	2	60	60	57	55			
			FA	68	1	0	0	1	0			
			FA	68	2	56	57	52	49			
			FA	69	1	1	0	0	0			

		FA 69	2	54	57	51	49	
		FA 76	1	0	0	1	0	
		FA 76	2	53	56	49	47	
		FA 79	1	0	1	0	0	
		FA 79	2	51	55	49	45	
		FA 80	1	1	0	0	0	
		FA 80	2	50	55	49	45	
		FA 82	1	0	1	0	0	
		FA 82	2	49	52	48	42	
		FA 83	1	2	0	0	0	
		FA 83	2	46	51	45	42	
		FA 84	1	0	2	0	0	
		FA 84	2	46	49	45	42	
		FA 86	1	1	0	0	0	
		FA 86	2	44	47	42	39	
		FA 87	1	1	0	1	0	
		FA 87	2	43	47	40	35	
		FA 88	1	1	0	0	0	
		FA 88	2	41	46	39	34	
		FA 90	1	0	1	1	0	
		FA 90	2	41	44	37	30	
		FA 91	1	0	2	0	0	
		FA 91	2	40	42	37	30	
		FA 93	1	1	0	0	0	
		FA 93	2	37	41	34	29	
		FA 94	1	1	3	0	0	
		FA 94	2	36	38	33	28	
		FA 95	1	0	1	0	0	
		FA 95	2	35	37	32	27	
		FA 96	1	2	0	0	0	
		FA 96	2	32	35	32	26	
		FA 97	1	1	1	0	0	
		FA 97	2	30	32	28	26	
		FA 99	1	0	0	0	1	
		FA 99	2	26	31	24	20	
		FA 100	1	0	0	0	1	
		FA 100	2	23	30	23	18	
		FA 101	1	1	0	0	0	
		FA 101	2	22	26	22	17	
		FA 102	1	2	1	0	0	
		FA 102	2	20	25	22	17	
		FA 104	1	1	0	0	0	
		FA 104	2	17	21	21	16	
Spontaneous tumor pct: 40% in ctrl. -		Total	-	24	18	6	5	
ZYMBAL'S GLAND	(ZG)	FA 82	1	0	0	1	0	0.438 0.394 0.399
ADENOCARCINOMA	(902)	FA 82	2	49	53	47	42	
		FA 93	1	0	0	1	0	
		FA 93	2	38	41	33	29	
Spontaneous tumor pct: <= 1% in ctrl. -		Total	-	0	0	2	0	

/s/

Moh-Jee Ng
3/19/01 09:33:41 AM
BIOMETRICS

Karl Lin
3/19/01 09:54:50 AM
BIOMETRICS
Concur with review

Executive CAC
Date of Meeting: November 5, 2002

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Robin Huff, Ph.D., HFD-570, Alternate Member
Josie Yang, Ph.D., HFD-550, Alternate Member
Karen Davis-Bruno, HFD-510, Team Leader
Gemma Kuijpers, HFD-510, Presenting Reviewer

Author of Draft: Gemma Kuijpers

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

NDA # 21-318
Drug Name: Forteo™ (teriparatide, rhPTH1-34)
Sponsor: Eli Lilly Laboratories

BACKGROUND:
PTH (parathyroid hormone) is secreted by the parathyroid gland and is involved in the maintenance of Ca homeostasis. When it is administered in an intermittent manner by subcutaneous injection it has an anabolic effect on bone in humans and animals. The compound teriparatide (recombinant human PTH1-34, Forteo™) has been developed by Eli Lilly for the treatment of osteoporosis in postmenopausal women and men. The proposed dose is 20 mcg/day.

RAT CARCINOGENICITY STUDY:
In a previous study in male and female rats with s.c. doses of 5, 30, 75 mcg/kg/day, teriparatide caused a dose-dependent increase in the incidence of osteosarcomas and other bone tumors in all treatment groups. A follow-up s.c. carcinogenicity study with teriparatide was performed in female rats to evaluate the effects of dosing duration and age of animals at treatment onset. Animals were dosed from the age of 2 months or 6 months, for a duration of either 6 months or 24/20 months. Study doses were 5 and 30 mcg/kg/day, N/group was 60. Groups were labeled alphabetically (A through I) with suffix 1 indicating the 5 mcg/kg low dose, and suffix 2 the 30 mcg/kg high dose. Arm A was the negative (vehicle) control, and arm B the positive control (30 mcg/kg/day, 24mo). The most relevant study arms were those in which animals were dosed for 6 months with follow-up (H1 and H2, E1 and E2), or dosed continuously for 24-20 months (B, I1 and I2). Doses were expected to yield AUC multiples of 3x and 20x the human AUC at the 20 mcg/day clinical dose.

FOLLOW-UP RAT STUDY RESULTS:
Arms B and I2 were clearly positive with 9/60 and 5/60 osteosarcomas,

respectively. Also, 1/60 to 2/60 osteomas or osteblastomas were observed in each of these two treatment arms. One (1/60) osteosarcoma was observed in arm A. Two osteosarcomas (2/60) each were seen in the 6-month treatment arms with 30 mcg/kg/day in older animals (E2) and younger animals (H2). One (1/60) osteosarcoma and one (1/60) osteoma were observed in the 6-month treatment arm with 5 mcg/kg/day in younger animals (H1). No bone tumors were detected in the 5 mcg/kg/day arms in which animals were started on treatment at the skeletally mature age of 6 months, for a duration of either 6 or 20 months. Large, reversible increases in bone mass were seen in all treatment arms.

EXECUTIVE CAC RECOMMENDATIONS AND CONCLUSIONS:

- The Committee agreed that the tumor findings were clearly related to dose and treatment-duration

- The Committee felt that the study was well designed and informative, and that the results appeared to be consistent with those of the previous study.

- Considering the results of the previous and the current study with 5 and 30 mcg/kg, the Committee felt that the maturity of the skeleton at the time of treatment onset was an important factor determining bone tumor incidence.

- The Committee noted that although the 5 mcg/kg dose in mature animals produced no osteosarcomas or other bone tumors, due to the relatively low statistical power of rodent bioassays especially for rare tumor types, this dose should not be considered a no-adverse-effect level.

- The Committee suggested that the results at 5 mcg/kg could be included in the product label with the animal dose represented by a human exposure multiple.

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

cc:\
/Division File, HFD 510
/KDavis-Bruno, HFD-510
/GKuijpers, HFD-510
/RHedin, HFD-510
/ASeifried, HFD-024

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joe Contrera
11/8/02 09:30:22 AM

APPEARS THIS WAY
ON ORIGINAL

Executive CAC
March 20, 2001

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Frank Sistare, Ph.D., HFD-910, Alternate Member
Jim Farrelly, Ph.D., HFD-530, Alternate Member
Karen Davis-Bruno, Ph.D., Team Leader
Gemma Kuijpers, Ph.D., Presenting Reviewer

Author of Draft: Gemma Kuijpers

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

NDA # 21,318
Drug Name: Forteo
Sponsor: Eli Lilly

LY333334 (Forteo^{R}) is the recombinant (1-34)-amino-acid fragment of human parathyroid hormone (rhPTH(1-34). When administered by daily s.c. injections, this compound causes an increase in osteoblastic bone formation resulting in increased bone mass and bone strength. The compound is under review for marketing for the indication of treatment of osteoporosis in postmenopausal women and men. One 2-year carcinogenicity study in the rat was carried out using doses of **0, 5, 30, 75 ug/kg/day**.

RAT CARCINOGENICITY STUDY:
The main result of the study was a dose-related statistically significant ($p<0.05$) increase in incidence of osteoblastoma and osteosarcoma at various bone sites in males and females in all dose groups. No bone tumors were seen in the control groups. The human exposure multiple in the dose groups varied from 1.6x to 42x. There was also a statistically significant positive dose-response relationship in the incidence of thyroid C-cell adenoma in males.

Executive CAC Recommendations and Conclusions:

- The Committee confirmed the validity of the study and the dose selection.
- The Committee concluded that the study is positive for carcinogenic findings, and that treatment of F344 rats with Forteo is associated with an increased incidence of osteosarcomas at exposure levels equivalent to intended human exposure.
- The Committee was concerned about the increased incidences in the treated groups of a number of combined neoplasms:
  - lung alveolar/bronchiolar neoplasms
  - thyroid gland C-cell adenoma and C-cell carcinoma (males)
  - skin epithelial cell neoplasms and keratoacanthoma (males and females)
  - clitoral gland (adenoma and carcinoma) in females
- The Committee recommended that additional statistical analyses of these combined tumor data be performed by CDER's Biostatistics Reviewer. Subsequent statistical analysis revealed that there was a statistically significant positive dose-response relationship in the incidence of combined thyroid C-cell adenoma and C-cell carcinoma in males, but not in the incidence of any other tumor combinations.
- The Committee recommended to the Division to request histopathologic evaluation of clitoral gland tissue from all treated animals by the Sponsor. Subsequent examination of the protocol, however, showed that clitoral gland tissue was not preserved unless a gross lesion was present. Therefore, the recommended evaluation could not be performed.
- The Committee recommended that the Division obtain historical control incidences from the testing laboratory in order to better evaluate any positive findings.

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
/Division File, HFD-510
/KDavisBruno, HFD-510
/GKuijpers, HFD-510
/RHedin, HFD-510
/ASeifried, HFD-024

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph DeGeorge
7/5/01 03:01:58 PM

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF CONSULTATION

Date: November 14, 2002
Between: Gemma Kuijpers, Ph.D. (HFD-510)
and
Joy D. Mele, M.S. (HFD-715)
Subject: Forteo follow-up rat study submitted July 30, 2002 (NDA 21,318)

The rat study data is summarized in the table below; see Appendix 1 for a schematic of the trial design.

The data

Obs	trt	onset	rtdur	obsdur	ost_sar	Number	ID	onset2	trtdur2	obsdur2
1	0	2	24	24	0	60	A	0	1	1
2	30	2	24	24	0	51	B	0	1	1
3	30	2	24	24	1	9	B	0	1	1
4	0	6	6	10	0	30	C	1	0	0
5	5	6	6	10	0	30	D1	1	0	0
6	30	6	6	10	0	30	D2	1	0	0
7	5	6	6	24	0	60	E1	1	0	1
8	30	6	6	24	0	58	E2	1	0	1
9	30	6	6	24	1	2	E2	1	0	1
10	0	2	6	6	0	30	F	0	0	0
11	5	2	6	6	0	30	G1	0	0	0
12	30	2	6	6	0	30	G2	0	0	0
13	5	2	6	24	1	1	H1	0	0	1
14	5	2	6	24	0	59	H1	0	0	1
15	30	2	6	24	1	2	H2	0	0	1
16	30	2	6	24	0	58	H2	0	0	1
17	5	6	20	24	0	60	I1	1	1	1
18	30	6	20	24	0	55	I2	1	1	1
19	30	6	20	24	1	5	I2	1	1	1

I believe that record #'s 3 and 19 drive the results found in the logistic regression analysis where dose and treatment duration were found to be the only significant factors related to the probability of having an osteosarcoma.

The results of a stepwise logistic regression analysis testing for all factors are:

Standard Parameter	DF	Wald Estimate	Error	Chi-Square	Pr > ChiSq
Intercept	1	-7.1144	1.2191	34.0541	<.0001
trt	1	0.1164	0.0399	8.5115	0.0035
trtdur2	1	1.5445	0.5340	8.3669	0.0038

So the logistic model is the following:

Logit = -7.1144 + 0.1164 TRT + 1.5445 Treatment duration

Where treatment takes on values of 0, 5 and 30 and duration is long (1) or short (0)

The table below shows the probability of having an osteosarcoma given specific values for dose and treatment duration.

Dose	Trt duration	Probability of an osteosarcoma
0	Short (6 months)	.0008
0	Long (24 months)	.0038
5	Short (6 months)	.00145

5	Long (24 months)	.00677
30	Short (6 months)	.02605
30	Long (24 months)	.11138

The table of odds ratios below show the significant risk due to longer duration and treatment.

Adjusted Odds Ratios

	Odds Ratio	Confidence Interval
Long vs short	4.68	1.65, 13.34
0 vs 5	1.79	1.21, 2.65
0 vs 30	32.89	3.15, 343.77

Let's say we want to know the contribution to the risk of an osteosarcoma given the other factors, then we could include those factors in the model and we would get the following probabilities of an osteosarcoma. You can see that the highest risk is with dose of 30, long treatment duration, early onset and long observation (p=.14) --- our model tells us, though, that this risk is not statistically significantly higher than the risk for short observation or late onset for dose 30+long treatment duration since neither of duration of observation or time of onset were significant risk factors.

Obs	trt	trtdur2	obsdur2	onset2	prob
1	0	0	0	1	0.00000
2	0	0	0	0	0.00000
3	0	1	1	0	0.00549
4	5	0	0	1	0.00000
5	5	0	1	1	0.00170
6	5	0	0	0	0.00000
7	5	0	1	0	0.00314
8	5	0	1	0	0.00314
9	5	1	1	1	0.00524
10	30	0	0	1	0.00000
11	30	0	1	1	0.02802
12	30	0	1	1	0.02802
13	30	0	0	0	0.00000
14	30	0	1	0	0.05047
15	30	0	1	0	0.05047
16	30	1	1	0	0.14091
17	30	1	1	0	0.14091
18	30	1	1	1	0.08170
19	30	1	1	1	0.08170

I would conclude that duration of treatment and dose are important predictors of risk of osteosarcoma with the risk highest in the high dose group with the longest treatment duration. The risk in the low dose group is greater than the risk in the control group (about 1.2 to 2.6 times) though the probability of a single case is very low in both groups (<.007 regardless of treatment duration). Although the risk in the 5 mg dose group is low, I would not conclude that there is no risk at that dose level.

Joy D. Mele, M.S.
Mathematical Statistician

cc:
Orig. NDA 21,318
HFD-510
HFD- 510 /RHedin, GKuijpers, BSchneider, EColman
HFD-715/JMele, TSahlroott; ENevius, CAnello

Appendix 1. Sponsor's schematic of trial design

Study Design Summary

Study Arm	Study No. Group No.	Age (Months) 2	8	14	20	26	Age During Treatment (Months)
A	R00100 01	Vehicle Control n = 60					
B	R00100 07	Positive Control (30 µg/kg) n = 60					2 - 26
C	R00200 01	Vehicle Control n = 30					
D1	R00200 02		5 µg/kg n = 30				6 - 12
D2	R00200 03		30 µg/kg n = 30				6 - 12
E1	R00200 04		5 µg/kg n = 60				6 - 12
E2	R00200 05		30 µg/kg n = 60				6 - 12
F	R00100 02	Vehicle Control n = 30					
G1	R00100 03	5 µg/kg n = 30					2 - 8
G2	R00100 04	30 µg/kg n = 30					2 - 8
H1	R00100 05	5 µg/kg n = 60					2 - 8
H2	R00100 06	30 µg/kg n = 60					2 - 8
I1	R00200 06		5 µg/kg n = 60				6 - 26
I2	R00200 07		30 µg/kg n = 60				6 - 26

Abbreviation: No. = number.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joy Mele
11/15/02 10:17:23 AM
BIOMETRICS

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA #: 21-318

Drug: Forteo (teriparatide)[1]

Sponsor: Eli Lilly and Company

Indication: [redacted]

Date of Submission: December 1, 2000

Statistical Reviewer: Joy Mele, M.S. (HFD-715)

Medical Reviewers: Efficacy: Bruce Schneider, M.D. (HFD-510)
Safety: Bruce Stadel, M.D. (HFD-510)

Volume Numbers in Statistical Section: Volumes 1.1-1.2, 1.204-1.305

Keywords:Clinical studies, NDA review, open-label

1 Teriparatide is also referred to as LY333334 in documents presented by the sponsor. In this review, the drug name will be abbreviated by PTH.

Introduction

The sponsor has presented the results of four Phase 3 clinical trials (Table 1) to demonstrate the efficacy and safety of teriparatide (PTH) for the treatment of osteoporosis in men and women. Two doses of PTH were studied (20 μg and 40 μg) but only the 20 μg dose is proposed for marketing. The 20 μg dose of PTH was studied in Trials B3D-MC-GHAC and B3D-MC-GHAJ; the other two studies (B3D-MC-GHAF and B3D-MC-GHAH) were of the 40 μg dose only. Trials B3D-MC-GHAC and B3D-MC-GHAJ were reviewed in an earlier document. Trials GHAF and GHAH provide further insight to the use of teriparatide in different populations (patients on HRT treatment and patients alternatively treated with alendronate) and are reviewed here.

Table 1. Brief Summary of Double-Blind, Randomized, Parallel, Controlled Clinical Trials

Study Number (# of sites)	Population	Treatment Arms (Rand. N)	Duration of Treatment	Primary Endpoint
B3D-MC-GHAC (99 USA)	Females W/vert. frac. ≥5 yrs PMP	PTH 20 (541) PTH 40 (552) PLA (544)	16-23 months (3 yrs planned)	New vertebral fractures
B3D-MC-GHAJ (37 USA)	Males Low BMD	PTH 20 (151) PTH 40 (139) PLA (147)	8-14 months (2 yrs planned)	Vertebral BMD
B3D-MC-GHAF (11 USA)	Females Low BMD ≥5 yrs PMP	PTH 40+HRT (122) PLA+HRT (125) About 50% on HRT pre-study	12-16 months (2 yrs planned)	Vertebral BMD
B3D-MC-GHAH (10 USA, CA. Europe, Mex)	Females Low BMD ≥5 yrs PMP	PTH 40 (73) Alendronate 10mg (73)	13-17 months (2 yrs planned)	Vertebral BMD

PMP=postmenopausal
PTH=teriparatide μg sc injection per day PLA=placebo
HRT=hormone replacement therapy

Following the closure of each trial, patients could opt to continue in an observational safety study, Study GHBJ. Study GHBJ provides valuable follow-up information after the withdrawal of PTH and therefore is reviewed in detail here.

Reviewer's Methods

For Studies GHAF and GHAH, this reviewer did not perform any additional analyses so only the sponsor's results are presented here. A brief summary of each study is given followed by a table of lumbar spine BMD results.

For Study GHBJ, the summary statistics presented here were computed by this reviewer using datasets provided by the sponsor. Note since GHBJ is an observational study, no comparative statistics were computed.

Study GHAH (5/97 to 4/99)

Study GHAH was a Phase 3, multicenter, double-blind, parallel, randomized study designed to compare daily doses of PTH 40 µg to alendronate 10 mg (ALEN10). All patients were also administered calcium and vitamin D.

Following a run-in of 2 months, patients were to be treated for 24 months; due to early termination of the trial, the median drug exposure was about 14 months (minimum of 1 day to a maximum of about 17 months).

A total of 146 patients (73 in each treatment group) were randomized to treatment. The primary reasons for treatment discontinuation in both treatment arms was ADE and patient decision (Table 2). There were 6 more patients in the ALEN group at the time of closure than in the PTH group due to more ADE's observed in the PTH group.

Table 2. Study GHAC Reasons for discontinuation of treatment

	ALEN10 (n=73)	**PTH 40 (n=73)**
ADE	7 (10%)	14 (19%)
Lost to follow-up	1 (1%)	0 (0%)
Patient decision	7 (10%)	4 (6%)
Protocol violation	1 (1%)	3 (4%)
Death	0 (0%)	1 (1%)
Study ended early	57 (78%)	51 (70%)

The treatment groups were well-balanced regarding baseline demographics (Table 3). About half the patients were over 65 years old (a younger population than GHAC) and the majority of the patients (95%) had not been treated previously with osteoporosis drugs.

Table 3. Study GHAH Baseline Demographics (Sponsor's Results)

	ALEN10 (n=73)	**PTH 40 (n=73)**
Age		
Mean (SD)	65 (9)	66 (8)
Range	35-80	47-85
≥65	55%	55%
BMI Mean (SD)	24 (3)	24 (4)
Caucasian	82%	82%
Years Postmenopausal	19 (10)	18 (9)
No Previous Osteo. Drug Treatment	95%	95%
Spinal BMD Mean (SD)	0.79 (0.1)	0.80 (0.1)

The BMD results at 6 sites show a statistically significant effect for PTH40 over alendronate 10. Also the results for PTH40 in this study are about 1-2% higher than what was observed in the PTH40 group in Study GHAC at 12 months.

Table 4. Sponsor's BMD Results for Study GHAH (Mean (SD)) at endpoint (LOCF)

	ALEN10 (n=73)	PTH 40 (n=73)
Lumbar spine	(n=66)	(n=62)
Baseline	0.80	0.80
% change	5.6%	12.2%*
Total hip	(n=63)	(n=61)
Baseline	0.73	0.73
% change	2.5%	4.0%*
Femoral neck	(n=63)	(n=61)
Baseline	0.65	0.65
% change	1.7%	4.8%*
Trochanter	(n=63)	(n=61)
Baseline	0.56	0.57
% change	3.9%	3.8%
Intertrochanter	(n=63)	(n=61)
Baseline	0.87	0.87
% change	2.3%	3.9%*
Wards triangle	(n=63)	(n=61)
Baseline	0.47	0.73
% change	3.9%	7.9%*

*Treatment difference significant at p<.05

Study GHAF (5/97 to 4/99)

Study GHAF was a Phase 3, multicenter, double-blind, parallel, randomized study designed to compare daily doses of PTH 40 µg in combination with hormone replacement therapy (HRT) to HRT alone in two groups of patients; patients previously treated with HRT and patients not previously treated with HRT. All patients were also administered calcium and vitamin D.

Following a run-in of 2 months, patients were to be treated for 18 months and then PTH treatment was withdrawn and patients were to be followed for 6 months. Due to early termination of the trial, the drug exposure was a median of about 14 months (range of 2 days to about 17 months).

A total of 247 patients (Table 5) were randomized to treatment stratifying on previous HRT (yes/no). The primary reasons for treatment discontinuation in both treatment arms was ADE and patient decision (Table 5).

Table 5. Study GHAF Reasons for discontinuation of treatment

	HRT (n=125)	HRT/PTH40 (n=122)
ADE	11 (9%)	18 (15%)
Lost to follow-up	1 (1%)	0 (0%)
Patient decision	5 (4%)	13 (11%)
Protocol violation	2 (2%)	0 (0%)
Lack of Efficacy	1 (1%)	0 (0%)
Study ended early	105 (84%)	91 (75%)

The treatment groups were well-balanced regarding baseline demographics (Table 6). About 1/3 of the patients were over 65 years old.

Table 6. Study GHAF Baseline Demographics (Sponsor's Results)

	No Prev HRT		Prev HRT	
	HRT (n=64)	HRT/PTH40 (n=61)	HRT (n=61)	HRT/PTH40 (n=61)
Age				
Mean (SD)	62 (7)	62 (7)	60 (8)	62 (8)
Range	45-79	50-81	36-79	47-79
≥65	33%	28%	25%	34%
BMI Mean (SD)	26 (5)	27 (4)	25 (4)	25 (5)
Caucasian	50%	43%	84%	92%
Hispanic	48%	56%	13%	8%
Years Postmenopausal	15 (7)	15 (8)	14 (8)	15 (9)
No Previous Osteo. Drug Treatment	100%	100%	0%	0%
Spinal BMD Mean (SD)	0.89 (0.2)	0.89 (0.2)	0.92 (0.2)	0.92 (0.2)

The addition of PTH to HRT resulted in about a 10% increase in BMD at the lumbar spine in patients with and without previous HRT therapy (Table 7 on the following page). Significant increases in BMD due to the addition of PTH were also realized at 5 other sites; total hip, femoral neck, trochanter, intertrochanter and Ward's triangle.

Table 7. Sponsor's BMD Results for Study GHAF
(Mean (SD)) at endpoint (LOCF)

	No Prev HRT		Prev HRT	
	HRT (n=64)	HRT/PTH40 (n=61)	HRT (n=61)	HRT/PTH40 (n=61)
Lumbar spine	(n=58)	(n=56)	(n=58)	(n=58)
Baseline	0.89	0.88	0.91	0.92
% change	+4.6%	+16.9%*	+1.5%	+11.2%*
Total hip	(n=57)	(n=52)	(n=57)	(n=58)
Baseline	0.85	0.85	0.84	0.81
% change	+2.9%	+7.3%*	+0.2%	+3.4%*
Femoral neck	(n=57)	(n=52)	(n=57)	(n=58)
Baseline	0.78	0.76	0.74	0.71
% change	+3.4%	+7.5%*	+0.7%	+3.2%*
Trochanter	(n=57)	(n=52)	(n=57)	(n=58)
Baseline	0.66	0.65	0.66	0.63
% change	+3.8%	+7.2%*	+0.4%	+3.3%*
Intertrochanter	(n=57)	(n=52)	(n=57)	(n=58)
Baseline	1.03	1.04	1.00	0.96
% change	+2.0%	+6.6%*	-0.1%	+3.6%*
Wards triangle	(n=57)	(n=52)	(n=57)	(n=58)
Baseline	0.61	0.59	0.59	0.56
% change	+4.4%	+11.2%*	+0.1%	+4.2%*

*Treatment difference significant at p<.05 compared to HRT alone.

Reviewer's overall comments on Studies GHAH and GHAF

The lumbar spine BMD results for Studies GHAH and GHAF are summarized in Table 8 with the results from GHAC (the fracture study in women) and GHAJ (a study of men). The PTH40 treatment effects seen in these four studies are comparable for patients completing 12 months of therapy.

Table 8. **Lumbar spine BMD** change from baseline results (Mean (SD))
for observed cases at Month 12

	Placebo	PTH 20	PTH 40	ALEN10	HRT	HRT/PTH40
Study GHAH	NA	NA	(n=52) +14.1% (9.4)	(n=58) +5.9% (4.8)	NA	NA
Study GHAF						
No prev. HRT	NA	NA	NA	NA	(n=54) +4.3% (4.3)	(n=48) +16.7% (9.7)
Prev. HRT					(n=55) +1.7% (3.3)	(n=50) +11.2% (6.4)
Study GHAC	(n=467) +0.8% (4.9)	(n=466) +8.3% (6.1)	(n=452) +11.9% (6.8)	NA	NA	NA
Study GHAJ	(n=42) +0.7% (4.7)	(n=40) +6.9% (4.6)	(n=36) +10.0% (5.8)	NA	NA	NA

In all 4 studies, nearly twice as many patients in the PTH40 group discontinued treatment due to an ADE (11%-19%) compared to the other treatment groups in the studies (5%-10%). From Dr. Stadel's review of safety, nausea was the only specific ADE with a statistically significant difference or trend between treatment groups.

Study GHBJ (ongoing)

Study GHBJ is an observational study originally designed to monitor, for two years, safety and BMD in patients previously enrolled in a PTH study. After PTH was stopped in their previous study, patients were permitted to take an alternative osteoporosis drug or remain untreated. The study was not blinded.

The primary objective of this trial was to collect additional safety data on patients previously treated with PTH; the safety data has been reviewed by Dr. Bruce Stadel. Secondary objectives included monitoring BMD at the spine, hip, total body and radius. Also data on vertebral and non-vertebral fractures were collected. The protocol was amended in early 2000 (about one year into the study) to include monitoring of spinal fractures by scheduling lumbar spine x-rays after 12 months of follow-up (FU).

Visits were planned at Month 0 (Visit 1), Month 12 (Visit 2) and Month 24 (Visit 3) or at the time of discontinuation. Month 0 occurred approximately 6 months after discontinuation of drug in the prior double-blind (DB) trial. For the submission reviewed here, data was available up to Visit 2.

Table 9 shows the number of patients enrolled in GHBJ by prior study. All randomized patients were eligible to be enrolled in GHBJ including early discontinuations from double-blind treatment. Most of the patients came from Studies GHAC and GHAJ (see Table 10 for the number of patients in each study by treatment group); the two primary studies reviewed in an earlier document by this reviewer. Only the results for these two studies will be examined in detail here.

Table 9 Patients enrolling in GHBJ by prior study

Prior Study	# Randomized in Prior Study	# Enrolled in GHBJ (% of randomized)
GHAC	1637	**1262 (77%)**
GHAJ	437	**355 (81%)**
GHAF	247	191 (77%)
GHAH	146	105 (72%)
GHAL	6	3 (50%)
GHAU	13	10 (77%)
GHAV	6	4 (67%)

The median time of follow-up was about 18 months at the time of the second GHBJ visit (Table 10) for GHAC patients and about 17 months for GHBJ patients. Follow-up was computed from the time of drug discontinuation to Visit 2; long FU times were for patients who discontinued DB treatment early.

Table 10. Duration of treatment exposure and observational follow-up for GHBJ patients

	Placebo	PTH20	PTH40
GHAC[1]	**N=410**	**N=432**	**N=411**
DB treatment exposure (months, median (range))	19 (2-24)	19 (0.4-24)	19 (0.8-25)
Duration of FU (months, median (range))	18 (5-39)	18 (4-38)	18 (5-38)
GHAJ	**N=127**	**N=120**	**N=107**
DB treatment exposure (months, median (range))	11 (1-14)	11 (1-14)	11 (0.4-15)
Duration of FU (months, median (range))	17.5 (6-30)	17 (5-28)	17.5 (6-30)

The demographics for the patients continuing into GHBJ from GHAC and GHAJ were similar to the demographics of the patients originally randomized in these studies; about

1 Exposure and duration of follow-up were similar for patients taking and not taking osteoporosis drugs during follow-up.

¾ of the women were over 65 while about 1/3 of the men were over 65, 99% of the patients were Caucasian and about 85% of the patients had not been previously treated with osteoporosis drugs before entering their previous clinical trial.

GHBJ patients had the option of taking an osteoporosis drug after discontinuing their double-blind treatment. About 40% of GHAC patients and 20% of GHAJ took bisphosphonates during the observational follow-up (Table 11).

Table 11. % of patients using osteoporosis drugs during observational follow-up

	Placebo	PTH20	PTH40
GHAC	N=410	N=432	N=411
Any Osteo. Trt	57%	53%	52%
Bisphos. Trt.	44%	40%	40%
GHAJ	N=127	N=120	N=107
Any Osteo. Trt	29%	16%	22%
Bisphos. Trt.	23%	15%	14%

The sponsor compared the demographics of patients taking osteoporosis drugs and those not taking the drugs during GHBJ. For GHAC, the two subgroups differed significantly on weight, BMI, baseline lumbar spine BMD, baseline vertebral fractures and prior use of osteoporosis drugs; a significant treatment by subgroup interaction was observed for baseline vertebral fractures. For GHAJ, the two subgroups differed significantly on age and baseline lumbar spine BMD; no significant treatment by subgroup interactions were observed. The sponsor concluded that the use of osteoporosis drugs in GHBJ may influence interpretation of fracture risk (*and seemingly, other outcomes as well*) and this reviewer concurs.

This reviewer presents results by bisphosphonate use since there is a clinical interest in how patients fare after being switched from PTH to a bisphosphonate and since the subgroups differ on important prognostic variables.

On the following pages, this reviewer examines the lumbar spine BMD data collected in GHBJ in detail and summarizes the vertebral fracture data. Less attention is paid here to the fracture data due to the lack of blinding during GHBJ and the addition of assessment of fractures to the protocol after unblinding.

Table 12 summarizes the lumbar spine BMD data during double blind (DB) treatment and during GHBJ (observational follow-up (FU)). For the FU period, this reviewer computed the change from the DB endpoint. Only patients with follow-up data are included in this table; a small number of patients had only Visit1 data (about 6 months without treatment) and are included in this table with the patients with Visit 2 data (about 18 months without treatment). Only the GHAC data is broken down by bisphosphonate use because the sample sizes are sufficiently large to obtain reasonable estimates (fewer than 20 patients per arm used bisphosphonates in Study GHAJ).

Overall, placebo patients show an increase in BMD during follow-up while PTH patients show a mean decrease for both dose groups in both studies. The decrease for PTH patients on bisphosphonates is about half the decrease seen for patients not on medication.

Table 12. Lumbar spine BMD (mean) at baseline and endpoint during double-blind treatment and after about 18 months of untreated follow-up

	Placebo	PTH20	PTH40
Study GHAC	(n=402)	(n=422)	(n=404)
Baseline	*0.83*	*0.83*	*0.82*
DB change	+0.009	+0.07	+0.10
DB % change	+1.2%	+9.5%	+13.4%
Endpoint	*0.84*	*0.90*	*0.93*
FU change from DB-EP	**+0.02**	**-0.01**	**-0.03**
FU % change from DB-EP	**+2.9%**	**-1.7%**	**-3.1%**
Study GHAC On FU BISPHOS	(n=179)	(n=168)	(n=160)
Baseline	*0.80*	*0.79*	*0.78*
DB change	+0.008	+0.08	+0.11
DB % change	+1.1%	+10.4%	+14.0%
Endpoint	*0.81*	*0.87*	*0.89*
FU change from DB-EP	**+0.04**	**-0.006**	**-0.02**
FU % change from DB-EP	**+4.6%**	**-0.7%**	**-1.8%**
Not On FU BISPHOS	(n=223)	(n=254)	(n=244)
Baseline	*0.85*	*0.86*	*0.85*
DB change	+0.01	+0.07	+0.11
DB % change	+1.2%	+8.9%	+13.0%
Endpoint	*0.86*	*0.92*	*0.95*
FU change from DB-EP	**+0.01**	**-0.02**	**-0.04**
FU % change from DB-EP	**+1.5%**	**-2.5%**	**-4.0%**
Study GHAJ	(n=125)	(n=116)	(n=105)
Baseline	*0.85*	*0.90*	*0.87*
DB change	+0.007	+0.06	+0.08
DB % change	+0.8%	+6.3%	+9.7%
Endpoint	*0.86*	*0.95*	*0.95*
FU change from DB-EP	**+0.007**	**-0.01**	**-0.03**
FU % change from DB-EP	**+1.1%**	**-1.3%**	**-3.2%**

Figure 1 on the following page illustrates the lumbar spine BMD change from baseline data for both the double blind endpoint and the GHBJ visits. Note that only patients with complete data are included in this graph in order to show how the BMD for the same group of patients changes over time. Change from baseline instead of percent