

Table 6. Analysis of Dose-Mortality Trend for Male Rats

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	0.09	0.7654
	Depart from Trend	0.23	0.8936
	Homogeneity	0.31	0.8574
Kruskal-Wallis	Dose-Mortality Trend	0.00	0.9929
	Depart from Trend	0.42	0.8110
	Homogeneity	0.42	0.9363

Source: _____

Figure 1. Cumulative Percentages of Death in Male Rats

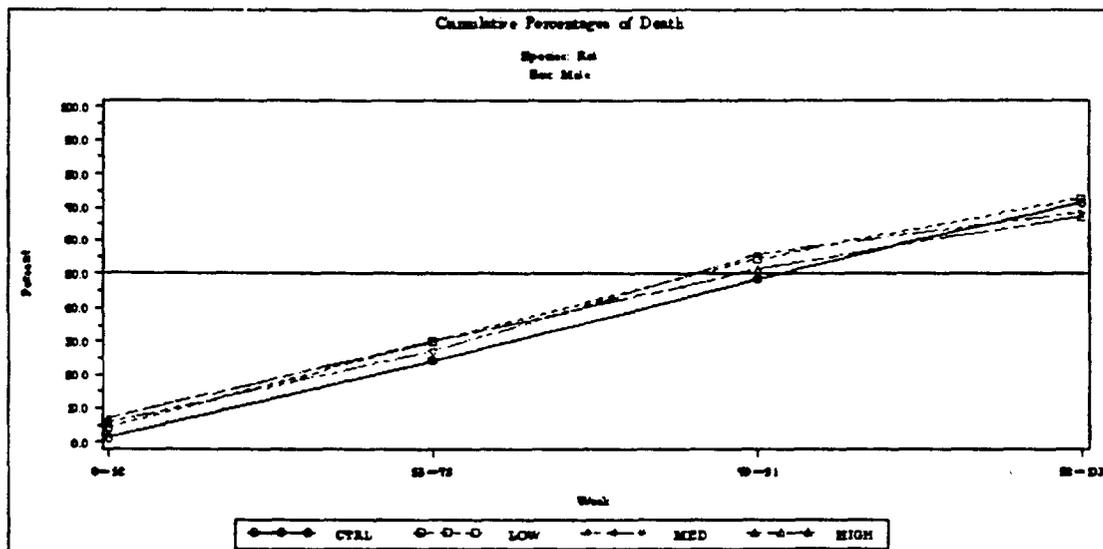


Figure 2. Kaplan-Meier Survival Functions for Male Rats

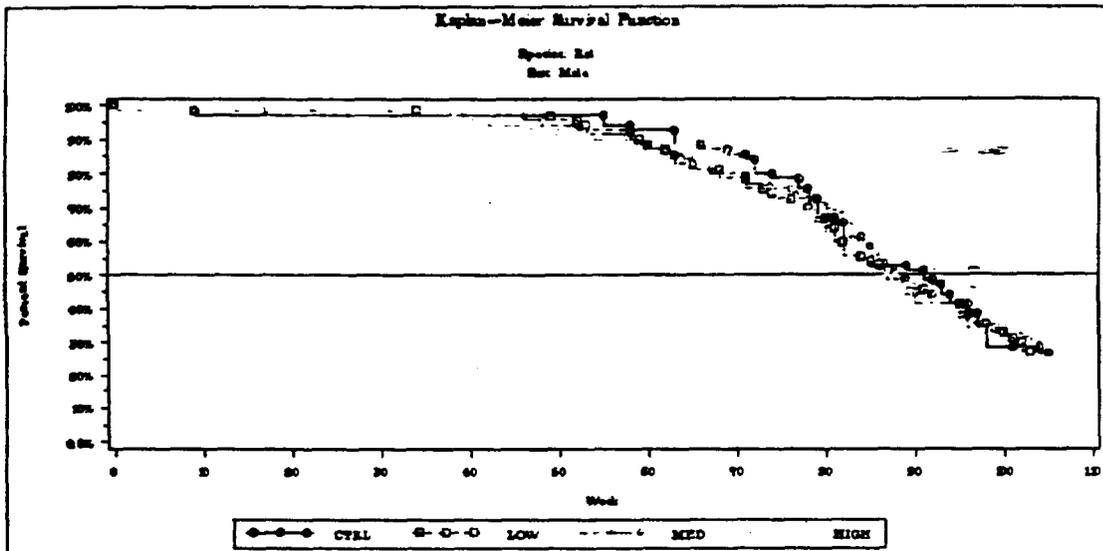


Table 7. Statistical-Decision Rule

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.

Table 8. Trend Test for Male Rats

Analysis of Carcinogenic Potential in Male Rat

Test of Dose-Response (Tumor) Positive Linear Trend

Study No. 951159

Run Date & Time: May 17, 2000 (14:08)

Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.1 0.5 2)
 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 TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLES-----	EXACT ASYMP PROB PROB /CONT CORR =P(STAT .GE. OBSERVED)
ADRENAL GLAND	(1) IN 92-103	1	0 0 1 0	
CORTICAL ADENOMA [B].	(14) IN 92-103	2	16 13 8 11	
		IN 104-105	1	0 0 0 1	
		IN 104-105	2	20 19 22 22	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 1 1	0.170 0.139 0.260
ADRENAL GLAND	(1) IN 92-103	1	1 0 0 0	1.000 0.763 0.911
CORTICAL CARCINOMA [M].	(15) IN 92-103	2	15 13 9 11	
Spontaneous tumor pct: 1% in ctrl. - Total			-	1 0 0 0	
ADRENAL GLAND	(1) IN 53-78	1	1 0 0 0	0.555 0.559 0.604
PHEOCHROMOCYTOMA [B].	(48) IN 53-78	2	15 18 15 16	
		IN 79-91	1	4 4 3 2	
		IN 79-91	2	13 13 17 12	
		IN 92-103	1	4 3 2 0	
		IN 92-103	2	12 10 7 11	
		IN 104-105	1	1 1 5 6	
		IN 104-105	2	19 18 17 17	
Spontaneous tumor pct: 14% in ctrl. - Total			-	10 8 10 8	
ADRENAL GLAND	(1) IN 79-91	1	1 0 0 0	0.087 0.070 0.104
PHEOCHROMOCYTOMA [M].	(49) IN 79-91	2	16 17 20 14	
		IN 92-103	1	1 1 1 1	
		IN 92-103	2	15 12 8 10	
		IN 104-105	1	0 0 1 3	
		IN 104-105	2	20 19 21 20	
Spontaneous tumor pct: 3% in ctrl. - Total			-	2 1 2 4	
MAMMARY GLAND	(10) IN 79-91	1	1 1 2 0	0.779 0.774 0.827
FIBROADENOMA [B].	(17) IN 79-91	2	16 16 17 11	
		IN 92-103	1	1 0 0 1	
		IN 92-103	2	12 13 6 8	
		IN 104-105	1	3 2 0 0	
		IN 104-105	2	16 15 19 21	
		FA 87	1	0 0 0 1	
		FA 87	2	37 35 32 32	
Spontaneous tumor pct: 7% in ctrl. - Total			-	5 3 2 2	
MAMMARY GLAND	(10) IN 79-91	1	1 1 1 0	0.747 0.742 0.815
ADENOCARCINOMA [M].	(2) IN 79-91	2	16 16 18 12	
		IN 104-105	1	2 0 1 1	
		IN 104-105	2	17 17 18 20	
Spontaneous tumor pct: 4% in ctrl. - Total			-	3 1 2 1	
MESENTERY	(11) FA 79	1	1 0 0 0	1.000 0.788 0.923
LEIOMYOSARCOMA [M].	(37) FA 79	2	52 49 51 49	
Spontaneous tumor pct: 1% in ctrl. - Total			-	1 0 0 0	
OTHER TISSUE(S)	(12) IN 79-91	1	0 1 0 0	0.753 0.746 0.906
GRANULAR CELL TUMOR [B].	(23) IN 79-91	2	17 16 20 15	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 1 0 0	
PANCREAS	(14) IN 79-91	1	0 1 0 0	0.927 0.889 0.943
ACINAR ADENOMA [B].	(1) IN 79-91	2	17 16 20 15	
		IN 92-103	1	1 0 0 0	

		IN 92-103	2	15	13	9	11	
		IN 104-105	1	0	1	0	0	
		IN 104-105	2	20	18	22	23	
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	2	0	0	
PANCREAS	(14)	IN 53-78	1	1	0	0	1	0.275 0.274 0.317
ISLET CELL ADENOMA [B].	(34)	IN 53-78	2	15	18	15	15	
		IN 79-91	1	1	1	4	1	
		IN 79-91	2	16	16	16	14	
		IN 92-103	1	2	1	2	2	
		IN 92-103	2	14	12	7	9	
		IN 104-105	1	3	3	3	4	
		IN 104-105	2	17	16	19	19	
Spontaneous tumor pct: 10%	in ctrl.	- Total	-	7	5	9	8	
PANCREAS	(14)	IN 53-78	1	0	0	0	1	0.501 0.512 0.576
ISLET CELL CARCINOMA [M].	(35)	IN 53-78	2	16	18	15	15	
		IN 79-91	1	2	0	0	1	
		IN 79-91	2	15	17	20	14	
		IN 92-103	1	1	1	2	1	
		IN 92-103	2	15	12	7	10	
		IN 104-105	1	4	0	2	1	
		IN 104-105	2	16	19	20	22	
Spontaneous tumor pct: 10%	in ctrl.	- Total	-	7	1	4	4	
PARATHYROID	(15)	IN 53-78	1	0	0	0	1	0.253 0.261 0.350
ADENOMA [B].	(5)	IN 53-78	2	16	17	15	14	
		IN 92-103	1	1	1	0	0	
		IN 92-103	2	15	12	8	11	
		IN 104-105	1	0	0	2	1	
		IN 104-105	2	19	19	19	21	
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	1	2	2	
PITUITARY	(16)	IN 79-91	1	0	1	0	0	0.753 0.746 0.906
GLIOMA [B], pars nervosa.	(22)	IN 79-91	2	17	16	20	15	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	1	0	0	
PITUITARY	(16)	IN 0-52	1	0	1	0	1	0.475 0.475 0.499
ADENOMA [B], pars distali	(3)	IN 0-52	2	1	2	4	4	
		IN 53-78	1	5	7	5	5	
		IN 53-78	2	6	6	4	4	
		IN 79-91	1	7	6	10	4	
		IN 79-91	2	5	6	7	3	
		IN 92-103	1	8	1	4	3	
		IN 92-103	2	1	4	3	1	
		IN 104-105	1	11	15	11	9	
		IN 104-105	2	8	4	11	14	
		FA 58	1	1	0	0	0	
		FA 58	2	67	66	65	64	
		FA 60	1	0	1	1	0	
		FA 60	2	66	62	62	64	
		FA 61	1	0	0	0	1	
		FA 61	2	66	62	62	63	
		FA 62	1	0	1	0	0	
		FA 62	2	66	61	62	63	
		FA 63	1	1	0	1	0	
		FA 63	2	65	61	61	63	
		FA 64	1	0	0	1	0	
		FA 64	2	65	60	60	63	
		FA 66	1	1	0	0	0	
		FA 66	2	64	58	59	63	
		FA 70	1	0	0	0	1	
		FA 70	2	61	57	57	60	
		FA 71	1	1	0	1	1	
		FA 71	2	60	57	56	59	
		FA 73	1	0	1	0	2	
		FA 73	2	59	54	56	55	
		FA 74	1	0	0	0	1	
		FA 74	2	59	53	56	54	
		FA 76	1	0	1	1	1	
		FA 76	2	56	51	53	52	

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FA 77	1	0	0	1	0			
FA 77	2	56	51	52	52			
FA 78	1	1	1	0	0			
FA 78	2	54	50	52	52			
FA 79	1	1	0	0	1			
FA 79	2	52	49	51	48			
FA 80	1	0	1	0	1			
FA 80	2	51	48	51	46			
FA 81	1	2	0	0	0			
FA 81	2	49	47	50	44			
FA 82	1	0	2	0	0			
FA 82	2	47	43	49	44			
FA 83	1	0	0	0	1			
FA 83	2	46	42	48	43			
FA 84	1	1	1	1	1			
FA 84	2	45	41	45	42			
FA 85	1	0	0	0	1			
FA 85	2	43	39	43	41			
FA 86	1	0	0	0	1			
FA 86	2	41	38	41	40			
FA 88	1	0	0	1	1			
FA 88	2	41	36	37	35			
FA 89	1	1	1	0	1			
FA 89	2	40	35	36	34			
FA 90	1	0	0	1	0			
FA 90	2	37	34	33	34			
FA 92	1	1	0	0	1			
FA 92	2	35	32	31	33			
FA 93	1	1	0	0	2			
FA 93	2	33	31	31	30			
FA 94	1	2	0	0	0			
FA 94	2	31	31	31	29			
FA 95	1	0	1	0	1			
FA 95	2	31	30	31	28			
FA 97	1	1	0	0	0			
FA 97	2	28	27	26	28			
FA 98	1	1	0	0	0			
FA 98	2	26	27	25	28			
FA 99	1	0	3	0	3			
FA 99	2	25	24	25	25			
FA 100	1	0	1	1	0			
FA 100	2	25	23	24	25			
FA 101	1	1	0	0	0			
FA 101	2	24	23	24	25			
FA 102	1	0	1	1	0			
FA 102	2	20	21	23	24			
FA 103	1	0	2	0	0			
FA 103	2	20	19	23	24			
FA 105	1	1	0	0	0			
FA 105	2	15	15	15	18			
Spontaneous tumor pct: 70% in ctrl. - Total	-	49	48	41	44			
PITUITARY (16) FA 47	1	0	0	0	1	0.245	0.044	0.140
LEIOMYOSARCOMA [M]. (37) FA 47	2	69	69	68	66			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			
PITUITARY (16) IN 104-105	1	0	0	0	1	0.273	0.056	0.164
ADENOMA [B], pars interme (4) IN 104-105	2	20	19	22	22			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			
PROSTATE (17) IN 0-52	1	0	0	0	1	0.384	0.107	0.257
ADENOMA [B]. (5) IN 0-52	2	1	3	4	4			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			
SKELETAL MUSCLE (18) IN 104-105	1	0	1	0	0	0.761	0.768	0.910
NERVE SHEATH TUMOR, MALIG (44) IN 104-105	2	20	18	22	23			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0			
SKELETAL MUSCLE (18) FA 89	1	1	0	0	0	1.000	0.782	0.920
RHABDOMYOSARCOMA [M]. (51) FA 89	2	40	36	35	35			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			

SKIN	(19)	IN 53-78	1	0	0	1	0			
FIBROMA [B].	(18)	IN 53-78	2	16	18	13	16		0.235	0.234 0.292
			IN 79-91	1	1	0	1	1			
			IN 79-91	2	16	17	19	14			
			IN 92-103	1	2	2	0	0			
			IN 92-103	2	14	11	9	11			
			IN 104-105	1	0	0	1	3			
			IN 104-105	2	20	19	21	20			
			FA 74	1	0	0	1	0			
			FA 74	2	59	53	55	55			
Spontaneous tumor pct: 4%		in ctrl.	- Total	-	3	2	4	4			
SKIN	(19)	IN 92-103	1	1	0	0	0		0.436	0.241 0.398
FIBROSARCOMA [M].	(19)	IN 92-103	2	15	13	9	11			
			FA 78	1	0	0	0	1			
			FA 78	2	55	51	52	51			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	1			
SKIN	(19)	IN 53-78	1	0	0	1	1		0.166	0.163 0.224
KERATOACANTHOMA [B].	(36)	IN 53-78	2	16	18	14	15			
			IN 79-91	1	0	0	1	1			
			IN 79-91	2	17	17	19	14			
			IN 92-103	1	1	1	0	0			
			IN 92-103	2	15	12	9	11			
			IN 104-105	1	0	1	0	1			
			IN 104-105	2	20	18	22	22			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	2	2	3			
SKIN	(19)	IN 79-91	1	1	0	0	1		0.647	0.674 0.757
LIPOMA [B].	(38)	IN 79-91	2	16	17	20	14			
			IN 92-103	1	1	2	1	0			
			IN 92-103	2	15	11	8	11			
			FA 74	1	0	0	1	0			
			FA 74	2	59	53	55	55			
Spontaneous tumor pct: 3%		in ctrl.	- Total	-	2	2	2	1			
SKIN	(19)	FA 84	1	1	0	0	0		1.000	0.789 0.924
LIPOSARCOMA [M].	(39)	FA 84	2	45	42	46	43			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	0			
SKIN	(19)	IN 92-103	1	0	0	1	0		0.574	0.708 0.839
NERVE SHEATH TUMOR, BENIG	(43)	IN 92-103	2	16	13	8	11			
			FA 73	1	0	1	0	0			
			FA 73	2	59	54	56	57			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	1	1	0			
SKIN	(19)	IN 92-103	1	1	0	1	0		0.345	0.314 0.452
NERVE SHEATH TUMOR, MALIG	(44)	IN 92-103	2	15	13	8	11			
			IN 104-105	1	0	0	0	1			
			IN 104-105	2	20	19	22	22			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	1	1			
SKIN	(19)	FA 96	1	0	0	1	0		0.487	0.563 0.785
OSTEOSARCOMA [M].	(46)	FA 96	2	31	29	28	28			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	1	0			
SKIN	(19)	IN 92-103	1	2	0	1	0		0.970	0.959 0.975
PAPILLOMA [B].	(47)	IN 92-103	2	14	13	8	11			
			IN 104-105	1	1	3	1	0			
			IN 104-105	2	19	16	21	23			
Spontaneous tumor pct: 4%		in ctrl.	- Total	-	3	3	2	0			
SKIN	(19)	FA 89	1	0	1	0	0		0.723	0.744 0.901
RHABDOMYOSARCOMA [M].	(51)	FA 89	2	41	35	36	35			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	1	0	0			
SKIN	(19)	IN 104-105	1	0	1	0	0		0.321	0.252 0.408
SARCOMA [M].	(52)	IN 104-105	2	20	18	22	23			
			FA 53	1	0	0	0	1			
			FA 53	2	69	67	66	64			

Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	1			
SKIN (19) IN 79-91	1	0	1	0	0	0.753	0.746	0.906
SEBACEOUS GLAND ADENOMA (54) IN 79-91	2	17	16	20	15			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0			
SKIN (19) IN 104-105	1	1	0	0	0	1.000	0.803	0.928
SQUAMOUS CELL CARCINOMA (56) IN 104-105	2	19	19	22	23			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			
SKIN (19) IN 104-105	1	1	0	0	0	1.000	0.803	0.928
BASAL CELL CARCINOMA (M) (8) IN 104-105	2	19	19	22	23			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			
SKIN (19) IN 92-103	1	0	0	0	1	0.224	0.034	0.119
BASAL CELL TUMOR, BENIGN (9) IN 92-103	2	16	13	9	10			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			
BONE (2) IN 104-105	1	0	0	1	0	0.535	0.597	0.803
OSTEOMA (B) (45) IN 104-105	2	20	19	21	23			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0			
BONE (2) FA 69	1	1	0	0	0	1.000	0.792	0.923
OSTEOSARCOMA (M) (46) FA 69	2	61	57	57	62			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			
BONE (2) FA 96	1	0	1	0	0	0.735	0.747	0.902
AMELOBLASTOMA, MALIGNANT (6) FA 96	2	31	28	29	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0			
SMALL INTESTINE (20) FA 66	1	1	0	0	0	1.000	0.791	0.923
ADENOCARCINOMA (M) (2) FA 66	2	64	58	59	63			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0			
SPLEEN (21) IN 79-91	1	0	0	1	0	0.507	0.554	0.786
HEMANGIOSARCOMA (M) (29) IN 79-91	2	17	17	19	15			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0			
SYSTEMIC (22) FA 58	1	1	0	0	0	1.000	0.871	0.942
GRANULOCYTIC LEUKEMIA (M) (26) FA 58	2	67	66	65	64			
		FA 77	1	1	0	0		
		FA 77	2	55	51	53	52	
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	0	0			
SYSTEMIC (22) IN 79-91	1	0	1	0	0	0.341	0.314	0.418
HISTIOCYTIC SARCOMA (M) (32) IN 79-91	2	17	16	20	15			
		IN 104-105	1	0	0	0	1	
		IN 104-105	2	20	19	22	22	
		FA 101	1	1	1	0	0	
		FA 101	2	24	22	24	25	
		FA 103	1	0	0	0	1	
		FA 103	2	20	21	23	23	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	2	0	2			
SYSTEMIC (22) IN 104-105	1	1	0	0	0	0.597	0.621	0.692
LYMPHOMA, MALIGNANT (M) (41) IN 104-105	2	19	19	22	23			
		FA 34	1	0	1	0	0	
		FA 34	2	69	69	69	70	
		FA 67	1	0	0	1	0	
		FA 67	2	62	58	58	63	
		FA 69	1	0	0	0	1	
		FA 69	2	62	57	57	61	
		FA 71	1	0	1	0	0	
		FA 71	2	61	56	57	60	
		FA 86	1	0	1	1	0	
		FA 86	2	41	37	40	41	
		FA 87	1	0	0	0	1	
		FA 87	2	41	37	39	37	
		FA 89	1	0	0	1	0	
		FA 89	2	41	36	35	35	
		FA 98	1	1	0	0	0	

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Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0	
KIDNEY (5) IN 104-105	1	1	0	0	0	1.000 0.803 0.928
LIPOMA [B]. (38) IN 104-105	2	19	19	22	23	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0	
KIDNEY (5) IN 104-105	1	0	0	0	1	0.273 0.056 0.164
LIPOSARCOMA [M]. (39) IN 104-105	2	20	19	22	22	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1	
KIDNEY (5) IN 92-103	1	1	0	0	0	0.392 0.352 0.491
ADENOMA [B]. (5) IN 92-103	2	15	13	9	11	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	1	1	
LARGE INTESTINE (6) IN 79-91	1	0	0	1	0	0.507 0.554 0.786
LEIOMYOSARCOMA [M]. (37) IN 79-91	2	17	17	19	15	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0	
LIVER (7) IN 79-91	1	0	0	0	1	0.217 0.033 0.119
CHOLANGIOCARCINOMA [M]. (13) IN 79-91	2	17	17	20	14	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1	
LIVER (7) IN 79-91	1	1	0	1	0	0.301 0.250 0.348
HEPATOCELLULAR ADENOMA [B] (30) IN 79-91	2	16	17	19	15	
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	1	2	
LIVER (7) IN 53-78	1	0	3	1	1	0.272 0.272 0.324
HEPATOCELLULAR CARCINOMA (31) IN 53-78	2	16	15	14	15	
Spontaneous tumor pct: 4% in ctrl. - Total	-	3	4	6	5	
LUNG (8) IN 104-105	1	1	0	0	0	1.000 0.803 0.928
ADENOCARCINOMA [M]. (2) IN 104-105	2	19	19	22	23	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0	
LYMPH NODE (9) IN 92-103	1	1	1	0	1	0.642 0.576 0.695
HEMANGIOSARCOMA [M]. (29) IN 92-103	2	15	12	9	10	
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	1	0	1	
LYMPH NODE (9) IN 104-105	1	1	0	0	0	1.000 0.803 0.928
LYMPHANGIOSARCOMA [M]. (40) IN 104-105	2	19	19	22	23	
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0	

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Spontaneous tumor pct: 3%		FA 98	2	26	27	25	28	
	in ctrl.	- Total	-	2	3	3	2	
TESTIS	(23)) IN 53-78	1	1	0	0	0	0.939 0.848 0.931
INTERSTITIAL-CELL TUMOR [(33)) IN 53-78	2	15	18	15	16	
		IN 79-91	1	0	1	0	0	
		IN 79-91	2	17	16	20	15	
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	1	0	0	
TESTIS	(23)) IN 53-78	1	1	1	0	0	0.942 0.851 0.931
MESOTHELIOMA [M].	(42)) IN 53-78	2	15	17	15	16	
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	1	0	0	
TESTIS	(23)) IN 104-105	1	0	1	0	0	0.761 0.768 0.910
SEMINOMA [M].	(55)) IN 104-105	2	20	18	22	23	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	1	0	0	
THORACIC CAVITY	(24)) IN 104-105	1	1	0	0	0	1.000 0.803 0.928
MESOTHELIOMA [M].	(42)) IN 104-105	2	19	19	22	23	
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	0	0	0	
THYMUS	(25)) IN 79-91	1	1	0	0	0	0.160 0.074 0.139
THYMOMA [B].	(58)) IN 79-91	2	16	17	20	15	
		IN 104-105	1	0	0	0	2	
		IN 104-105	2	20	19	22	21	
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	0	0	2	
THYROID	(26)) IN 53-78	1	2	0	0	0	0.561 0.572 0.631
C-CELL ADENOMA [B].	(10)) IN 53-78	2	14	18	15	16	
		IN 79-91	1	2	1	0	0	
		IN 79-91	2	15	16	20	15	
		IN 92-103	1	3	0	0	0	
		IN 92-103	2	13	13	9	11	
		IN 104-105	1	2	1	2	5	
		IN 104-105	2	18	18	20	18	
Spontaneous tumor pct: 13%	in ctrl.	- Total	-	9	2	2	5	
THYROID	(26)) IN 79-91	1	0	0	2	0	0.867 0.884 0.930
C-CELL CARCINOMA [M].	(11)) IN 79-91	2	17	17	18	15	
		IN 104-105	1	1	2	0	0	
		IN 104-105	2	19	17	22	23	
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	2	2	0	
THYROID	(26)) IN 79-91	1	0	0	1	0	0.507 0.554 0.786
FOLLICULAR ADENOCARCINOMA	(20)) IN 79-91	2	17	17	19	15	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	0	1	0	
THYROID	(26)) IN 104-105	1	0	1	1	0	0.661 0.757 0.870
FOLLICULAR ADENOMA [B].	(21)) IN 104-105	2	20	18	21	23	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	1	1	0	
BRAIN	(3)) IN 104-105	1	0	1	0	0	0.761 0.768 0.910
GRANULAR CELL TUMOR, BENI	(24)) IN 104-105	2	20	18	22	23	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	0	1	0	0	
BRAIN	(3)) IN 104-105	1	1	0	0	0	0.983 0.908 0.955
ASTROCYTOMA [M].	(7)) IN 104-105	2	19	19	22	23	
		FA 81	1	1	1	0	0	
		FA 81	2	50	46	50	44	
Spontaneous tumor pct: 3%	in ctrl.	- Total	-	2	1	0	0	
ZYMBAL'S GLAND	(30)) FA 66	1	1	0	0	0	0.396 0.352 0.491
ADENOCARCINOMA [M].	(2)) FA 66	2	64	58	59	63	
		FA 72	1	0	0	0	1	
		FA 72	2	60	55	56	57	
		FA 86	1	0	0	1	0	
		FA 86	2	41	38	40	41	
Spontaneous tumor pct: 1%	in ctrl.	- Total	-	1	0	1	1	
HARDERIAN GLAND	(4)) FA 96	1	0	1	0	0	0.735 0.747 0.902
ADENOCARCINOMA [M].	(2)) FA 96	2	31	28	29	28	

Analysis of Female Rats

Table 9. Number of Female Rats Died by Treatment by Time

Number of Animals
Species: Rat
Sex: Female

	Treatment Group				Total N
	CTRL	LOW	MED	HIGH	
	N	N	N	N	
Week					
0-52	5	3	2	5	15
53-78	18	24	24	22	88
79-91	18	13	13	16	60
92-103	7	12	10	12	41
104-105	22	18	21	15	76
Total	70	70	70	70	280

Source: _____

Table 10. Analysis of Mortality for Female Rats by Treatment by Time

Analysis of Mortality
Species: Rat
Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
	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
Week												
0-52	5	70	7.1	3	70	4.3	2	70	2.9	5	70	7.1
53-78	18	65	32.8	24	67	38.6	24	68	37.1	22	65	38.6
79-91	18	47	58.6	13	43	57.1	13	44	55.7	16	43	61.4
92-103	7	29	68.6	12	30	74.3	10	31	70.0	12	27	78.6
104-105	22	70	31.4	18	70	25.7	21	70	30.0	15	70	21.4

Table 11. Analysis of Dose-Mortality Trend for Female Rats

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	1.14	0.2856
	Depart from Trend	0.75	0.6869
	Homogeneity	1.89	0.5953
Kruskal-Wallis	Dose-Mortality Trend	0.94	0.3320
	Depart from Trend	0.54	0.7642
	Homogeneity	1.48	0.6872

Source: _____

Figure 3. Cumulative Percentages of Death in Female Rats

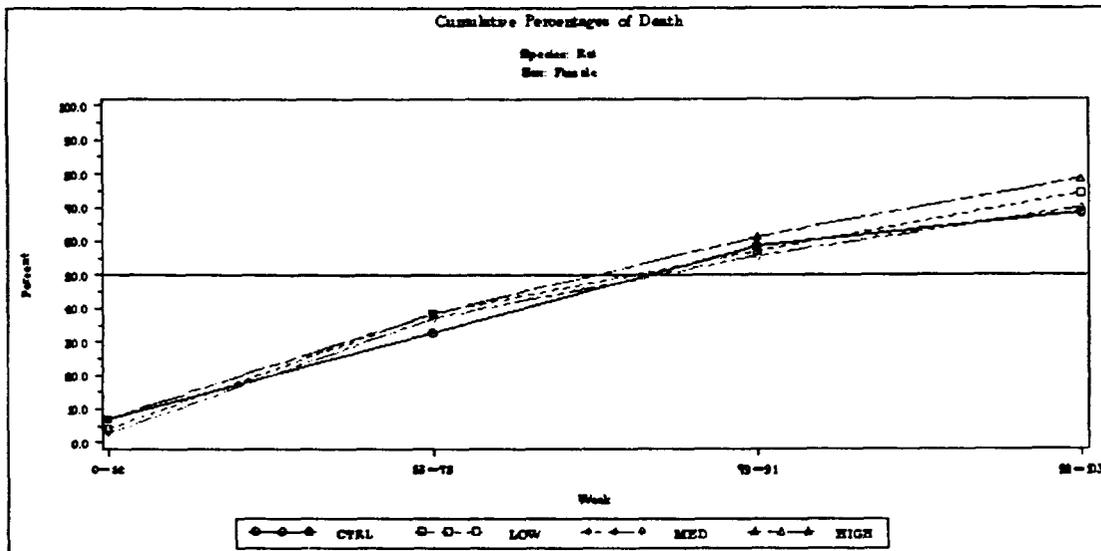
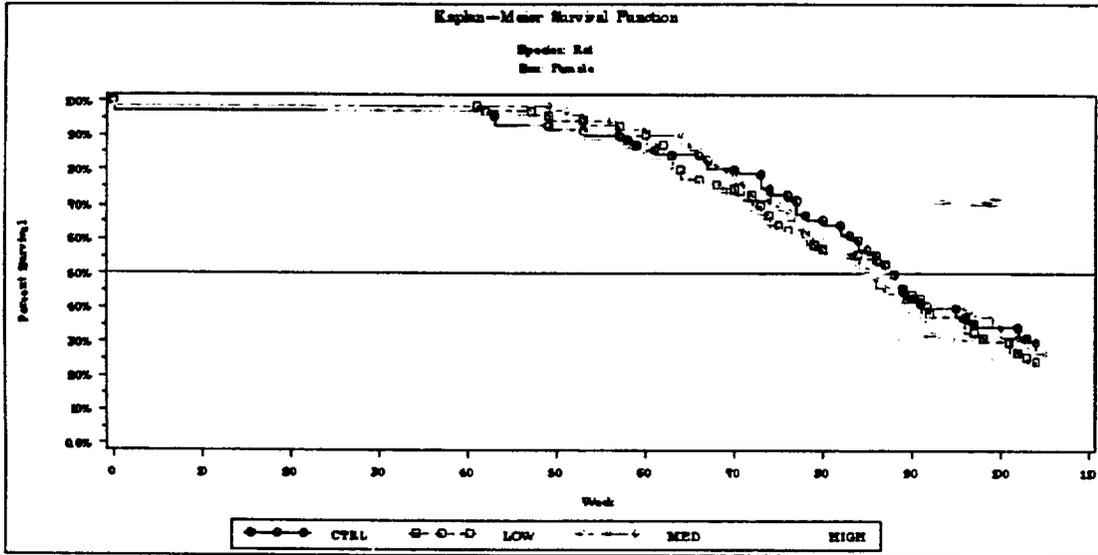


Figure 4. Kaplan-Meier Survival Functions for Female Rats



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Table 12. Trend Test for Female Rats

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.	
<ol style="list-style-type: none"> 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:	
<ol style="list-style-type: none"> 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	
<ol style="list-style-type: none"> 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. 951159
 Run Date & Time: May 17, 2000 (14:28)
 Source: _____

Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.1 0.5 2)
 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 TIME TYPES STRATA	ROW NO.	2xC CONTINGENCY -----TABLES-----	EXACT ASYMP ASYMP PROB PROB PROB /CONT CORR =P(STAT .GE. OBSERVED)
ADRENAL GLAND	(1) IN 92-103	1	0 1 0 0	0.825 0.838 0.924
CORTICAL CARCINOMA [M].	(15) IN 92-103	2	7 10 10 12	
		FA 103	1	0 1 0 0	
		FA 103	2	24 18 22 16	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 2 0 0	
MAMMARY GLAND	(10) IN 53-78	1	4 5 4 5	0.460 0.460 0.488
FIBROADENOMA [B].	(17) IN 53-78	2	13 18 17 13	
		IN 79-91	1	5 8 7 5	
		IN 79-91	2	10 3 5 9	
		IN 92-103	1	4 9 5 6	

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IN 92-103	2		3	3	4	6		
IN 104-105	1		14	11	13	9		
IN 104-105	2		8	7	8	6		
FA 24	1		0	0	0	1		
FA 24	2		70	70	70	69		
FA 47	1		0	0	0	1		
FA 47	2		67	69	70	67		
FA 49	1		1	1	1	0		
FA 49	2		66	67	69	67		
FA 56	1		0	0	0	1		
FA 56	2		64	66	67	63		
FA 62	1		0	0	0	1		
FA 62	2		60	63	64	59		
FA 66	1		1	0	1	0		
FA 66	2		59	56	60	56		
FA 70	1		0	0	0	1		
FA 70	2		58	53	56	51		
FA 74	1		0	1	1	1		
FA 74	2		55	48	52	46		
FA 78	1		0	0	1	0		
FA 78	2		50	44	45	44		
FA 83	1		0	0	0	1		
FA 83	2		45	40	40	41		
FA 85	1		1	0	0	0		
FA 85	2		41	39	38	37		
FA 87	1		0	0	1	0		
FA 87	2		39	38	33	36		
FA 88	1		1	1	0	0		
FA 88	2		36	36	32	35		
FA 89	1		1	1	0	1		
FA 89	2		34	34	32	32		
FA 100	1		0	0	1	0		
FA 100	2		25	22	25	18		
Spontaneous tumor pct: 46%		in ctrl.	-	32	37	35	33	

MAMMARY GLAND	(10)	IN 79-91	1	1	0	0	0	0.948	0.866	0.937
FIBROMA [B].	(18)	IN 79-91	2	17	13	13	16			
			IN 92-103	1	0	1	0	0			
			IN 92-103	2	7	11	10	12			
Spontaneous tumor pct: 1%			in ctrl.	-	1	1	0	0			

MAMMARY GLAND	(10)	IN 104-105	1	0	0	1	0	0.473	0.530	0.773
FIBROSARCOMA [M].	(19)	IN 104-105	2	22	18	20	15			
Spontaneous tumor pct: <= 1%			in ctrl.	-	0	0	1	0			

MAMMARY GLAND	(10)	IN 53-78	1	2	2	2	0	0.958	0.955	0.963
ADENOCARCINOMA [M].	(2)	IN 53-78	2	13	20	20	20			
			IN 79-91	1	5	6	0	4			
			IN 79-91	2	12	7	13	12			
			IN 92-103	1	3	5	2	2			
			IN 92-103	2	4	7	8	10			
			IN 104-105	1	7	5	10	4			
			IN 104-105	2	15	13	11	11			
			FA 56	1	0	0	1	1			
			FA 56	2	64	66	66	63			
			FA 58	1	1	0	0	0			
			FA 58	2	62	65	65	62			
			FA 60	1	0	1	0	0			
			FA 60	2	61	64	65	61			
			FA 63	1	0	1	0	0			
			FA 63	2	60	60	64	58			
			FA 69	1	0	0	1	0			
			FA 69	2	58	53	56	53			
			FA 74	1	1	0	0	1			
			FA 74	2	54	49	53	46			
			FA 78	1	1	0	0	0			
			FA 78	2	49	44	46	44			
			FA 83	1	1	0	0	0			
			FA 83	2	44	40	40	42			
Spontaneous tumor pct: 30%			in ctrl.	-	21	20	16	12			

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MAMMARY GLAND	(10)	IN 79-91	1	1	0	0	0	0.981	0.947	0.970
ADENOMA [B].	(5)	IN 79-91	2	17	13	13	16			
			IN 92-103	1	1	0	0	0			
			IN 92-103	2	6	12	10	12			
			IN 104-105	1	2	1	1	0			
			IN 104-105	2	20	17	20	15			
Spontaneous tumor pct: 6%		in ctrl.	- Total	-	4	1	1	0			
OVARY	(13)	IN 92-103	1	0	1	0	0	0.829	0.777	0.914
GRANULOSA-THECA CELL TUMO	(27)	IN 92-103	2	7	11	10	12			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	1	0	0			
OVARY	(13)	IN 92-103	1	0	0	1	0	0.536	0.511	0.812
GRANULOSA-THECA CELL TUMO	(28)	IN 92-103	2	7	12	9	12			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	1	0			
OVARY	(13)	FA 97	1	0	0	1	0	0.490	0.549	0.782
THECA-CELL TUMOR, MALIGNA	(57)	FA 97	2	26	26	27	22			
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	1	0			
PANCREAS	(14)	IN 53-78	1	0	0	0	1	0.888	0.873	0.913
ISLET CELL ADENOMA [B].	(34)	IN 53-78	2	18	24	24	21			
			IN 92-103	1	2	1	1	0			
			IN 92-103	2	5	11	9	12			
			IN 104-105	1	2	1	1	0			
			IN 104-105	2	20	17	20	15			
Spontaneous tumor pct: 6%		in ctrl.	- Total	-	4	2	2	1			
PANCREAS	(14)	IN 92-103	1	0	0	1	0	0.669	0.737	0.844
ISLET CELL CARCINOMA [M].	(35)	IN 92-103	2	7	12	9	12			
			IN 104-105	1	1	0	1	0			
			IN 104-105	2	21	18	20	15			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	2	0			
PARATHYROID	(15)	IN 79-91	1	0	0	0	1	0.483	0.469	0.596
ADENOMA [B].	(5)	IN 79-91	2	17	13	12	13			
			IN 92-103	1	0	1	0	0			
			IN 92-103	2	7	10	10	11			
			IN 104-105	1	1	0	1	0			
			IN 104-105	2	20	18	20	15			
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	1	1	1			
PITUITARY	(16)	IN 53-78	1	0	1	0	0	0.838	0.836	0.882
CARCINOMA [M], pars dista	(12)	IN 53-78	2	18	23	23	22			
			IN 104-105	1	2	1	0	0			
			IN 104-105	2	20	16	21	15			
			FA 78	1	0	0	1	0			
			FA 78	2	50	43	45	44			
			FA 82	1	1	0	0	0			
			FA 82	2	45	39	40	42			
			FA 92	1	0	0	1	0			
			FA 92	2	29	29	30	27			
			FA 93	1	0	0	0	1			
			FA 93	2	29	26	29	25			
			FA 96	1	1	0	0	0			
			FA 96	2	27	26	29	22			
			FA 99	1	0	0	1	0			
			FA 99	2	25	21	26	22			
Spontaneous tumor pct: 6%		in ctrl.	- Total	-	4	2	3	1			
PITUITARY	(16)	IN 0-52	1	0	0	1	0	0.474	0.476	0.496
ADENOMA [B], pars distali	(3)	IN 0-52	2	2	1	0	4			
			IN 53-78	1	3	5	4	4			
			IN 53-78	2	2	3	3	5			
			IN 79-91	1	6	2	4	2			
			IN 79-91	2	1	0	2	2			
			IN 92-103	1	2	2	3	2			
			IN 92-103	2	1	0	2	1			
			IN 104-105	1	17	15	19	14			
			IN 104-105	2	4	2	0	1			
			FA 41	1	0	1	0	0			

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FA 41	2	70 68 70 69
FA 42	1	1 0 0 0
FA 42	2	69 68 70 69
FA 43	1	1 0 0 0
FA 43	2	67 68 70 68
FA 47	1	0 1 0 0
FA 47	2	67 67 70 68
FA 49	1	1 0 0 0
FA 49	2	66 67 70 67
FA 51	1	0 0 1 1
FA 51	2	65 66 68 66
FA 53	1	1 0 1 1
FA 53	2	64 66 67 64
FA 57	1	1 1 1 0
FA 57	2	63 64 65 62
FA 58	1	0 0 0 1
FA 58	2	63 64 65 61
FA 59	1	1 0 0 0
FA 59	2	61 64 65 61
FA 60	1	0 1 1 0
FA 60	2	61 63 64 61
FA 61	1	1 0 0 0
FA 61	2	60 62 64 60
FA 62	1	0 1 0 1
FA 62	2	60 61 64 59
FA 63	1	0 1 0 0
FA 63	2	60 59 64 58
FA 64	1	0 2 1 0
FA 64	2	60 56 63 58
FA 65	1	0 0 2 2
FA 65	2	60 55 61 56
FA 66	1	0 1 0 0
FA 66	2	60 54 61 56
FA 67	1	1 0 2 0
FA 67	2	58 53 58 56
FA 68	1	0 1 1 3
FA 68	2	58 52 57 53
FA 69	1	0 0 1 1
FA 69	2	58 52 56 52
FA 70	1	2 0 1 2
FA 70	2	56 52 55 50
FA 72	1	0 1 0 0
FA 72	2	56 50 53 49
FA 73	1	1 2 0 1
FA 73	2	55 48 53 47
FA 74	1	2 1 2 0
FA 74	2	53 47 51 47
FA 75	1	0 2 1 0
FA 75	2	52 44 49 45
FA 76	1	1 1 1 1
FA 76	2	51 43 48 44
FA 77	1	0 0 2 0
FA 77	2	51 43 46 44
FA 78	1	2 1 0 0
FA 78	2	48 42 46 44
FA 79	1	0 2 2 0
FA 79	2	47 40 42 43
FA 80	1	1 1 2 1
FA 80	2	46 39 40 42
FA 83	1	1 0 0 2
FA 83	2	44 39 40 40
FA 84	1	0 1 1 1
FA 84	2	43 38 38 38
FA 85	1	1 0 0 1
FA 85	2	41 38 38 36
FA 86	1	1 0 0 0
FA 86	2	39 38 36 36
FA 87	1	2 1 1 1
FA 87	2	37 36 33 35
FA 88	1	1 1 0 2
FA 88	2	36 35 32 33

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FA 89	1	2	3	1	2			
FA 89	2	33	31	31	31			
FA 90	1	1	1	0	2			
FA 90	2	31	30	31	27			
FA 91	1	1	1	0	0			
FA 91	2	29	29	31	27			
FA 92	1	0	2	0	1			
FA 92	2	29	27	31	26			
FA 93	1	0	0	0	2			
FA 93	2	29	26	29	24			
FA 95	1	0	0	0	1			
FA 95	2	29	26	29	22			
FA 96	1	1	1	1	0			
FA 96	2	27	25	28	22			
FA 97	1	1	3	0	0			
FA 97	2	25	22	28	22			
FA 98	1	0	1	0	0			
FA 98	2	25	21	27	22			
FA 99	1	0	0	0	4			
FA 99	2	25	21	27	18			
FA 100	1	0	0	1	0			
FA 100	2	25	21	25	18			
FA 101	1	0	1	0	0			
FA 101	2	25	20	24	18			
FA 102	1	1	2	2	0			
FA 102	2	24	18	22	18			
FA 103	1	1	0	1	1			
FA 103	2	23	18	21	15			
FA 104	1	1	0	1	0			
FA 104	2	21	17	20	15			
FA 105	1	0	0	1	0			
FA 105	2	17	14	15	11			
Spontaneous tumor pct: 86% in ctrl. - Total	-	60	63	63	57			
SKIN (19) IN 79-91	1	0	0	0	1	0.266	0.052	0.155
FIBROMA [B]. (18) IN 79-91	2	18	13	13	15			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1			
SKIN (19) IN 79-91	1	1	0	0	0	0.858	0.831	0.909
KERATOACANTHOMA [B]. (36) IN 79-91	2	17	13	13	16			
	IN 104-105	1	1	0	1	0		
	IN 104-105	2	21	18	20	15		
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	1	0			
SKIN (19) IN 92-103	1	1	0	0	0	1.000	0.876	0.946
LIPOMA [B]. (38) IN 92-103	2	6	12	10	12			
	IN 104-105	1	1	0	0	0		
	IN 104-105	2	21	18	21	15		
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	0	0			
SKIN (19) IN 104-105	1	0	1	0	0	0.271	0.202	0.353
LIPOSARCOMA [M]. (39) IN 104-105	2	22	17	21	15			
	FA 89	1	0	0	0	1		
	FA 89	2	35	35	32	32		
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	1			
SKIN (19) IN 79-91	1	0	1	0	0	0.700	0.752	0.900
SARCOMA [M]. (52) IN 79-91	2	18	12	13	16			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0			
SKIN (19) FA 92	1	0	1	0	0	0.752	0.747	0.904
SEBACEOUS ADENOCARCINOMA (53) FA 92	2	29	29	31	27			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0			
SKIN (19) IN 104-105	1	0	0	1	0	0.473	0.530	0.773
BASAL CELL CARCINOMA [M]. (8) IN 104-105	2	22	18	20	15			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0			
SPLEEN (21) FA 85	1	0	0	1	0	0.480	0.560	0.783
HEMANGIOSARCOMA [M]. (29) FA 85	2	42	39	37	37			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0			

SYSTEMIC	(22)	IN 92-103	1	0	1	0	0	0.652	0.745	0.863
HISTIOCYTIC SARCOMA [M].	(32)	IN 92-103	2	7	11	10	12			
			FA 85	1	0	0	1	0			
			FA 85	2	42	39	37	37			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	1	0			
SYSTEMIC	(22)	IN 79-91	1	1	1	0	0	0.162	0.158	0.218
LYMPHOMA, MALIGNANT [M].	(41)	IN 79-91	2	17	12	13	16			
			IN 92-103	1	0	1	0	0			
			IN 92-103	2	7	11	9	11			
			IN 104-105	1	0	0	1	1			
			IN 104-105	2	22	18	20	14			
			FA 51	1	0	0	0	1			
			FA 51	2	65	67	69	66			
			FA 92	1	0	0	1	0			
			FA 92	2	29	30	30	27			
			FA 103	1	0	0	0	1			
			FA 103	2	24	19	22	15			
Spontaneous tumor pct: 1% in ctrl. - Total				-	1	2	2	3			
THYMUS	(25)	IN 79-91	1	0	1	1	0	0.339	0.303	0.401
THYMOMA [B].	(58)	IN 79-91	2	18	12	12	15			
			IN 92-103	1	1	0	0	0			
			IN 92-103	2	6	12	10	12			
			IN 104-105	1	1	0	0	2			
			IN 104-105	2	21	18	21	12			
Spontaneous tumor pct: 3% in ctrl. - Total				-	2	1	1	2			
THYROID	(26)	IN 53-78	1	0	0	1	0	0.590	0.609	0.680
C-CELL ADENOMA [B].	(10)	IN 53-78	2	18	24	23	22			
			IN 79-91	1	2	2	0	0			
			IN 79-91	2	16	11	13	16			
			IN 92-103	1	0	0	0	2			
			IN 92-103	2	7	12	10	10			
			IN 104-105	1	0	1	3	0			
			IN 104-105	2	22	17	18	15			
Spontaneous tumor pct: 3% in ctrl. - Total				-	2	3	4	2			
THYROID	(26)	FA 86	1	0	0	1	0	0.476	0.561	0.783
C-CELL CARCINOMA [M].	(11)	FA 86	2	40	39	35	36			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0			
URINARY BLADDER	(27)	IN 53-78	1	0	1	0	0	0.824	0.835	0.922
PAPILLOMA [B].	(47)	IN 53-78	2	18	22	24	22			
			FA 70	1	0	1	0	0			
			FA 70	2	58	52	56	51			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	2	0	0			
UTERUS	(28)	FA 78	1	0	0	0	1	0.266	0.199	0.350
ENDOMETRIAL STROMAL SARCO	(16)	FA 78	2	50	44	46	43			
			FA 104	1	0	1	0	0			
			FA 104	2	22	17	21	15			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	1			
UTERUS	(28)	IN 79-91	1	1	0	0	0	1.000	0.788	0.920
LEIOMYOSARCOMA [M].	(37)	IN 79-91	2	17	13	13	16			
Spontaneous tumor pct: 1% in ctrl. - Total				-	1	0	0	0			
UTERUS	(28)	IN 0-52	1	0	0	1	0	0.089	0.084	0.109
POLYP [B].	(50)	IN 0-52	2	5	3	1	5			
			IN 53-78	1	0	1	0	2			
			IN 53-78	2	18	23	24	20			
			IN 79-91	1	0	1	2	1			
			IN 79-91	2	18	12	11	15			
			IN 92-103	1	0	1	1	0			
			IN 92-103	2	7	11	9	12			
			IN 104-105	1	2	3	1	4			
			IN 104-105	2	20	15	20	11			
Spontaneous tumor pct: 3% in ctrl. - Total				-	2	6	5	7			

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VAGINA	(29)	IN 92-103	1	0	0	0	1	0.292	0.064	0.179
GRANULAR CELL TUMOR, BENI	(24)	IN 92-103	2	7	12	10	11			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	0	0	1			
VAGINA	(29)	IN 92-103	1	1	0	0	0	1.000	0.812	0.931
GRANULAR CELL TUMOR, MALI	(25)	IN 92-103	2	6	12	10	12			
Spontaneous tumor pct: 1%			in ctrl. - Total	-	1	0	0	0			
BRAIN	(3)	IN 104-105	1	0	0	0	1	0.197	0.025	0.101
GRANULAR CELL TUMOR, BENI	(24)	IN 104-105	2	22	18	21	14			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	0	0	1			
BRAIN	(3)	FA 71	1	0	0	1	0	0.476	0.584	0.746
GRANULAR CELL TUMOR, MALI	(25)	FA 71	2	56	52	54	49			
			FA 86	1	0	0	1	0			
			FA 86	2	40	39	35	36			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	0	2	0			
BRAIN	(3)	FA 102	1	0	0	0	1	0.204	0.028	0.107
ASTROCYTOMA [M].	(7)	FA 102	2	25	21	24	17			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	0	0	1			
ZYMBAL'S GLAND	(30)	FA 90	1	1	0	0	0	1.000	0.784	0.922
ADENOCARCINOMA [M].	(2)	FA 90	2	31	32	31	29			
Spontaneous tumor pct: 1%			in ctrl. - Total	-	1	0	0	0			
KIDNEY	(5)	IN 104-105	1	0	1	0	0	0.710	0.730	0.901
LIPOMA [B].	(38)	IN 104-105	2	22	17	21	15			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	1	0	0			
LIVER	(7)	IN 104-105	1	2	1	2	1	0.547	0.554	0.663
HEPATOCELLULAR ADENOMA [B]	(30)	IN 104-105	2	20	17	19	14			
Spontaneous tumor pct: 3%			in ctrl. - Total	-	2	1	2	1			
LIVER	(7)	IN 104-105	1	0	1	0	0	0.710	0.730	0.901
HEPATOCELLULAR CARCINOMA	(31)	IN 104-105	2	22	17	21	15			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	1	0	0			

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Analysis of Male Mice

Table 13. Number of Male Mice Died by Treatment by Time

Number of Animals
Species: Mouse
Sex: Male

	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	
Week					
0-52	7	4	14	8	34
53-78	16	20	11	10	57
79-91	10	13	12	7	42
92-103	13	14	13	7	47
104-105	24	19	20	37	100
Total	70	70	70	70	280

Source: _____

Table 14. Analysis of Mortality for Male Mice by Treatment by Time

Analysis of Mortality
Species: Mouse
Sex: Male

	Dose											
	CTRL			LOW			MED			HIGH		
	NUM. of Dead	NUM. at Risk	CUMU Pct. Died									
Week												
0-52	7	70	10.0	4	70	5.7	14	70	20.0	8	70	12.8
53-78	16	63	32.9	20	66	34.3	11	66	35.7	10	61	27.1
79-91	10	47	47.1	13	46	52.9	12	45	52.9	7	61	37.1
92-103	13	37	65.7	14	33	72.9	13	33	71.4	7	44	47.1
104-105	24	70	34.3	19	70	27.1	20	70	28.6	37	70	52.9

Table 15. Analysis of Dose-Mortality Trend for Male Mice

Dose-Mortality Trend Tests

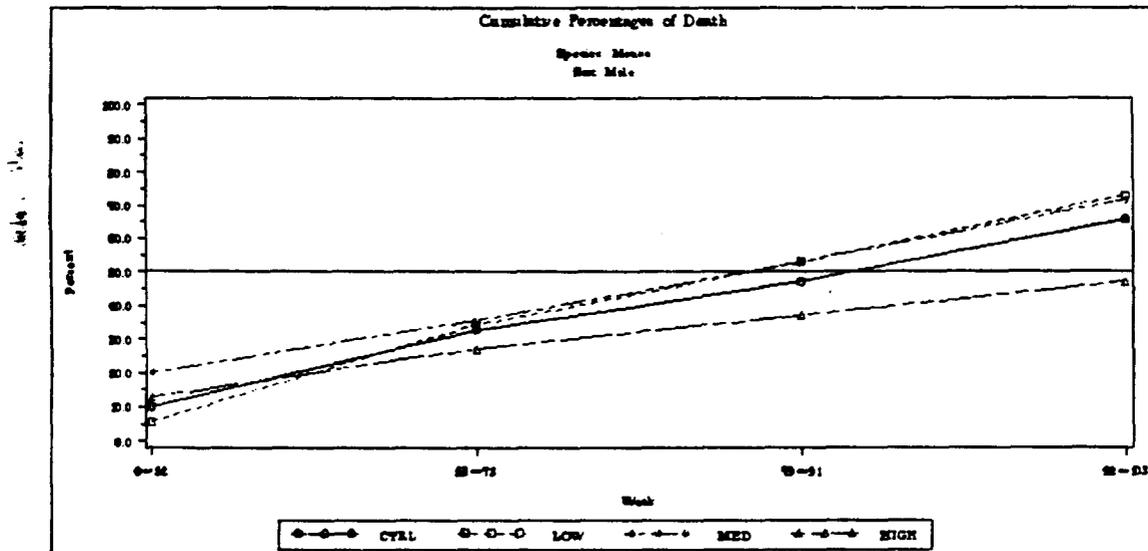
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1.

Species: Mouse
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	7.23	0.0072
	Depart from Trend	2.31	0.3152
	Homogeneity	9.54	0.0229
Kruskal-Wallis	Dose-Mortality Trend	3.95	0.0468
	Depart from Trend	1.66	0.4353
	Homogeneity	5.62	0.1318

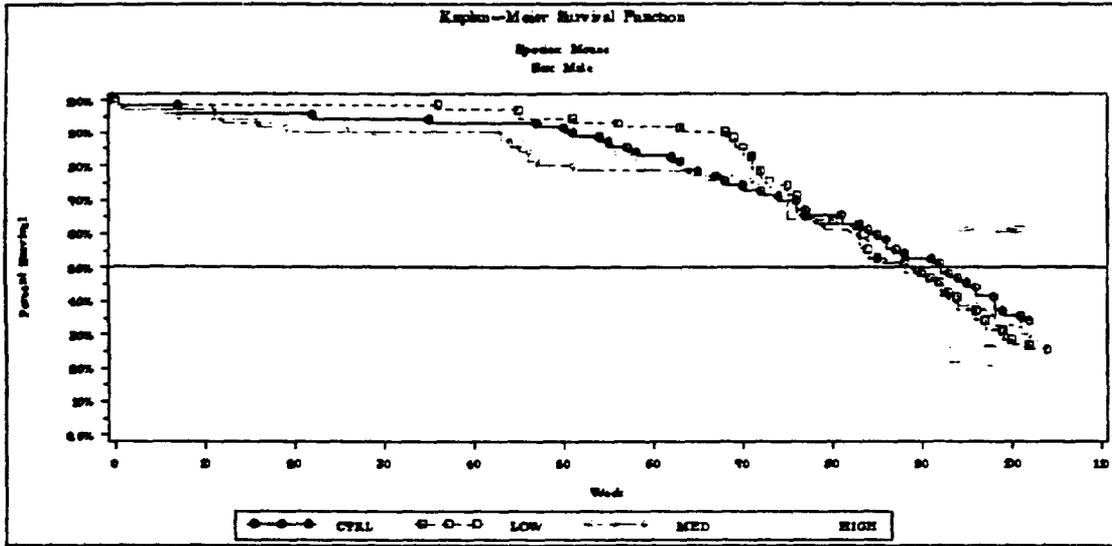
Source: _____

Figure 5. Cumulative Percentages of Death in Male Mice



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Figure 6. Kaplan-Meier Survival Functions for Male Mice



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Table 16. Trend Test for Male Mice

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.	
<ol style="list-style-type: none"> 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:	
<ol style="list-style-type: none"> 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	
<ol style="list-style-type: none"> 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 Male Mouse
 Test of Dose-Response (Tumor) Positive Linear Trend
 Study No. 951021

Run Date & Time: May 17, 2000 (14:35)

Source:

Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.1 0.3 1)
 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 TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLES-----	EXACT ASYMP ASYMP PROB PROB PROB /CONT CORR =P(STAT .GE. OBSERVED)
ADRENAL GLAND	(1) IN 104-105	1	1 1 0 1	0.691 0.630 0.842
PHEOCHROMOCYTOMA [B].	(32) IN 104-105	2	23 18 20 36	
Spontaneous tumor pct: 1%		in ctrl. - Total	-	1 1 0 1	
ADRENAL GLAND	(1) IN 104-105	1	0 0 0 1	0.370 0.102 0.453
SPINDLE CELL TUMOR [B].	(35) IN 104-105	2	24 19 20 36	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 0 1	

ADRENAL GLAND	(1)	IN 53-78	1	1	0	0	0	
CORTICAL ADENOMA [B].	(5)	IN 53-78	2	15	20	11	9	0.942 0.904 0.976
			IN 79-91	1	1	0	0	0	
			IN 79-91	2	9	13	12	7	
			IN 92-103	1	0	0	1	0	
			IN 92-103	2	13	14	12	7	
			IN 104-105	1	1	0	0	0	
			IN 104-105	2	23	19	20	37	
Spontaneous tumor pct: 4%		in ctrl.	- Total	-	3	0	1	0	
PREPUTIAL/CLITO	(14)	IN 104-105	1	1	0	0	0	
HEMANGIOSARCOMA [M].	(13)	IN 104-105	2	23	19	20	37	1.000 0.849 0.985
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	0	
SEMINAL VESICLE	(15)	IN 104-105	1	0	0	0	1	
ADENOCARCINOMA [M].	(1)	IN 104-105	2	24	19	20	36	0.370 0.102 0.453
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	0	1	
SYSTEMIC	(19)	FA 87	1	1	0	0	0	
GRANULOCYTIC LEUKEMIA [M]	(11)	FA 87	2	40	37	37	46	0.546 0.385 0.709
			FA 100	1	0	0	0	1	
			FA 100	2	26	22	25	41	
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	1	
SYSTEMIC	(19)	IN 104-105	1	1	0	0	0	
HISTIOCYTIC SARCOMA [M].	(16)	IN 104-105	2	23	19	20	37	1.000 0.849 0.985
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	0	
SYSTEMIC	(19)	IN 53-78	1	0	1	0	0	
LYMPHOMA, MALIGNANT [M].	(24)	IN 53-78	2	16	18	11	10	0.969 0.959 0.981
			IN 92-103	1	1	0	0	0	
			IN 92-103	2	11	12	12	6	
			FA 44	1	0	0	1	0	
			FA 44	2	66	69	62	63	
			FA 46	1	0	0	1	0	
			FA 46	2	66	68	59	62	
			FA 72	1	0	1	0	0	
			FA 72	2	52	57	53	54	
			FA 83	1	1	0	0	0	
			FA 83	2	45	45	43	51	
			FA 85	1	1	0	0	0	
			FA 85	2	42	39	41	49	
			FA 88	1	1	0	0	0	
			FA 88	2	38	37	37	44	
			FA 93	1	1	1	0	0	
			FA 93	2	35	31	32	44	
			FA 98	1	0	0	1	0	
			FA 98	2	31	24	25	44	
			FA 100	1	0	1	0	1	
			FA 100	2	26	21	25	41	
Spontaneous tumor pct: 7%		in ctrl.	- Total	-	5	4	3	1	
BONE	(2)	IN 104-105	1	0	1	0	0	
OSTEOMA [B].	(29)	IN 104-105	2	24	18	20	37	0.760 0.789 0.974
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	1	0	0	
TESTIS	(20)	IN 104-105	1	1	0	0	0	
INTERSTITIAL CELL TUMOR [(17)	IN 104-105	2	23	19	20	37	1.000 0.849 0.985
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	0	
TESTIS	(20)	IN 104-105	1	1	0	0	0	
LEIOMYOMA [B].	(18)	IN 104-105	2	23	19	20	37	1.000 0.849 0.985
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	0	
THYROID	(21)	IN 104-105	1	1	0	0	0	
FOLLICULAR ADENOMA [B].	(8)	IN 104-105	2	23	19	20	37	1.000 0.849 0.985
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	0	
BRAIN	(3)	FA 87	1	0	0	0	1	
ASTROCYTOMA [M].	(4)	FA 87	2	41	37	37	45	0.285 0.063 0.382
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	0	0	1	

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HARDERIAN GLAND	(5)	IN 104-105	1	0	0	0	1	0.370	0.102	0.453
ADENOCARCINOMA [M].	(1)	IN 104-105	2	24	19	20	36			
Spontaneous tumor pct: <= 1%			in ctrl.	-	0	0	0	1			
HARDERIAN GLAND	(5)	IN 53-78	1	0	3	0	1	0.085	0.077	0.126
ADENOMA [B].	(3)	IN 53-78	2	16	17	11	9			
			IN 79-91	1	0	2	1	1			
			IN 79-91	2	10	11	11	6			
			IN 92-103	1	1	2	2	2			
			IN 92-103	2	12	12	11	5			
			IN 104-105	1	2	2	1	5			
			IN 104-105	2	22	17	19	32			
Spontaneous tumor pct: 4%			in ctrl.	-	3	9	4	9			
KIDNEY	(6)	IN 92-103	1	1	2	0	0	0.915	0.853	0.974
ADENOMA [B].	(3)	IN 92-103	2	12	12	13	7			
Spontaneous tumor pct: 1%			in ctrl.	-	1	2	0	0			
LIVER	(8)	IN 92-103	1	0	0	0	1	0.552	0.543	0.769
HEMANGIOSARCOMA [M].	(13)	IN 92-103	2	13	14	12	6			
			IN 104-105	1	0	1	0	0			
			IN 104-105	2	24	18	20	37			
			FA 57	1	1	0	0	0			
			FA 57	2	60	65	56	59			
			FA 101	1	0	0	1	0			
			FA 101	2	26	20	24	38			
Spontaneous tumor pct: 1%			in ctrl.	-	1	1	1	1			
LIVER	(8)	IN 0-52	1	1	0	0	0	0.937	0.928	0.963
HEPATOCELLULAR ADENOMA [B]	(14)	IN 0-52	2	6	4	14	9			
			IN 53-78	1	1	0	0	1			
			IN 53-78	2	15	19	11	9			
			IN 79-91	1	1	2	1	0			
			IN 79-91	2	9	11	11	7			
			IN 92-103	1	1	0	0	0			
			IN 92-103	2	12	14	13	7			
			IN 104-105	1	0	4	2	1			
			IN 104-105	2	24	15	18	36			
			FA 72	1	0	1	0	0			
			FA 72	2	52	57	53	54			
Spontaneous tumor pct: 6%			in ctrl.	-	4	7	3	2			
LIVER	(8)	IN 53-78	1	1	0	0	1	0.911	0.902	0.947
HEPATOCELLULAR CARCINOMA	(15)	IN 53-78	2	15	20	11	9			
			IN 79-91	1	2	0	2	0			
			IN 79-91	2	8	12	9	7			
			IN 92-103	1	0	1	2	0			
			IN 92-103	2	13	12	11	7			
			IN 104-105	1	3	1	0	1			
			IN 104-105	2	21	18	20	36			
			FA 82	1	0	0	1	0			
			FA 82	2	46	45	43	51			
			FA 90	1	0	1	0	0			
			FA 90	2	38	35	35	44			
			FA 102	1	0	1	0	0			
			FA 102	2	25	19	23	38			
Spontaneous tumor pct: 9%			in ctrl.	-	6	4	5	2			
LUNG	(9)	IN 0-52	1	1	0	0	0	0.386	0.382	0.478
ADENOCARCINOMA [M].	(1)	IN 0-52	2	6	4	14	9			
			IN 53-78	1	0	1	0	0			
			IN 53-78	2	16	18	11	10			
			IN 79-91	1	1	0	0	0			
			IN 79-91	2	8	13	12	6			
			IN 92-103	1	1	1	1	1			
			IN 92-103	2	12	12	12	6			
			IN 104-105	1	2	5	2	8			
			IN 104-105	2	22	14	18	29			
			FA 56	1	0	1	0	0			
			FA 56	2	61	65	56	61			

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			FA 85	1	0	0	0	1	
			FA 85	2	43	39	41	48	
			FA 86	1	1	0	0	0	
			FA 86	2	41	37	38	47	
			FA 100	1	0	1	0	0	
			FA 100	2	26	21	25	42	
Spontaneous tumor pct: 9%				in ctrl. - Total	-	6	9	3	10
LUNG	(9)	IN 53-78	1	0	1	0	0	0.715 0.781 0.935
MESOTHELIOMA (M).	(26)	IN 53-78	2	16	18	11	10	
			FA 77	1	0	1	0	0	
			FA 77	2	49	49	49	52	
			FA 93	1	0	0	1	0	
			FA 93	2	36	32	31	44	
Spontaneous tumor pct: <= 1%				in ctrl. - Total	-	0	2	1	0
LUNG	(9)	IN 0-52	1	0	1	0	0	0.782 0.777 0.839
ADENOMA (B).	(3)	IN 0-52	2	7	3	14	9	
			IN 53-78	1	0	0	2	0	
			IN 53-78	2	16	20	9	10	
			IN 79-91	1	1	2	2	0	
			IN 79-91	2	9	11	10	7	
			IN 92-103	1	4	3	3	0	
			IN 92-103	2	9	11	10	7	
			IN 104-105	1	3	5	5	8	
			IN 104-105	2	21	14	15	29	
Spontaneous tumor pct: 11%				in ctrl. - Total	-	8	11	12	8

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Analysis of Female Mice

Table 17. Number of Female Mice Died by Treatment by Time

Number of Animals
Species: Mouse
Sex: Female

Week	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	
0-52	5	4	5	3	18
53-78	8	14	8	16	47
79-91	16	14	15	12	57
92-103	8	10	11	12	42
104-105	31	28	30	27	116
Total	70	70	70	70	280

Source: _____

Table 18. Analysis of Mortality for Female Mice by Treatment by Time

Analysis of Mortality
Species: Mouse
Sex: Female

Week	Dose											
	CTRL			LOW			MED			HIGH		
	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	5	70	7.1	4	70	5.7	6	70	8.6	3	70	4.3
53-78	8	65	20.0	14	66	25.7	8	64	20.0	16	67	27.1
79-91	16	56	42.9	14	52	45.7	15	56	41.4	12	51	44.3
92-103	8	40	55.7	10	38	60.0	11	41	57.1	12	39	61.4
104-105	31	70	44.3	28	70	40.0	30	70	42.9	27	70	38.6

Table 19. Analysis of Dose-Mortality Trend for Female Mice

Dose-Mortality Trend Tests

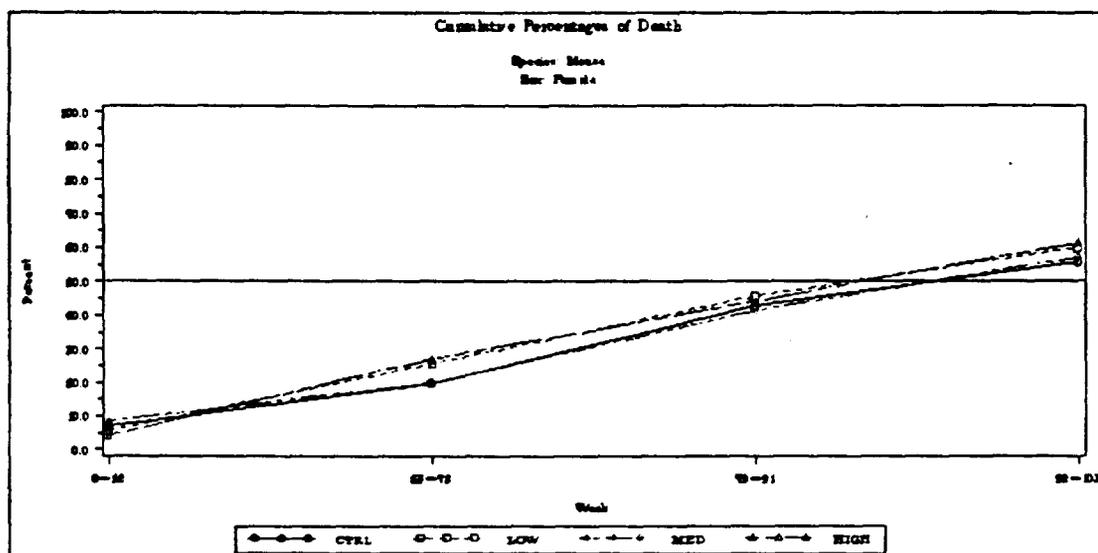
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1.

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.12	0.7343
	Depart from Trend	0.23	0.8914
	Homogeneity	0.35	0.9513
Kruskal-Wallis	Dose-Mortality Trend	0.03	0.8585
	Depart from Trend	0.17	0.9187
	Homogeneity	0.20	0.8774

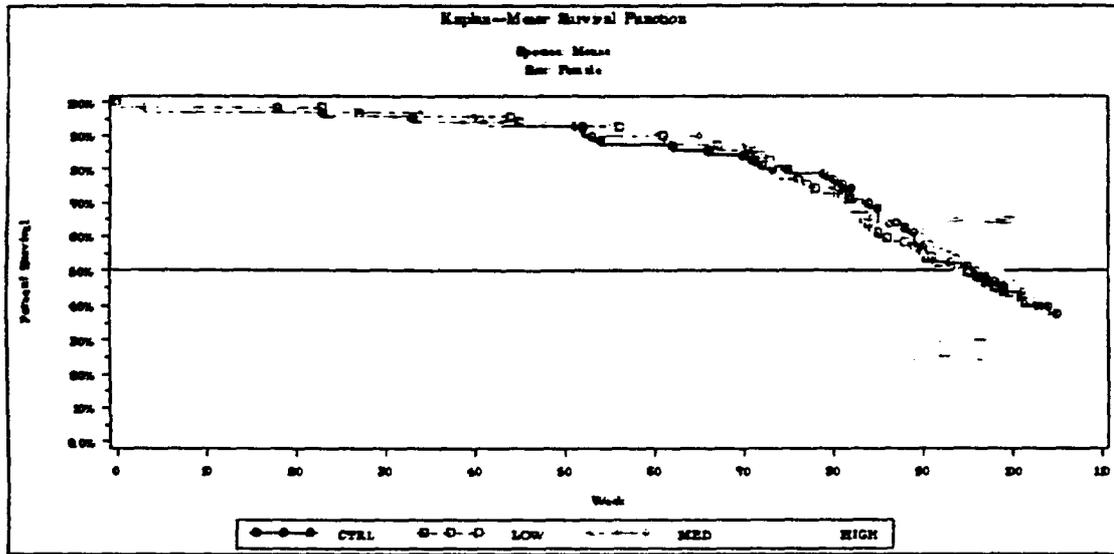
Source: _____

Figure 7. Cumulative Percentages of Death in Female Mice



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Figure 8. Kaplan-Meier Survival Functions for Female Mice



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Table 20. Trend Test for Female Mice

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 Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Study No. 951021

Run Date & Time: May 17, 2000 (14:42)

Source:

Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.1 0.3 1)
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 TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP /CONT	PROB CORR
ADRENAL GLAND	(1)) IN 92-103	1	0 0 1 0	0.897	0.870	0.969	
SPINDLE CELL TUMOR (B).	(35)) IN 92-103	2	9 10 10 12				
		IN 104-105	1	2 0 0 0				
		IN 104-105	2	29 28 30 27				
Spontaneous tumor pct: 3%		in ctrl. - Total	-	2 0 1 0				
ADRENAL GLAND	(1)) IN 92-103	1	0 1 0 0	0.644	0.719	0.931	
CORTICAL ADENOMA (B).	(5)) IN 92-103	2	9 9 11 12				
		IN 104-105	1	0 0 1 0				
		IN 104-105	2	31 28 29 27				

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Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	1	0	
MAMMARY GLAND	(10)	IN 79-91	1	0	1	0 0
ADENOCARCINOMA [M].	(1)	IN 79-91	2	14	11	15 11
		IN 92-103	1	0	0	1 0
		IN 92-103	2	7	10	9 12
		IN 104-105	1	1	0	0 2
		IN 104-105	2	29	27	28 24
		FA 74	1	0	0	0 1
		FA 74	2	55	56	54 55
		FA 90	1	1	1	0 0
		FA 90	2	41	38	42 39
		FA 93	1	1	0	0 0
		FA 93	2	38	37	38 38
		FA 95	1	1	0	1 0
		FA 95	2	35	35	35 35
Spontaneous tumor pct: 6% in ctrl. - Total	-	4	2	2	3	
MAMMARY GLAND	(10)	IN 104-105	1	1	0	0 0
ADENOMA [B].	(3)	IN 104-105	2	29	27	28 26
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0	
OVARY	(11)	IN 79-91	1	0	0	0 1
HEMANGIOSARCOMA [M].	(13)	IN 79-91	2	16	13	15 11
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1	
OVARY	(11)	IN 104-105	1	0	2	0 0
LUTEAL CELL TUMOR [B].	(21)	IN 104-105	2	31	26	30 27
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	2	0	0	
OVARY	(11)	FA 99	1	0	1	0 0
LUTEAL CELL TUMOR [M].	(22)	FA 99	2	33	31	34 36
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0	
OVARY	(11)	IN 104-105	1	0	1	0 2
CYSTADENOMA [B].	(6)	IN 104-105	2	31	27	30 25
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	2	
OVARY	(11)	IN 104-105	1	0	0	1 1
GONADAL STROMAL TUMOR [B]	(9)	IN 104-105	2	31	28	29 26
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	1	
PARATHYROID	(12)	IN 104-105	1	0	0	1 0
ADENOMA [B].	(3)	IN 104-105	2	29	24	29 24
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0	
PITUITARY	(13)	IN 92-103	1	1	0	0 0
ADENOMA [B], pars distali	(2)	IN 92-103	2	8	10	11 11
		IN 104-105	1	1	0	0 2
		IN 104-105	2	30	28	30 25
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	0	2	
SKELETAL MUSCLE	(16)	FA 97	1	1	0	0 0
RHABDOMYOSARCOMA [M].	(34)	FA 97	2	34	34	33 36
		FA 102	1	0	0	0 1
		FA 102	2	31	30	29 31
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	1	
SKIN	(17)	FA 88	1	0	0	0 1
HEMANGIOSARCOMA [M].	(13)	FA 88	2	45	42	45 44
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1	
SKIN	(17)	IN 104-105	1	1	0	0 0
LEIOMYOSARCOMA [M].	(19)	IN 104-105	2	30	28	30 27
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0	
SKIN	(17)	FA 100	1	0	0	1 0
NERVE SHEATH TUMOR, MALIG	(28)	FA 100	2	32	31	33 35
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0	
SKIN	(17)	IN 79-91	1	1	0	0 0

PAPILLOMA [B].	(31)	IN 79-91	2	15	14	15	12	
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	0	
SKIN	(17)	IN 79-91	1	1	0	0	0	1.000 0.801 0.985
SWEAT GLAND ADENOMA [B].	(36)	IN 79-91	2	15	14	15	12	
Spontaneous tumor pct: 1%		in ctrl.	- Total	-	1	0	0	0	
SPLEEN	(18)	IN 53-78	1	0	1	0	0	0.146 0.127 0.304
HEMANGIOSARCOMA [M].	(13)	IN 53-78	2	9	13	8	16	
			IN 92-103	1	0	0	0	1	
			IN 92-103	2	9	10	11	11	
			IN 104-105	1	0	0	1	0	
			IN 104-105	2	31	28	29	27	
			FA 89	1	0	0	0	1	
			FA 89	2	44	41	44	41	
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	1	1	2	
SYSTEMIC	(19)	IN 0-52	1	0	1	0	0	0.766 0.765 0.843
HISTIOCYTIC SARCOMA [M].	(16)	IN 0-52	2	5	3	6	3	
			IN 79-91	1	0	1	0	0	
			IN 79-91	2	13	12	14	11	
			IN 104-105	1	0	3	1	0	
			IN 104-105	2	31	25	29	26	
			FA 54	1	1	0	0	0	
			FA 54	2	62	66	64	67	
			FA 70	1	0	0	1	0	
			FA 70	2	60	61	62	62	
			FA 72	1	0	0	1	0	
			FA 72	2	58	60	59	61	
			FA 73	1	0	0	0	2	
			FA 73	2	57	59	58	58	
			FA 75	1	1	0	0	0	
			FA 75	2	56	56	56	56	
			FA 81	1	0	0	0	1	
			FA 81	2	54	52	52	50	
			FA 82	1	0	0	1	0	
			FA 82	2	53	51	51	50	
			FA 84	1	1	0	0	0	
			FA 84	2	51	49	50	49	
			FA 85	1	1	1	0	0	
			FA 85	2	48	44	47	46	
			FA 87	1	1	0	0	0	
			FA 87	2	47	42	45	46	
			FA 93	1	1	0	0	0	
			FA 93	2	39	38	40	39	
			FA 98	1	0	1	0	0	
			FA 98	2	34	32	34	36	
			FA 104	1	0	0	0	1	
			FA 104	2	31	28	30	26	
Spontaneous tumor pct: 9%		in ctrl.	- Total	-	6	7	4	4	
SYSTEMIC	(19)	IN 79-91	1	0	1	0	0	0.719 0.717 0.972
LEUKEMIA [M], eosinophili	(20)	IN 79-91	2	16	13	15	12	
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	1	0	0	
SYSTEMIC	(19)	IN 0-52	1	0	0	1	0	0.982 0.979 0.986
LYMPHOMA, MALIGNANT [M].	(24)	IN 0-52	2	5	4	3	3	
			IN 53-78	1	1	0	2	1	
			IN 53-78	2	6	11	6	15	
			IN 79-91	1	1	0	0	1	
			IN 79-91	2	10	11	14	10	
			IN 92-103	1	1	0	1	1	
			IN 92-103	2	7	8	10	11	
			IN 104-105	1	9	10	8	6	
			IN 104-105	2	22	18	22	21	
			FA 34	1	0	0	1	0	
			FA 34	2	67	68	68	68	
			FA 41	1	0	0	1	0	
			FA 41	2	67	68	66	67	
			FA 66	1	1	0	0	0	
			FA 66	2	60	63	63	62	

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FA 72	1	1	0	0	0						
FA 72	2	57	60	60	61						
FA 73	1	0	1	0	0						
FA 73	2	57	58	58	60						
FA 77	1	0	1	0	0						
FA 77	2	56	53	56	56						
FA 78	1	0	1	0	0						
FA 78	2	56	52	56	53						
FA 79	1	1	0	0	0						
FA 79	2	55	52	56	51						
FA 82	1	0	0	1	0						
FA 82	2	53	51	51	50						
FA 84	1	1	2	0	1						
FA 84	2	51	47	50	48						
FA 86	1	0	1	0	0						
FA 86	2	48	42	47	46						
FA 87	1	1	0	0	0						
FA 87	2	47	42	45	46						
FA 89	1	1	0	0	0						
FA 89	2	43	41	44	42						
FA 90	1	1	0	0	0						
FA 90	2	42	40	44	40						
FA 101	1	1	1	0	0						
FA 101	2	31	30	33	33						
FA 103	1	0	1	0	0						
FA 103	2	31	28	30	30						
Spontaneous tumor pct: 29%	in ctrl.	-	Total	-	20	18	15	10			
BONE	(2)	IN 79-91	1	0	0	1	0	0.936	0.914	0.975
OSTEOMA [B].	(29)	IN 79-91	2	16	14	14	12			
			IN 104-105	1	2	2	0	0			
			IN 104-105	2	29	26	30	27			
Spontaneous tumor pct: 3%	in ctrl.	-	Total	-	2	2	1	0			
BONE	(2)	FA 40	1	0	0	1	0	0.500	0.550	0.920
OSTEOSARCOMA [M].	(30)	FA 40	2	67	68	67	67			
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	0	1	0			
THYROID	(21)	IN 104-105	1	1	0	0	1	0.412	0.269	0.623
POLLICULAR ADENOMA [B].	(8)	IN 104-105	2	30	28	30	26			
Spontaneous tumor pct: 1%	in ctrl.	-	Total	-	1	0	0	1			
URETER	(22)	IN 104-105	1	1	0	0	0	1.000	0.808	0.985
HEMANGIOMA [B].	(12)	IN 104-105	2	30	28	30	27			
Spontaneous tumor pct: 1%	in ctrl.	-	Total	-	1	0	0	0			
URINARY BLADDER	(23)	IN 79-91	1	0	1	0	0	0.719	0.717	0.972
MESENCHYOMA [B].	(25)	IN 79-91	2	16	13	15	12			
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	1	0	0			
URINARY BLADDER	(23)	IN 104-105	1	0	0	0	1	0.232	0.041	0.332
PAPILLOMA [B].	(31)	IN 104-105	2	31	28	30	26			
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	0	0	1			
UTERUS	(24)	IN 104-105	1	3	1	1	0	0.764	0.748	0.886
ADENOCARCINOMA [M].	(1)	IN 104-105	2	28	27	29	27			
			FA 103	1	0	0	0	1			
			FA 103	2	31	29	30	29			
Spontaneous tumor pct: 4%	in ctrl.	-	Total	-	3	1	1	1			
UTERUS	(24)	IN 79-91	1	0	0	0	1	0.310	0.233	0.574
GRANULAR CELL TUMOR, BENI	(10)	IN 79-91	2	16	14	15	11			
			IN 92-103	1	0	1	0	0			
			IN 92-103	2	9	9	11	12			
Spontaneous tumor pct: <= 1%	in ctrl.	-	Total	-	0	1	0	1			
UTERUS	(24)	IN 53-78	1	0	0	1	0	0.408	0.380	0.663
HEMANGIOMA [B].	(12)	IN 53-78	2	9	14	7	16			
			IN 104-105	1	1	0	0	1			
			IN 104-105	2	30	28	30	26			
Spontaneous tumor pct: 1%	in ctrl.	-	Total	-	1	0	1	1			

UTERUS	(24)	IN 0-52	1	0	0	1	0	0.802	0.818	0.932
HEMANGIOSARCOMA [M].	(13)	IN 0-52	2	5	4	5	3			
			IN 104-105	1	0	0	1	0			
			IN 104-105	2	31	28	29	27			
			FA 53	1	1	0	0	0			
			FA 53	2	64	66	64	67			
			FA 82	1	1	0	0	0			
			FA 82	2	52	51	52	50			
			FA 86	1	0	0	1	0			
			FA 86	2	48	43	46	46			
Spontaneous tumor pct: 3%			in ctrl. - Total	-	2	0	3	0			
UTERUS	(24)	IN 53-78	1	0	2	0	0	0.698	0.708	0.855
LEIOMYOMA [B].	(18)	IN 53-78	2	9	12	8	16			
			IN 92-103	1	0	1	0	0			
			IN 92-103	2	9	9	11	12			
			IN 104-105	1	0	1	1	1			
			IN 104-105	2	31	27	29	26			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	4	1	1			
UTERUS	(24)	IN 92-103	1	0	0	0	1	0.300	0.304	0.592
LEIOMYOSARCOMA [M].	(19)	IN 92-103	2	9	10	11	11			
			IN 104-105	1	0	1	1	0			
			IN 104-105	2	31	27	29	27			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	1	1	1			
UTERUS	(24)	IN 92-103	1	0	0	0	1	0.285	0.063	0.390
LYMPHANGIOMA [B].	(23)	IN 92-103	2	9	10	11	11			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	0	0	1			
UTERUS	(24)	IN 0-52	1	0	1	0	0	0.722	0.710	0.978
MESENCHYMOMA [B].	(25)	IN 0-52	2	5	3	6	3			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	1	0	0			
UTERUS	(24)	IN 104-105	1	1	0	0	0	1.000	0.808	0.985
MYXOMA [B].	(27)	IN 104-105	2	30	28	30	27			
Spontaneous tumor pct: 1%			in ctrl. - Total	-	1	0	0	0			
UTERUS	(24)	IN 104-105	1	0	0	0	1	0.232	0.041	0.332
ADENOMA [B].	(3)	IN 104-105	2	31	28	30	26			
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	0	0	1			
UTERUS	(24)	IN 53-78	1	0	1	1	2	0.805	0.801	0.858
POLYP [B].	(33)	IN 53-78	2	9	12	7	13			
			IN 79-91	1	1	1	1	1			
			IN 79-91	2	15	11	14	11			
			IN 92-103	1	1	0	1	1			
			IN 92-103	2	8	10	10	11			
			IN 104-105	1	9	7	4	3			
			IN 104-105	2	22	21	26	24			
			FA 74	1	0	0	0	1			
			FA 74	2	57	58	56	57			
			FA 76	1	0	1	0	0			
			FA 76	2	56	55	56	56			
			FA 81	1	0	1	0	0			
			FA 81	2	54	51	52	51			
			FA 84	1	0	1	0	0			
			FA 84	2	52	48	50	49			
Spontaneous tumor pct: 16%			in ctrl. - Total	-	11	12	7	8			
UTERUS	(24)	IN 79-91	1	0	0	1	0	0.236	0.228	0.418
ENDOMETRIAL STROMAL SARCO	(7)	IN 79-91	2	15	14	14	12			
			IN 104-105	1	0	1	1	2			
			IN 104-105	2	31	27	29	25			
			FA 87	1	1	0	0	0			
			FA 87	2	47	42	45	46			
Spontaneous tumor pct: 1%			in ctrl. - Total	-	1	1	2	2			
VAGINA	(25)	FA 51	1	0	0	1	0	0.503	0.553	0.921
GRANULAR CELL TUMOR, BENI	(10)	FA 51	2	65	65	65	66			

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Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	1	0						
VAGINA	(25)	IN 79-91	1	1	0	0	0	0.727	0.717	0.876
POLYP [B].	(33)	IN 79-91	2	15	12	15	12			
			IN 104-105	1	0	1	0	1			
			IN 104-105	2	30	27	30	26			
			FA 62	1	1	0	0	0			
			FA 62	2	60	62	64	63			
			FA 81	1	0	1	0	0			
			FA 81	2	53	50	52	50			
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	2	0	1						
VAGINA	(25)	FA 93	1	1	0	0	0	1.000	0.814	0.985
ENDOMETRIAL STROMAL SARCO	(7)	FA 93	2	38	38	40	38			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0						
CERVIX	(4)	IN 79-91	1	0	1	0	0	0.632	0.613	0.829
LEIOMYOMA [B].	(18)	IN 79-91	2	16	13	15	12			
			IN 104-105	1	2	0	0	1			
			IN 104-105	2	29	28	30	26			
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	1	0	1						
CERVIX	(4)	FA 94	1	0	0	0	1	0.250	0.048	0.352
LEIOMYOSARCOMA [M].	(19)	FA 94	2	37	38	39	37			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1						
CERVIX	(4)	IN 53-78	1	0	1	0	0	0.781	0.777	0.894
POLYP [B].	(33)	IN 53-78	2	9	13	8	16			
			IN 92-103	1	0	0	0	1			
			IN 92-103	2	9	10	11	11			
			IN 104-105	1	1	3	1	0			
			IN 104-105	2	30	25	29	27			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	4	1	1						
HARDERIAN GLAND	(5)	IN 79-91	1	0	0	2	0	0.128	0.115	0.207
ADENOMA [B].	(3)	IN 79-91	2	16	14	13	12			
			IN 92-103	1	0	1	1	1			
			IN 92-103	2	9	9	10	11			
			IN 104-105	1	1	1	2	3			
			IN 104-105	2	30	27	28	24			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	2	5	4						
KIDNEY	(6)	IN 104-105	1	0	0	2	0	0.478	0.550	0.854
ADENOMA [B].	(3)	IN 104-105	2	31	28	28	27			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	2	0						
LARGE INTESTINE	(7)	IN 104-105	1	1	0	0	0	1.000	0.808	0.985
LEIOMYOSARCOMA [M].	(19)	IN 104-105	2	30	28	30	27			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	0	0	0						
LIVER	(8)	IN 92-103	1	0	0	0	1	0.238	0.186	0.401
HEMANGIOSARCOMA [M].	(13)	IN 92-103	2	9	10	11	11			
			IN 104-105	1	1	0	0	1			
			IN 104-105	2	30	28	30	26			
			FA 44	1	0	1	0	0			
			FA 44	2	67	67	66	67			
Spontaneous tumor pct: 1% in ctrl. - Total	-	1	1	0	2						
LIVER	(8)	IN 92-103	1	1	0	0	0	1.000	0.903	0.986
HEPATOCELLULAR ADENOMA [B]	(14)	IN 92-103	2	8	10	11	12			
			IN 104-105	1	1	0	0	0			
			IN 104-105	2	30	28	30	27			
Spontaneous tumor pct: 3% in ctrl. - Total	-	2	0	0	0						
LIVER	(8)	IN 92-103	1	0	0	0	1	0.285	0.063	0.390
HEPATOCELLULAR CARCINOMA	(15)	IN 92-103	2	9	10	11	11			
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1						
LUNG	(9)	IN 79-91	1	2	0	1	1	0.844	0.838	0.906
ADENOCARCINOMA [M].	(1)	IN 79-91	2	14	14	14	11			
			IN 92-103	1	0	0	2	1			

			IN 92-103	2	9	9	9	11	
			IN 104-105	1	4	0	3	0	
			IN 104-105	2	27	28	27	27	
			FA 74	1	0	1	0	0	
			FA 74	2	57	57	56	58	
			FA 94	1	0	1	0	0	
			FA 94	2	37	37	39	38	
Spontaneous tumor pct: 9%		in ctrl.	- Total	-	6	2	6	2	
LUNG	(9)	IN 53-78	1	0	1	0	0	0.284 0.279 0.377
ADENOMA [B].	(3)	IN 53-78	2	9	13	8	16	
			IN 79-91	1	0	1	1	1	
			IN 79-91	2	16	13	14	11	
			IN 92-103	1	1	1	0	0	
			IN 92-103	2	8	9	11	12	
			IN 104-105	1	3	5	6	6	
			IN 104-105	2	28	23	24	21	
Spontaneous tumor pct: 6%		in ctrl.	- Total	-	4	8	7	7	
LUNG	(9)	IN 104-105	1	0	1	0	0	0.732 0.729 0.972
RHABDOMYOSARCOMA [M].	(34)	IN 104-105	2	31	27	30	27	
Spontaneous tumor pct: <= 1%		in ctrl.	- Total	-	0	1	0	0	

END-OF-FILE

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Meeting Date: December 14, 2000 Time: 3:30 – 4:40 PM Location: Conf. Rm. K

NDA 21-223 Zometa (zoledronic acid for injection)

Type of Meeting: End of Review

External participant: Novartis Pharmaceuticals Corporation

Meeting Chair: Dr. David Orloff

External participant lead: Dr. Thomas Koestler, Vice President, Global DRA

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. John Jenkins, Director, ODEII
Dr. David Orloff, Director, DMEDP
Dr. Eric Colman, Clinical Team Leader, DMEDP
Dr. Douglas Throckmorton, Deputy Director, DCRDP
Dr. Bruce Stadel, Clinical Reviewer, DMEDP
Mr. Randy Hedin, Project Manager, DMEDP

External participant Attendees and titles:

Dr. Mathias Hukkelhoven, Vice President U.S. DRA
Dr. David Parkinson, Vice President, Oncology
Dr. Gregory Burke, Vice President, Oncology
Dr. Paul Gallo, Statistician, Oncology
Dr. Thomas Koestler, Vice President, Global DRA
Dr. John Seaman, Director, Oncology

Meeting Objectives:

Meeting requested by Novartis Pharmaceuticals Corporation to discuss the approvable letter, and what the Division would consider as a complete response.

Discussion Points and Decisions (agreements) reached:

- The firm presented background information on the adverse events reported in the ongoing bone metastases trials (Studies 010, 011, and 039). See attached slides. The Division agreed with the company that there was not a strong or consistent renal adverse event signal observed in the hypercalcemia of malignancy trials;

however, an obvious signal did emerge from the bone metastases trials. Preliminary data indicate that increasing the length of the infusion from 5 to 15 minutes decreases the risk for elevations in serum creatinine in patients treated with repeat doses of the 4-mg dose of zoledronate.

- The Division quoted the approvable letter issued September 21, 2000, that stated, "In order to address this outstanding safety concern, you must provide the complete study reports for clinical trial 010, 011, and 039." If the firm wishes to submit a response that falls short of this, the Division advised that the nature of such a response be proposed in correspondence in advance of such a submission for our review and concurrence. The Division stated that it is happy to work with the sponsor towards a submission including interim safety data from the ongoing bone metastases trials, along with certain other information requested in the letter, as a complete response to the approvable letter which would meet our needs for assessment of the renal and overall safety of Zometa.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Signature, minutes preparer: _____

Concurrence Chair: _____

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/s/

David Orloff
1/12/01 12:51:26 PM

Randy Hedin
1/12/01 12:49:06 PM

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Meeting Date: June 8, 2000 Time: 10:00 – 10:20 PM Location: 14B-45

NDA 21-223 Zometa (zoledronic acid for injection)

Type of Meeting: Teleconference

External participant: Novartis Pharmaceuticals Corporation

Meeting Chair: Dr. Eric Colman

External participant lead: Ms. Ellen Cutler

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Eric Colman, Medical Team Leader, DMEDP
Dr. Bruce Stadel, Medical Reviewer, DMEDP
Mr. Randy Hedin, Project Manager, DMEDP

External participant Attendees and titles:

Dr. Gregory Burke, Clinical Research, Oncology
Ms. Ellen Cutler, Drug Regulatory Affairs
Dr. Deborah Dunsire, Oncology Business Unit
Dr. Mathias Hukkelhoven, Drug Regulatory Affairs
Dr. Thomas Koestler, Drug Regulatory Affairs
Dr. Deborah Matos, Biostatistics
Dr. John Seaman, Clinical Research, Oncology
Dr. Mark Amman, Drug Regulatory Affairs
Mr. Russ Hume, Liason Officer

Meeting Objectives:

Teleconference to discuss the unblinded data package on renal safety that is to be submitted on June 9, 2000, and its' effect on the review of the NDA.

Discussion Points and Decisions (agreements) reached:

- The firm stated that it is concerned that the unblinded data package on renal safety will be releasable to the public if the NDA is approved. This issue was discussed with no decision made on the procedure to follow.

Post meeting note: The firm stated in a telephone call to the Project Manager after the meeting that they will submit the unblinded data package on renal safety to the IND with a cover letter to the NDA referring to it. The Project Manager stated that he would check with other team members, and inform them if this is not acceptable.

- The firm asked if the Division agreed that the proposed June 9, 2000 submission would be a major amendment and extend the user-fee clock three months, and the Division stated that it would.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Signature, minutes preparer: _____

[Handwritten signature]

Concurrence Chair: _____

[Handwritten initials]

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Screening of New NDA
(Japobrata Choudhury)

NDA #: 21-223

Priority Classification:

Trade Name: Zometa

Sponsor: NOVARTIS

Generic Name: zoledronic acid

Indication: Treatment of
tumor-induced hypercalcemia

No. of Controlled Studies: 2

Date of Submission: 12-21-99

User Fee Goal Date:

Volume numbers in statistical section: Volumes 1.1, 1.61, 1.64 to 1.74, 1.140
to 1.158, amendment dated 01-07-00

Date of 45 Day Meeting: 1-2⁷~~0~~-00

Anticipated Review Completion Date:

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CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	yes
Original protocols & subsequent amendments available in the NDA	yes
Designs utilized appropriate for the indications requested	Some subjectivity was involved
Endpoints and methods of analysis spelled out in the protocols	Yes
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	None in what is available to us
Appropriate references included for novel statistical-methodology (if present)	Yes
Sufficient data listings and intermediate analysis tables to permit a statistical review	
Data from primary studies on diskettes and/or CANDAs submitted	See a CD-ROM
Intent-to-treat analyses	Mentioned in report
Effects of dropouts on primary analyses investigated	No
Gender, racial, and geriatric subgroups investigated	yes

Company Finished Product Active Substance		NOVARTIS zoledronic acid 42446	Reference therapy controlled studies in patients		Page 4	
Ref. (Vol. & Page)	Protocol. No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No. & Race (w,b,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen Duration of Therapy Dosage	General Results & Adverse Events % AEs % SAEs	
1.6. Reference therapy controlled studies in patients						
report: Vol: 64 p. 8-2 listings: Vol: 159 p. CD-Rom Crf: Vol: 159 p. CD-rom	protocol: 036 Invest.: Dr A. Lortholary, France start: 23-Dec-97 end: 13-Oct-99	design, goal & population: randomized, double-blind study of 2 doses of zoledronate and Aredia in treatment of tumor-induced hypercalcemia evaluations: corrected serum calcium concentration, safety and tolerability	total: 149 (143w, 2b, 4o) age: 28-84 (59.7) yr groups: 46 (20m,26f) 51 (28m,23f) 52 (27m,25f)	form: intravenous duration: once in Stage 1; once 56 days later for Stage 2 (retreatment) for relapse or refractory TIH doses: zol. 4 mg Aredia 90 mg	Both zoledronate doses are highly efficacious. Zoledronate 4 mg is the recommended dose for the initial treatment of TIH 94 54 96 63 90 46	
report: Vol: 70 p. 8-1 listings: Vol: 159 p. CD-rom Crf: Vol: 159 p. CD-rom	protocol: 037 Invest.: Dr. P Major, Canada start: 07-Jan-98 end: 19-Sep-99	design, goal & population: randomized, double-blind study of 2 doses of zoledronate and Aredia in treatment of tumor-induced hypercalcemia evaluations: corrected serum calcium concentration, safety and tolerability	total: 138 (85w, 43b, 10o) age: 21-94 (59.1) yr groups: 40 (26m,14f) 47 (37m,10f) 51 (31m,20f)	form: intravenous duration: once in Stage 1; once 56 days later for Stage 2 (retreatment) for relapse or refractory TIH doses: zol. 4 mg Aredia 90 mg	Both zoledronate doses are highly efficacious. Zoledronate 4 mg is the recommended dose for the initial treatment of TIH. 95 50 96 49 94 37	

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Figure 2-1. 95% confidence interval for complete response rates by Day 10 in Study 036

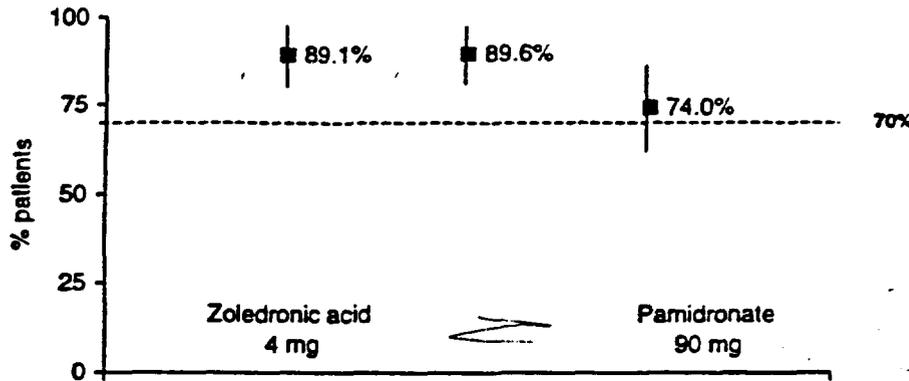
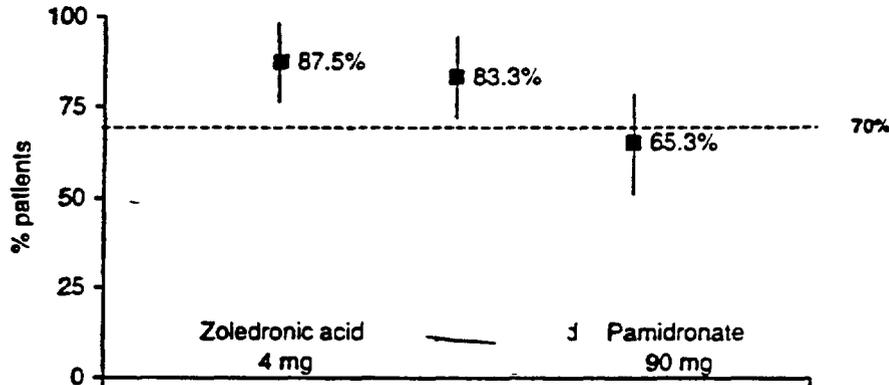


Figure 2-2. 95% confidence interval for complete response rates by Day 10 in Study 037



In both studies, the percentage of patients with complete responses by Day 10 was similar for both zoledronic acid groups and lower for the pamidronate 90 mg group. In Study 036, the complete response rates by Day 10 were higher for the two zoledronic acid groups than for pamidronate 90 mg ($p < 0.15$) (see Figure 2-3).

In Study 037, the complete response rate by Day 10 was statistically significantly higher in the zoledronic acid 4 mg group compared with the pamidronate 90 mg group ($p = 0.018$) (see Figure 2-4), compared with pamidronate 90 mg ($p < 0.07$). No significant differences in complete response rates by Day 10 were observed for other between-treatment comparisons.

study day for patients in Studies 036 and 037 are presented graphically in Figures 2-5 and 2-6, respectively.

Table 2-7. Number of patients with complete response by study day and treatment group in Studies 036 and 037

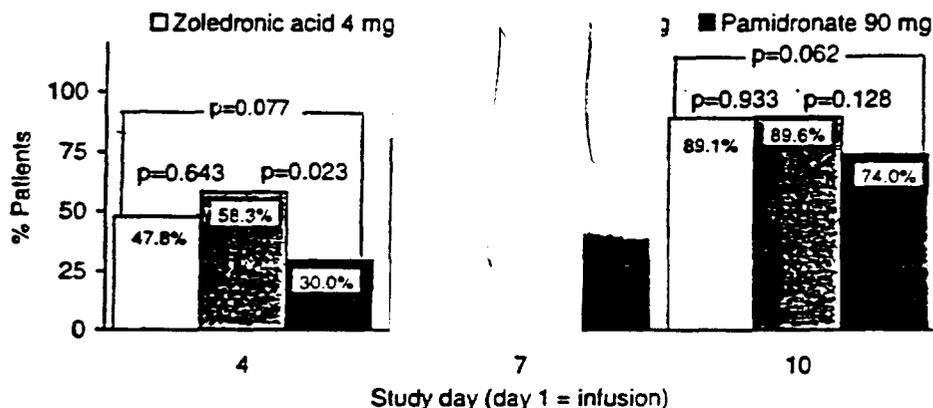
Day	Study 036		Study 037	
	Zoledronic acid 4 mg N=46 n (%)	Pamidronate 90 mg N=50 n (%)	Zoledronic acid 4 mg N=40 n (%)	Pamidronate 90 mg N=49 n (%)
4	22 (47.8) ¹	15 (30.0)	17 (42.5)	18 (36.7)
7	37 (80.4)	36 (72.0)	34 (85.0) ²	27 (55.1)
10	41 (89.1) ¹	37 (74.0)	35 (87.5) ²	32 (65.3)

¹ Denotes 0.05 < p < 0.10.

² Denotes statistical significance at 0.05 level, two-sided vs. pamidronate 90 mg.

Source: Clinical Study reports for Studies 036 and 037; Post-text Table 9.1-1.

Figure 2-5. Complete response rates by study day and treatment group in Study 036



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in the percentage of complete response were not only above the -10% preset non-inferiority limit but also above 0%. This indicates that both zoledronic acid doses are superior to pamidronate 90 mg.

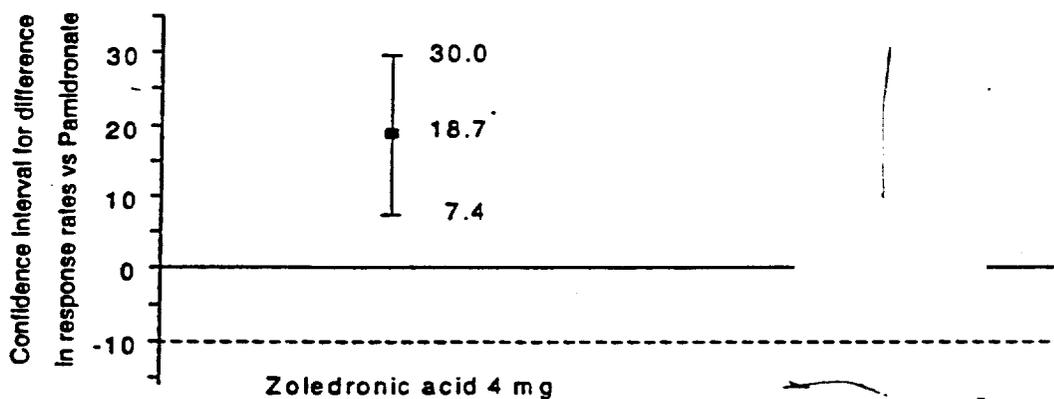
The between-treatment analysis of complete responders at Day 10 is summarized in Table 2-16. The 95% confidence intervals for complete response rates of both zoledronic acid groups compared with pamidronate 90 mg are presented graphically in Figure 2-7.

Table 2-16. Summary of between-treatment analysis of complete responders in the pooled analysis

	Difference Zoledronic acid 4 mg - pamidronate 90 mg	Difference pamidronate 90 mg	Difference zoledronic acid 4 mg
Estimate (%)	18.7	17.0	-1.7
95% confidence interval	7.4-30.0	5.5-28.4	-11.5-8.1
p-value	0.002	0.015	0.674

Source: Appendix 3.2

Figure 2-7. 95% confidence intervals for complete response rates vs. pamidronate 90 mg



The frequency of patients with complete responses by Day 10 was comparable for both zoledronic acid groups and lower for the pamidronate 90 mg group (see Figure 2-8). The complete response rate by Day 10 was significantly higher in the zoledronic acid 4 groups compared with the pamidronate 90 mg group ($p = 0.002$ and $p = 0.015$, respectively). No significant differences in complete response rates by Day 10 were observed between the zoledronic acid groups.

Electronic Mail Message

Date: 1/27/00 9:43:43 AM
From: Gemma Kuijpers
To: Randy Hedin
Subject: 11 am filing meeting

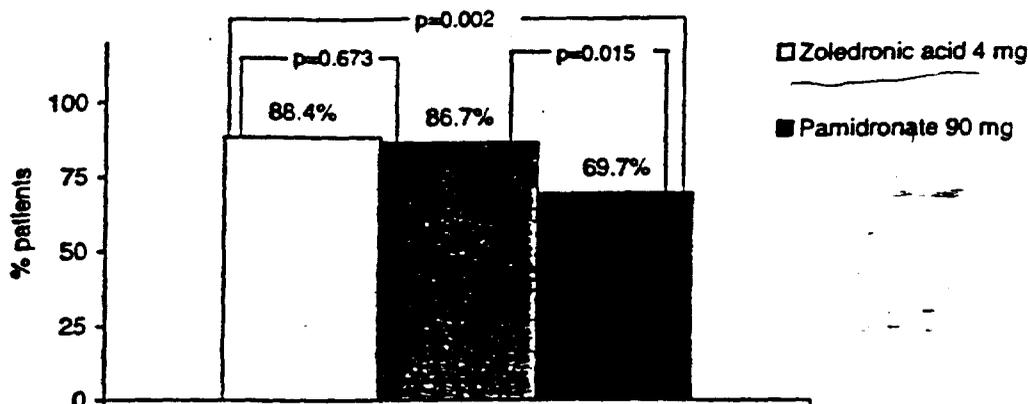
(KUIJPERSG)
(HEDINR)

Hi Randy

I will be late for the meeting (appr. 20 minutes).
(The NDA is fileable for Pharm/Tox)
I will be there at about 11.20am.
Gemma

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Figure 2-8. Complete response rates by treatment group in the pooled analysis



2.5.6. Secondary efficacy results

Complete response by study day

The frequency of patients with complete responses increased over time from Day 4 to Day 10 in all treatment groups. Onset of normalization of CSC occurred by Day 4 in about half of the patients treated with zoledronic acid (45.3% for 4 mg), while only 33% of the pamidronate 90 mg patients had such a normalization by Day 4. The frequency of patients with complete responses was higher in the zoledronic acid 4 mg group compared with pamidronate 90 mg by Days 7 and 10 ($p \leq 0.005$), and the frequency of patients with complete responses was significantly higher in the zoledronic acid 4 mg group compared with the pamidronate 90 mg group by Days 4, 7, and 10 ($p < 0.05$). The numbers of patients with complete responses by Days 4, 7, and 10 are summarized by treatment group in Table 2-17.

Table 2-17. Number of patients with complete response by study day and treatment group in the pooled analysis

Day	Zol 4 mg	Pam 90 mg	p-value vs. Pam 90 mg
	N=86 n (%)	N=99 n (%)	
4	39 (45.3)	33 (33.3)	0.104
7	71 (82.6)	63 (63.6)	0.005
10	76 (88.4)	69 (69.7)	0.002

Source: Appendix 3.2.

Corrected serum calcium values

CSC values decreased from baseline through Day 10 in all treatment groups. The decrease from baseline in CSC values was statistically significantly lower in the zoledronic acid 4 and 8 mg groups, compared with the pamidronate 90 mg group at Days 7 and 10. No significant

Electronic Mail Message

Date: 1/27/00 8:36:05 AM
From: Paul Stinavage (STINAVAGEP)
To: Randy Hedin (HEDINR)
Cc: Sheldon Markofsky (MARKOFSKYS)
Subject: NDA 21-223, Zometa

I looked at the jackets for this application that you sent up. The application is FILEABLE from a product quality microbiology perspective.

I will not be able to attend the filing meeting scheduled for 11:00 this morning.

Paul

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