CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
CARCINOGENICITY STUDIES

NDA/BLA #:	NDA209176
Drug Name:	Radicava® (edaravone) Injection, 30 mg/100 mL, 60 mg/100 mL
Indication(s):	The treatment for Amyotrophic Lateral Sclerosis (ALS)
Applicant:	Mitsubishi Tanabe Pharma Corporation (MTPC).
	525 Washington Blvd., Suite 400, Jersey City, NJ 07310, USA
Laboratory:	(b) (4)
Date(s):	Consultation Received on 1/11/2022
Documents Reviewed:	Rat study B180275 and the electronic tumor.xpt file and SEND datasets were submitted on 1/11/2022 (via NDA209176/S-0173)
Review Priority:	Regular Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Feng Zhou, MS
Concurring Reviewers:	Karl Lin, Ph. D., Team Leader
Medical Division:	CDER/ON/DN1
Nonclinical Team:	David Carbone, Ph.D; Sally Yasuda, Ph.D
Project Manager:	Michelle Mathers, RPM
Keywords:	Carcinogenicity, Dose response

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1   Summary

This review evaluates statistically the data of the 104-weeks oral gavage carcinogenicity study of edaravone in rats. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality). From the statistical point of view, the review concludes that edaravone had no carcinogenic effect.

Rat Study: Rats (60/sex/group) were dosed by oral gavage with edaravone daily for up to 104 weeks. The respective edaravone doses in the water control (WC, received water for injection), vehicle control (VC, received 1% w/v tragacanth gum aqueous solution), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 50, 100, and 200 mg/kg/day in males and 0, 0, 50, 100, and 250 mg/kg/day in females. The treatments were terminated at Weeks 104 for all male rats and at Week 93 for all female rats.

The survival analyses didn't show any statistically significant positive dose response relationship in mortality in males and females when compared with vehicle control group or water control group. The mortality rates for the water control group were statistically significantly higher than that for the mid and high dosed groups in males and the high dosed group in females. The respective survival rates in the WC, VC, LD, MD, and HD of edaravone at the time they were terminated were 32%, 48%, 42%, 55%, and 60% in males and 30%, 37%, 37%, 40%, and 52% in females.

The tumor analysis results showed that there were no statistically significant positive dose response relationships between the treated groups and vehicle control group or water control group for male and female rats.

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2   Background

Based on the interactions with Agency, the sponsor, Mitsubishi Tanabe Pharma Corporation (MTPC), agreed to conduct a two-year carcinogenicity study of edaravone in rat as post-marketing requirement PMR 3208-2 after approval of Radicava® (edaravone) Injection 30 mg/100 mL dated May 5, 2017. The sponsor hereby submitted the final nonclinical reports: Study B180275: "A 104-week oral repeated dose carcinogenicity study of edaravone in rats" on 1/11/2022 (via NDA209176/S-0173) to fulfils the aforementioned the post-marketing requirement PMR 3208-2.

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases. Results of this review have been discussed with the nonclinical team.

3   Rat Study- B180275

Study Report: **b180275-pre-clinical-study-report.pdf (statistical report on page 838)**
SAS data: **tumor.xpt and SEND dataset**

The objective of this study was to evaluate the carcinogenic potential of the test item, edaravone, following daily oral administration (gavage) to rats for 104 weeks. The respective edaravone doses in the water control (WC), vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were displayed in following table:

Group Number[a]	Test Article	Dose Level mg/kg/day	Concentration (mg/mL)	Number of Animals Male	Number of Animals Female
0	Water Control[b]	0	0	60	60
1	Vehicle Control[c]	0	0	60	60
2	Edaravone	50	5	60	60
3	Edaravone	100	10	60	60
4	Edaravone	200	20	60	-
4	Edaravone	250	25	-	60

a : Group number assigned in tumor submission data files (see Section 3 Data Files and Analysis Dataset)
b : Administered with the water control (water for injection)
c : Administered with the vehicle ⬛⬛⬛ (b) (4) gum aqueous solution)
- : Not applicable

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

3.1   Sponsor's Analyses

3.1.1   Survival Analysis

The survival rate was presumed by Kaplan-Meier's method. The statistical analyses were performed between the water control group and each test article-treated group and between the vehicle control group and each test article-treated group, respectively. A dose-related trend of

the survival rate was examined by Tarone method. The comparison of survival rate was performed by the log-rank test. These tests were conducted at the two-tailed significance level of 5%.

Sponsor's concluded results: There was no treatment-related change in survival rate. No treatment-related increase in the cause of death and premature sacrifice was observed.

3.1.2   Tumor Data Analysis

The statistical analyses of tumor data were performed between the water control group and each test article-treated group and between the vehicle control group and each test article treated group, respectively. As for the prevalence of the tumor, statistical analysis was performed as follows; high incidence tumors (10 or more animals per sex) were assessed by Peto's method1 for trend and to separately compare the incidence between the statistical control group and each test article-treated group. However, low incidence tumors (not more than 10 animals per sex) were assessed by Peto's exact test1 for trend and pairwise comparison. For the incidence of tumors, the following partitions (in weeks) were used: Week 1 to 52, Week 53 to 78, Week 79 to 92, Week 93 to 104 (males only), and the scheduled terminal necropsy.

The analysis of positive trends in the incidence was conducted at the significance level of 0.5% (one tailed-level) for common tumors (background rate: more than 1%) and 2.5% (one tailed-level) for rare tumors (background rate: 1% or less). Pairwise comparisons were conducted at the significance level of 1% (one tailed-level) for common tumors and 5% (one tailed-level) for rare tumors.

Sponsor's findings: No test article-related neoplasms proliferative changes were observed for both males and females, there were no statistically significant differences in tumor incidence amongst the groups.

3.2   Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 1/11/2022 via NDA209176/S-0173. The vehicle control group was compared to each of treated group and water control group for the survival analyses and the tumor analyses

3.2.1   Data Quality

The sponsor submitted both tumor.xpt file and SEND database on 1/11/2022 (via NDA209176/S-0173). The were some discrepancies between the analyses results based on the tumor.xpt and that based on the SEND database. The discrepancy didn't change the results of all analyses and effect on the statistical conclusion. The analyses results in this report were based on the SEND database.

3.2.2   Survival Analysis

The survival distributions of rates in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions were tested using the log-rank test. The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data of all treatment groups are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings: The treatments were terminated at Weeks 104 for all male rats and at Week 93 for all female rats. This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the groups were 41 (68%), 31 (52%), 35 (58%), 27 (45%), and 24 (40%) in male rats and 42 (70%), 38 (63%), 38 (63%), 36 (60%) and 29 (48%) in female rats in the WC, VC, LD, MD, and HD groups, respectively. The survival analyses didn't show any statistically significant positive dose response relationship in mortality in males and females when compared with vehicle control group or water control group. The mortality rates for the water control group were statistically significantly higher than that for the mid and high dosed groups in males and the high dosed group in females.

3.2.3   Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the papers of Bailer and Portier [2] and Bieler and Williams [3]. In this method an animal that lives the full study period (w_{max}) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of $s_h = 1$. An animal that dies at week w_h without developing the tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{max}}\right)^k < 1$. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor of the tumor type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

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The adjusted levels of significance for testing a positive dose response in the 2-year rats study are 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparison in the 2-year rat study are 0.01 and 0.05 for a common tumor and a rare tumor, respectively. A rare tumor is defined as one in which the tumor rate is less than 1% in the vehicle control group.

This reviewer performed separate sets of tumor data analyses to test the positive dose responses in tumor incidence rates using the vehicle control and the water control, respectively and to test the pairwise comparisons between the vehicle control or the water control group and each of the low, medium, high groups. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A, 3B, 4A, and 4B in the appendix for the comparison with vehicle control group and water control group for male rats and female rats, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of treated groups and control.

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Male Rats

Organ name	Tumor name	0 mg/kg/day Vehicle (VC) P - Trend	50 mg/kg/day Low (L) P – L vs. VC	100 mg/kg/day Mid (M) P – M vs. VC	200 mg/kg/day High (H) P – H vs VC
Gland, Adrenal	Pheochromocytoma, Malignant	0/60 (48) 0.0393	2/60 (46) 0.2368	0/60 (49) NC	4/60 (53) 0.0717
Organ name	**Tumor name**	**0 mg/kg/day Water C (WC) P - Trend**	**50 mg/kg/day Low (L) P – L vs. WC**	**100 mg/kg/day Mid (M) P – M vs. WC**	**200 mg/kg/day High (H) P – H vs. WC**
Gland, Adrenal	Pheochromocytoma, Malignant	0/60 (44) 0.0434	2/60 (46) 0.2584	0/60 (49) NC	4/60 (53) 0.0845

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.   The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, there were no statistically significant positive dose response relationships between the treated groups and vehicle control group or water control group for male and female rats.

Feng Zhou
Mathematical Statistician

Concurring Reviewer: Karl Lin, Ph.D., Team Leader, Biometrics-6
Dr. David Carbone
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Dr. Karl Lin

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4   Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

Week / Type of Death	Water Control No. of Death	Water Control Cum %	Vehicle Control No. of Death	Vehicle Control Cum %	Low Dose No. of Death	Low Dose Cum %	Mid Dose No. of Death	Mid Dose Cum %	High Dose No. of Death	High Dose Cum %
0 - 52	1	1.67	2	3.33	2	3.33	1	1.67	.	.
53 - 78	9	16.67	7	15.00	8	16.67	9	16.67	3	5.00
79 - 92	15	41.67	9	30.00	7	28.33	8	30.00	7	16.67
93 - 104	16	68.33	13	51.67	18	58.33	9	45.00	14	40.00
Terminal sacrifice	19	31.67	29	48.33	25	41.67	33	55.00	36	60.00
Total	60	.	60	.	60	.	60	.	60	.

Table 1B: Intercurrent Mortality Rate in Female Rats

Week / Type of Death	Water Control No. of Death	Water Control Cum %	Vehicle Control No. of Death	Vehicle Control Cum %	Low Dose No. of Death	Low Dose Cum %	Mid Dose No. of Death	Mid Dose Cum %	High Dose No. of Death	High Dose Cum %
0 - 52	5	8.33	2	3.33	2	3.33	1	1.67	5	8.33
53 - 78	18	38.33	14	26.67	21	38.33	26	45.00	9	23.33
79 - 92	19	70.00	21	61.67	15	63.33	9	60.00	15	48.33
93 - 104	.	.	1	63.33	.	.	.	.	.	.
Terminal sacrifice	18	30.00	22	36.67	22	36.67	24	40.00	31	51.67
Total	60	.	60	.	60	.	60	.	60	.

Table 2A: Intercurrent Mortality Comparison in Male Rats

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High
Dose-Response (Likelihood Ratio)	0.0528	0.5185	0.5040	0.1300
Homogeneity (Log-Rank)	0.1488	0.5141	0.5006	0.1254
Test	**All Dose Groups**	**WC vs. Low**	**WC vs. Mid**	**WC vs. High**
Dose-Response (Likelihood Ratio)	0.0006	0.2913	0.0187	0.0009
Homogeneity (Log-Rank)	0.0047	0.2835	0.0171	0.0007

Table 2B: Intercurrent Mortality Comparison in Female Rats

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High
Dose-Response (Likelihood Ratio)	0.1014	0.6990	0.7478	0.1595
Homogeneity (Log-Rank)	0.3028	0.6952	0.7444	0.1546
Test	**All Dose Groups**	**WC vs. Low**	**WC vs. Mid**	**WC vs. High**
Dose-Response (Likelihood Ratio)	0.0201	0.6140	0.5800	0.0199
Homogeneity (Log-Rank)	0.1463	0.6083	0.5748	0.0180

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Table 3A: Tumor Rates and P-Values for Trend and Pairwise Comparisons with Vehicle Control in Male Rats

Organ name	Tumor name	0 mg/kg/day Vehicle (VC) P - Trend	50 mg/kg/day Low (L) P – L vs. VC	100 mg/kg/day Mid (M) P – M vs. VC	200 mg/kg/day High (H) P – H vs VC
Body Cavity, Cranial	Schwannoma, Malignant	0/60 (48) 0.7563	1/60 (47) 0.4947	0/60 (49) NC	0/60 (53) NC
Bone	Osteosarcoma, Malignant	0/60 (48) 0.2704	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5248
Bone, Mandible	Carcinoma, Squamous Cell, Malignant	0/60 (48) 0.0721	0/60 (46) NC	0/60 (49) NC	2/60 (53) 0.2729
Brain	Astrocytoma, Malignant	1/60 (48) 0.6097	2/60 (47) 0.4920	3/60 (50) 0.3242	1/60 (53) 0.7766
Eye	Melanoma, Malignant	0/60 (48) 0.5204	0/60 (46) NC	1/60 (49) 0.5052	0/60 (53) NC
Gland, Adrenal	Carcinoma, Adrenocortical, Malignant	1/60 (48) 0.8586	1/60 (47) 0.7474	1/60 (49) 0.7577	0/60 (53) 1.0000
	Pheochromocytoma, Benign	5/60 (48) 0.8767	7/60 (47) 0 3644	6/60 (49) 0.5147	3/60 (53) 0.8951
	Pheochromocytoma, Malignant	0/60 (48) 0.0393	2/60 (46) 0 2368	0/60 (49) NC	4/60 (53) 0.0717
Gland, Mammary	Adenocarcinoma, Malignant	0/60 (48) 0.2741	0/60 (46) NC	0/60 (49) NC	1/60 (54) 0.5294
	Fibroadenoma, Benign	0/60 (48) 0.8247	2/60 (47) 0 2421	0/60 (49) NC	0/60 (53) NC
Gland, Pituitary	Adenoma, Anterior Lobe Pituitary Gland, Benign	21/60 (51) 0.7486	25/60 (52) 0 3065	26/60 (55) 0.3318	21/60 (56) 0.7215
	Adenoma, Pars Intermedia, Benign	0/60 (48) 0.8254	2/60 (46) 0 2368	0/60 (49) NC	0/60 (53) NC
	Carcinoma, Pars Distalis, Malignant	3/60 (48) 0.9589	0/60 (46) 1.0000	2/60 (49) 0.8255	0/60 (53) 1.0000
Gland, Preputial	Adenoma, Benign	0/60 (48) 0.2704	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5248
Gland, Thyroid	Adenoma, C-Cell, Benign	6/60 (48) 0.5337	3/60 (46) 0 9105	2/60 (50) 0.9742	6/60 (54) 0.7006
	Adenoma, Follicular Cell, Benign	2/60 (48) 0.1315	4/60 (47) 0 3286	2/60 (49) 0.6992	6/60 (53) 0.1691
	Carcinoma, C-Cell, Malignant	0/60 (48) 0.3400	1/60 (46) 0.4894	2/60 (49) 0.2526	1/60 (54) 0.5294
	Carcinoma, Follicular Cell, Malignant	0/60 (48) 0.7563	1/60 (47) 0.4947	0/60 (49) NC	0/60 (53) NC
Gland, Zymbal	Adenoma, Benign	1/60 (48) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
	Carcinoma, Malignant	0/60 (48) 0.7551	1/60 (46) 0.4894	0/60 (49) NC	0/60 (53) NC
Heart	Schwannoma, Malignant	1/60 (48) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000

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Organ name	Tumor name	0 mg/kg/day Vehicle (VC) P - Trend	50 mg/kg/day Low (L) P – L vs. VC	100 mg/kg/day Mid (M) P – M vs. VC	200 mg/kg/day High (H) P – H vs VC
Kidney	Carcinoma, Urothelial, Malignant	0/60 (48) 0.2704	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5248
	Liposarcoma, Malignant	0/60 (48) 0.7551	1/60 (46) 0.4894	0/60 (49) NC	0/60 (53) NC
Liver	Adenoma, Hepatocellular, Benign	1/60 (48) 0.8254	0/60 (46) 1.0000	1/60 (49) 0.7577	0/60 (53) 1.0000
	Cholangiocarcinoma, Malignant	0/60 (48) 0.5204	0/60 (46) NC	1/60 (49) 0.5052	0/60 (53) NC
	Sarcoma, Histiocytic, Malignant	0/60 (48) 0.2741	0/60 (46) NC	0/60 (49) NC	1/60 (54) 0.5294
Lung/Bronchus	Adenoma, Bronchioloalveolar, Benign	0/60 (48) 0.7551	1/60 (46) 0.4894	0/60 (49) NC	0/60 (53) NC
	Carcinoma, Bronchioloalveolar, Malignant	0/60 (48) 0.5204	0/60 (46) NC	1/60 (49) 0.5052	0/60 (53) NC
Lymph Node, Mesenteric	Hemangioma, Benign	0/60 (48) 0.2704	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5248
	Hemangiosarcoma, Malignant	0/60 (48) 0.2704	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5248
Muscle	Rhabdomyosarcoma, Malignant	0/60 (48) 0.2704	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5248
Pancreas	Adenoma, Acinar Cell, Benign	1/60 (48) 0.8586	1/60 (47) 0.7474	1/60 (49) 0.7577	0/60 (53) 1.0000
	Carcinoma, Islet Cell, Malignant	3/60 (48) 0.8860	1/60 (46) 0 9362	1/60 (49) 0.9438	1/60 (53) 0.9523
	Adenoma, Islet Cell, Benign	6/60 (48) 0.4652	6/60 (47) 0.6055	8/60 (49) 0.4031	7/60 (53) 0.5769
Site, Uncertain Primary	Leukemia, Granulocytic, Malignant	0/60 (48) 0.2741	0/60 (46) NC	0/60 (49) NC	1/60 (54) 0.5294
	Lymphoma, Malignant	2/60 (48) 0.9496	1/60 (46) 0.8710	1/60 (49) 0.8827	0/60 (53) 1.0000
	Mast Cell Tumor, Malignant	0/60 (48) 0.5204	0/60 (46) NC	1/60 (49) 0.5052	0/60 (53) NC
	Sarcoma, Histiocytic, Malignant	0/60 (48) 0.8586	3/60 (47) 0 1171	0/60 (49) NC	0/60 (53) NC
Skin	Carcinoma, Squamous Cell, Malignant	1/60 (48) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
	Fibroma, Benign	0/60 (48) 0.5829	1/60 (46) 0.4894	3/60 (49) 0.1250	0/60 (53) NC
	Hair Follicle Neoplasm, Benign	0/60 (48) 0.6482	1/60 (46) 0.4894	1/60 (49) 0.5052	0/60 (53) NC
	Hemangiosarcoma, Malignant	1/60 (48) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
	Melanoma, Malignant	0/60 (48) 0.2704	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5248
	Papilloma, Squamous Cell, Benign	0/60 (48) 0.2080	0/60 (46) NC	1/60 (49) 0.5052	1/60 (53) 0.5248
	Basal Cell Tumor, Benign	0/60 (48)	1/60 (46)	0/60 (49)	1/60 (53)

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Organ name	Tumor name	0 mg/kg/day Vehicle (VC) P - Trend	50 mg/kg/day Low (L) P – L vs. VC	100 mg/kg/day Mid (M) P – M vs. VC	200 mg/kg/day High (H) P – H vs VC
		0.3356	0.4894	NS	0.5248
	Carcinoma, Basal Cell, Malignant	1/60 (48)	1/60 (46)	0/60 (49)	0/60 (53)
		0.9410	0.7419	1.0000	1.0000
	Keratoacanthoma, Benign	4/60 (48)	7/60 (47)	3/60 (49)	2/60 (53)
		0.9314	0 2495	0.7907	0.9187
Small Intestine, Duodenum	Adenocarcinoma, Malignant	1/60 (49)	0/60 (46)	0/60 (49)	0/60 (53)
		1.0000	1.0000	1.0000	1.0000
Spleen	Hemangiosarcoma, Malignant	1/60 (49)	0/60 (46)	0/60 (49)	0/60 (53)
		1.0000	1.0000	1.0000	1.0000
Subcutis	Fibroma, Benign	3/60 (48)	4/60 (47)	4/60 (49)	3/60 (53)
		0.6285	0.4881	0.5116	0.7071
	Fibrosarcoma, Malignant	1/60 (48)	0/60 (46)	2/60 (49)	0/60 (53)
		0.7593	1.0000	0.5078	1.0000
	Hemangiosarcoma, Malignant	0/60 (48)	1/60 (47)	0/60 (49)	0/60 (53)
		0.7563	0.4947	NC	NC
	Lipoma, Benign	2/60 (48)	3/60 (47)	2/60 (49)	0/60 (53)
		0.9472	0.4899	0.6992	1.0000
	Schwannoma, Malignant	0/60 (48)	1/60 (46)	0/60 (49)	0/60 (53)
		0.7551	0.4894	NC	NC
Testis	Leydig Cell Tumor, Benign	1/60 (48)	1/60 (46)	1/60 (49)	3/60 (53)
		0.1642	0.7419	0.7577	0.3471
Thymus	Granular Cell Tumor, Malignant	1/60 (48)	0/60 (46)	0/60 (49)	0/60 (53)
		1.0000	1.0000	1.0000	1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.   The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 3B: Tumor Rates and P-Values for Trend and Pairwise Comparisons with Vehicle Control in Female Rats

Organ name	Tumor name	0 mg/kg/day Vehicle (VC) P - Trend	50 mg/kg/day Low (L) P - L vs. VC	100 mg/kg/day Mid (M) P - M vs. VC	250 mg/kg/day High (H) P - H vs. VC
Bone, Mandible	Carcinoma, Squamous Cell, Malignant	0/60 (33)	0/60 (30)	1/60 (30)	1/60 (34)
		0.1976	NC	0.4762	0.5075
Eye	Melanoma, Malignant	0/60 (33)	0/60 (30)	0/60 (30)	1/60 (34)
		0.2677	NC	NC	0.5075
Gland, Adrenal	Adenoma, Adrenocortical, Benign	0/60 (33)	1/60 (30)	2/60 (30)	2/60 (34)
		0.1565	0.4762	0.2227	0.2537
	Carcinoma, Adrenocortical, Malignant	1/60 (33)	0/60 (30)	0/60 (30)	0/60 (34)
		1.0000	1.0000	1.0000	1.0000
	Pheochromocytoma, Benign	1/60 (33)	1/60 (30)	0/60 (30)	2/60 (34)
		0.2753	0.7296	1.0000	0.5114
Gland, Mammary	Adenocarcinoma, Malignant	17/60 (41)	14/60 (37)	21/60 (42)	20/60 (43)

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Organ name	Tumor name	0 mg/kg/day Vehicle (VC) P - Trend	50 mg/kg/day Low (L) P - L vs. VC	100 mg/kg/day Mid (M) P - M vs. VC	250 mg/kg/day High (H) P - H vs. VC
		0.2787	0.7113	0.2879	0.4030
	Adenoma, Benign	3/60 (33)	1/60 (30)	1/60 (30)	2/60 (35)
		0.6413	0 9313	0.9313	0.8398
	Fibroadenoma, Benign	27/60 (44)	20/60 (39)	23/60 (41)	20/60 (41)
		0.8459	0.8743	0.7622	0.9170
	Sarcoma, Malignant	0/60 (33)	0/60 (30)	0/60 (30)	1/60 (35)
		0.2734	NC	NC	0.5147
	Tumor, Mixed, Benign	0/60 (33)	0/60 (30)	1/60 (30)	0/60 (34)
		0.5039	NC	0.4762	NC
	Sarcoma Arising in Fibroadenoma, Malignant	2/60 (33)	0/60 (30)	0/60 (30)	0/60 (34)
		1.0000	1.0000	1.0000	1.0000
Gland, Pituitary	Adenoma, Anterior Lobe Pituitary Gland, Benign	29/60 (45)	31/60 (46)	31/60 (47)	23/60 (43)
		0.9095	0.4699	0.5263	0.8966
	Carcinoma, Pars Distalis, Malignant	8/60 (36)	9/60 (34)	8/60 (33)	5/60 (36)
		0.8817	0.4458	0.5336	0.8902
Gland, Thyroid	Adenoma, C-Cell, Benign	3/60 (34)	2/60 (30)	1/60 (30)	2/60 (34)
		0.6866	0.7810	0.9270	0.8220
	Adenoma, Follicular Cell, Benign	0/60 (33)	1/60 (30)	0/60 (30)	0/60 (34)
		0.7402	0.4762	NC	NC
	Carcinoma, C-Cell, Malignant	1/60 (33)	0/60 (30)	0/60 (30)	0/60 (34)
		1.0000	1.0000	1.0000	1.0000
Gland, Zymbal	Carcinoma, Malignant	1/60 (33)	0/60 (30)	0/60 (30)	0/60 (34)
		1.0000	1.0000	1.0000	1.0000
Kidney	Carcinoma, Urothelial, Malignant	0/60 (33)	0/60 (30)	1/60 (30)	0/60 (34)
		0.5039	NC	0.4762	NC
Liver	Adenoma, Hepatocellular, Benign	0/60 (33)	0/60 (30)	1/60 (30)	0/60 (34)
		0.5039	NC	0.4762	NC
Ovary	Thecoma, Benign	1/60 (33)	0/60 (30)	0/60 (30)	0/60 (34)
		1.0000	1.0000	1.0000	1.0000
Pancreas	Adenoma, Islet Cell, Benign	0/60 (33)	0/60 (30)	1/60 (30)	1/60 (34)
		0.1976	NS	0.4762	0.5075
Site, Uncertain Primary	Lymphoma, Malignant	0/60 (33)	1/60 (30)	0/60 (30)	0/60 (34)
		0.7402	0.4762	NC	NC
	Sarcoma, Histiocytic, Malignant	0/60 (33)	0/60 (30)	0/60 (30)	1/60 (34)
		0.2677	NC	NC	0.5075
Skin	Adenoma, Sebaceous, Benign	1/60 (33)	0/60 (30)	0/60 (30)	0/60 (34)
		1.0000	1.0000	1.0000	1.0000
	Carcinoma, Malignant	0/60 (33)	0/60 (30)	0/60 (30)	1/60 (34)
		0.2677	NC	NC	0.5075
	Papilloma, Squamous Cell, Benign	0/60 (33)	0/60 (30)	1/60 (30)	0/60 (34)
		0.5039	NC	0.4762	NC
	Keratoacanthoma, Benign	0/60 (33)	0/60 (30)	1/60 (30)	0/60 (34)
		0.5039	NS	0.4762	NS
Small Intestine,	Leiomyoma, Benign	1/60 (33)	0/60 (30)	0/60 (30)	0/60 (34)

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Organ name	Tumor name	0 mg/kg/day Vehicle (VC) P - Trend	50 mg/kg/day Low (L) P - L vs. VC	100 mg/kg/day Mid (M) P - M vs. VC	250 mg/kg/day High (H) P - H vs. VC
Jejunum		1.0000	1.0000	1.0000	1.0000
Subcutis	Fibroma, Benign	1/60 (33) 1.0000	0/60 (30) 1.0000	0/60 (30) 1.0000	0/60 (34) 1.0000
	Fibrosarcoma, Malignant	0/60 (33) 0.5039	0/60 (30) NC	1/60 (30) 0.4762	0/60 (34) NC
	Lipoma, Benign	0/60 (33) 0.6322	1/60 (30) 0.4762	1/60 (30) 0.4762	0/60 (34) NC
Thymus	Thymoma, Malignant	0/60 (33) 0.2734	0/60 (30) NC	0/60 (30) NC	1/60 (35) 0.5147
Uterus	Granular Cell Tumor, Benign	1/60 (33) 0.4653	0/60 (30) 1.0000	0/60 (30) 1.0000	1/60 (34) 0.7612
	Polyp, Endometrial Stromal, Benign	2/60 (34) 0.8978	6/60 (32) 0 1103	2/60 (30) 0.6445	1/60 (34) 0.8806
Vagina	Granular Cell Tumor, Benign	3/60 (34) 0.8588	1/60 (30) 0 9270	0/60 (30) 1.0000	1/60 (34) 0.9431
	Granular Cell Tumor, Malignant	1/60 (33) 1.0000	0/60 (30) 1.0000	0/60 (30) 1.0000	0/60 (34) 1.0000
	Leiomyosarcoma, Malignant	0/60 (33) 0.2677	0/60 (30) NC	0/60 (30) NC	1/60 (34) 0.5075
	Polyp, Vaginal, Benign	0/60 (33) 0.2677	0/60 (30) NC	0/60 (30) NC	1/60 (34) 0.5075

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.   The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons with Water Control in Male Rats

Organ name	Tumor name	0 mg/kg/day Water C (WC) P - Trend	50 mg/kg/day Low (L) P – L vs. WC	100 mg/kg/day Mid (M) P – M vs. WC	200 mg/kg/day High (H) P – H vs. WC
Body Cavity, Cranial	Schwannoma, Malignant	0/60 (44) 0.7720	1/60 (47) 0.5165	0/60 (49) NC	0/60 (53) NC
Body Cavity, Oral	Papilloma, Squamous Cell, Benign	1/60 (44) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
Body Cavity, Scrotum	Mesothelioma, Malignant	2/60 (44) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
Bone	Osteosarcoma, Malignant	0/60 (44) 0.2760	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5464
Bone, Mandible	Carcinoma, Squamous Cell, Malignant	0/60 (44) 0.0752	0/60 (46) NC	0/60 (49) NC	2/60 (53) 0.2960
Brain	Astrocytoma, malignant	0/60 (44) 0.4486	2/60 (47) 0.2640	3/60 (50) 0.1462	1/60 (53) 0.5464

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Organ name	Tumor name	0 mg/kg/day Water C (WC) P - Trend	50 mg/kg/day Low (L) P – L vs. WC	100 mg/kg/day Mid (M) P – M vs. WC	200 mg/kg/day High (H) P – H vs. WC
Eye	Melanoma, Malignant	0/60 (44) 0.5313	0/60 (46) NC	1/60 (49) 0.5269	0/60 (53) NC
Gland, Adrenal	Adenoma, Adrenocortical, Benign	2/60 (44) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
	Carcinoma, Adrenocortical, Malignant	0/60 (44) 0.6626	1/60 (47) 0.5165	1/60 (49) 0.5269	0/60 (53) NC
	Pheochromocytoma, Benign	10/60 (46) 0.9932	7/60 (47) 0.8692	6/60 (49) 0.9350	3/60 (53) 0.9967
	Pheochromocytoma, Malignant	0/60 (44) 0.0434	2/60 (46) 0.2584	0/60 (49) NC	4/60 (53) 0.0845
Gland, Mammary	Adenocarcinoma, Malignant	0/60 (44) 0.2798	0/60 (46) NC	0/60 (49) NC	1/60 (54) 0.5510
	Fibroadenoma, Benign	1/60 (44) 0.9511	2/60 (47) 0.5250	0/60 (49) 1.0000	0/60 (53) 1.0000
Gland, Pituitary	Adenoma, Anterior Lobe Pituitary Gland, Benign	24/60 (52) 0.8623	25/60 (52) 0.5000	26/60 (55) 0.5311	21/60 (56) 0.8658
	Adenoma, Pars Intermedia, Benign	2/60 (44) 0.9864	2/60 (46) 0.7084	0/60 (49) 1.0000	0/60 (53) 1.0000
	Carcinoma, Pars Distalis, Malignant	3/60 (44) 0.9651	0/60 (46) 1.0000	2/60 (49) 0.8511	0/60 (53) 1.0000
Gland, Preputial	Adenoma, Benign	0/60 (44) 0.2760	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5464
Gland, Prostate	Adenocarcinoma, Malignant	1/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
Gland, Thyroid	Adenoma, C-Cell, Benign	2/60 (44) 0.1185	3/60 (46) 0.5213	2/60 (50) 0.7383	6/60 (54) 0.2114
	Adenoma, Follicular Cell, Benign	5/60 (45) 0.4806	4/60 (47) 0.7788	2/60 (49) 0.9566	6/60 (53) 0.6152
	Carcinoma, C-Cell, Malignant	2/60 (44) 0.7625	1/60 (46) 0.8873	2/60 (49) 0.7312	1/60 (54) 0.9129
	Carcinoma, Follicular Cell, Malignant	0/60 (44) 0.7720	1/60 (47) 0.5165	0/60 (49) NC	0/60 (53) NC
Gland, Zymbal	Carcinoma, Malignant	0/60 (44) 0.7708	1/60 (46) 0.5111	0/60 (49) NC	0/60 (53) NC
Kidney	Carcinoma, Urothelial, Malignant	0/60 (44) 0.2760	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5464
	Lipoma, Benign	1/60 (44) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
	Liposarcoma, Malignant	0/60 (44) 0.7708	1/60 (46) 0.5111	0/60 (49) NC	0/60 (53) NC
	Nephroblastoma, Malignant	1/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
Large Intestine, Cecum	Adenoma, Benign	1/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000

File Name: NDA209176Carcin_Rat.doc

Organ name	Tumor name	0 mg/kg/day Water C (WC) P - Trend	50 mg/kg/day Low (L) P – L vs. WC	100 mg/kg/day Mid (M) P – M vs. WC	200 mg/kg/day High (H) P – H vs. WC
Liver	Adenoma, Hepatocellular, Benign	4/60 (45) 0.9962	0/60 (46) 1.0000	1/60 (49) 0.9777	0/60 (53) 1.0000
	Carcinoma, Hepatocellular, Malignant	1/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
	Cholangiocarcinoma, Malignant	0/60 (44) 0.5313	0/60 (46) NC	1/60 (49) 0.5269	0/60 (53) NC
	Hemangiosarcoma, Malignant	1/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
	Sarcoma, Histiocytic, Malignant	0/60 (44) 0.2798	0/60 (46) NC	0/60 (49) NC	1/60 (54) 0.5510
Lung/Bronchus	Adenoma, Bronchioloalveolar, Benign	0/60 (44) 0.7708	1/60 (46) 0.5111	0/60 (49) NC	0/60 (53) NC
	Carcinoma, Bronchioloalveolar, Malignant	0/60 (44) 0.5313	0/60 (46) NC	1/60 (49) 0.5269	0/60 (53) NC
Lymph Node, Mesenteric	Hemangioma, Benign	0/60 (44) 0.2760	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5464
	Hemangiosarcoma, Malignant	1/60 (44) 0.5411	0/60 (46) 1.0000	0/60 (49) 1.0000	1/60 (53) 0.7968
Mesentery	Fibrosarcoma, Pleomorphic, Malignant	1/60 (44) 1.0000	0/60 (46) 1.0000	0/60 (49) 1.0000	0/60 (53) 1.0000
Muscle	Rhabdomyosarcoma, Malignant	0/60 (44) 0.2760	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5464
Pancreas	Adenoma, Acinar Cell, Benign	0/60 (44) 0.6626	1/60 (47) 0.5165	1/60 (49) 0.5269	0/60 (53) NC
	Adenoma, Islet Cell, Benign	3/60 (44) 0.2283	6/60 (47) 0.2767	8/60 (49) 0.1363	7/60 (53) 0.2460
	Carcinoma, Islet Cell, Malignant	0/60 (44) 0.3417	1/60 (46) 0.5111	1/60 (49) 0.5269	1/60 (53) 0.5464
Site, Uncertain Primary	Leukemia, Granulocytic, Malignant	1/60 (45) 0.5431	0/60 (46) 1.0000	0/60 (49) 1.0000	1/60 (54) 0.7959
	Lymphoma, Malignant	0/60 (44) 0.6640	1/60 (46) 0.5111	1/60 (49) 0.5269	0/60 (53) NC
	Mast Cell Tumor, Malignant	0/60 (44) 0.5313	0/60 (46) NC	1/60 (49) 0.5269	0/60 (53) NC
	Sarcoma, Histiocytic, Malignant	0/60 (44) 0.8715	3/60 (47) 0.1335	0/60 (49) NC	0/60 (53) NC
Skin	Fibroma, Benign	0/60 (44) 0.6043	1/60 (46) 0.5111	3/60 (49) 0.1420	0/60 (53) NC
	Hair Follicle Neoplasm, Benign	0/60 (44) 0.6640	1/60 (46) 0.5111	1/60 (49) 0.5269	0/60 (53) NC
	Melanoma, Malignant	0/60 (44) 0.2760	0/60 (46) NC	0/60 (49) NC	1/60 (53) 0.5464
	Papilloma, Squamous Cell, Benign	0/60 (44) 0.2168	0/60 (46) NC	1/60 (49) 0.5269	1/60 (53) 0.5464
	Basal Cell Tumor, Benign	0/60 (44) 0.3497	1/60 (46) 0.5111	0/60 (49) NS	1/60 (53) 0.5464
	Carcinoma, Basal Cell, Malignant	0/60 (44)	1/60 (46)	0/60 (49)	0/60 (53)

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Organ name	Tumor name	0 mg/kg/day Water C (WC) P - Trend	50 mg/kg/day Low (L) P – L vs. WC	100 mg/kg/day Mid (M) P – M vs. WC	200 mg/kg/day High (H) P – H vs. WC
		0.7708	0.5111	NS	NS
	Keratoacanthoma, Benign	8/60 (46)	7/60 (47)	3/60 (49)	2/60 (53)
		0.9958	0.7284	0.9807	0.9960
Spleen	Sarcoma, Malignant	1/60 (45)	0/60 (46)	0/60 (49)	0/60 (53)
		1.0000	1.0000	1.0000	1.0000
Subcutis	Fibroma, Benign	6/60 (45)	4/60 (47)	4/60 (49)	3/60 (53)
		0.9071	0.8594	0.8743	0.9524
	Fibrosarcoma, Malignant	1/60 (45)	0/60 (46)	2/60 (49)	0/60 (53)
		0.7699	1.0000	0.5322	1.0000
	Fibrosarcoma, Pleomorphic, Malignant	1/60 (45)	0/60 (46)	0/60 (49)	0/60 (53)
		1.0000	1.0000	1.0000	1.0000
	Hemangiosarcoma, Malignant	0/60 (44)	1/60 (47)	0/60 (49)	0/60 (53)
		0.7720	0.5165	NC	NC
	Lipoma, Benign	4/60 (45)	3/60 (47)	2/60 (49)	0/60 (53)
		0.9927	0.8004	0.9165	1.0000
	Schwannoma, Malignant	0/60 (44)	1/60 (46)	0/60 (49)	0/60 (53)
		0.7708	0.5111	NC	NC
Testis	Leydig Cell Tumor, Benign	2/60 (45)	1/60 (46)	1/60 (49)	3/60 (53)
		0.3387	0.8832	0.8941	0.5778

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.   The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons with Water Control in Female Rats

Organ name	Tumor name	0 mg/kg/day Water (WC) P - Trend	50 mg/kg/day Low (L) P - L vs. WC	100 mg/kg/day Mid (M) P - M vs. WC	250 mg/kg/day High (H) P - H vs. WC
Bone	Hemangioma, Benign	1/60 (31)	0/60 (30)	0/60 (30)	0/60 (34)
		1.0000	1.0000	1.0000	1.0000
Bone, Mandible	Carcinoma, Squamous Cell, Malignant	1/60 (31)	0/60 (30)	1/60 (30)	1/60 (34)
		0.4684	1.0000	0.7459	0.7764
Eye	Melanoma, Malignant	0/60 (30)	0/60 (30)	0/60 (30)	1/60 (34)
		0 2742	NC	NC	0.5312
Gland, Adrenal	Adenoma, Adrenocortical, Benign	2/60 (31)	1/60 (30)	2/60 (30)	2/60 (34)
		0.4909	0.8751	0.6813	0.7278
	Carcinoma, Adrenocortical, Malignant	1/60 (30)	0/60 (30)	0/60 (30)	0/60 (34)
		1.0000	1.0000	1.0000	1.0000
	Pheochromocytoma, Benign	0/60 (30)	1/60 (30)	0/60 (30)	2/60 (34)
		0 1278	0.5000	NC	0.2783
Gland, Harderian	Adenocarcinoma, Malignant	1/60 (30)	0/60 (30)	0/60 (30)	0/60 (34)
		1.0000	1.0000	1.0000	1.0000
Gland, Mammary	Adenocarcinoma, Malignant	17/60 (38)	14/60 (37)	21/60 (42)	20/60 (43)

Organ name	Tumor name	0 mg/kg/day Water (WC) P - Trend	50 mg/kg/day Low (L) P - L vs. WC	100 mg/kg/day Mid (M) P - M vs. WC	250 mg/kg/day High (H) P - H vs. WC
		0 3594	0.7997	0.4028	0.5254
	Adenoma, Benign	0/60 (30)	1/60 (30)	1/60 (30)	2/60 (35)
		0 1481	0.5000	0.5000	0.2861
	Fibroadenoma, Benign	29/60 (44)	20/60 (39)	23/60 (41)	20/60 (41)
		0 9113	0.9426	0.8750	0.9656
	Sarcoma, Malignant	0/60 (30)	0/60 (30)	0/60 (30)	1/60 (35)
		0 2800	NC	NC	0.5385
	Tumor, Mixed, Benign	1/60 (30)	0/60 (30)	1/60 (30)	0/60 (34)
		0.8249	1.0000	0.7542	1.0000
Gland, Pituitary	Adenoma, Anterior Lobe Pituitary Gland, Benign	27/60 (44)	31/60 (46)	31/60 (47)	23/60 (43)
		0.8672	0.3531	0.4061	0.8314
	Carcinoma, Pars Distalis, Malignant	9/60 (34)	9/60 (34)	8/60 (33)	5/60 (36)
		0 9330	0.6080	0.6874	0.9475
Gland, Thyroid	Adenoma, C-Cell, Benign	3/60 (32)	2/60 (30)	1/60 (30)	2/60 (34)
		0.7045	0.8022	0.9355	0.8407
	Adenoma, Follicular Cell, Benign	1/60 (30)	1/60 (30)	0/60 (30)	0/60 (34)
		0 9430	0.7542	1.0000	1.0000
Kidney	Carcinoma, Urothelial, Malignant	0/60 (30)	0/60 (30)	1/60 (30)	0/60 (34)
		0 5161	NC	0.5000	NC
Liver	Adenoma, Hepatocellular, Benign	2/60 (31)	0/60 (30)	1/60 (30)	0/60 (34)
		0 9420	1.0000	0.8751	1.0000
Pancreas	Adenoma, Islet Cell, Benign	0/60 (30)	0/60 (30)	1/60 (30)	1/60 (34)
		0 2073	NS	0.5000	0.5312
Site, Uncertain Primary	Leukemia, Granulocytic, Malignant	1/60 (30)	0/60 (30)	0/60 (30)	0/60 (34)
		1.0000	1.0000	1.0000	1.0000
	Lymphoma, Malignant	1/60 (31)	1/60 (30)	0/60 (30)	0/60 (34)
		0 9400	0.7459	1.0000	1.0000
	Sarcoma, Histiocytic, Malignant	0/60 (30)	0/60 (30)	0/60 (30)	1/60 (34)
		0 2742	NC	NC	0.5312
Skin	Carcinoma, Malignant	0/60 (30)	0/60 (30)	0/60 (30)	1/60 (34)
		0 2742	NC	NC	0.5312
	Papilloma, Squamous Cell, Benign	0/60 (30)	0/60 (30)	1/60 (30)	0/60 (34)
		0 5161	NC	0.5000	NC
	Keratoacanthoma, Benign	0/60 (30)	0/60 (30)	1/60 (30)	0/60 (34)
		0 5161	NS	0.5000	NS
Subcutis	Fibrosarcoma, Malignant	0/60 (30)	0/60 (30)	1/60 (30)	0/60 (34)
		0 5161	NC	0.5000	NC
	Lipoma, Benign	1/60 (30)	1/60 (30)	1/60 (30)	0/60 (34)
		0.8607	0.7542	0.7542	1.0000
Thymus	Thymoma, Malignant	0/60 (30)	0/60 (30)	0/60 (30)	1/60 (35)
		0 2800	NC	NC	0.5385
Uterus	Granular Cell Tumor, Benign	0/60 (30)	0/60 (30)	0/60 (30)	1/60 (34)
		0 2742	NC	NC	0.5312
	Polyp, Endometrial Stromal, Benign	5/60 (32)	6/60 (32)	2/60 (30)	1/60 (34)

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Organ name	Tumor name	0 mg/kg/day Water (WC) P - Trend	50 mg/kg/day Low (L) P - L vs. WC	100 mg/kg/day Mid (M) P - M vs. WC	250 mg/kg/day High (H) P - H vs. WC
		0 9865	0.5000	0.9379	0.9900
Vagina	Granular Cell Tumor, Benign	0/60 (30)	1/60 (30)	0/60 (30)	1/60 (34)
		0 3411	0.5000	NC	0.5312
	Leiomyosarcoma, Malignant	0/60 (30)	0/60 (30)	0/60 (30)	1/60 (34)
		0 2742	NC	NC	0.5312
	Polyp, Vaginal, Benign	0/60 (30)	0/60 (30)	0/60 (30)	1/60 (34)
		0 2742	NC	NC	0.5312

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.   The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

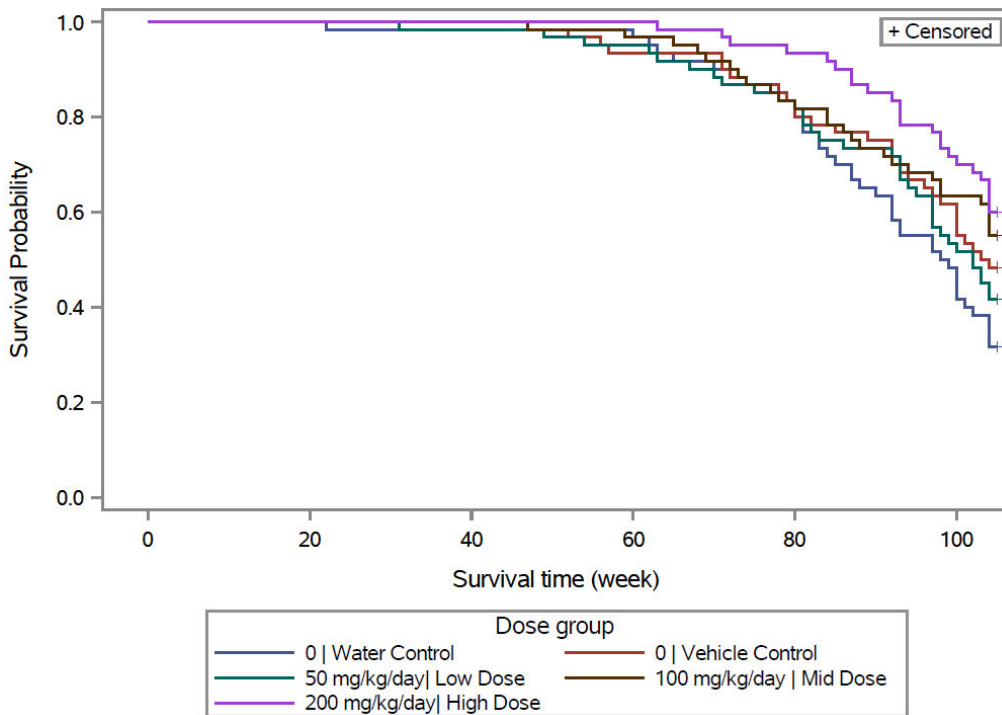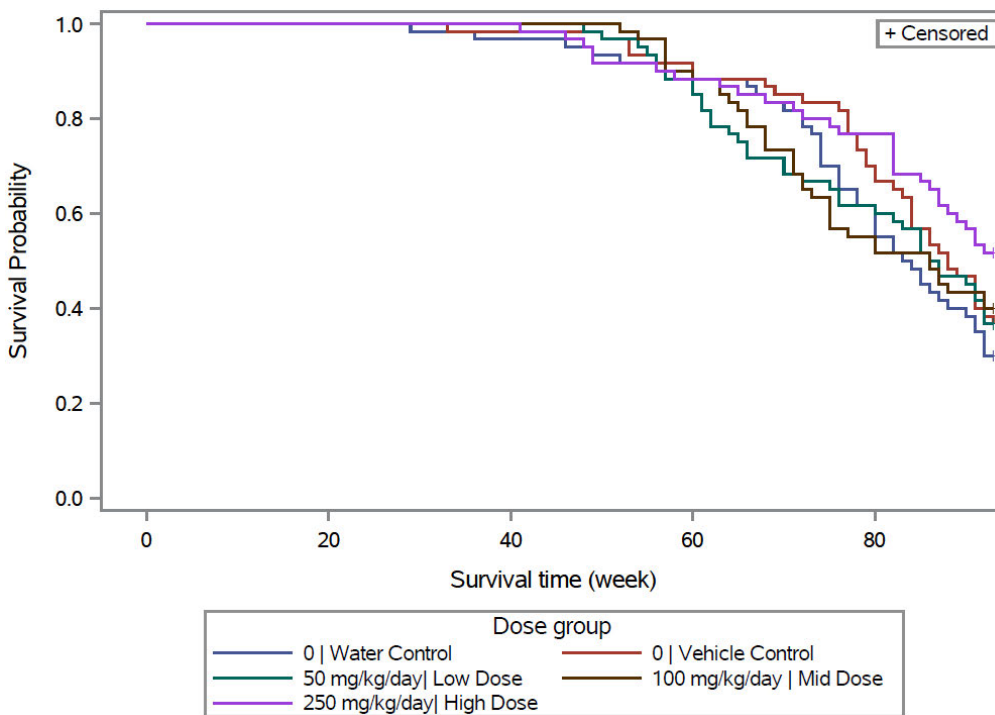**Figure 1A: Kaplan-Meier Survival Functions for Male Rats**

Figure 1B: Kaplan-Meier Survival Functions for Female Rats

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