§ Summary of Subgroups for Spine (L1- L4) BMD: Mean Relative Change from Baseline to Last Value (ITT):

BMD Subgroup	Placebo	Oral Ibandronate		
		0.5 mg	1.0 mg	2.5 mg
	% change (n)	% change (n)	% change (n)	% change (n)
Vitamin D (ng/ml)				
1st tertile (0–33)	-0.9371 (56)	-0.6145 (54)	0.1685 (56)	1.3372 (63) *
2nd tertile (> 33–45)	-1.1218 (45)	-0.3163 (55)	0.2586 (51)	2.4276 (43) *
3rd tertile (> 45)	-1.5689 (48)	-0.7366 (48)	0.4821 (53) *	2.3321 (46) *
Calcium Compliance				
Compliant	-0.9845 (128)	-0.5827 (130)	0.5398 (138) *	2.2486 (128) *
Non-compliant	-2.3709 (22)	-0.3773 (27)	-1.1962 (22)	0.3545 (25) *
Weight (kg)				
1st tertile (0-65.3)	-0.8904 (49)	-1.1194 (51)	-0.2041 (60)	1.2891 (49) *
2nd tertile (65.3 -76.8)	-2.3632 (41)	-0.8980 (50)	0.3047 (54) *	2.4543 (52) *
3rd tertile (> 76.8)	-0.4964 (58)	0.2911 (55)	0.8760 (45)	2.1602 (50) *

* Difference between active group and placebo was significant ($p < 0.05$).

Vitamin D at Baseline

Compared to results for the main ITT population, the mean relative change in BMD in the 2.5 mg groups of the 2nd (> 33- 45 ng/ ml) and 3rd (> 45 ng/ ml) tertiles showed increases over that for the primary analysis 2.5 mg group.

However, patients with the lowest Vitamin D concentrations (1st tertile, 0– 33 ng/ ml) showed a smaller treatment effect in all active groups (less increase or a greater decrease in spine BMD), relative to the results of the primary analysis groups. The degree of change in BMD within each of the three Vitamin D tertiles was dose-dependent, with the 1.0 mg and 2.5 mg groups in all tertiles showing an absolute increase from baseline to last value. For the 2.5 mg groups in all tertiles, there was a significant increase in BMD versus placebo from baseline to last value.

Calcium Compliance

Patients in all groups who complied with the calcium supplement regimen displayed better results (either less reduction or an increase) in mean relative change from baseline spine BMD as compared to non- compliant patients.

However, the number of non-compliant patients for any group was very low (N≤27). In the non-compliant subgroup, mean relative spine BMD for the ibandronate groups was improved over that of placebo. However, relative change was decreased from baseline for all but the 2.5 mg group, which differed significantly from placebo.

Weight at Baseline

Treatment groups were analyzed by patient weight at baseline (1st tertile, 0– 65.3 kg; 2nd tertile, >65.3– 76.8 kg, 3rd tertile, >76.8 kg). Patients in the 1st tertile had the smallest increase in lumbar spine BMD compared to those in the 2nd and 3rd tertiles. The mean relative change from baseline BMD (as compared to placebo) in all 3 tertiles showed dose-dependent increases similar to those seen in the primary analysis, but the differences within the tertiles between active drug groups and placebo generally were not as pronounced.

Nevertheless, for all 2.5 mg groups in the Weight subgroup, the difference from placebo was significant.

§ The three variables, baseline PTH, weight and pre-menopausal treatment, in which there were baseline imbalances, were entered separately, pair-wise and combined into the primary efficacy ANOVA model.

Covariate in ANOVA model	0.5mg vs. Placebo	1.0mg vs. Placebo	2.5mg vs. Placebo
Separately			
PTH	0.0029	0.0011	0.0440
Treatment	0.0311	<0.0001	<0.0001
Weight	0.0004	0.0027	0.0105
Treatment	0.1008	<0.0001	<0.0001
Pre-menopausal Treatment	0.5715	0.2540	0.5327
Treatment	0.1223	0.0002	<0.0001
Pair-wise			
PTH	0.0077	0.0039	0.1359
Weight	0.0009	0.0216	0.0333
Treatment	0.0325	<0.0001	<0.0001
PTH	0.0026	0.0014	0.0461
Pre-menopausal Treatment	0.5394	0.3256	0.5696
Treatment	0.0360	<0.0001	<0.0001
Weight	0.0003	0.0033	0.0124
Pre-menopausal Treatment	0.4170	0.3396	0.7188
Treatment	0.1352	<0.0001	<0.0001

* ANOVA also included terms for treatment and Strata.

Baseline PTH and weight were considered significant predictors of the primary efficacy parameter for all treatments when entered separately into the model. As both baseline PTH and weight increased, the primary efficacy parameter (i. e. relative change in BMD

(L2-L4) at Month 24) increased. When baseline PTH and weight were added to the model in a pair-wise manner, only weight was found to be a significant predictor in the 2.5mg group. Pre-menopausal treatment was found not to be a significant predictor in any of the treatment groups.

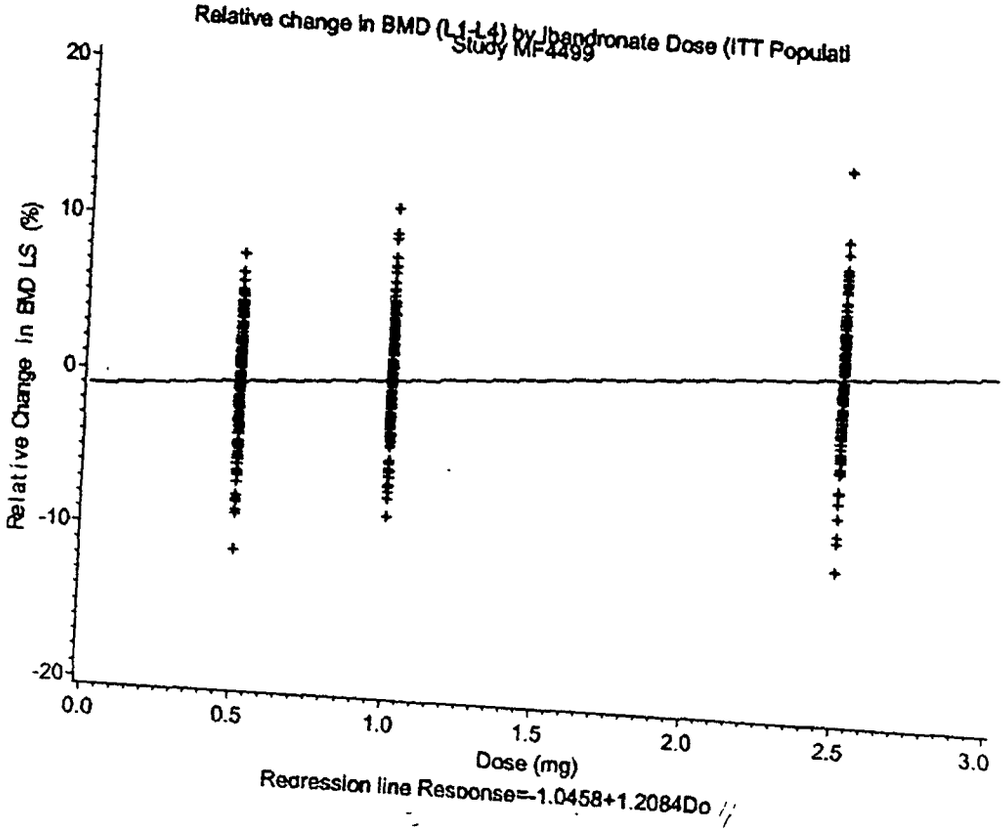
For all ANOVA models fitted to the 1.0mg and 2.5mg groups versus placebo, treatment group was found to be a highly significant predictor of the primary efficacy parameter.

§ The continuous variables, PTH and weight were split into three groups based on the distribution of the data (i. e. <33rd percentile, 33rd- 66th percentile and >66th percentile).

Mean (& 95% CI) of Difference Between Ibandronate Groups vs. Placebo for Relative Change in BMD Lumbar Spine (L1- L4) from Baseline at Month 24 (ITT Population):

Subgroup	0.5mg vs. placebo	1.0mg vs. placebo	2.5mg vs. placebo
Weight 1 (<65.3kg)	0.013 (-1.280, 1.306)	1.037 (-0.202, 2.275)	2.289 (0.965, 3.613)
Weight 2 (≥65.3kg, ≤76.8kg)	1.181 (-0.290, 2.651)	2.344 (0.899, 3.790)	4.385 (2.924, 5.846)
Weight 3 (>76.8kg)	0.604 (-0.797, 2.004)	1.138 (-0.342, 2.618)	2.414 (0.971, 3.857)
Pre-menopausal Treatment = Yes	-0.075 (-1.372, 1.221)	1.587 (0.341, 2.833)	3.070 (1.713, 4.427)
Pre-menopausal Treatment = No	1.159 (0.154, 2.164)	1.465 (0.438, 2.492)	3.098 (2.104, 4.093)
PTH 1 (<29.7pmol/l)	0.335 (-1.091, 1.760)	0.785 (-0.599, 2.169)	2.344 (0.910, 3.778)
PTH 2 (≥29.7pmol/l, ≤42.3pmol/l)	0.603 (-0.795, 2.001)	1.440 (0.070, 2.810)	3.652 (2.304, 5.000)
PTH 3 (>42.3pmol/l)	1.042 (-0.344, 2.429)	2.294 (0.908, 3.680)	3.088 (1.650, 4.526)

§ Dose Response



Analysis of Variance

	SS	df	MS	F-value	p-value
Due to linear regression	489.1913	1	489.1913	33.9197	< 0.0001
Departures from linearity	5.0233	1	5.0233	0.3483	0.5554
Error	6735.0991	467	14.42205375		
Total	7229.3137	469			

From the analysis of variance, we can see that the variation due to the linear regression is highly significant, and the variation due to departures from linearity is not significant. From this we can conclude that there is a linear dose-response relationship and from the regression line conclude that a unit increase in dose, results in a 1.2084 fold increase from baseline of BMD (L1- L4) at Month 24.

2.3.3.2.6 Reviewer's Comments and Conclusions on Study MF 4499

This study has provided statistical evidence in favor of the efficacy of 1.0 mg and 2.5 mg doses of ibandronate (not 0.5 mg). This reviewer's analyses with the data supplied to the electronic document room (EDR) support these findings.

If statistical significance is not mentioned, then the comparison is only numerical. "Strata" (the only factor other than treatment pre-specified in the Data Analysis Plan, for inclusion in ANOVA of primary analysis) was a significant covariate. However, there were no significant Strata by Treatment interactions. For all active groups, the highest treatment effect estimates were found in Strata D, the high-risk patients. Compared to the results of the main ITT population, greater increases in lumbar spine BMD were seen in all ibandronate groups of Strata C and D. Thus, the greatest treatment effect of ibandronate on lumbar spine BMD in this study was observed in osteopenic patients who were at least three years postmenopausal.

The following subgroup analyses were exploratory:

For each active group versus placebo comparison, the highest mean difference in relative change in BMD (L1- L4) from baseline was found in patients weighing between 65.3kg to 76.8kg (Weight 2, middle group).

The difference in relative change in BMD between the 0.5mg and 1.0mg groups versus placebo increased as the baseline PTH increased. For the 2.5mg group versus placebo comparison, the highest mean difference in BMD was found for patients with a baseline PTH value between 29.7pmol/ l and 42.3pmol/ l (PTH 2, middle group).

Treatment differences between the 2.5mg group and placebo were similar for patients taking pre-menopausal treatments to those not taking the pre-menopausal treatments. This was also true for the comparison between the 1.0mg group and placebo.

Age (≤55 or >55) was a significant covariate. However, the interaction with treatment was not significant. For all active groups, the highest treatment effect estimates were found in patients aged > 55 years old.

There was no significant Race by Treatment interaction. Caucasians were found to have higher treatment effect estimates then non-Caucasians.

The overall Center by Treatment interaction p-value was .3190 (NDA page 1633 of the Study Report). Center by Treatment interaction (p= 0.0797) was significant only with respect to 1.0 mg ibandronate. Centers 22051, 22054 and 22848 were found to have the

highest treatment effect estimates. However, these centers did not have excessive number of patients (had only 44, 12 and 46 patients (in all treatment arms) in each center respectively).

For "Vitamin D at Baseline", patients with the lowest Vitamin D concentrations (1st tertile, 0– 33 ng/ ml) showed a smaller treatment effect in all active groups, relative to the results of the primary analysis groups.

For "Calcium Compliance," the number of non-compliant patients for any group was very low (N≤27). In the non-compliant subgroup, mean relative spine BMD for the ibandronate groups was improved over that of placebo. However, relative change was decreased from baseline for all but the 2.5 mg group, which differed significantly from placebo.

Weight was found to be significant predictors of the primary efficacy parameter. As weight increased, the primary efficacy parameter (i. e. relative change in BMD (L2- L4) at Month 24) increased. Treatment groups were analyzed by patient weight at baseline (1st tertile, 0– 65.3 kg; 2nd tertile, >65.3– 76.8 kg, 3rd tertile, >76.8 kg). Patients in the 1st tertile had the smallest increase in lumbar spine BMD compared to those in the 2nd and 3rd tertiles.

Analyses adjusting for baseline imbalances, showed the overall statistically significant difference among the treatment groups.

There was a linear dose-response relationship. A unit increase in dose resulted, on an average, in 1.2084 fold increase from baseline of BMD (L1- L4) at Month 24.

2.4 Findings in Special/Subgroup Populations

This reviewer has reviewed only the primary efficacy variable.

In the fracture Study 4411, all the significant treatment by factor interaction occurred for the 2.5mg vs placebo comparisons and the factors were: Baseline lumbar spine T-score, age, weight, years since menopause, vitamin D status. The significant treatment by Baseline lumbar spine T-score interaction was qualitative.

In the prevention Study 4499, no significant interaction could be detected (except for the 1.0mg vs placebo comparison, for which the treatment by weight interaction p-value was 0.0965) from all analyses that could be obtained from the sponsor. Nonetheless, non-significant variation in subgroup results have been discussed above.

2.5 CONCLUSION

(2 studies for 2 indications)

In spite of some statistically significant interactions in Study 4411 [quantitative, i.e., not qualitative (except for Treatment by Baseline BMD T-score), i.e., better ibandronate treatment response relative to placebo in almost all subgroups, except for BMD T-score >-2.0 SD], both studies reviewed provided statistically significant evidence in favor of their respective primary efficacy conclusion.

/S/

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot

Dr. Wilson

CC:
Archival NDA 21-455/N_000

HFD-510/Dr. Colman
HFD-510/Dr. Kehoe
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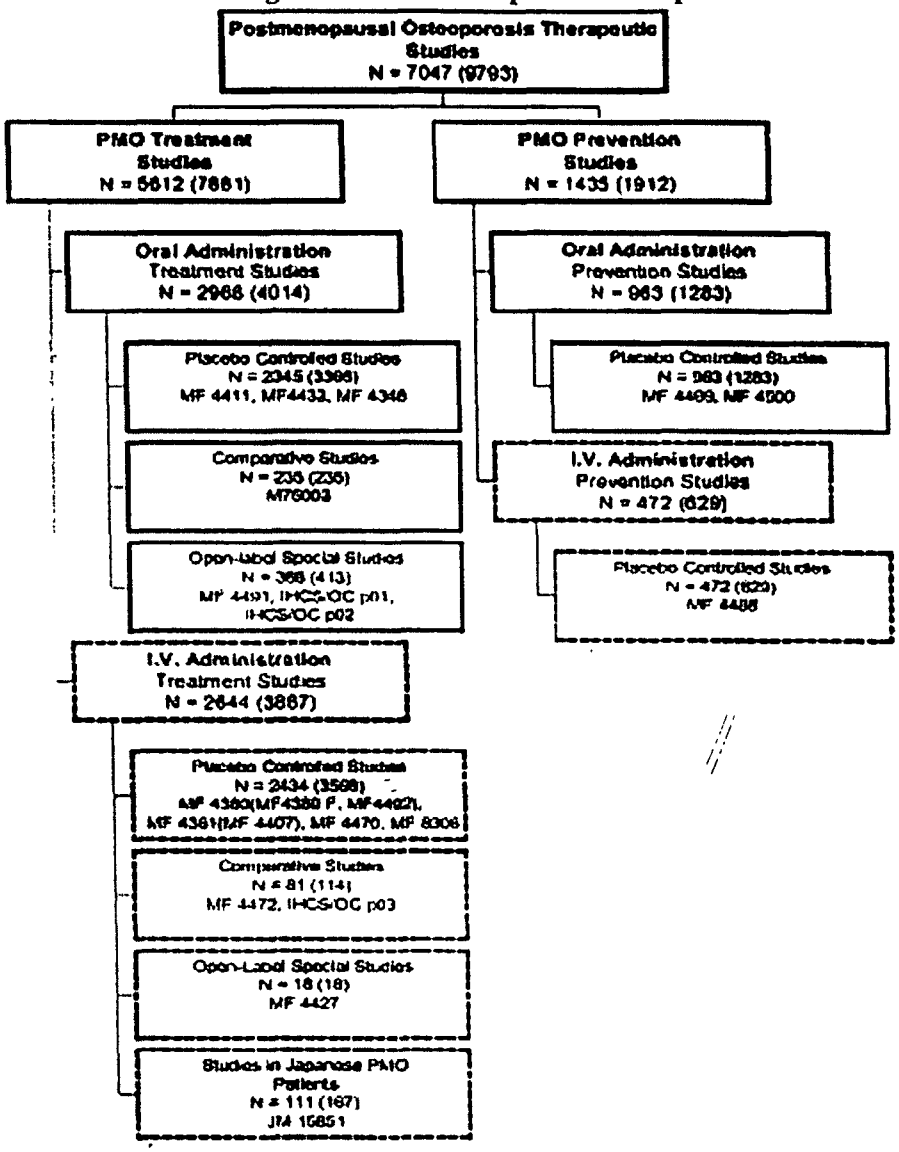
HFD-715/Dr. Nevius
HFD-715/Dr. Wilson
HFD-715/Dr. Sahlroot
HFD-715/Dr. Choudhury

J.Choudhury:7-3110: 05/15/03

This review consists of 69 pages of text and 3 pages of appendices.

2.6 APPENDIX

Chart 0.1.1
Overview of the Clinical Program for Postmenopausal Osteoporosis:



Notes: N = number of patients randomized to ibandronate with the total number of patients randomized provided in brackets. Patients that continued in follow- up intravenous administration extension studies are not re-counted. Study numbers in brackets indicate follow-up studies to that before the brackets. Stippled boxes indicate studies which provide relevant additional information in support of the safety information from the administration of ibandronate in the treatment or prevention of post- menopausal osteoporosis.

Table 0.1.2

Oral Ibandronate PMO Treatment Studies

Protocol	Phase	Design	Dose (mg)	Frequency[1]	Patients Treated (N)	Duration	Post-treatment Fasting	Location	Primary efficacy variable[2]
MF 4411 [7009]	3	Multicenter, double-blind, placebo-controlled, parallel	Placebo 2.5 20	daily daily intermittent Total =	975 977 977 2929	3 years	at least 1 hour	Europe North America	New vertebral fractures
MF 4411 [7011]	2	Single-center, double-blind, placebo-controlled, parallel and cross-over	Placebo 2.5 20	daily daily intermittent Total =	83 81 78 240	1 year	at least 1 hour	Europe	Spine BMD (L2-L4)
MF 4348 [7010]	2	Single-center, double-blind, placebo-controlled, dose-finding, parallel	Placebo 0.25 0.5 1.0 2.5 5.0	daily daily daily daily daily daily Total =	30 30 30 30 30 30 180	1 year	at least 1 hour	Europe	Spine BMD (L2-L4)
M 75003 [7013]	3	Multicenter, double-blind, parallel	2.5 20	daily weekly Total =	121 114 235	48 weeks	at least 1 hour	Europe North America	Spine BMD (L1-L4)
MF 4391 [7012]	3	Multicenter, open-label, parallel	2.5 2.5	daily daily Total =	106 107 213	1 year	30 minutes 60 minutes	Europe North America	Spine BMD (L1-L4)

1 Intermittent treatment of 20 mg qd for 12 doses at the start of every 3 months. Patients received matching placebo on days without active treatment.
2 LSBMD Lumbar Spine Bone Mineral Density.

Table 0.1.3

Oral Ibandronate PMO Prevention Studies

Protocol	Phase	Design	Dose (mg)	Frequency	Patients Treated (N)	Duration	Pre-treatment Fasting	Location	Stratification	Primary efficacy variable[1]
MF 4499 [7014]	2/3	Multicenter, double-blind, placebo-controlled, parallel, dose-finding	placebo 0.5 1.0 2.5	daily daily daily daily Total =	162 162 166 163 653	2 years	at least 30 minutes	North America	by baseline LS BMD and time since menopause	Spine BMD (L1-L4)
MF 4500 [7015]	2/3	Multicenter, double-blind, placebo-controlled, parallel, dose-finding	placebo 5 10 20 Total =	weekly weekly weekly weekly	158 156 154 159 630	2 years	at least 30 minutes[2]	Europe	by baseline LS BMD and time since menopause	Spine BMD (L1-L4)

1 LS BMD (L1-L4) = Lumbar Spine Bone Mineral Density (L1-L4)
2 The post-dose fasting period was changed from at least 60 minutes to at least 30 minutes during the study

Table 0.1.4

Intravenous Ibandronate PMO Treatment Studies

Protocol	Phase	Design	Dose (mg)	Frequency	Patients Treated (N)	Planned Duration	Pre-treatment Fasting	Location	Primary efficacy variable[1]
MF 4336 [7020]	3	Multicenter, double-blind, placebo-controlled, parallel, randomized, intravenous	placebo 0.5 1.0 Total =	quarterly quarterly quarterly	946 951 [illegible] 2462	3 years	no fasting required	Europe North America	vertebral fracture
MF 4476 [7025]	2/3	Multicenter, double-blind, placebo-controlled, parallel, randomized, intravenous, dose-finding	placebo 1.0 2.0 Total =	quarterly quarterly quarterly	128 131 261 520	2 years[2]	no fasting required	Europe	LS BMD (L2-L4)
MF 4561 [7018]	2	Multicenter, double-blind, placebo-controlled, parallel, randomized, intravenous, dose-finding	placebo 0.25 0.5 1.0 2.0 Total =	quarterly quarterly quarterly quarterly quarterly	20 24 27 26 27 126	1 year	no fasting /required	Europe	LS BMD (L2-L4)

1 LS BMD (L2-L4) = Lumbar Spine Bone Mineral Density (L2-L4)
2 This study was prematurely terminated due to the insufficient fracture risk reduction observed with 1.0 mg i.v. ibandronate in MF 4336

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/s/

Japobrata Choudhury
5/15/03 03:14:26 PM
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Steve Wilson
5/15/03 03:25:50 PM
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Todd Sahlroot
5/16/03 08:32:13 AM
BIOMETRICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

NDA:	21-455
Name of drug:	Bonviva® (ibandronate sodium)
Applicant:	Hoffmann-La Roche Inc.
Indication:	Treatment and prevention of postmenopausal osteoporosis
Documents reviewed:	\\CDSESUB1\N21455\N_000\2002-07-15\pharmtox\tox\j8.pdf \\CDSESUB1\N21455\N_000\2002-07-15\pharmtox\tox\j14.pdf \\CDSESUB1\N21455\N_000\2002-07-15\pharmtox\tox\j15.pdf
Project manager:	Randy Hedin (HFD-510)
Pharmacological reviewer:	Gemma Kuijpers, Ph.D. (HDF-510)
Dates:	Received 7/15/02; user fee (10 months) 5/16/03
Statistical reviewer:	Cynthia Liu, MA (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
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Biometrics division director:	Ed Nevius, Ph.D. (HFD-715)

Keywords: NDA review, carcinogenicity studies, survival, neoplastic lesions

TABLE OF CONTENTS

Summary of Statistical Review

- Documents of three oncogenicity studies (1 rat and 2 mice) with two sexes each, submitted by the sponsor along with electronic data sets, were reviewed.

- Dose levels for the 104-week oral gavage Wistar rat study were 0, 3, 7, and 15 mg/kg/day; 0, 5, 20, and 40 mg/kg/day for the 18-month oral gavage NMRI mouse study; and 0, 5, 20, and 80 mg/kg/day for the 90-week drinking water NMRI mouse study.

- According to the sponsor, the increased mortality rates observed in the high-dose groups in both sexes in the 18-month oral gavage mouse study were a result of respiratory distress due to the irritant nature of the dosing solutions. Thus, an additional set of the control and high-dose group animals were studies. Also, the 90-week drinking water mouse study was therefore conducted.

- Since the reductions in body weight and dose levels for the 3 carcinogenicity studies were in a reasonable range according to the reviewing pharmacologist, although there were significant positive trends in mortality in the male rat study and in the male and female oral gavage mouse study, the toxicity effects on survival were considered not to be detrimental in those cases.

- The number of animals with adequate treatment exposure was generally sufficient with respect to the duration of each study, except the high-dose females in the oral gavage mouse study, where most of them died early as a result of respiratory distress.

- The only significant tumor findings among the 3 carcinogenicity studies were observed in the cases of subcapsular cell adenoma Type A, Type B, and/or subcapsular cell adenocarcinoma of the adrenal gland in the females of the drinking water mouse study, where significant positive trends were associated with a significantly increased tumor incidence in the high-dose group when compared to the control. However, the males in this study did not exhibit such significant findings, nor were the two sexes in the oral gavage mouse study.

- There were no analyses of combining tumors, tissues, and/or related hyperplastic lesions required by the reviewing pharmacologist.

Introduction

The sponsor has submitted three oncogenicity studies (1 rat and 2 mice) with two sexes each, conducted by laboratories in German, for the new drug application (NDA 21-455) for Bonviva® (ibandronate sodium) Tablets. The purpose of these three oncogenicity studies was to determine any effects of the test article on the incidence and morphology of tumors following oral gavage administration once daily to the rats for at least 104 weeks and oral gavage and drinking water administration to the mice for at least 18 months and 90 weeks, respectively.

This reviewer has performed her own independent statistical analyses on survival and neoplastic lesions, using the electronic data sets submitted by the sponsor. The FDA's Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (May 2001) was used as a reference. The 6 study designs are briefly described below, followed by this reviewer's analysis methods and discussion in regard to the differences, if any, between the sponsor and reviewer's results.

Study Design

The group designation, dose level, and number of animals per group for the rat and mouse studies are provided below. The report numbers for the oral gavage rat study, oral gavage mouse study, and drinking water mouse study are J8, J14, and J15, respectively.

Group	Rat (Oral Gavage)			Mouse (Oral Gavage)			Mouse (Drinking Water)		
	Dose Level mg/kg/day	# Animals per group		Dose Level Mg/kg/day	# Animals per group		Dose Level mg/kg/day	# Animals per group	
		M	F		M	F		M	F
1. Control	0	50	50	0	140	140	0	100	100
2. Low	3	50	50	5	55	55	5	50	50
3. Mid	7	50	50	20	55	55	20	50	50
4. High	15	50	50	40	85	85	80	50	50

As indicated in the sponsor's oral gavage mouse study report (J14), the original sample sizes were 110 for the control and 55 for each of the ibandronate treated groups (denoted as subset 0). However, due to the high mortality, particularly in the 40-mg/kg/day group, an additional 30 animals for the control and high-dose groups each were studied (denoted as subset 1) for both sexes.

Reviewer's Analysis Methods

Survival. Evaluations of dose-response trend in mortality and group comparisons were conducted using Cox-Tarone binary regression (parametric) and Gehan-Breslow (nonparametric) tests. The former method is weighted more heavily toward late incidences and the latter method is weighted more heavily toward early incidences due to treatment. As a result, both are valuable tools for incidence data with onset times. Kaplan-Meier product limit survival curves were a supplementary tool to examine the survival distribution patterns among the study groups. One-sided tail probabilities for trend and group comparisons are evaluated at the 5% significance level.

Neoplastic Lesions. To minimize Type I (false positive) error rate, neoplastic lesions were chosen for statistical analyses if more than 1 occurrence was observed in any of the study groups. For example, 1, 0, 1, and 0 corresponding to the incidences of Groups 1-4 would not be chosen for the analysis; while 1, 0, 2, and 0 for Groups 1-4, respectively, would be.

The occult tumors (incidental and/or fatal) were analyzed by interval-based exact permutation test incorporating cause of death information. The cut-off points used for the intervals were Weeks 0-52, 53-78, 79-92, 93-before terminal sacrifice, and terminal sacrifice for the rat study, which are based on the suggestions from National Toxicology Program (NTP). Since the durations of the two mouse studies were shorter than 104 weeks, this reviewer used Weeks 0-26, 27-52, 53-before terminal sacrifice, and terminal sacrifice for the 18-month oral gavage mouse study and Weeks 0-26, 27-52, 53-78, 79-before terminal sacrifice, and terminal sacrifice for the 90-week drinking water mouse study. The palpable (superficial) tumors were also analyzed by interval-based exact permutation test as in the case of fatal tumors, using the first palpation time (provided in the sponsor's electronic data files) as the tumor onset time. SAS PROC MULTTEST (1999) was used to implement the interval-based exact permutation test. Comparisons of control versus treated groups were performed only if there was a significant trend in the incidence data.

The benign and malignant neoplastic lesions, which met the selection criterion for the analysis, were evaluated individually as well as combined. In the cases of multiple-organ findings (e.g., hemangioma, hemangiosarcoma, lipoma, liposarcoma, fibroma, and fibrosarcoma), the incidences were counted by animal as well as by tissue type. They were evaluated statistically if they met the selection criterion for the analysis. The statistical results for these cases may be biased because not all the animals were examined for every tissue. This reviewer has selected combined tumor types and/or combined organ types, where appropriate, for the analyses based on the work of McConnell et al. (1986). There were no combined cases required by the reviewing pharmacologist.

Since whether tumor incidence rates increase as doses increase is the main concern of the FDA/CDER pre-clinical review team regardless of the real direction indicated by the data, upper-tailed probabilities (p-values) were, therefore, always computed in testing for positive trend and group comparisons. The following table provides the criterion for determining the statistical significance according to the FDA's guidance (May 2001).

	Test for Positive Trend	Control-High Pairwise Comparisons
Standard 2-Year Studies with 2 Species and 2 Sexes	Common and rare tumors are tested at 0.005 and 0.025 significance levels, respectively.	Common and rare tumors are tested at 0.01 and 0.05 significance levels, respectively.

Since no specific criterion is given in the guidance for any traditional study with duration time shorter than 104 weeks, in order to be consistent with the rat study, this reviewer used the same (above) criterion for those two mouse studies as well. Common tumor is defined as a tumor type with background (control) rate >1% and rare tumor with background (control) rate ≤1%. The concurrent control and historical control (where applicable) data were both taken into consideration in determining commonality of a tumor.

In the sponsor's electronic tumor data files for the two mouse studies (J14 and J15), some animals were coded as planned intermittent sacrifice animals, which were not mentioned in the study designs. For the purpose of statistical analyses, this reviewer changed their codes to natural death category due to the fact that they did not die during the terminal sacrifice interval. Also, terminal sacrifice animals in the electronic tumor data file for J14 were mistakenly coded as natural death animals and vice versa. In addition, in the sponsor's tumor analyses for those two mouse studies, the animals that died before their first tumor was noted were excluded from the set of total number of animals at risk. This reviewer thinks that those animals should not be excluded due to the following two reasons: (1) survival time-adjusted analysis, as opposed to unadjusted analysis, has been widely used for tumor analyses to adjust for any intercurrent mortality differences among the study groups and (2) excluding any randomized animals would reduce the power of the test. Therefore, those animals were included in this reviewer's tumor analyses. Nevertheless, it did not cause any major discrepancies between the sponsor and this reviewer's results and conclusion.

Due to the high mortality occurring in the higher dose groups in both subset 0 and subset 1 of the oral gavage mouse study (J14), the sponsor combined the two sets of data to perform the

tumor analyses. It is not clear to this reviewer if subset 1 animals were part of the original randomized animals. Also, the first days of treatment for subsets 0 and 1 animals were about 8 weeks apart; therefore, it is possible that the subset 1 animals may be 8 weeks older than the subset 0 animals when the treatment started.

Arithmetic dose levels were used for all the analyses in this review.

Reviewer's Results and Discussion

The 104-Week Rat Study – Oral Gavage (Report No. J8)

Survival. There was a significant positive trend ($p = 0.0139$) in mortality in the male rats (Table 1), which was driven by the significantly higher mortality rates in the mid- (7 mg/kg/day) and high-dose (15 mg/kg/day) groups when compared to the control ($p = 0.0385$ and 0.0234, respectively, based on Gehan-Breslow test). However, the female rats did not show such significant findings. In fact, a negative trend in mortality (not statistically significant) was observed in the females (Table 2), which was associated with a marginally significantly decreased ($p = 0.0431$) mortality rate in the low-dose group (3 mg/kg/day), but not in the mid- and high-dose groups, when compared to the control.

The Kaplan-Meier product limit survival curves for the male and female rats are depicted in Figures 1 and 2, respectively, which show at least 70% of the male rats and 80% of the female rats in each group still surviving at the beginning of Week 90. This indicates that there was sufficient number of animals with adequate treatment exposure in this 104-week oral gavage Wistar rat study, according to the FDA's guidance (May 2001).

Neoplastic Lesions. According to the sponsor, there were significant positive trends in the incidences of benign (fibrous) histiocytomas of the skin in the males and of c-cell adenoma in the females (both $p < 0.05$), which were judged to be not significant based on this reviewer's analyses ($p = 0.0506$ and 0.0650, respectively).

In summary, there were no significant positive trends in the incidences of any common tumors at the $p \leq 0.005$ significance level and of any rare tumors at the $p \leq 0.025$ significance level in either of the two sexes in this Wistar rat study, as shown in Tables 3 (males) and 4 (females).

The 18-Month Mouse Study – Oral Gavage (Report No. J14)

Survival. There were highly significant positive trends ($p = 0.0000$) in mortality in both sexes based on either subset 0 or subset 0+1 (pooled data), as shown in Tables 5 (males) and 6 (females). The significant trends were mainly due to the highly significantly increased

mortality rates in the mid- (20 mg/kg/day) and high-dose (40 mg/kg/day) groups (at least or approximately two-fold increase) when compared to the control ($p \leq 0.0001$ for all cases, based on Gehan-Breslow test). Subset 1, where only the control and high-dose groups were evaluated, also exhibited similar significant positive findings in both sexes.

As depicted in Figures 3-5 for the male and Figures 6-8 for the female Kaplan-Meier product limit survival curves, significantly more animals in the mid- and particularly the high-dose groups died early than the control and low-dose group animals. There were at least 50% of the males in each group still surviving at the beginning of Week 60 in this 18-month NMRI mouse study. However, only around 27% and 38% of the high-dose females in subset 0 and subset 0+1, respectively, were still surviving at the beginning of Week 60, which may imply not having enough high-dose females with adequate treatment exposure for oncogenic evaluation. According to the sponsor, the increased mortality rates in the higher dose groups in both sexes of this study were a result of respiratory distress due to the irritant nature of the dosing solutions. Therefore, another mouse study with drinking water (see below) was conducted.

Neoplastic Lesions. Since a high mortality was observed in the high-dose group in subset 0, to increase the power of the test, this reviewer performed the tumor analyses on the combined data set (subset 0+1). There were no significant positive trends in the incidences of any common tumors at the $p \leq 0.005$ significance level and of any rare tumors at the $p \leq 0.025$ significance level in either of the two sexes, based on the pooled data (subset 0+1) of the oral gavage NMRI mouse study, as shown in Tables 7 (males) and 8 (females). This reviewer also performed an additional set of analyses for the females by excluding the high-dose group and found no significant findings as well.

The 90-Week Mouse Study – Drinking Water (Report No. J15)

Survival. There was a borderline significant decrease in mortality in the low-dose group (5 mg/kg/day) of the males (Table 9, $p = 0.0496$ based on Gehan-Breslow test) when compared to the control, but not in the mid- (20 mg/kg/day) or high-dose (80 mg/kg/day) groups of this sex. In addition, a significant decrease ($p = 0.0293$) in mortality was also observed in the female high-dose group (Table 10). However, neither of these significant group comparisons was associated with any significant trends in either sex. In fact, both sexes showed a negative trend in mortality (not statistically significant) in this study.

The male and female Kaplan-Meier product limit survival curves are depicted in Figures 9 and 10, respectively, which show at least 80% of the male mice and 65% of the female mice in each group still surviving at the beginning of Week 80. This indicates that there was

sufficient number of animals with adequate treatment exposure in this 90-week drinking water NMRI mouse study, according to the FDA's Guidance (May 2001).

Neoplastic Lesions. The subcapsular cell adenoma Type A of the adrenal gland in the females showed incidence rates of 0/100, 1/50, 1/50, and 3/50 for control, low-, mid-, and high-dose groups, respectively, with a trend p-value 0.0228, which was judged to be statistically significant by this reviewer due to an 0% incidence rate in the concurrent control (rare tumor type). The Type A/Type B combined (0/100, 1/50, 1/50, and 4/50 corresponding to Groups 1-4) and Type A/Type B/Adenocarcinoma combined (0/100, 1/50, 2/50, and 4/50 corresponding to Groups 1-4) also exhibited a significant positive trend with p-value 0.0069 and 0.0099, respectively (Table 12). Evidently, those significant trends were driven by the increased incidences in the high-dose (80 mg/kg/day) groups. The p-values for control versus high-dose comparison in these cases were 0.0594, 0.0223, and 0.0223, respectively. This reviewer also performed an additional set of analyses using logistic regression method for those 3 tumor types and found the results (see below) were even more significant than those using exact permutation test.

	Exact Permutation Test		Logistic Regression Test	
Female – Adrenal Gland	Trend p	Groups 1 vs. 4 p	Trend p	Groups 1 vs. 4 p
Subcap. cell adenoma Type A	0.0228 *	0.0594	0.0134 *	0.0406 #
Subcap. cell adenoma Type A/B	0.0069 *	0.0223 #	0.0026 *	0.0144 #
Subcap. cell adenoma Type A/B/Adenocarcinoma	0.0099 *	0.0223 #	0.0051 *	0.0144 #
* = Significant trend at $p \leq 0.025$ for rare tumor type # = Significant group comparison at $p \leq 0.05$ for rare tumor type				

The p-value 0.0594 was borderline not significant at $p \leq 0.05$ for control versus high-dose comparison; however, since logistic regression test showed a marginally significant p-value, 0.0406, special attention should be paid to this case.

No other significant findings were observed in the females. Also, none of the tumors in the males showed significant findings (Table 11) in this drinking water NMRI mouse study.

Conclusion

Since the reductions in body weight and dose levels for the 104-week rat study, 18-month oral gavage mouse study, and 90-week drinking water mouse study were in a reasonable

range according to the reviewing pharmacologist, although there were significant positive trends in mortality in the male rat study and in the male and female oral gavage mouse study, the toxicity effects on survival were considered not to be detrimental in those cases.

The only significant tumor findings among the rat and mouse studies were observed in the cases of subcapsular cell adenoma Type A, Type B, and/or subcapsular cell adenocarcinoma of the adrenal gland in the females of the drinking water mouse study, where significant positive trends were associated with a significantly increased tumor incidence in the high-dose group when compared to the control. They were judged to be rare tumors by this reviewer due to 0% incidence rates in the concurrent controls. The males in this study did not exhibit such significant findings, nor were the two sexes in the oral gavage mouse study; in fact;.the tumor incidences in these cases were all in a negative direction with concurrent control rates >1% except subcapsular cell adenoma Type A of the females in the oral gavage mouse study (0.7%).

Based on the examinations of the validity of the study designs, the number of animals with adequate treatment exposure was generally sufficient with respect to the duration of each study, except the high-dose females in the oral gavage mouse study, where most of them died early as a result of respiratory distress due to the irritant nature of the dosing solutions.

Labeling Comments

[redacted] However, there were significant positive trends and control versus high-dose comparisons in the incidences of subcapsular cell adenoma Type A, Type B, and/or subcapsular cell adenocarcinoma of the adrenal gland observed in the females of the 90-week drinking water mouse study based on this reviewer's analyses, even though the males in this study and the males and females in the 18-month oral gavage study did not show such significant findings.

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

CC: HFD-510/RHedin, KDavisbruno, GKuijpers
HFD-715/ENevius, KLin, TSahlroot, CLiu
HFD-700/CAnello

Appendix I – Tables for 104-Week Oral Gavage Rat Study

104 Week Oral Gavage Carcinogenicity Study with BM 21.0955.Na in the Rat

Table 1 (Report No. J8)
Results of Statistical Analyses of Mortality Data for Male Rats

Group	1	2	3	4
Dose	0	3	7	15
Number of Deaths				
Weeks 0-52	0	1	5	7
Weeks 53-78	0	3	2	3
Weeks 79-92	5	6	3	4
Weeks 93-before term sac	5	1	7	3
Terminal Sacrifice Weeks	40	39	33	33
Unadjusted Mortality	10/50 (0.20)	11/50 (0.22)	17/50 (0.34)	17/50 (0.34)
Kaplan-Meier Estimate (Final)	0.200	0.220	0.340	0.340

	Cox-Tarone Test	Gehan-Breslow Test
Groups 1 vs. 2-4 Trend (one-sided p)	0.0237 ≤ p ≤ 0.0274 + *	0.0139 + *
Departure from Trend (two-sided p)	0.6612	0.7167
Homogeneity (two-sided p)	0.1791	0.1384
Groups 1 vs. 2 (one-sided p)	0.4253 +	0.2830 +
Groups 1 vs. 3 (one-sided p)	0.0688 +	0.0385 + *
Groups 1 vs. 4 (one-sided p)	0 0546 +	0.0234 + *

+ = Effect in the positive (increasing) direction
* = Significant at p ≤ 0.05

Table 2 (Report No. J8)
Results of Statistical Analyses of Mortality Data for Female Rats

Group	1	2	3	4
Dose	0	3	7	15
Number of Deaths				
Weeks 0-52	3	0	1	3
Weeks 53-78	3	2	2	2
Weeks 79-92	5	2	7	2
Weeks 93-before term sac	7	7	8	6
Terminal Sacrifice Weeks	32	39	32	37
Unadjusted Mortality	18/50 (0.36)	11/50 (0.22)	18/50 (0.36)	13/50 (0.26)
Kaplan-Meier Estimate (Final)	0.360	0.220	0 360	0 260

	Cox-Tarone Test	Gehan-Breslow Test
Groups 1 vs. 2-4 Trend (one-sided p)	0.3041 ≤ p ≤ 0.3246 –	0.3044 ≤ p ≤ 0.3045 –
Departure from Trend (two-sided p)	0.1892	0.1785
Homogeneity (two-sided p)	0.3044	0 2948
Groups 1 vs. 2 (one-sided p)	0.0741 –	0.0431 – *
Groups 1 vs. 3 (one-sided p)	0.4480 –	0.4073 –
Groups 1 vs. 4 (one-sided p)	0.1893 –	0.1529 –

– = Effect in the negative (decreasing) direction
* = Significant at p ≤ 0.05

Table 3 (Report No. J8)
Results of Statistical Analyses of Neoplastic Lesions for Male Rats

Group	1	2	3	4
Dose (mg/kg/day)	0	3	7	15
Mesenteric Lymph Node – Hemangioma				
Fatal Incidence	0	0	0	0
Incidental Incidence	9	6	1	2
Total Incidence Rate	9/50	6/50	1/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9912				
Kidney – Lipoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	2	0	0
Total Incidence Rate	0/50	2/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7759				
Urinary Bladder – Transitional Cell Papilloma				
Fatal Incidence	0	0	0	0
Incidental Incidence	9	2	0	0
Total Incidence Rate	0/50	2/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7567				
Thymus – Thymoma				
Fatal Incidence	0	1	0	0
Incidental Incidence	0	1	0	1
Total Incidence Rate	0/50	2/50	0/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5082				
Pancreas – Islet Cell Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	1	3	1	1
Total Incidence Rate	1/50	3/50	1/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6195				
Pancreas – Islet Cell Carcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	0	2	0
Total Incidence Rate	0/50	0/50	2/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4552				
Pancreas – Islet Cell Adenoma/Carcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	1	3	3	1
Total Incidence Rate	1/50	3/50	3/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5386				
Thyroid Gland – C-Cell Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	0	0	2
Total Incidence Rate	2/50	0/50	0/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.2713				
Thyroid Gland – C-Cell Carcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	1	5	0	2
Total Incidence Rate	1/50	5/50	0/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5324				

Table 3 (Report No. J8) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Rats

Group	1	2	3	4
Dose (mg/kg/day)	0	3	7	15
Thyroid Gland – C-Cell Adenoma/Carcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	3	5	0	4
Total Incidence Rate	3/50	5/50	0/50	4/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.3877				
Adrenal Gland – Cortical Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	1	2	0
Total Incidence Rate	0/50	1/50	2/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5419				
Adrenal Gland – Cortical Adenoma/Carcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	1	3	0
Total Incidence Rate	0/50	1/50	3/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4919				
Adrenal Gland – Phaeochromocytoma				
Fatal Incidence	2	0	0	0
Incidental Incidence	3	0	0	0
Total Incidence Rate	5/50	0/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 1.0000				
Adrenal Gland – Ganglioneuroma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	2	0	0
Total Incidence Rate	0/50	2/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7759				
Pituitary Gland – Adenoma, Pleomorphic, P. Dist.				
Fatal Incidence	0	0	0	0
Incidental Incidence	4	2	4	3
Total Incidence Rate	4/50	2/50	4/50	3/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4734				
Pituitary Gland – Hemorrhagic Adenoma, P. Dist.				
Fatal Incidence	0	0	0	0
Incidental Incidence	9	6	8	6
Total Incidence Rate	9/50	6/50	8/50	6/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6383				
Pituitary Gland – Pleomorphic/Hemorrhagic/Spongiocytic Adenoma, P. Dist.				
Fatal Incidence	0	0	0	0
Incidental Incidence	13	8	13	9
Total Incidence Rate	13/50	8/50	13/50	9/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5948				
Skin – Squamous Cell Papilloma				
Total Incidence Rate	2/50	0/50	1/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8624				

Table 3 (Report No. J8) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Rats

Group	1	2	3	4
Dose (mg/kg/day)	0	3	7	15
Skin – Squamous Cell Papilloma/Carcinoma, Keratinizing				
Total Incidence Rate	2/50	1/50	1/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9021				
Skin – Malignant Pleomorphic Fibrous Histiocytoma				
Total Incidence Rate	2/50	0/50	0/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5966				
Skin – Histiocytoma, Benign				
Total Incidence Rate	0/50	0/50	0/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0506				
Skin – Malignant Pleomorphic Fibrous Histiocytoma/Histiocytoma, Benign				
Total Incidence Rate	2/50	0/50	0/50	3/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.1080				
Mammary Gland – Fibroma				
Total Incidence Rate	1/50	4/50	1/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8888				
Mammary Gland – Fibroma/Fibroadenoma				
Total Incidence Rate	2/50	4/50	1/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 7985				
Hemolymphoreticular System (MPS) – Histiocytic Sarcoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	1	2	0
Total Incidence Rate	0/50	1/50	2/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5426				
Testes – Leydig Cell Tumor				
Fatal Incidence	0	0	0	0
Incidental Incidence	1	1	0	2
Total Incidence Rate	1/50	1/50	0/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.2096				
Multiple Organs – Lipoma (from Body Cavity, Kidney, and Skin)				
Fatal Incidence	0	0	0	0
Incidental Incidence	1	2	1	0
Total Incidence Rate	1/50	2/50	1/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8397				
Multiple Organs – Hemangioma/Hemangiosarcoma (from Mesenteric Lymph Node and Spleen)				
Fatal Incidence	0	0	0	0
Incidental Incidence	10	6	1	2
Total Incidence Rate	10/50	6/50	1/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9952				
Multiple Organs – Fibroma/Fibrosarcoma (from Mammary Gland and Skin)				
Total Incidence Rate	2/50	4/50	2/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7710				

Table 4 (Report No. J8)
Results of Statistical Analyses of Neoplastic Lesions for Female Rats

Group	1	2	3	4
Dose (mg/kg/day)	0	3	7	15
Liver – Hepatocellular Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	1	0	0
Total Incidence Rate	2/50	1/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9889				
Mesenteric Lymph Node – Hemangioma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	2	1	0
Total Incidence Rate	0/50	2/50	1/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7476				
Thymus – Thymoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	1	5	3	1
Total Incidence Rate	1/50	5/50	3/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7720				
Ovary – Granulosa Cell Tumor				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	0	0	0
Total Incidence Rate	2/50	0/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 1.0000				
Ovary – Granulosa Cell Tumor/Theca Granulosa Cell Tumor				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	1	1	0
Total Incidence Rate	2/50	1/50	1/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 9316				
Pancreas – Islet Cell Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	4	0	0
Total Incidence Rate	0/50	4/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8857				
Thyroid Gland – C-Cell Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	0	1	2
Total Incidence Rate	0/50	0/50	1/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 0650				
Thyroid Gland – C-Cell Carcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	6	0	0	1
Total Incidence Rate	6/50	0/50	0/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9870				
Thyroid Gland – C-Cell Adenoma/Carcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	6	0	1	3
Total Incidence Rate	6/50	0/50	1/50	3/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 7532				

Table 4 (Report No. J8) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Rats

Group	1	2	3	4
Dose (mg/kg/day)	0	3	7	15
Thyroid Gland – Follicular Cell Carcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	1	0	2
Total Incidence Rate	2/50	1/50	0/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 4573				
Pituitary Gland – Adenoma Pleomorphic, P. Dist.				
Fatal Incidence	1	0	0	0
Incidental Incidence	6	1	12	5
Total Incidence Rate	7/50	1/50	12/50	5/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4087				
Pituitary Gland – Hemorrhagic Adenoma, P. Dist.				
Fatal Incidence	0	0	1	0
Incidental Incidence	23	33	15	22
Total Incidence Rate	23/50	33/50	16/50	22/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8296				
Pituitary Gland – Pleomorphic/Hemorrhagic/Spongiocytic Adenoma, P. Dist.				
Fatal Incidence	1	0	1	0
Incidental Incidence	30	35	27	27
Total Incidence Rate	31/50	35/50	28/50	27/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8757				
Mammary Gland – Fibroma				
Total Incidence Rate	2/50	1/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9878				
Mammary Gland – Fibroadenoma				
Total Incidence Rate	10/50	15/50	10/50	13/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4540				
Mammary Gland – Fibroma/Fibroadenoma				
Total Incidence Rate	12/50	16/50	10/50	13/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6323				
Mammary Gland – Adenocarcinoma				
Total Incidence Rate	4/50	2/50	1/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7897				
Mammary Gland – Fibroadenoma/Adenocarcinoma				
Total Incidence Rate	14/50	16/50	11/50	15/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5648				
Mammary Gland – Fibroma/Fibroadenoma/Adenocarcinoma				
Total Incidence Rate	16/50	17/50	11/50	15/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7193				
Mammary Gland – Cystic Adenoma				
Total Incidence Rate	0/50	0/50	2/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5111				

Table 4 (Report No. J8) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Rats

Group	1	2	3	4
Dose (mg/kg/day)	0	3	7	15
Mammary Gland – Papillary Cystadenoma				
Total Incidence Rate	0/50	2/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8208				
Uterus – Polyp				
Fatal Incidence	0	0	0	0
Incidental Incidence	4	4	6	5
Total Incidence Rate	4/50	4/50	6/50	5/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.3587				
Uterus – Adenocarcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	1	0	2
Total Incidence Rate	0/50	1/50	0/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.1230				
Multiple Organs – Hemangioma/Hemangiosarcoma (from Mesenteric Lymph Node and Body Cavity)				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	2	1	1
Total Incidence Rate	0/50	2/50	1/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4413				
Multiple Organs – Lipoma (from Stomach and Body Cavity)				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	2	1	0
Total Incidence Rate	0/50	2/50	1/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7364				
Multiple Organs – Lipoma/Liposarcoma (from Stomach and Body Cavity)				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	2	1	1
Total Incidence Rate	0/50	2/50	1/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4266				

Figure 1 (Report No. J8)
Kaplan-Meier Product Limit Survival Curves for Male Rats

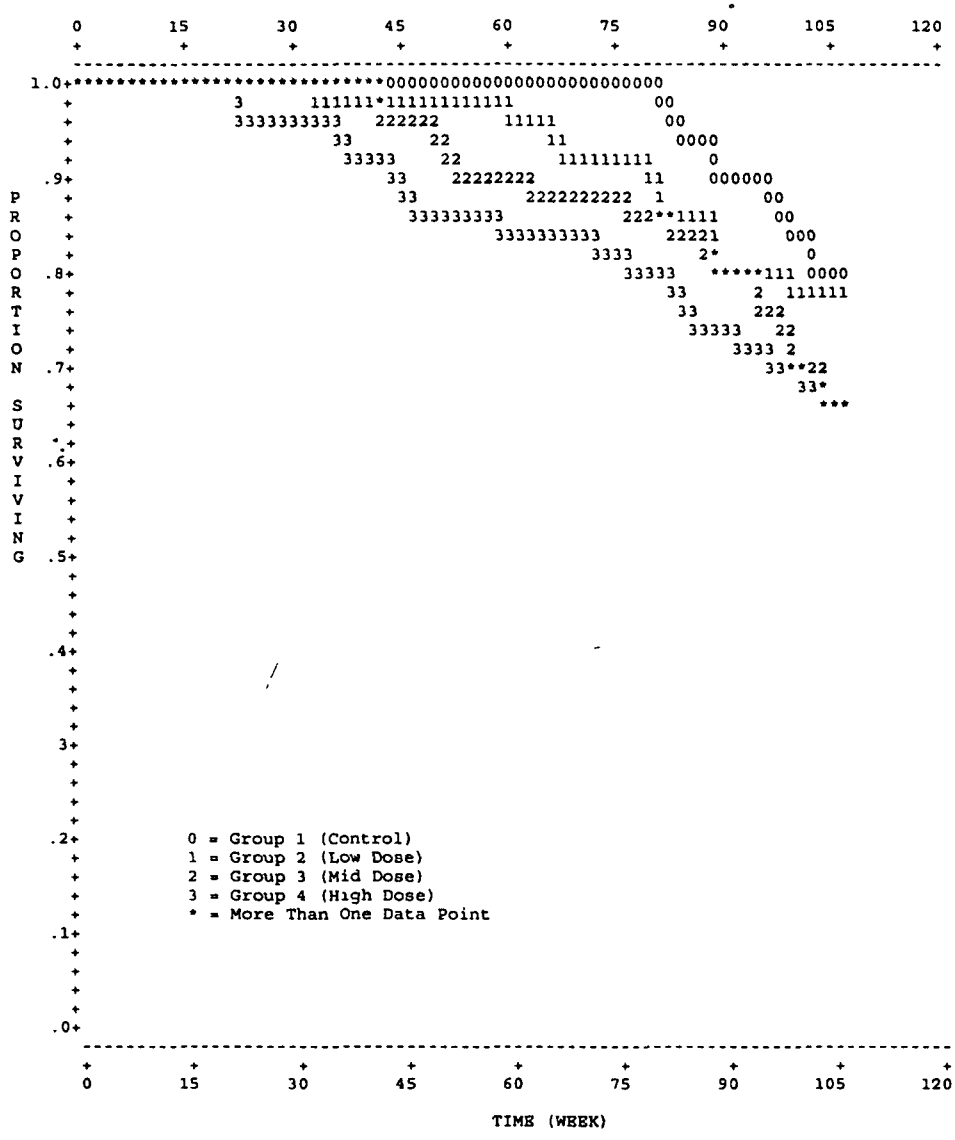
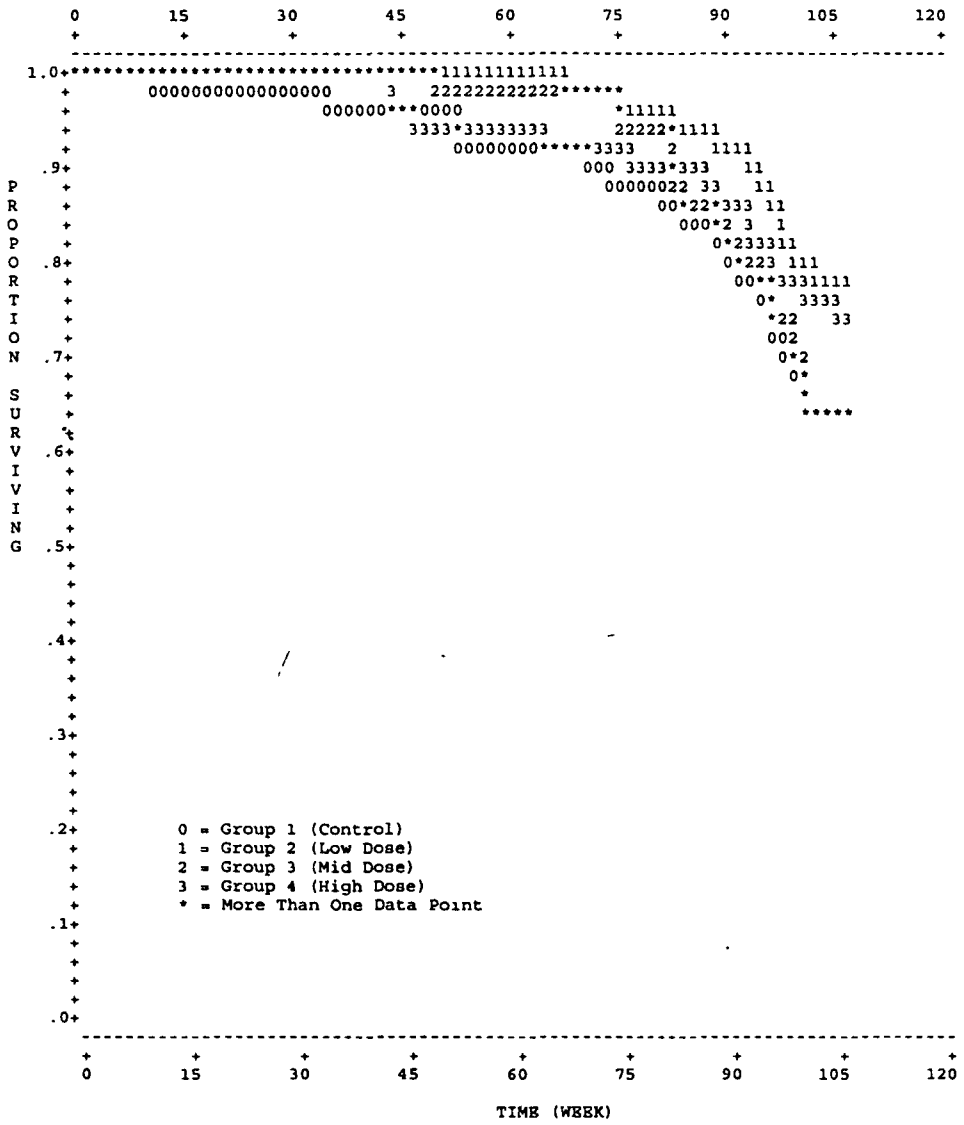


Figure 2 (Report No. J8)
Kaplan-Meier Product Limit Survival Curves for Female Rats



Appendix II – Tables for 18-Month Oral Gavage Mouse Study

Carcinogenicity Study in Mice with BM 21.0955.Na Administered by Oral Gavage

Table 5 (Report No. J14)
Results of Statistical Analyses of Mortality Data for Male Mice Administered by Oral Gavage

Group	1	2	3	4
Dose	0	5	20	40
Subset 0 (main study)				
Unadjusted Mortality	23/100	11/55	26/55	35/55
Kaplan-Meier Estimate (Final)	0.209	0.200	0.473	0.636
Cox-Tarone Test: One-sided p-value	0.0000 + **	0.4997 +	0.0001 + **	0.0000 + **
Gehan-Breslow Test: One-sided p-value	0 0000 + **	0 4466 +	0.0000 + **	0 0000 + **
Subset 1 (additional study)				
Unadjusted Mortality	7/30			15/30
Kaplan-Meier Estimate (Final)	0.233			0.500
Cox-Tarone Test: One-sided p-value				0.0177 + *
Gehan-Breslow Test: One-sided p-value				0.0066 + **
Subset 0+1 (pooled data)				
Unadjusted Mortality	30/140	11/55	26/55	50/85
Kaplan-Meier Estimate (Final)	0.214	0 200	0.473	0.603
Cox-Tarone Test: One-sided p-value	0.0000 + **	0.4684 –	0.0000 + **	0.0000 + **
Gehan-Breslow Test: One-sided p-value	0.0000 + **	0.4773 +	0.0000 + **	0 0000 + **
Number of Deaths				
Weeks 0-26	0	3	6	10
Weeks 27-52	3	2	8	23
Weeks 53-before term sac	27	6	12	17
Terminal Sacrifice Weeks	110	44	29	35

P-value under Group 1 is for trend probability; p-values under the other groups are for group comparison probability of that treated group versus the control (Group 1)

+ = Effect in the positive (increasing) direction
– = Effect in the negative (decreasing) direction
* = Significant at $p \leq 0.05$
** = Significant at $p \leq 0.01$

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Table 6 (Report No. J14)
Results of Statistical Analyses of Mortality Data for Female Mice Administered by Oral Gavage

Group	1	2	3	4
Dose	0	5	20	40
Subset 0 (main study)				
Unadjusted Mortality	26/110	19/55	27/55	49/55
Kaplan-Meier Estimate (Final)	0 239	0 345	0.491	0.891
Cox-Tarone Test: One-sided p-value	0.0000 + **	0.0509 +	0.0001 + **	0.0000 + **
Gehan-Breslow Test: One-sided p-value	0.0000 + **	0.0243 + *	0.0000 + **	0.0000 + **
Subset 1 (additional study)				
Unadjusted Mortality	11/30			19/30
Kaplan-Meier Estimate (Final)	0.367			0.633
Cox-Tarone Test: One-sided p-value				0.0111 + *
Gehan-Breslow Test: One-sided p-value				0.0032 + **
Subset 0+1 (pooled data)				
Unadjusted Mortality	37/140	19/55	27/55	68/85
Kaplan-Meier Estimate (Final)	0.270	0 345	0.491	0 800
Cox-Tarone Test: One-sided p-value	0.0000 + **	0.1031 +	0.0002 + **	0.0000 + **
Gehan-Breslow Test: One-sided p-value	0.0000 + **	0.0528 +	0.0001 + **	0.0000 + **
Number of Deaths				
Weeks 0-26	1	4	9	31
Weeks 27-52	6	4	5	14
Weeks 53-before term sac	30	11	13	23
Terminal Sacrifice Weeks	103	36	28	17

P-value under Group 1 is for trend probability; p-values under the other groups are for group comparison probability of that treated group versus the control (Group 1).

+ = Effect in the positive (increasing) direction
* = Significant at $p \leq 0.05$
** = Significant at $p \leq 0.01$

Table 7 (Report No. J14)
Results of Statistical Analyses of Neoplastic Lesions for Male Mice Administered by Oral Gavage

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	40
Liver – Hepatocellular Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	2	1	2
Total Incidence Rate	0/140	2/55	1/55	2/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.1943				
Liver – Hepatocellular Carcinoma				
Fatal Incidence	2	1	0	0
Incidental Incidence	5	1	0	2
Total Incidence Rate	7/140	2/55	0/55	2/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6970				
Liver – Hepatocellular Adenoma/Carcinoma				
Fatal Incidence	2	1	0	0
Incidental Incidence	5	3	1	4
Total Incidence Rate	7/140	4/55	1/55	4/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4766				
Liver – Hemangiosarcoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	0	0	0
Total Incidence Rate	2/140	0/55	0/55	0/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 1.0000				
Adrenal Gland – Subcap. Cell Adenoma Type B				
Fatal Incidence	0	0	0	0
Incidental Incidence	15	8	1	4
Total Incidence Rate	15/140	8/54	1/54	4/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8582				
Adrenal Gland – Subcap. Cell Adenoma Mixed				
Fatal Incidence	0	0	0	0
Incidental Incidence	13	7	3	2
Total Incidence Rate	13/140	7/54	3/54	2/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9010				
Adrenal Gland – Subcap. Cell Adenoma Type B/Mixed				
Fatal Incidence	0	0	0	0
Incidental Incidence	28	15	4	6
Total Incidence Rate	28/140	15/54	4/54	6/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9613				
Adrenal Gland – Cortical Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	19	6	2	6
Total Incidence Rate	19/140	6/54	2/54	6/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7689				
Adrenal Gland – Medullary Malignant Pheochromocytoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	0	0	0
Total Incidence Rate	2/140	0/54	0/54	0/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 1.0000				

Table 7 (Report No. J14) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Mice Administered by Oral Gavage

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	40
Adrenal Gland – Medullary Benign Pheochromocytoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	1	0	0
Total Incidence Rate	2/140	1/54	0/54	0/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 8697				
Adrenal Gland – Medullary Benign/Malignant Pheochromocytoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	4	1	0	0
Total Incidence Rate	4/140	1/54	0/54	0/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9673				
Lung – Bronchiolo-Alveolar Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	23	10	11	13
Total Incidence Rate	23/140	10/55	11/55	13/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0797				
Lung – Bronchiolo-Alveolar Carcinoma				
Fatal Incidence	3	1	0	0
Incidental Incidence	12	8	1	2
Total Incidence Rate	15/140	9/55	1/55	2/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9782				
Lung – Bronchiolo-Alveolar Adenoma/Carcinoma				
Fatal Incidence	3	1	0	0
Incidental Incidence	34	18	12	15
Total Incidence Rate	37/140	19/55	12/55	15/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4657				
Urinary Bladder – Transitional Cell Carcinoma				
Fatal Incidence	1	1	0	1
Incidental Incidence	6	1	0	1
Total Incidence Rate	7/139	2/55	0/55	2/82
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7223				
Pituitary Gland – Adenoma, Pars Distalis				
Fatal Incidence	0	0	0	0
Incidental Incidence	4	0	0	1
Total Incidence Rate	4/134	0/53	0/53	1/83
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6727				
Pituitary Gland – Adenoma, Pars Intermedia				
Fatal Incidence	1	0	0	0
Incidental Incidence	2	0	0	0
Total Incidence Rate	3/134	0/53	0/53	0/83
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 1 0000				
Harderian Gland – Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	11	10	5	4
Total Incidence Rate	11/140	10/55	5/55	4/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5182				

Table 7 (Report No. J14) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Mice Administered by Oral Gavage

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	40
Harderian Gland – Adenocarcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	0	0	0
Total Incidence Rate	2/140	0/55	0/55	0/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 1.0000				
Harderian Gland – Adenoma/Adenocarcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	13	10	5	4
Total Incidence Rate	13/140	10/55	5/55	4/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6439				
Lymphoreticular/Hematopoietic System/Malignant Lymphoma				
Fatal Incidence	3	0	0	2
Incidental Incidence	4	2	0	1
Total Incidence Rate	7/140	2/55	0/55	3/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5116				
Multiple Organs – Hemangiosarcoma (from Liver and Abdominal Cavity)				
Fatal Incidence	1	0	0	0
Incidental Incidence	2	0	0	0
Total Incidence Rate	3/140	0/55	0/55	0/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 1.0000				

Table 8 (Report No. J14)
Results of Statistical Analyses of Neoplastic Lesions for Female Mice Administered by Oral Gavage

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	40
Liver – Hepatocellular Carcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	3	0	0	0
Total Incidence Rate	3/140	0/55	0/55	0/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 1.0000				
Adrenal Gland – Subcap. Cell Adenoma Mixed				
Fatal Incidence	0	0	0	0
Incidental Incidence	4	0	2	0
Total Incidence Rate	4/139	0/55	2/55	0/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7018				
Adrenal Gland – Subcap. Cell Adenoma Type A				
Fatal Incidence	0	0	0	0
Incidental Incidence	1	2	0	0
Total Incidence Rate	1/139	2/55	0/55	0/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6445				
Adrenal Gland – Subcap. Cell Adenoma Type B				
Fatal Incidence	0	0	0	0
Incidental Incidence	3	1	0	0
Total Incidence Rate	3/139	1/55	0/55	0/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9060				
Adrenal Gland – Subcap. Cell Adenoma Type A/Type B/Mixed				
Fatal Incidence	0	0	0	0
Incidental Incidence	8	3	2	0
Total Incidence Rate	8/139	3/55	2/55	0/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8999				
Lung – Bronchiolo-Alveolar Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	7	8	4	7
Total Incidence Rate	7/140	8/55	4/55	7/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0620				
Lung – Bronchiolo-Alveolar Carcinoma				
Fatal Incidence	4	1	1	0
Incidental Incidence	10	7	2	0
Total Incidence Rate	14/140	8/55	3/55	0/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9887				
Lung – Bronchiolo-Alveolar Adenoma/Carcinoma				
Fatal Incidence	4	1	1	0
Incidental Incidence	17	14	6	7
Total Incidence Rate	21/140	15/55	7/55	7/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 6328				
Thymus – Malignant Thymoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	1	0	0
Total Incidence Rate	2/133	1/55	0/54	0/81
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8308				

Table 8 (Report No. J14) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Mice Administered by Oral Gavage

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	40
Thymus – Benign/Malignant Thymoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	3	1	0	0
Total Incidence Rate	3/133	1/55	0/54	0/81
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9073				
Thyroid Gland – Follicular Cell Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	4	1	0	0
Total Incidence Rate	4/139	1/55	0/55	0/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9485				
Ovary – Tubulostromal Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	25	7	4	3
Total Incidence Rate	25/139	7/54	4/54	3/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9397				
Ovary – Tubulostromal Carcinoma				
Fatal Incidence	1	0	0	0
Incidental Incidence	4	3	0	0
Total Incidence Rate	5/139	3/54	0/54	0/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9557				
Ovary – Tubulostromal Adenoma/Carcinoma				
Fatal Incidence	1	0	0	0
Incidental Incidence	29	9	4	3
Total Incidence Rate	30/139	9/54	4/54	3/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9819				
Ovary – Benign Granulosa Cell Tumor				
Fatal Incidence	0	0	0	0
Incidental Incidence	9	1	0	0
Total Incidence Rate	9/139	1/54	0/54	0/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9975				
Ovary – Malignant Granulosa Cell Tumor				
Fatal Incidence	1	0	0	0
Incidental Incidence	1	2	1	1
Total Incidence Rate	2/139	2/54	1/54	1/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.2393				
Ovary – Benign/Malignant Granulosa Cell Tumor				
Fatal Incidence	1	0	0	0
Incidental Incidence	10	3	1	1
Total Incidence Rate	11/139	3/54	1/54	1/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8640				
Ovary – Benign Luteoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	4	2	0	0
Total Incidence Rate	4/139	2/54	0/54	0/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9331				

Table 8 (Report No. J14) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Mice Administered by Oral Gavage

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	40
Ovary – Benign Sertoli Cell Tumor				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	1	0	1
Total Incidence Rate	2/139	1/54	0/54	1/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.3044				
Ovary – Benign/Malignant Sertoli Cell Tumor				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	2	0	1
Total Incidence Rate	2/139	2/54	0/54	1/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5396				
Ovary – Cystadenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	4	0	0	0
Total Incidence Rate	4/139	0/54	0/54	0/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 1.0000				
Ovary – Cystadenoma/Cystadenocarcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	5	1	0	0
Total Incidence Rate	5/139	1/54	0/54	0/84
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9710				
Uterus – Stromal Polyp				
Fatal Incidence	0	0	0	0
Incidental Incidence	4	4	2	2
Total Incidence Rate	4/140	4/55	2/55	2/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.2557				
Pituitary Gland – Adenoma, Pars Distalis				
Fatal Incidence	2	0	0	0
Incidental Incidence	26	9	10	1
Total Incidence Rate	28/138	9/54	10/53	1/82
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9174				
Harderian Gland – Adenoma				
Fatal Incidence	1	0	0	0
Incidental Incidence	11	1	2	2
Total Incidence Rate	12/140	1/55	2/54	2/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6105				
Harderian Gland – Adenoma/Adenocarcinoma				
Fatal Incidence	1	0	0	0
Incidental Incidence	12	1	2	2
Total Incidence Rate	13/140	1/55	2/54	2/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6650				
Lymphoreticular/Hematopoietic System – Malignant Lymphoma				
Fatal Incidence	14	3	4	1
Incidental Incidence	11	5	2	1
Total Incidence Rate	25/140	8/55	6/55	2/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9631				

Table 8 (Report No. J14) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Mice Administered by Oral Gavage

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	40
Phagocytic System – Histiocytic Sarcoma				
Fatal Incidence	3	1	0	1
Incidental Incidence	4	1	2	0
Total Incidence Rate	7/140	2/55	2/55	1/85
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6277				

Figure 3 (Report No. J14)
Kaplan-Meier Product Limit Survival Curves for Male Mice Administered by Oral Gavage for Subset 0 (main study)

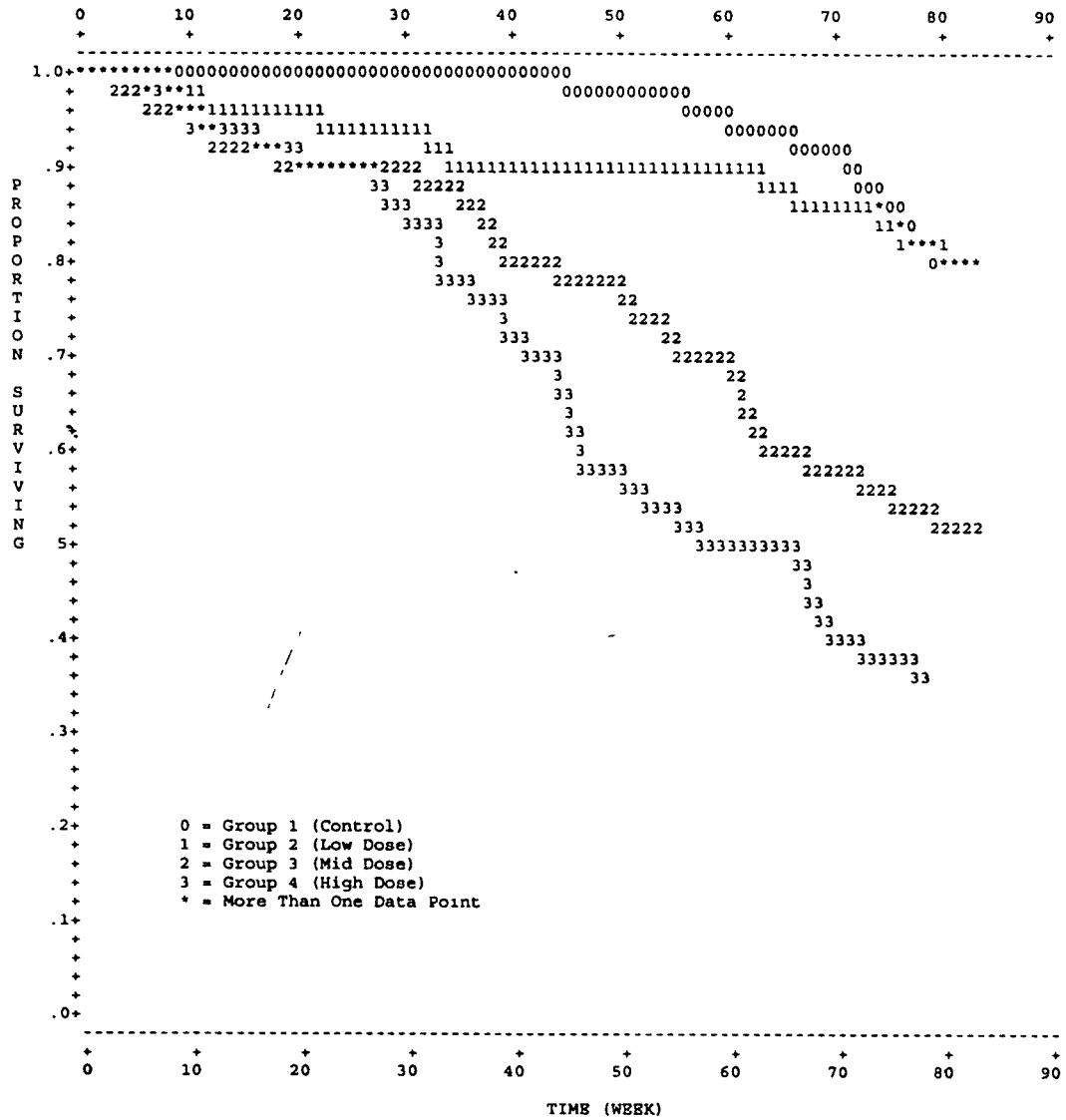


Figure 4 (Report No. J14)
Kaplan-Meier Product Limit Survival Curves for Male Mice Administered by Oral Gavage for Subset 1 (additional study)

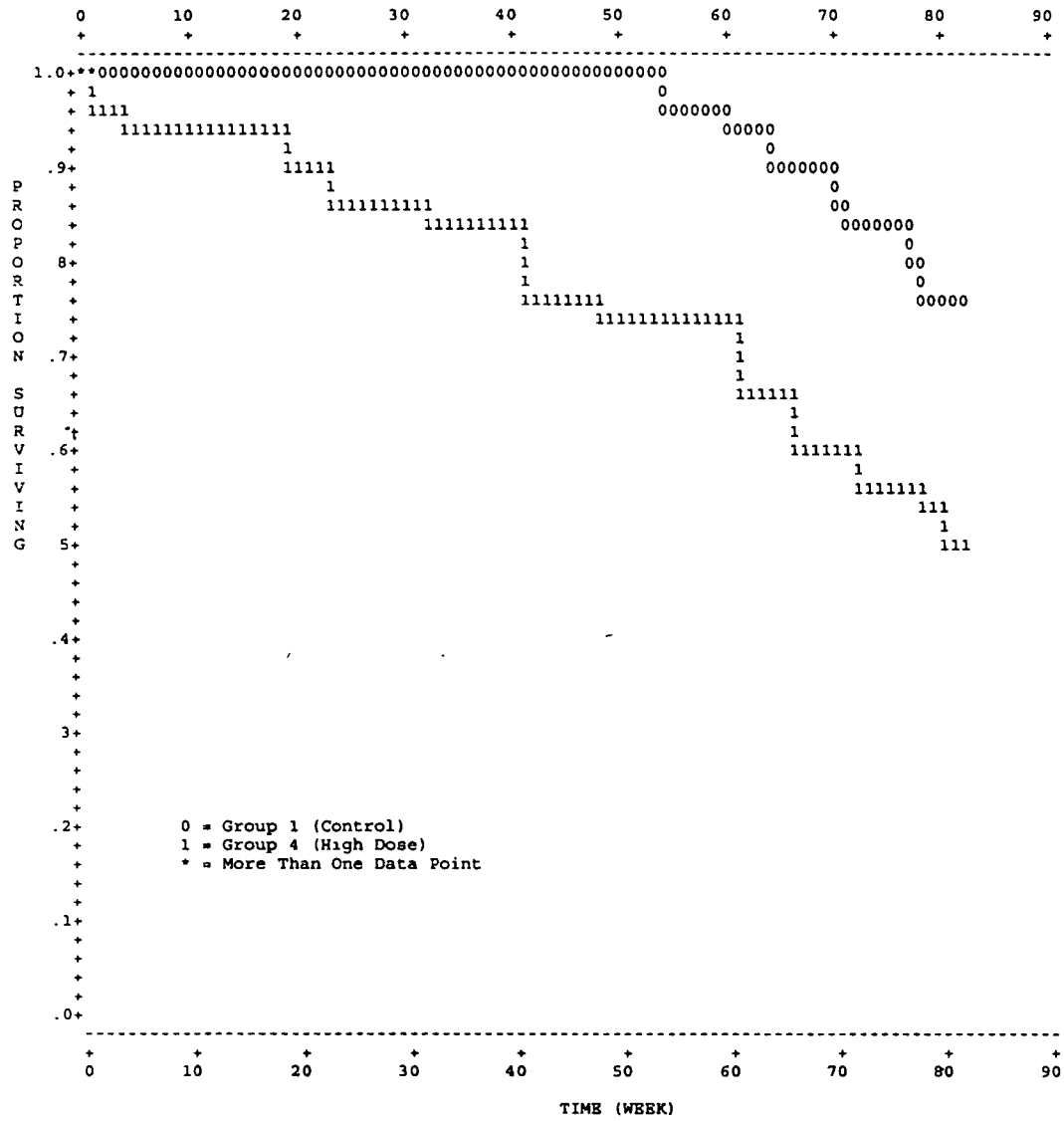


Figure 5 (Report No. J14)
Kaplan-Meier Product Limit Survival Curves for Male Mice Administered by Oral Gavage for Subset 0+1 (pooled data)

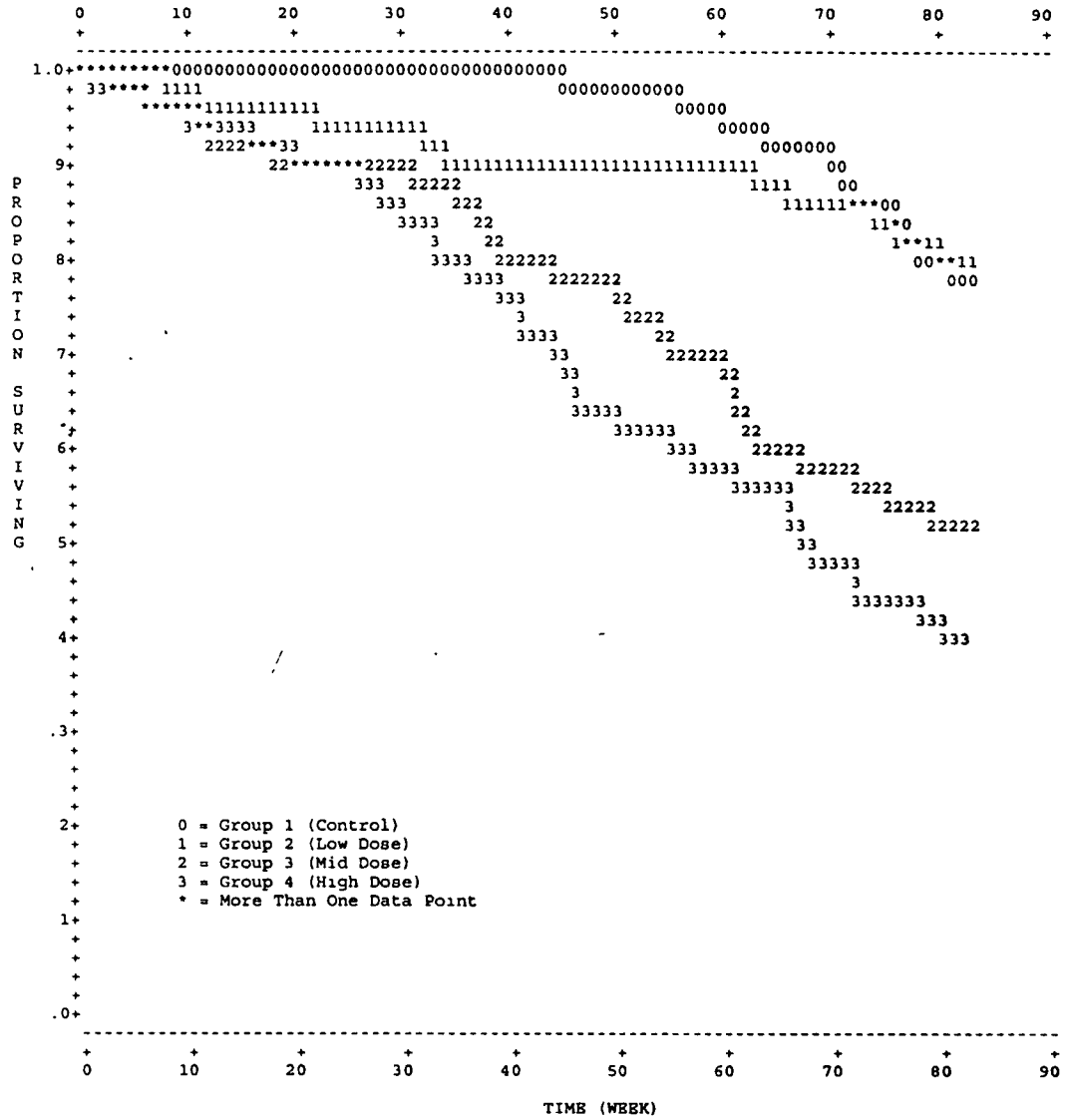


Figure 6 (Report No. J14)
Kaplan-Meier Product Limit Survival Curves for Female Mice Administered by Oral Gavage for Subset 0 (main study)

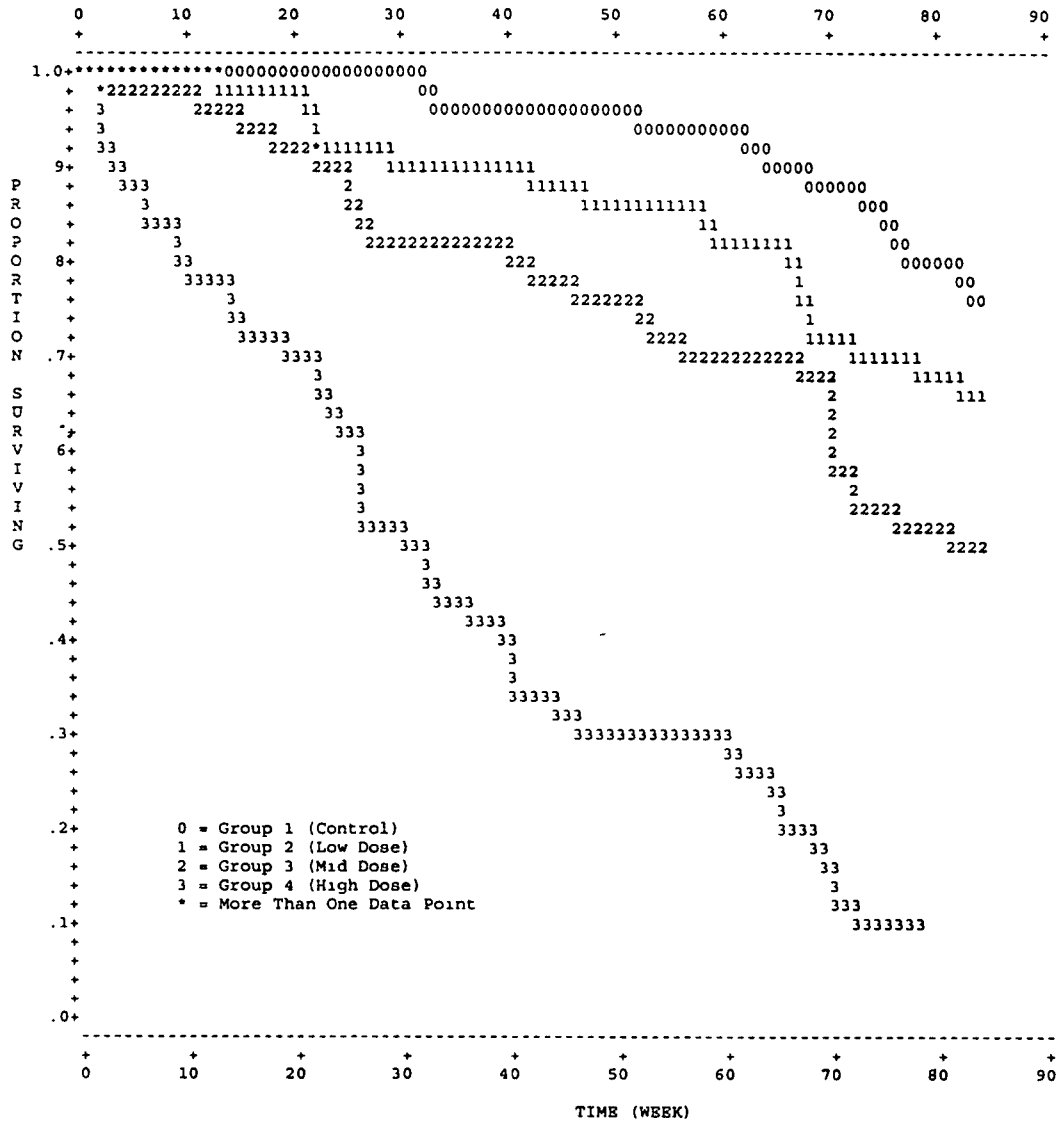


Figure 7 (Report No J14)

Kaplan-Meier Product Limit Survival Curves for Female Mice Administered by Oral Gavage for Subset 1 (additional study)

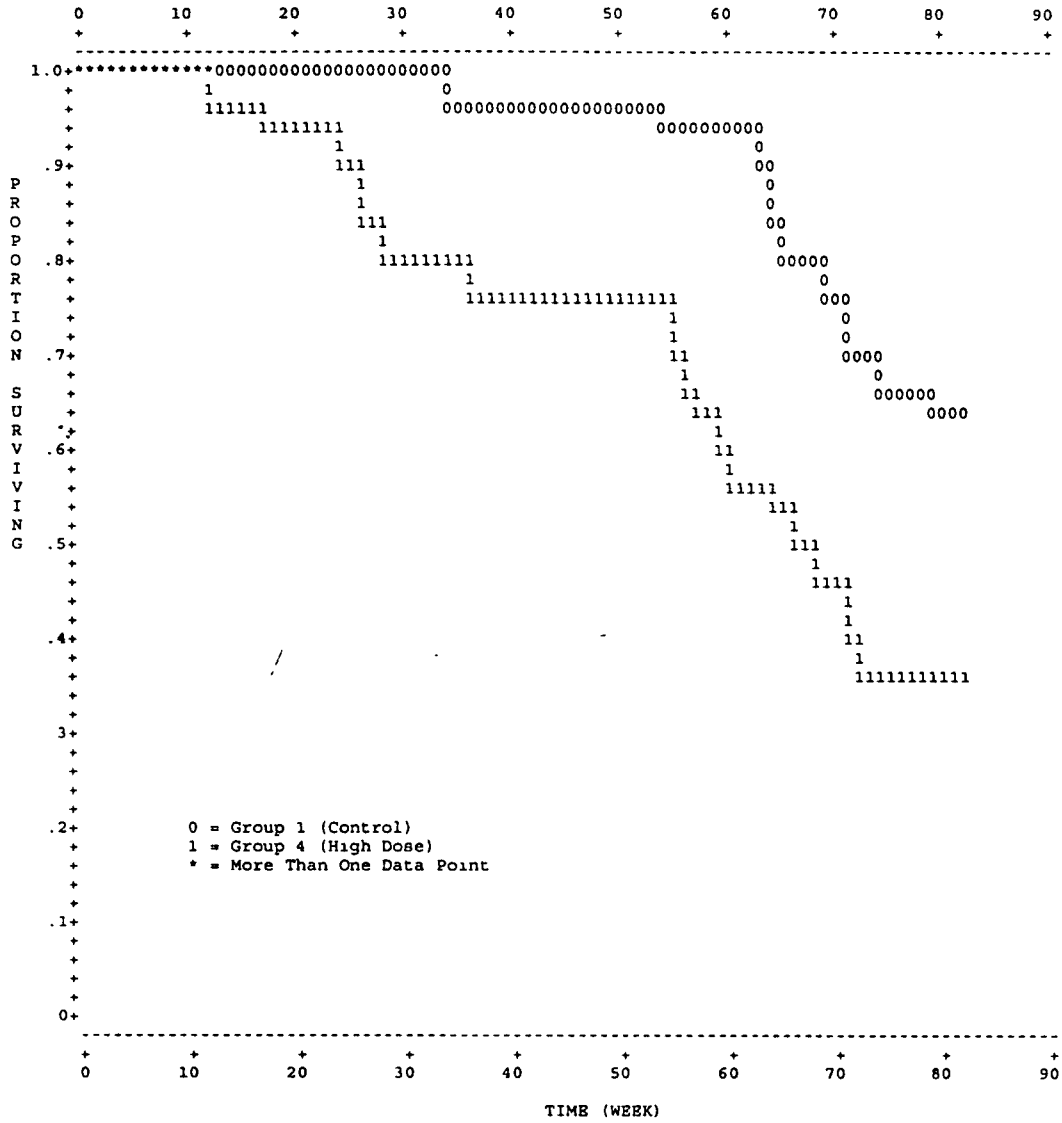
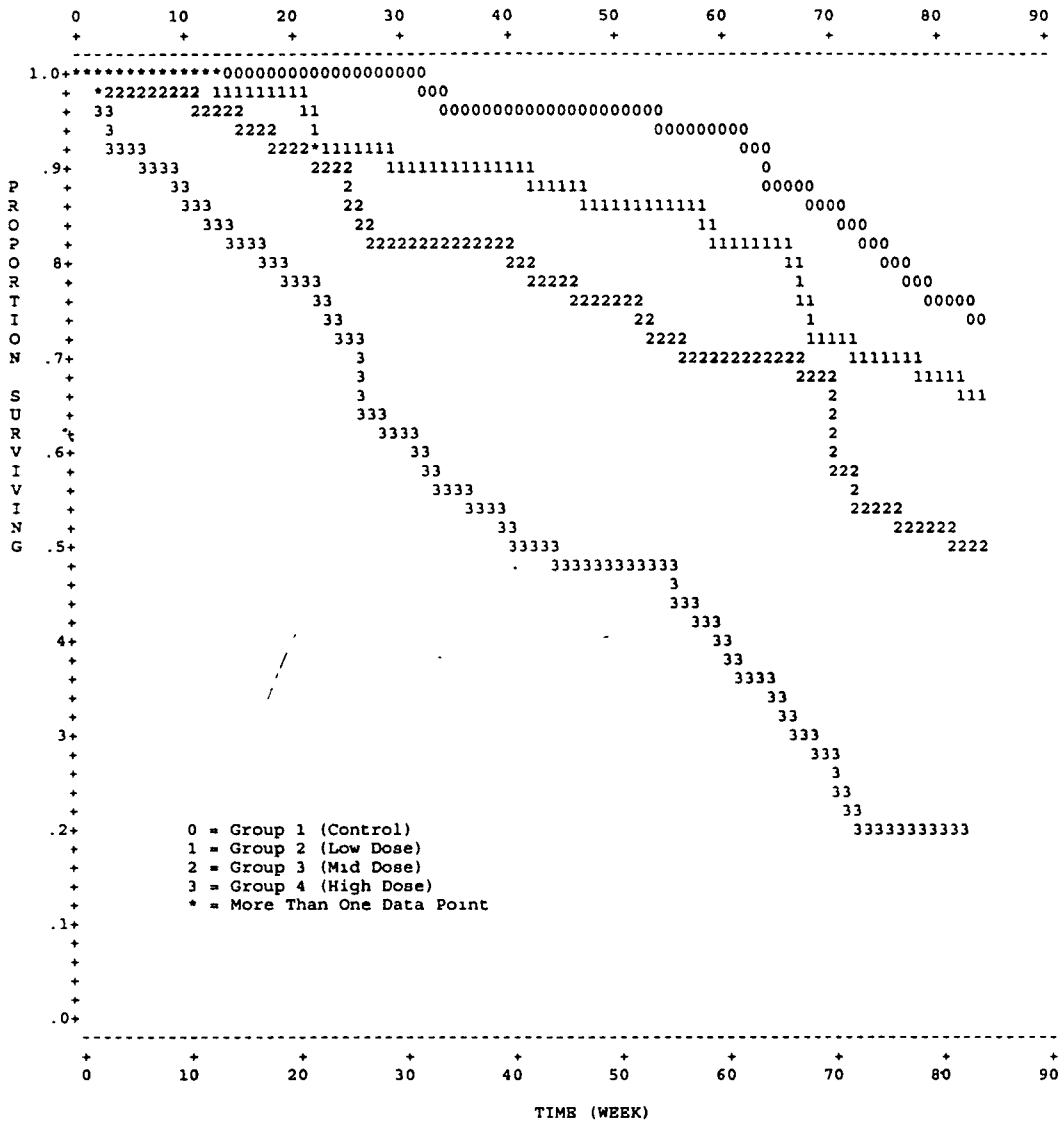


Figure 8 (Report No. J14)
Kaplan-Meier Product Limit Survival Curves for Female Mice Administered by Oral Gavage for Subset 0+1 (pooled data)



Appendix III – Tables for 90-Week Drinking Water Mouse Study

Carcinogenicity Study in Mice with BM 21.0955.Na in Drinking Water

Table 9 (Report No. J15)
Results of Statistical Analyses of Mortality Data for Male Mice Administered by Drinking Water

Group	1	2	3	4
Dose	0	5	20	80
Number of Deaths				
Weeks 0-26	1	0	0	0
Weeks 27-52	2	1	0	1
Weeks 53-78	11	4	4	5
Weeks 79-before term sac	13	2	5	4
Terminal Sacrifice Weeks	73	43	41	40
Unadjusted Mortality	27/100 (0.27)	7/50 (0.14)	9/50 (0.18)	10/50 (0.20)
Kaplan-Meier Estimate (Final)	0.275	0.140	0 180	0.200

	Cox-Tarone Test	Gehan-Breslow Test
Groups 1 vs. 2-4 Trend (one-sided p)	0.3187 ≤ p ≤ 0.3645 –	0.3246 ≤ p ≤ 0 3248 –
Departure from Trend (two-sided p)	0.1594	0.1669
Homogeneity (two-sided p)	0 2718	0.2854
Groups 1 vs. 2 (one-sided p)	0.0614 –	0.0496 – *
Groups 1 vs. 3 (one-sided p)	0.1348 –	0.0907 –
Groups 1 vs. 4 (one-sided p)	0.2328 –	0.1940 –

– = Effect in the negative (decreasing) direction
* = Significant at p ≤ 0.05

Table 10 (Report No. J15)
Results of Statistical Analyses of Mortality Data for Female Mice Administered by Drinking Water

Group	1	2	3	4
Dose	0	5	20	80
Number of Deaths				
Weeks 0-26	2	0	0	0
Weeks 27-52	6	2	4	0
Weeks 53-78	19	9	11	7
Weeks 79-before term sac	23	7	5	10
Terminal Sacrifice Weeks	50	32	30	33
Unadjusted Mortality	50/100 (0.50)	18/50 (0.36)	20/50 (0.40)	17/50 (0.34)
Kaplan-Meier Estimate (Final)	0.500	0.360	0.400	0 340

	Cox-Tarone Test	Gehan-Breslow Test
Groups 1 vs. 2-4 Trend (one-sided p)	0.0633 ≤ p ≤ 0.0748 –	0.0526 ≤ p ≤ 0.0527 –
Departure from Trend (two-sided p)	0.3575	0.4550
Homogeneity (two-sided p)	0.2200	0.2408
Groups 1 vs. 2 (one-sided p)	0.0925 –	0.0994 –
Groups 1 vs. 3 (one-sided p)	0.2147 –	0.2458 –
Groups 1 vs. 4 (one-sided p)	0.0415 – *	0.0293 – *

– = Effect in the negative (decreasing) direction
* = Significant at p ≤ 0.05

Table 11 (Report No. J15)
Results of Statistical Analyses of Neoplastic Lesions for Male Mice Administered by Drinking Water

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	80
Liver – Hepatocellular Adenoma				
Fatal Incidence	1	0	0	1
Incidental Incidence	8	3	6	4
Total Incidence Rate	9/100	3/50	6/50	5/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.3432				
Liver – Hepatocellular Carcinoma				
Fatal Incidence	3	0	0	1
Incidental Incidence	1	1	1	0
Total Incidence Rate	4/100	1/50	1/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7227				
Liver – Hepatocellular Adenoma/Carcinoma				
Fatal Incidence	4	0	0	2
Incidental Incidence	9	4	7	4
Total Incidence Rate	13/100	4/50	7/50	6/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4787				
Liver – Hemangiosarcoma				
Fatal Incidence	1	0	0	0
Incidental Incidence	1	2	1	0
Total Incidence Rate	2/100	2/50	1/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8622				
Adrenal Gland – Subcap. Cell Adenoma Type B				
Fatal Incidence	0	0	0	0
Incidental Incidence	9	6	2	1
Total Incidence Rate	9/100	6/50	2/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9825				
Adrenal Gland – Subcap. Cell Adenoma Mixed				
Fatal Incidence	0	0	0	0
Incidental Incidence	8	4	6	2
Total Incidence Rate	8/100	4/50	6/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8378				
Adrenal Gland – Subcap. Cell Adenoma Type B/Mixed/Subcap. Cell Adenocarcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	18	11	8	3
Total Incidence Rate	18/100	11/50	8/50	3/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9930				
Lung and Bronchi – Pulmonary Adenoma				
Fatal Incidence	1	0	0	2
Incidental Incidence	32	20	23	14
Total Incidence Rate	33/100	20/50	23/50	16/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6464				
Lung and Bronchi – Pulmonary Adenocarcinoma				
Fatal Incidence	3	1	2	2
Incidental Incidence	9	7	3	4
Total Incidence Rate	12/100	8/50	5/50	6/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5984				

Table 11 (Report No. J15) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Mice Administered by Drinking Water

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	80
Lung and Bronchi – Pulmonary Adenoma/Adenocarcinoma				
Fatal Incidence	3	1	2	4
Incidental Incidence	38	25	23	18
Total Incidence Rate	41/100	26/50	25/50	22/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 4995				
Urinary Bladder – Transitional Cell Papilloma				
Fatal Incidence	0	0	0	0
Incidental Incidence	3	0	0	1
Total Incidence Rate	3/100	0/50	0/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6014				
Urinary Bladder – Benign Mesenchymal Tumor				
Fatal Incidence	0	0	0	0
Incidental Incidence	6	4	7	2
Total Incidence Rate	6/100	4/50	7/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7468				
Urinary Bladder – Malignant Mesenchymal Tumor				
Fatal Incidence	1	0	0	0
Incidental Incidence	1	0	1	1
Total Incidence Rate	2/100	0/50	1/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4161				
Urinary Bladder – Benign/Malignant Mesenchymal Tumor				
Fatal Incidence	1	0	0	0
Incidental Incidence	7	4	8	3
Total Incidence Rate	8/100	4/50	8/50	3/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6842				
Pituitary Gland – Adenoma, Pars Intermedia				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	0	0	2
Total Incidence Rate	0/99	0/50	0/50	2/49
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0404				
Harderian Gland – Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	9	8	6	5
Total Incidence Rate	9/100	8/50	6/50	5/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5750				
Harderian Gland – Adenoma/Adenocarcinoma				
Fatal Incidence	1	0	0	0
Incidental Incidence	9	8	6	5
Total Incidence Rate	10/100	8/50	6/50	5/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6269				
Prostate Gland – Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	1	1	2	1
Total Incidence Rate	1/100	1/49	2/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.3435				

Table 11 (Report No. J15) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Male Mice Administered by Drinking Water

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	80
Hematopoietic Tissue – Lymphoma				
Fatal Incidence	4	2	1	2
Incidental Incidence	2	6	2	1
Total Incidence Rate	6/100	8/50	3/50	3/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7284				
Hematopoietic Tissue – Malignant Mast Cell Tumor				
Fatal Incidence	1	0	0	0
Incidental Incidence	0	2	0	0
Total Incidence Rate	1/100	2/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8560				
Multiple Organs – Hemangiosarcoma (from Liver, Abdominal Cavity, and Femur with Marrow)				
Fatal Incidence	1	1	0	0
Incidental Incidence	1	3	1	9
Total Incidence Rate	2/100	4/50	1/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 9228				
Multiple Organs – Hemangioma/Hemangiosarcoma (from Liver, Abdominal Cavity, and Femur with Marrow)				
Fatal Incidence	1	1	0	0
Incidental Incidence	2	3	1	9
Total Incidence Rate	3/100	4/50	1/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 9543				

Table 12 (Report No. J15)
Results of Statistical Analyses of Neoplastic Lesions for Female Mice Administered by Drinking Water

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	80
Liver – Hepatocellular Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	0	0	0
Total Incidence Rate	2/100	0/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 1.0000				
Liver – Hepatocellular Adenoma/Carcinoma				
Fatal Incidence	0	0	0	1
Incidental Incidence	2	0	0	0
Total Incidence Rate	2/100	0/50	0/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 5393				
Liver – Hemangioma/Hemangiosarcoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	0	0	1
Total Incidence Rate	2/100	0/50	0/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5420				
Adrenal Gland – Subcap. Cell Adenoma Type A				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	1	1	3
Total Incidence Rate	0/100	1/50	1/50	3/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0228 *				
Groups 1 vs. 4 One-sided (Upper-tailed) p = 0.0594				
Adrenal Gland – Subcap. Cell Adenoma Type A/Type B				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	1	1	4
Total Incidence Rate	0/100	1/50	1/50	4/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 0069 *				
Groups 1 vs. 4 One-sided (Upper-tailed) p = 0.0223 #				
Adrenal Gland – Subcap. Cell Adenoma Type A/Type B/Subcap. Cell Adenocarcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	0	1	2	4
Total Incidence Rate	0/100	1/50	2/50	4/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.0099 *				
Groups 1 vs. 4 One-sided (Upper-tailed) p = 0.0223 #				
Groups 1 vs. 3 One-sided (Upper-tailed) p = 0.1377				
Adrenal Gland – Pheochromocytoma				
Fatal Incidence	0	0	0	1
Incidental Incidence	1	0	0	1
Total Incidence Rate	1/100	0/50	0/50	2/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.1244				
Lung and Bronchi – Pulmonary Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	18	11	6	12
Total Incidence Rate	18/100	11/50	6/50	12/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.3784				

* = Significant at $p \leq 0.025$ for trend for rare tumor type
# = Significant at $p \leq 0.050$ for group comparison for rare tumor type

Table 12 (Report No. J15) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Mice Administered by Drinking Water

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	80
Lung and Bronchi – Pulmonary Adenocarcinoma				
Fatal Incidence	2	0	0	0
Incidental Incidence	3	1	1	3
Total Incidence Rate	5/100	1/50	1/50	3/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.3803				
Lung and Bronchi – Pulmonary Adenoma/Adenocarcinoma				
Fatal Incidence	2	0	0	0
Incidental Incidence	21	12	7	15
Total Incidence Rate	23/100	12/50	7/50	15/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.3312				
Urinary Bladder – Benign/Malignant Mesenchymal Tumor				
Fatal Incidence	0	1	0	0
Incidental Incidence	1	1	0	0
Total Incidence Rate	1/98	2/50	0/46	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8480				
Ovary – Tubulostromal Adenoma				
Fatal Incidence	0	1	1	0
Incidental Incidence	20	13	10	11
Total Incidence Rate	20/100	14/50	11/50	11/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7034				
Ovary – Tubulostromal Adenocarcinoma				
Fatal Incidence	0	1	0	0
Incidental Incidence	0	1	0	0
Total Incidence Rate	0/100	2/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.7119				
Ovary – Tubulostromal Adenoma/Adenocarcinoma				
Fatal Incidence	0	1	1	0
Incidental Incidence	20	13	10	11
Total Incidence Rate	20/100	14/50	11/50	11/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 7034				
Ovary – Benign Granulosa Cell Tumor				
Fatal Incidence	0	0	0	0
Incidental Incidence	5	2	2	1
Total Incidence Rate	5/100	2/50	2/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.8461				
Ovary – Malignant Granulosa Cell Tumor				
Fatal Incidence	3	2	0	0
Incidental Incidence	1	2	0	0
Total Incidence Rate	4/100	4/50	0/50	0/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9913				
Ovary – Benign/Malignant Granulosa Cell Tumor				
Fatal Incidence	3	2	0	0
Incidental Incidence	6	4	2	1
Total Incidence Rate	9/100	6/50	2/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.9874				

Table 12 (Report No. J15) (Continued)
Results of Statistical Analyses of Neoplastic Lesions for Female Mice Administered by Drinking Water

Group	1	2	3	4
Dose (mg/kg/day)	0	5	20	80
Ovary – Benign Luteoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	1	1	2	1
Total Incidence Rate	1/100	1/50	2/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4036				
Uterus – Leiomyoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	2	0	2	1
Total Incidence Rate	2/100	0/50	2/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.4184				
Thyroid Gland – Follicular Cell Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	1	2	2	1
Total Incidence Rate	1/98	2/50	2/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0 4952				
Mammary Area – Adenocarcinoma				
Total Incidence Rate	3/98	1/50	1/50	1/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6911				
Pituitary Gland – Adenoma, Pars Distalis				
Fatal Incidence	4	1	0	2
Incidental Incidence	27	18	11	16
Total Incidence Rate	31/100	19/50	11/49	18/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6336				
Pituitary Gland – Adenoma/Adenocarcinoma, Pars Distalis				
Fatal Incidence	4	1	0	2
Incidental Incidence	28	18	12	16
Total Incidence Rate	32/100	19/50	12/49	18/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.6792				
Harderian Gland – Adenoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	3	4	1	2
Total Incidence Rate	3/100	4/50	1/50	2/49
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5994				
Harderian Gland – Adenoma/Adenocarcinoma				
Fatal Incidence	0	0	0	0
Incidental Incidence	3	4	2	2
Total Incidence Rate	3/100	4/50	2/50	2/49
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5911				
Hematopoietic Tissue – Lymphoma				
Fatal Incidence	22	8	8	11
Incidental Incidence	15	10	4	9
Total Incidence Rate	37/100	18/50	12/50	20/50
Groups 1 vs. 2-4 One-sided (Upper-tailed) Trend p = 0.5748				

Figure 9 (Report No. J15)
Kaplan-Meier Product Limit Survival Curves for Male Mice Administered by Drinking Water

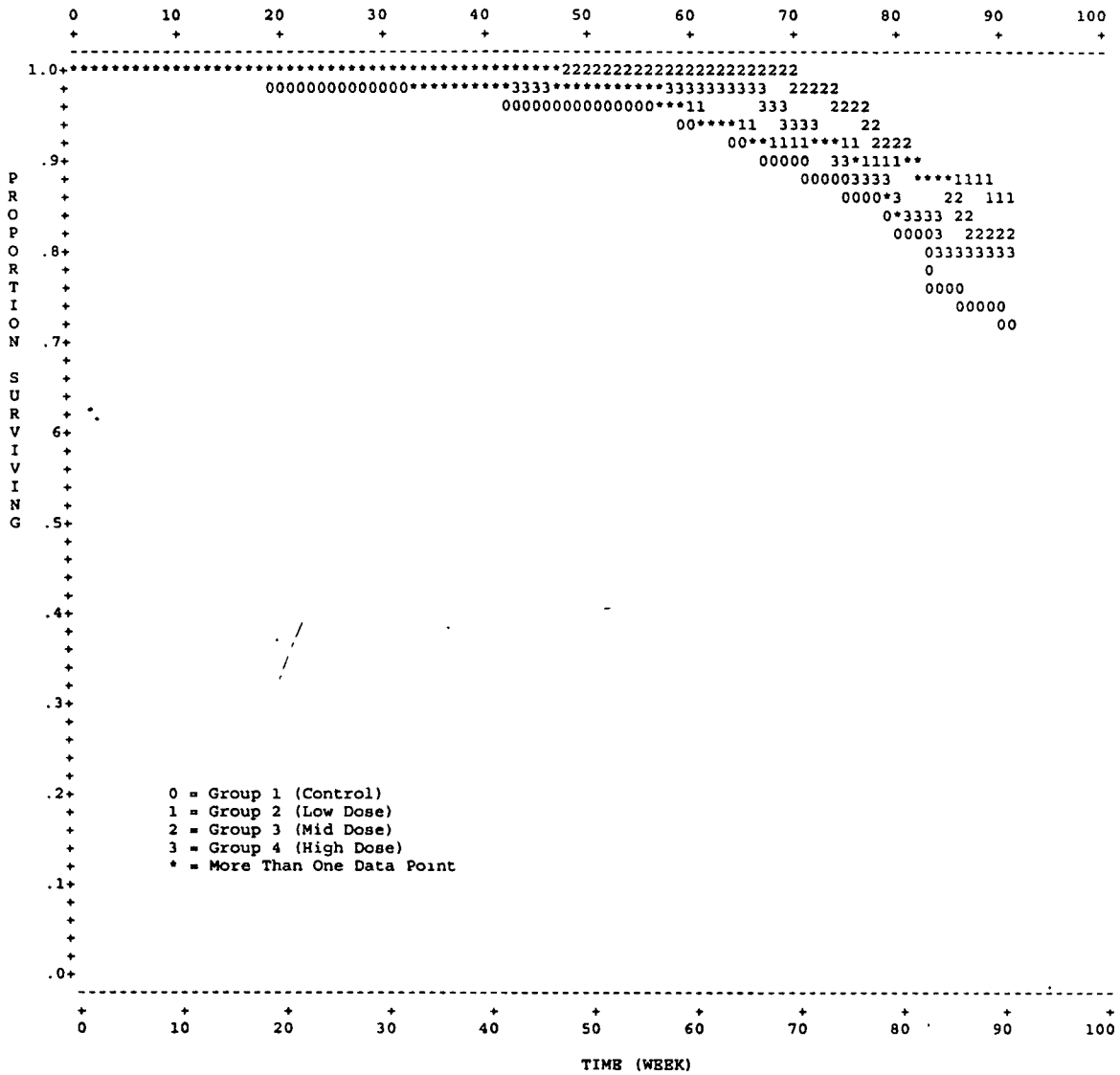
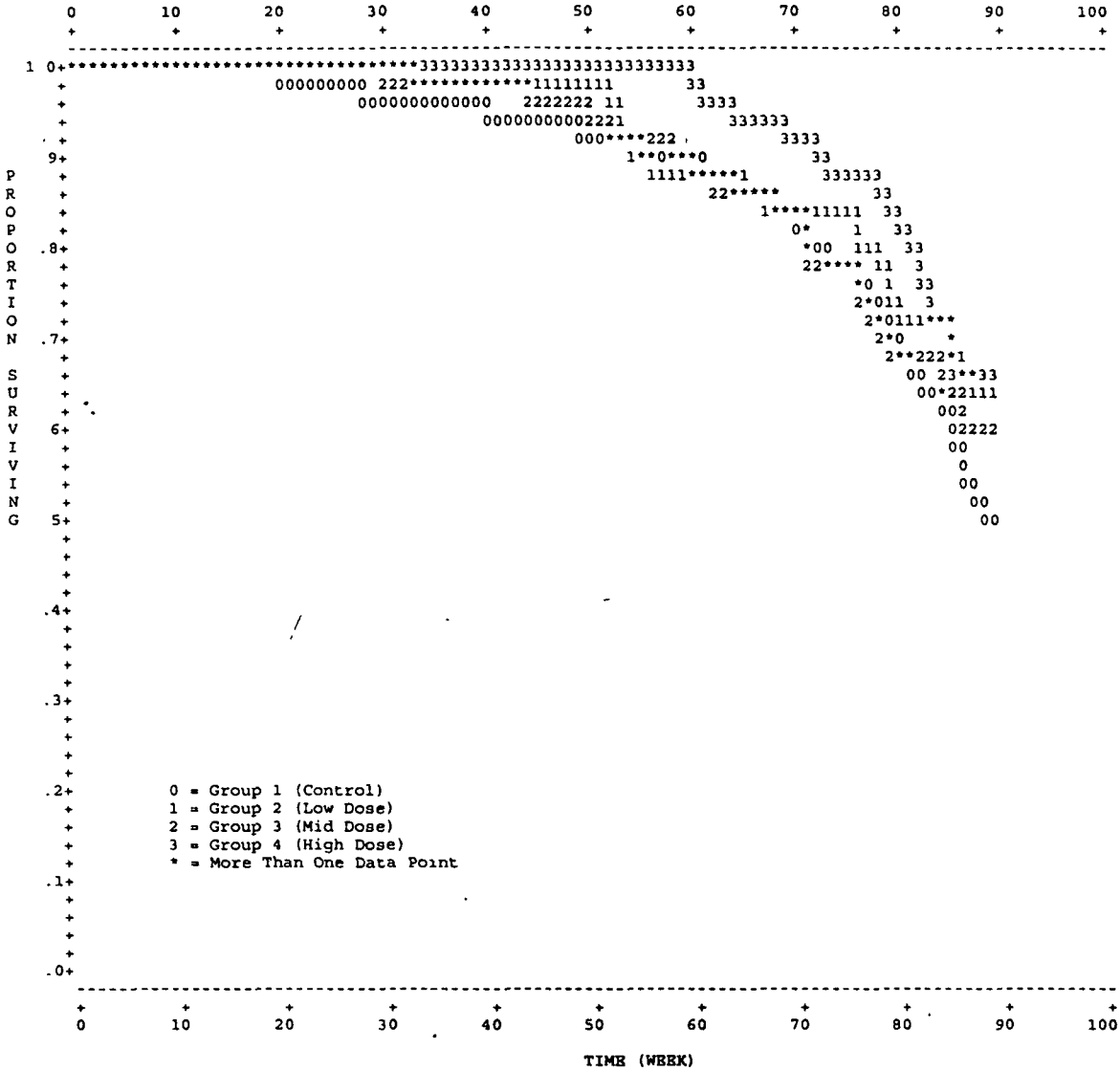


Figure 10 (Report No. J15)
Kaplan-Meier Product Limit Survival Curves for Female Mice Administered by Drinking Water



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/s/

Karl Lin
3/4/03 11:28:09 AM
BIOMETRICS
Cynthia Liu is the statistical reviewer of the carcinogenicity studies in this submission. She finished this review and is on maternity leave. The review report is put in the DFS by Karl lin.

Karl Lin
3/4/03 11:32:35 AM
BIOMETRICS
Concur with review

Executive CAC
Date of Meeting: February 11, 2003

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Abby Jacobs, Ph.D., HFD-540, Alternate Member
Jim Farrelly, Ph.D., HFD-530, Alternate Member
Karen Davis-Bruno, Ph.D., HFD-510, Team Leader
Gemma Kuijpers, Ph.D., HFD-510, Presenting Reviewer

Author of Draft: Gemma Kuijpers

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

NDA #: 21-455
Drug Name: Bonviva® (ibandronate sodium)
Sponsor: Hoffman-La Roche Inc.

Background
Ibandronate is a bisphosphonate, a compound which inhibits osteoclastic bone resorption and increases bone mass, particularly in cancellous bone. The proposed indication is treatment and prevention of postmenopausal osteoporosis (2.5 mg/day, orally). Target organs for toxicity are kidney, liver, GI tract, lung and testis. Doses for both the rat and the mouse carcinogenicity studies were selected by the sponsor based on data from dose-range finding studies.

Rat Carcinogenicity Study Results (Oral Gavage)
A 104-week study was carried out in Wistar rats at doses of 0, 3, 7, 15 mg/kg/day (N=50/sex/grp), by oral gavage. Doses were selected based on data from a 3-month oral gavage study with 0, 10, 20, 30, 40, 50 mg/kg/day, in which mortality was seen in males and females at 20 mg/kg/day and dose-related decreases in body weight had been observed at all doses. In the 104-week carcinogenicity study, there were reductions in survival in MD and HD males of 17%, and dose-related decreases in body weight in both sexes of up to 10%. No decrease in survival was observed in females. Increased incidence and severity of kidney tubular epithelial hypertrophy was observed in all treated groups. Effects related to the pharmacodynamic action of the drug were seen in all treated groups. Neoplastic findings included skin fibrous histiocytoma in males (Ctrl-LD-MD-HD: 0-0-0-2), and thyroid C-cell adenoma in females (Ctrl-LD-MD-HD: 0-0-1-2). These were statistically significant according to Sponsor's analysis (trend test), but not according to CDER Biometrics' analysis using p-values for rare tumors. Historical control incidences for skin histiocytoma in males ranged from 0-5%, and for thyroid C-cell adenoma in females from 0-24%.

Mouse Carcinogenicity Study Results (Oral Gavage)
An 18-month study was carried out in Crl:NMRI/BR mice at doses of 0, 10, 20, 40 mg/kg/day by oral gavage. The study was started with Subset 0 consisting of N=110-55-

55-55/sex. However, due to mortality resulting from local respiratory tract irritation in the high dose groups Subset 1 was added after 8 weeks consisting of N= 30-0-0-30/sex (Total N=140-55-55-85). Doses were selected based on data from two 3-month oral gavage studies with 0, 20, 40, 60, 80, 100 mg/kg/day, and with 0, 10, 15, 20, 30, 40 mg/kg/day, in which mortality was observed at 40 mg/kg/day. In the 18-month carcinogenicity study, there were reductions in survival in MD and HD males and females of up to 40% (HD males) and 80% (HD females). There were slight, dose-related decreases in body weight in both sexes of up to 10%, respiratory tract and GI lesions in MD and HD, and bone effects in all treated. Neoplastic findings included hepatocellular adenoma (0%-3.7%-1.9%-2.6%) in males, and Harderian gland adenoma in males (8%, 19%, 9%, 5%), significant according to Sponsor's trend test (liver adenoma) and/or pairwise comparison (control vs. LD, both tumors). In females, there was an increase in lung bronchioalveolar adenoma in the LD group (5%-15%-8%-11%), significant in that group according to Sponsor. However, these findings were not significant according to CDER Biometrics' analysis.

Mouse Carcinogenicity Study Results (Drinking Water)
A 90-week study was carried out in Crl:NMRI/Br mice at doses of 0, 5, 20, 80 mg/kg/day (N=100-50-50-50/sex), by drinking water administration. Doses were selected based on data from two 3-month studies, one with 0, 50, 100, 200, 400, 800 mg/kg/day and one with 0, 10, 20, 30, 40, 50 mg/kg/day. Respiratory disturbance were seen at 100 (males) and 200 (females) mg/kg/day and mortality at 400 (males) and 800 (females) mg/kg/day. In the 90-week carcinogenicity study, there was no effect on survival, slight trachea/larynx lesions in MD and HD males, and no other significant toxicity. Dose-related bone effects (moderate to severe in HD groups) were observed in all treatment groups. Neoplastic findings included pituitary adenoma in males (0%-0%-0%-4%), significant according to Sponsor's analysis. In females, there was a dose-related increase in the incidence of adrenal subcapsular adenoma, type A (0%-2%-2%-6%), subcapsular cell adenoma, type A/B combined (0%-2%-2%-8%), and subcapsular adenoma, type A/B/adenocarcinoma combined (0%-2%-4%-8%). These findings were statistically significant according to Sponsor's analysis (trend test, and pairwise control-HD comparison) and CDER Biometrics' analysis (trend test). The control incidences for adrenal subcapsular adenoma and adenocarcinoma in the other mouse gavage study were 0.7% and 0%, respectively.

Executive CAC Recommendations and Conclusions:

Rat Study:

- The Committee felt that the study including the dose selection was adequate for males and females based on mortality in the 3-month dose range finding study.
- The Committee concluded that there were no significant tumor findings. Based on the low incidence only in the HD group, the histocytoma finding in males (2/50 in HD) was not considered significant. The thyroid C-cell adenoma finding in females (1/49 in MD, 2/50 in HD) was not considered of biological significance due to low incidences and the fact that historical control values indicate this is a common tumor.

Mouse Study (Oral Gavage):

- The Committee felt that the study was adequate, based on dose-limiting mortality in the HD groups.
- The Committee concluded that there were no significant tumor findings. The liver hepatocellular adenoma finding in males was not considered a significant finding due to low incidences and absence of a clear dose response. The Harderian gland adenoma finding in LD males and the lung adenoma finding in LD females did not indicate a significant treatment-related finding.

Mouse Study (Drinking Water):

- The doses used in the drinking water study were suboptimal, and the MTD was not reached. However, the Committee felt that the two mouse studies (gavage and drinking water) taken together provided acceptable data and could be accepted as adequate.
- The Committee concluded that the drinking water study was positive for adrenal subcapsular tumors. Significant findings were adrenal subcapsular adenoma, type A, type A/B combined and typeA/B/carcinoma combined.
- The Committee recommended that historical control data for adrenal subcapsular tumors from the time this study was conducted (1993-1995) are obtained. Historical control data are required from the testing facility for control mice from drinking water studies or for untreated controls. In particular, individual study incidences as well as the range of tumor incidences need to be considered.
- The Committee recommended that Sponsor clarify the histological characterization of the adrenal subcapsular tumor types. Perspectives on the appropriateness of combining these types of tumors need to be requested.

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

cc:\
/Division File, HFD-510
KDavisbruno/Team leader, HFD-510
GKuijpers/Reviewer, HFD-510
RHedin/CSO/PM, HFD-510
/ASeifried, HFD-024

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

/s/

Joe Contrera
2/14/03 03:45:24 PM