CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19982

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Date: JUL 17 1991

volumes 1 to 3, Date of Document, Feb. 27,

2. Response to request for information, May 1, 1991.
3. Response to request for information, May 22, 1991.
4. Computer floppy diskettes and three sets of hard copy listings, May 30, 1991.

I. Background

Two animal carcinogenicity studies (one in rats, and one in mice) included in this NDA submission have been reviewed by the Division of Biometrics. This is a repeated mouse carcinogenicity study which was intended to evaluate the carcinogenic potential of Bisoprolol (CL 297,939) in mice for two years. Dr. Ernest J. Belair, HFD-110, who is the reviewing pharmacologist of this NDA has requested the Division of Biometrics to perform the statistical review and evaluation of this study. The data submitted on computer floppy diskettes were used in the reviewer's independent analyses.

II. The Mouse Study

II. a. Design

In this study, three groups of 60 :COBS:CD1(ICR)BR mice per sex received 8, 40, or 200 mg/kg/day of bisoprolol in the diet for two years. Two control groups of 60 mice per sex received drug-free rodent chow. An additional three groups of 48 mice/sex received the same bisoprolol doses (8, 40, or 200 mg/kg/day) which were used for determination of plasma drug concentrations. Animals used for the toxicology evaluation were assigned to study 87086. Animals used for pharmacokinetic evaluation were assigned to study 87201. In study 87086, clinical observations were recorded daily, physical examinations were conducted weekly, body weight and food consumption were recorded weekly. A gross postmortem examination was performed on all animals. Histopathological evaluation was performed only on animals in the high dose group (200 mg/kg/day) and the first untreated control group.

II. b. Sponsor's analyses

Kaplan-Meier mortality estimates were computed for all groups of each sex. Cox's logrank procedure ("Regression Models and Life Tables", Journal of the Royal Statistical Society, Series B, 34, 187-220, 1972) was used to test for heterogeneity in survival distributions among the groups for each sex. The trend test with ordinal dose scaling (Tarone, "Tests

for Trend in Life-table Analysis", Biometrika, 62, 679-682, 1975) was used to test the dose-response relationship. Two-tailed tests were performed in each case. The sponsor compared the mortality data between two control groups, among all groups, and between the high dose and one of the control groups. The results of the analyses are as follows:

Compare the mortality between two control groups:

The log-rank test and the Kaplan-Meier survival curves of two control groups (Figures 1A and 1B) revealed that the survival patterns in both control groups were not significant different (males: $p = 0.72$; females: $p = 0.82$). Therefore, both control groups were pooled for subsequent analyses.

Compare the mortality among all groups:

The Cox test and the Kaplan-Meier survival curves for all dose groups for male and female mice (Figures 2A and 2B) showed that there was no significant difference (at 0.05 level) in mortality among all groups either in males (heterogeneity p-value = 0.41, trend p-value = 0.36) or in females (heterogeneity p-value = 0.89, trend p-value = 0.76). Table 1 summarizes survival at selected time points, by dose group, for male and female mice.

Compare the mortality between the high dose and the first untreated control group:

A separate analysis comparing the survival of animals in the 200 mg/kg/day group to that of the control animals was also performed using the logrank test. It is noted that the animals in these two groups were evaluated histopathologically. The log-rank test and the Kaplan-Meier survival curves (Figures 3A and 3B) showed that there was no statistically significant difference in mortality between the high dose group and the first control group either in male ($p = 0.82$) or in female mice ($p = 0.91$).

The prevalence method described in the paper of Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) was used to test the difference between the high-dose group and the control group with respect to patterns of tumor occurrence. The analyses were implemented using a computer program developed by Kodell et al. ("CHRONIC: A SAS procedure for statistical analysis of carcinogenesis studies", Journal of Statistical Computation and Simulation, 16, 287-310). Since only two groups were examined microscopically, no trend analysis was performed. If fewer than five animals were observed to have a tumor in a particular organ, no statistical significance test was performed. The sponsor also indicated that no adjustment for the p-value has been made for the multiplicity of testing.

Table 2 showed the incidence of tumor-bearing animals by dose group, for specific organ types, as well as for selected groupings of tumors. Table

3 listed the summary table of mice with benign and/or malignant tumors. The results of the above analyses revealed that there was a statistically significant increase in bronchiolo-alveolar adenomas in treated females (12/60 in the high dose group versus 5/60 in the control group; p = 0.03). In female mice, the incidence of bronchiolo-alveolar adenocarcinomas was also higher in the 200 mg/kg/day group than in control group (6/60 versus 2/60). But this increase was not statistically significant (p = 0.08). An analysis of grouped lung tumors (bronchiolo-alveolar adenomas and bronchiolo-alveolar adenocarcinomas) indicated a significant increase in incidence in the 200 mg/kg/day dose group relative to control group (16/60 versus 7/60; p = 0.02). No corresponding increase in the incidence of these lung tumors was observed in males. Hence, the sponsor stated that "it seems likely that the occurrence of this statistically significant increase is simply a consequence of the multiple hypothesis tests applied to the data, and does not reflect a true effect of the compound."

Based on the above analyses, the sponsor concluded that "within the limits of biological variation, the incidence of each of the various tumor types observed in this study was comparable in the high-dose and control groups. All the tumors were considered to be spontaneous lesions unrelated to administration of bisoprolol."

II. c. Analyses and Comments

The sponsor submitted only data of the high dose (200 mg/kg/day) and first control groups which were evaluated histopathologically. Hence the following analyses used data of these two groups only. The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart ("Trend and Homogeneity Analyses of Proportions and Life Table Data", Computers and Biomedical Research, 10, 373-381, 1977) were used to test for heterogeneity in survival distributions between the high dose and the control groups. The p-values of the Cox test were 0.8958 and 0.3685 for females and males, respectively. The p-values of the generalized Wilcoxon test were 0.7097 and 0.8882 for females and males, respectively. Hence, there were no statistically significant difference (at 0.05 level) in the survival distribution in either female or male mice.

The Peto death-rate method (1980) using time intervals 0-50, 51-80, and 81-104 weeks was used to test the difference in intercurrent mortality rate between the high dose and the control groups for both male and female mice (see Table 4). The results of the analyses showed that there was no significant difference in intercurrent mortality rate in either male (p = 0.3243) or female mice (p = 0.3115).

The prevalence method described in the paper of Peto et al. (1980) and the exact permutation trend test were applied to test the differences in the tumor incidence rates between the high-dose and the control groups. The time intervals 0-50, 51-80, 81-104 and terminal sacrifice were used in those methods. The test results showed that there were statistically significant tumor occurrence differences between the high dose and control

groups in the lungs bronchiolo-alveolar adenoma (p = 0.0253) and salivary gland malignant lymphoma (p = 0.01349) in female mice. The incidence rates of these two tumors are given in Tables 5 and 6. The difference in tumor occurrence between the high dose and control groups of thymus gland malignant lymphoma in male mice was marginally statistically significant (p = 0.06013).

Upon FDA's request, the sponsor submitted three sets of historical control data on spontaneous neoplastic lesions on May 1, 1991. The first data set included the historical control incidences of pulmonary tumors in 18 months :CD-1 (ICR)BR mouse studies (see Table 7). The second data set included the historical control incidences of pulmonary tumors of the 21-24 months :CD-1 (ICR) BR mouse studies (see Table 8). The third historical control data set was from the Experimental Pathology Laboratories, Inc. Hazleton, WI. (see Table 9). From the above three sets of historical control data, we found that the number of animals with bronchiolo-alveolar adenoma in female high dose group in this study (12/60 = 20%) was above the historical range of incidences in the 18 months studies (Table 7: 1/50 = 2% to 13/148 = 8.78%), in the 21-24 months studies (Table 8: 4/72 = 5.55% to 4/50 = 8%), and in the third data set (Table 9: 0/108 = 0% to 2/49 = 4.08%).

The original mouse study was conducted by administering Bisoprolol to the animals at dosage levels of 0, 10, 50, or 250 mg/kg/day for 87 weeks. The results of the analyses of the original study showed that there are statistically significant dose-response relationships in the lungs metastatic adenocarcinoma (p = 0.03471), ovaries cystadenoma (p = 0.00893) in female mice, and lymph nodes hemangioma-abdominal lymph node (p = 0.0485) in male mice.

This repeated mouse study yielded significant results different from those of the original study (different tumors on different organs/tissues).

III. Summary

This is a repeated mouse carcinogenicity study which was intended to evaluate the carcinogenic potential of Bisoprolol in mice when administered continuously to the animals, via the diet, at dosage levels of 0, 8, 40, or 200 mg/kg/day for two years. The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distributions. The statistical methods described in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the difference in intercurrent mortality and incidental tumor rates between the high dose and control groups.

In this repeated mouse study, the results of the reviewer's analyses show that there is no significant difference in survival distribution in either female or male mice. Nor is there a significant difference in

intercurrent mortality rate in either female or male mice. However, there are statistically significant tumor occurrence differences between the high dose and control groups in lungs bronchiolo-alveolar adenoma ($p = 0.0253$) and salivary gland malignant lymphoma ($p = 0.01349$) in female mice. There is marginally statistically significant tumor occurrence difference between the high dose and control groups in thymus gland malignant lymphoma ($p = 0.06013$) in male mice.

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This repeated mouse study yielded significant results different from those of the original study (different tumors on different organs/tissues).

Figure 1a. Bisoprolol Mc)ncogenicity Study (87086)
Survival Curves for the Two Control Groups – Males

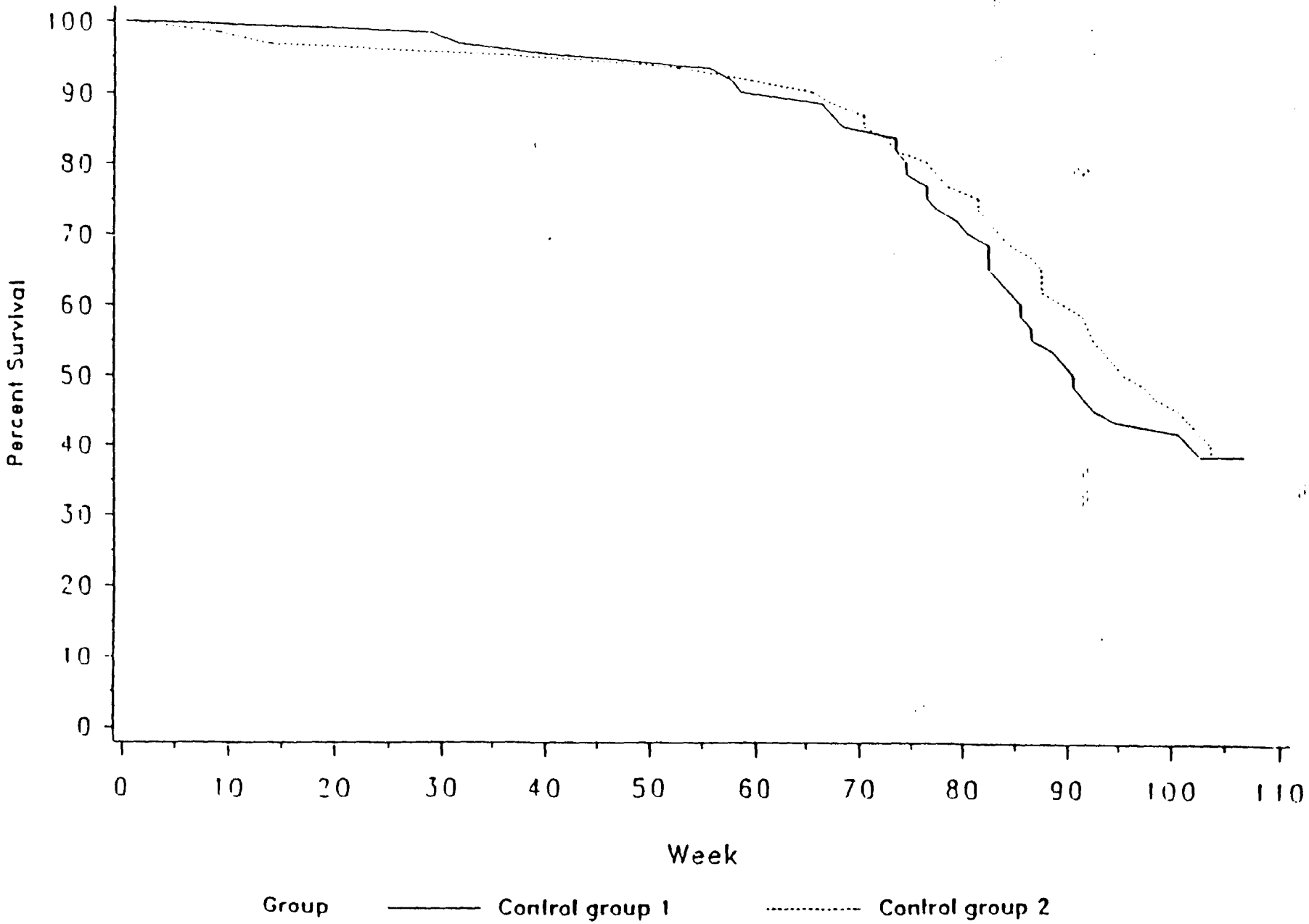

Figure 1b. Bisoprolol Mouse Oncogenicity Study (87086)
Survival Curves for the Two Control Groups – Females

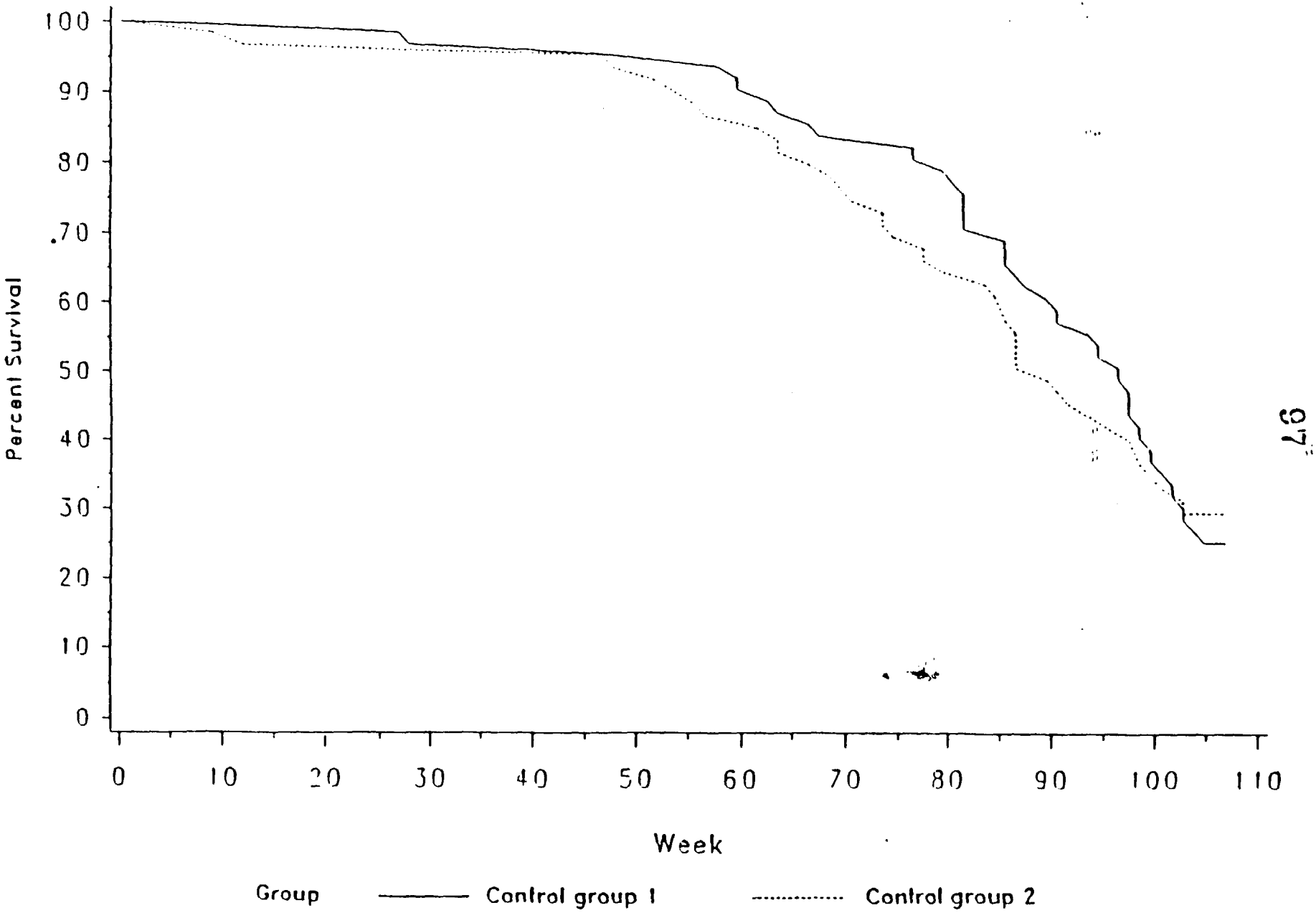

Figure 2a. Bisoprolol Mouse ɔgenicity Study (87086)
Survival Curves by Dose Groups – Males

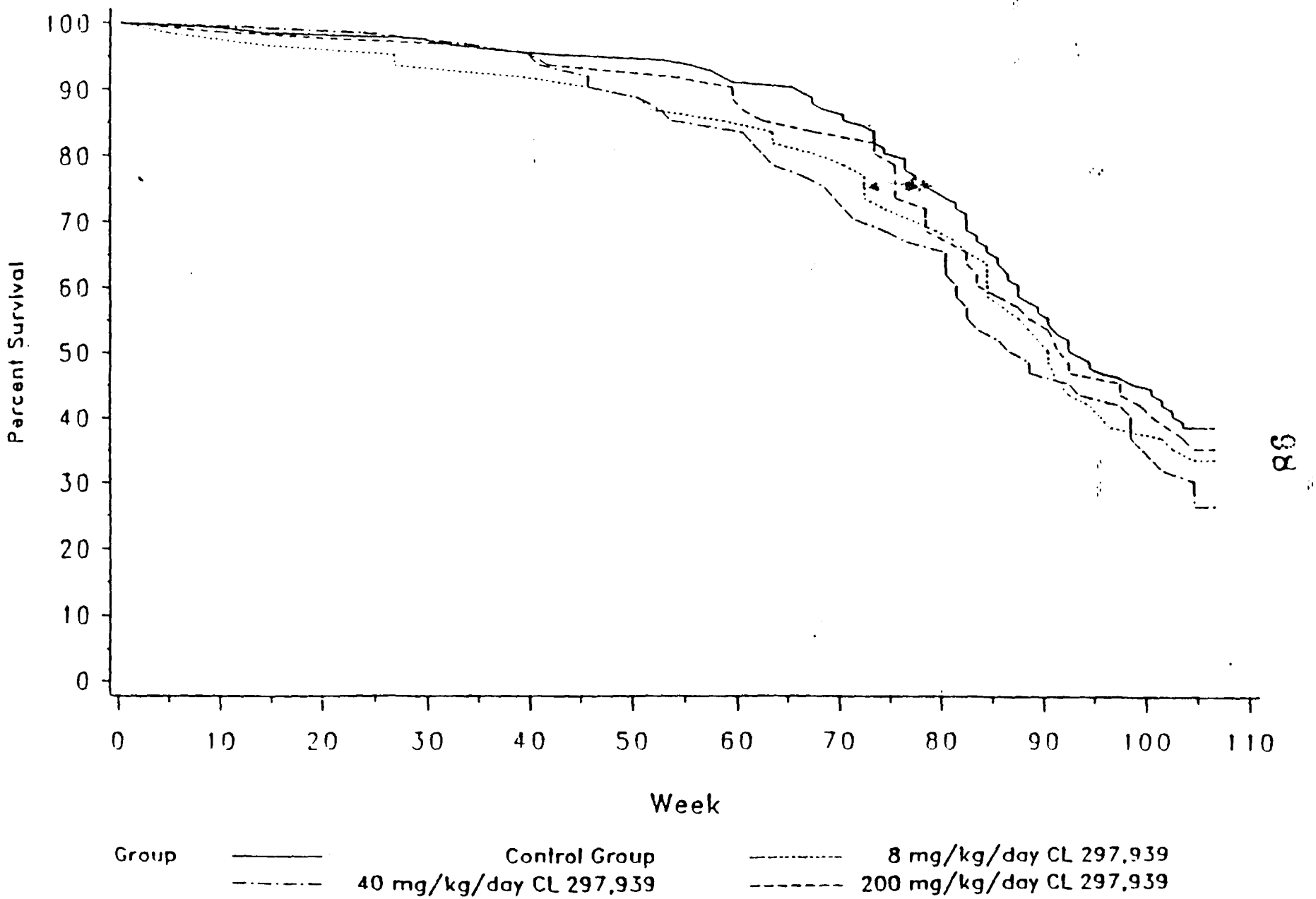

Figure 2b. Bisoprolol Mous ...icogenicity Study (87086)
Survival Curves by Dose Groups – Females

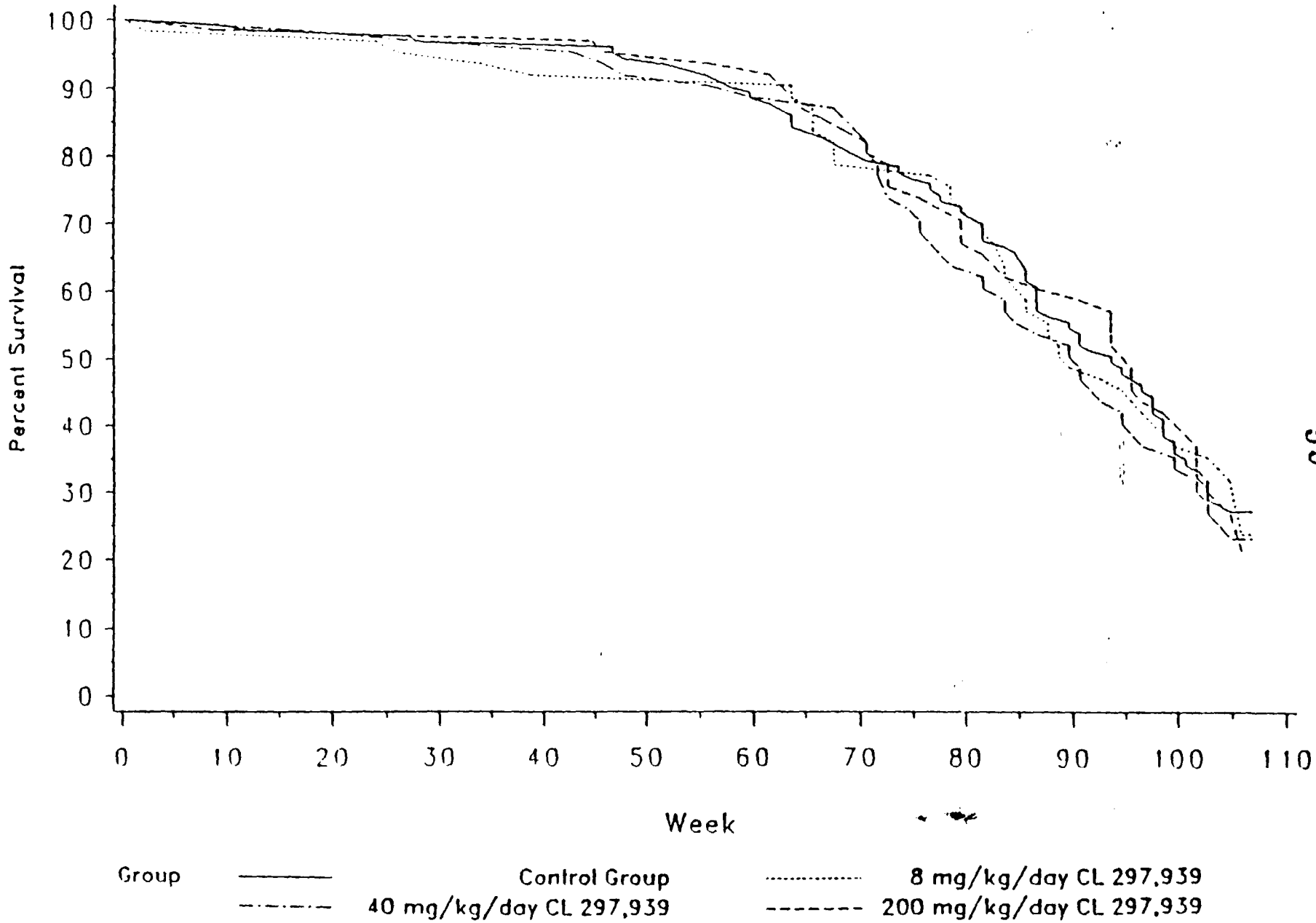

Figure 3a. Bisoprolol Mou icogenicity Study (87086)
Survival Curves : Animals Evaluated Histopathologically – Male s

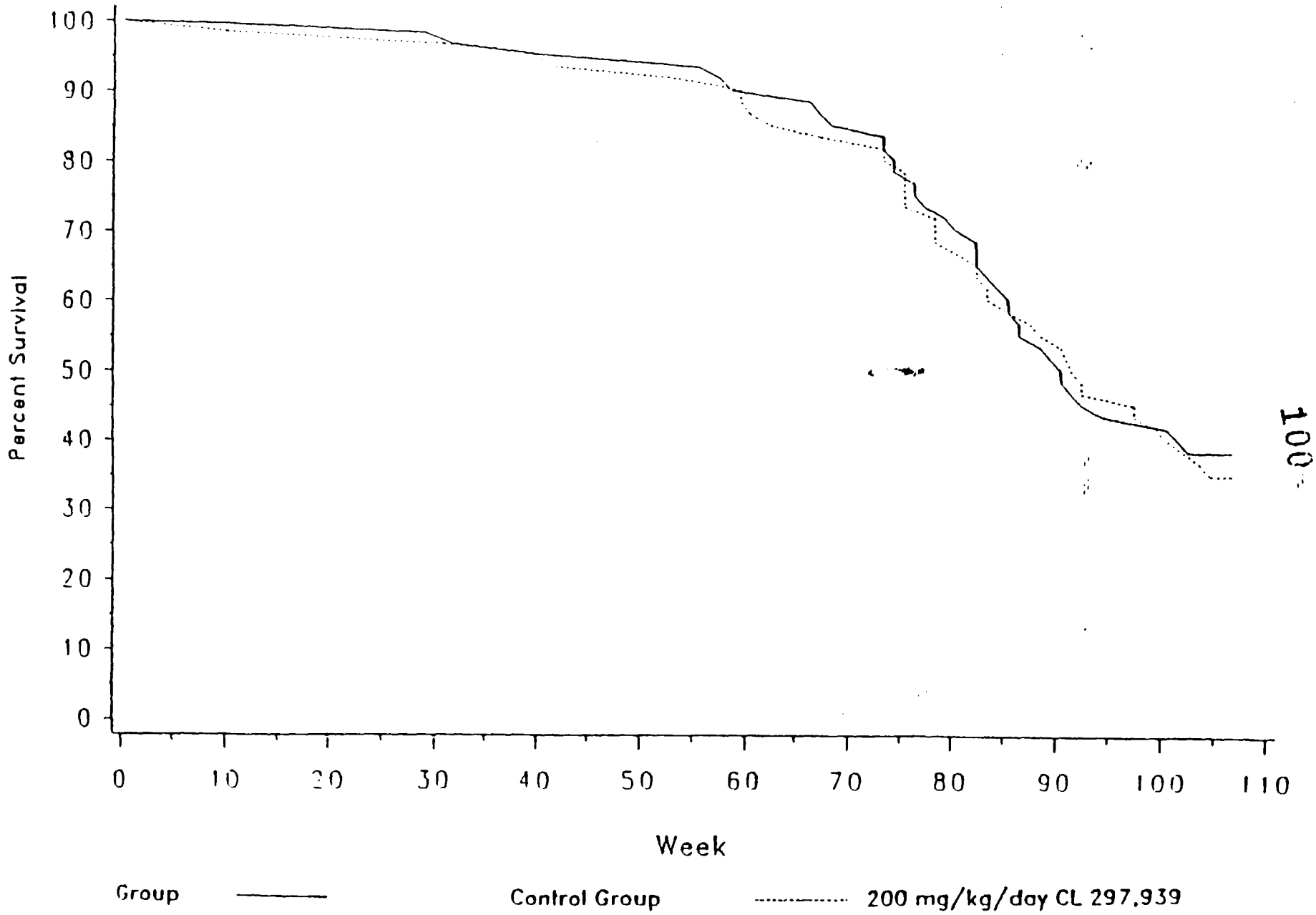

Figure 3b. Bisoprolol Mouse Oncogenicity Study (87086)
Survival Curves : Animals Evaluated Histopathologically -- Females

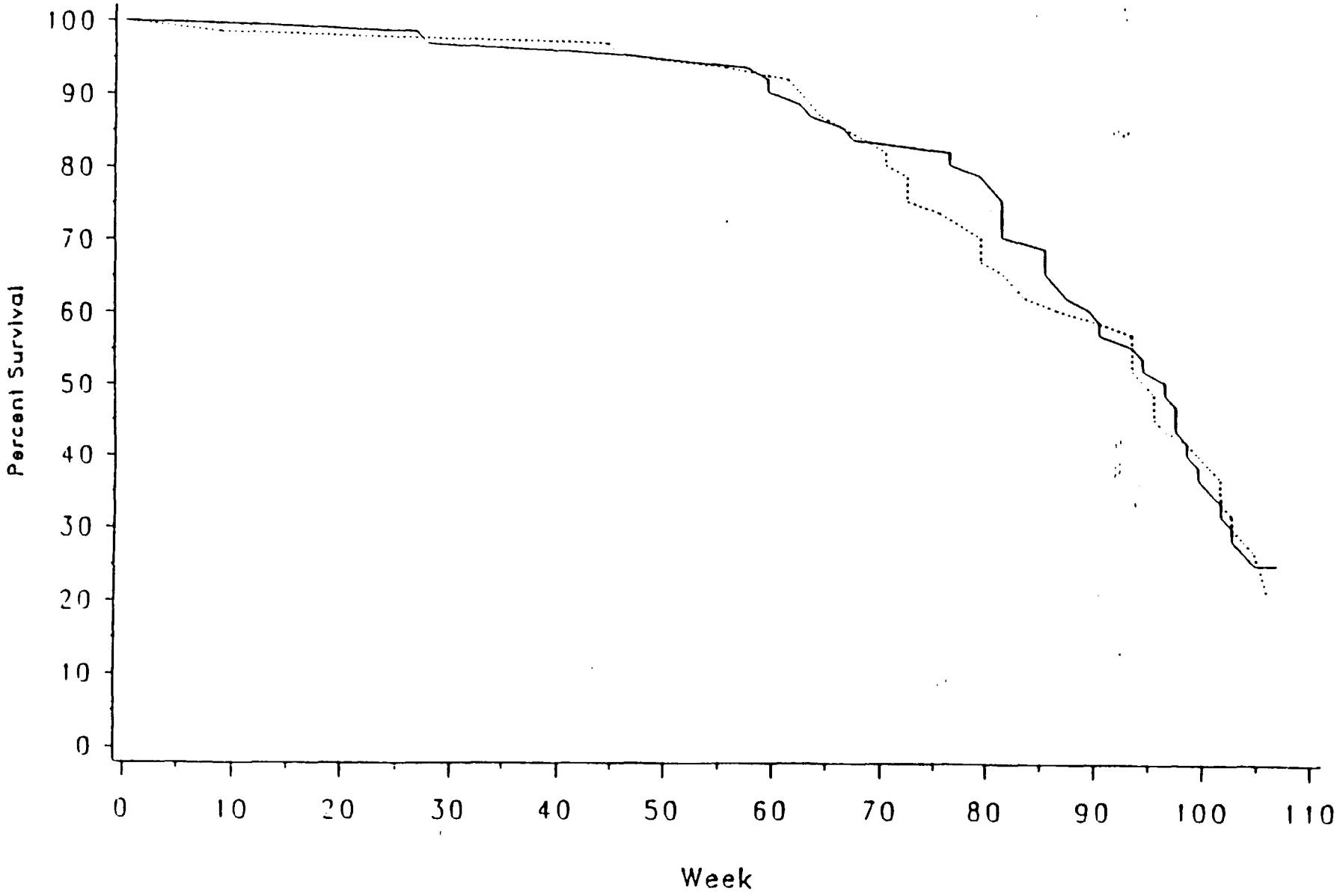

TABLE 1

BISOPROLOL: CARCINOGENICITY STUDY IN MICE (87086)
SURVIVAL AT SELECTED TIME POINTS

MALES

Time (Months)	Percent Survival			
	Untreated	8 mg/kg	40 mg/kg	200 mg/kg
12	94%	86%	87%	91%
15	90%	81%	77%	84%
18	76%	70%	66%	71%
20	62%	57%	50%	57%
21	54%	49%	46%	53%
22	48%	40%	42%	46%
23	44%	37%	35%	41%
24	38%	33%	27%	35%

Initially : n=60 animals in each dose group
n=120 animals in the control group

Logrank Test : Heterogeneity among mortality profiles, p = 0.41
Increasing mortality with dose, p = 0.36

FEMALES

Time (Months)	Percent Survival			
	Untreated	8 mg/kg	40 mg/kg	200 mg/kg
12	93%	91%	91%	94%
15	83%	87%	87%	86%
18	73%	75%	65%	71%
20	57%	56%	54%	60%
21	52%	48%	49%	57%
22	47%	44%	40%	48%
23	36%	37%	35%	40%
24	27%	24%	23%	21%

Initially : n=60 animals in each dose group
n=120 animals in the control group

Logrank Test : Heterogeneity among mortality profiles, p = 0.89
Increasing mortality with dose, p = 0.76

TABLE 2

BISOPROLOL: CARCINOGENICITY STUDY IN MICE (87086)

FREQUENCY OF TUMOR-BEARING ANIMALS BY DOSE GROUP

Organ	Tumor Type/ Grouping	MALES Untreated Control	MALES 200 mg/kg	MALES P-value*	FEMALES Untreated Control	FEMALES 200 mg/kg	FEMALES P-value*
Adrenals							
	Cortical Adenoma	0/59	0/58	-	1/58	0/59	-
	Pheochromocytoma	0/59	0/58	-	1/58	0/59	-
	Cortical Carcinoma	1/59	0/58	-	0/58	0/59	-
Bones							
	Chondroma	1/59	0/58	-	0/60	0/60	-
	Osteosarcoma	0/59	1/58	-	0/60	0/60	-
Epididymis							
	Carcinoma	1/59	0/59	-	-	-	-
Kidneys							
A:	Renal Cell Adenoma	0/60	1/59	-	0/60	0/60	-
B:	Renal Cell Carcinoma	0/60	1/59	-	0/60	0/60	-
	A or B	0/60	2/59	-	0/60	0/60	-

TABLE 2 (continued)

BISOPROLOL: CARCINOGENICITY STUDY IN MICE (87086)

FREQUENCY OF TUMOR-BEARING ANIMALS BY DOSE GROUP

Organ	Tumor Type/ Grouping	MALES Untreated Control	MALES 200 mg/kg	MALES P-value*	FEMALES Untreated Control	FEMALES 200 mg/kg	FEMALES P-value*
Liver							
	Kupffer Cell Sarcoma	0/60	0/59	-	1/60	0/60	-
	Hemangioma	0/60	1/59	-	1/60	0/60	-
	Hemangiosarcoma	0/60	3/59	-	1/60	1/60	-
	C: Hepatocellular Adenoma	5/60	1/59	0.95	2/60	1/60	-
	D: Hepatocellular Carcinoma	4/60	4/59	0.48	2/60	0/60	-
	E: Cholangiocarcinoma	1/60	0/59	-	0/60	0/60	-
	C, D or E	9/60	4/59	0.92	3/60	1/60	-
Lungs							
	F: Bronchiolo-Alveolar Adenoma	11/60	6/59	0.90	5/60	12/60	0.03
	G: Bronchiolo-Alveolar Adenocarcinoma	1/60	2/59	-	2/60	6/60	0.08
	F or G	12/60	8/59	0.82	7/60	16/60	0.02
Lymph Nodes							
	Hemangioma	0/56	2/57	-	1/59	0/59	-

TABLE 2 (continued)

BISOPROLOL: CARCINOGENICITY STUDY IN MICE (87086)

FREQUENCY OF TUMOR-BEARING ANIMALS BY DOSE GROUP

Organ	Tumor Type/ Grouping	MALES Untreated Control	MALES 200 mg/kg	MALES P-value*	FEMALES Untreated Control	FEMALES 200 mg/kg	FEMALES P-value*
Mammary Glands							
	H: Adenoma	0/53	0/52	-	1/58	0/59	-
	I: Adenocarcinoma	0/53	0/52	-	1/58	1/59	-
	J: Adenoacanthoma	0/53	0/52	-	0/58	1/59	-
	H, I or J	0/53	0/52	-	2/58	2/59	-
Ovaries							
	Granulosa Cell Tumor	-	-	-	1/59	3/58	-
	Hemangioma	-	-	-	0/59	1/58	-
	Hemangiosarcoma	-	-	-	1/59	0/58	-
Parathyroid Gland							
	Adenoma	0/53	0/44	-	0/44	1/54	-
Pituitary Gland							
	Adenoma	0/54	0/55	-	2/58	0/55	-
Prostate Gland							
	Adenocarcinoma	0/60	1/59	-	-	-	-

TABLE 2 (continued)

BISOPROLOL: CARCINOGENICITY STUDY IN MICE (87086)

FREQUENCY OF TUMOR-BEARING ANIMALS BY DOSE GROUP

Organ	Tumor Type/ Grouping	MALES Untreated Control	MALES 200 mg/kg	MALES P-value*	FEMALES Untreated Control	FEMALES 200 mg/kg	FEMALES P-value*
Seminal Vesicle							
	Hemangiosarcoma	1/60	0/59	-	-	-	-
Skeletal Muscle							
	Hemangiosarcoma	0/60	1/59	-	0/60	0/60	-
Skin							
	Fibroma	0/56	0/57	-	1/58	0/60	-
	Hemangioma	0/56	0/57	-	0/58	1/60	-
	Hemangiosarcoma	0/56	0/57	-	0/58	2/60	-
Spleen							
	Hemangioma	1/60	0/59	-	0/60	0/60	-
	Hemangiosarcoma	2/60	1/59	-	0/60	1/60	-
Stomach							
	Adenoma	1/59	0/59	-	0/60	1/60	-
	Hemangioma	1/59	0/59	-	0/60	0/60	-

TABLE 2 (continued)

BISOPROLOL: CARCINOGENICITY STUDY IN MICE (87086)

FREQUENCY OF TUMOR-BEARING ANIMALS BY DOSE GROUP

Organ	Tumor Type/ Grouping	MALES Untreated Control	MALES 200 mg/kg	MALES P-value*	FEMALES Untreated Control	FEMALES 200 mg/kg	FEMALES P-value*
Thyroid Glands							
	Adenoma	0/59	1/57	-	0/60	0/60	-
Uterus							
	Leiomyosarcoma	-	-	-	1/59	1/60	-
	Hemangioma	-	-	-	2/59	4/60	0.16
K:	Sarcoma, Stromal, Endometrium	-	-	-	4/59	4/60	0.47
L:	Sarcoma, Undifferentiated	-	-	-	0/59	1/60	-
	K or L	-	-	-	4/59	5/60	0.35
Vagina							
	Fibrosarcoma	-	-	-	0/53	1/57	-
All Organs							
	Hemangioma	2/60	3/59	0.30	4/60	6/60	0.21
	Hemangiosarcoma	3/60	5/59	0.24	2/60	4/60	0.20
	Hemangioma or Hemangiosarcoma	5/60	8/59	0.18	6/60	10/60	0.12

TABLE 2 (continued)

BISOPROLOL: CARCINOGENICITY STUDY IN MICE (87086)

FREQUENCY OF TUMOR-BEARING ANIMALS BY DOSE GROUP

Organ	Tumor Type/ Grouping	MALES Untreated Control	MALES 200 mg/kg	MALES P-value*	FEMALES Untreated Control	FEMALES 200 mg/kg	FEMALES P-value*
Hematopoietic System							
	Granulocytic Leukemia	0/60	1/59	-	0/60	0/60	-
	Histiocytic Sarcoma	0/60	3/60	-	5/60	5/60	0.47
	Malignant Lymphoma	3/60	5/60	0.22	7/60	11/60	0.16

* P-value from one-sided Peto analysis, testing for increased tumor prevalence in the 200 mg/kg group.

No p-value was calculated if fewer than five animals had the tumor of interest.

Table 3

Bisoprolol Mouse Carcinogenicity Study

Summary Table of Tumor Findings

	Males		Females	
	Controls[a]	200 mg/kg[b]	Controls[a]	200 mg/kg[b]
Mice with Tumors	29	27	32	41
Mice with Benign Tumors	18	11	15	18
Mice with Malignant Tumors	13	20	24	32
Mice with more than one Primary Tumor	4	7	9	14

a - N=60
b - N=59

Table 4
Intercurrent Mortality Rates
Male Mice

Weeks	Control 1			High		
	Start	D	%	Start	D	%
0-50	60	3	5	60	4	6.66
51-80	57	14	24.56	56	15	26.78
81-104	43	20	46.51	41	20	48.78
Term.	23			21		

Female Mice

Weeks	Control			High		
	Start	D	%	Start	D	%
0-50	60	3	5	60	3	5
51-80	57	10	17.54	57	15	26.31
81-104	47	32	68.08	42	27	64.28
Term.	15			15		

Notes: D: Deaths
%: Percent of death during the period

Table 5
Tumor Incidence Rates
Female Mice, Lungs Bronchiolo-alveolar adenoma

Weeks	Control		High	
	T	N	T	N
0-50	0	3	0	3
51-80	1	10	1	15
81-104	2	32	8	27
Terminal	2	15	3	15
Total	5	60	12	60

Table 6
Tumor Incidence Rates
Female Mice, Salivary Gland Malignant Lymphoma

Weeks	Control		High	
	T	N	T	N
0-50	0	3	0	3
51-80	0	10	2	15
81-104	0	32	4	27
Terminal	0	15	0	15
Total	0	60	6	60

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

EXPANDED TABLE OF PULMONARY TUMORS IN CD-1® MICE: 18 MONTHS

MALE

TUMOR	GROUP	A	B	C	D	E	F	G	H
	N=	50	48	50	50	49	49	150	50
bronchiolar/alveolar adenoma		—	—	—	4	—	—	18	—
alveolar type II adenoma		—	—	—	—	—	—	—	13
bronchiolar/alveolar carcinoma		2	—	—	—	—	—	5	—
alveolar type II carcinoma		—	8	4	—	4	7	—	—

FEMALE

	N=	50	48	50	50	50	50	148	50
bronchiolar/alveolar adenoma		—	—	—	1	—	—	13	—
alveolar type II adenoma		—	—	—	—	—	—	—	10
bronchiolar/alveolar carcinoma		2	—	—	—	—	—	6	—
alveolar type II carcinoma		—	7	8	—	6	5	—	1

CD-1® MOUSE: 18 MONTHS GLOSSARY OF SYNONYMS

The synonyms listed below are those found in the studies compiled:

LUNG:

alveolar type II adenoma
-alveologenic adenoma

alveolar type II carcinoma
-alveolar adenocarcinoma,
-alveologenic carcinoma/adenocarcinoma

bronchiolar carcinoma
-bronchiogenic carcinoma

STOMACH:

adenoma
-gastric adenoma
-mucosal adenoma

LIVER:

cholangiocarcinoma
-hepatobiliary carcinoma

nodular hepatocellular proliferation
-nodular hepatocytic hyperplasia

hepatocellular carcinoma
-hepatocellular carcinoma, papillary form

OVARY:

luteoma
-luteal cell tumor

UTERUS:

endometrial sarcoma
-endometrial stromal sarcoma

ADRENAL:

cortical adenocarcinoma
-cortical carcinoma

pheochromocytoma (M)
-medullary carcinoma

Table 8

EXPANDED TABLE OF PULMONARY TUMORS IN CD-1® MICE: 21-24 MONTHS

TUMOR		GROUP A	B	C	D	E	F	G
MALE								
	N =	50	81	70	68	71	70	70
bronchiolar/alveolar adenoma		5	6	—	—	8	—	—
bronchiolar/alveolar carcinoma		12	5	—	—	—	—	—
alveolar type II carcinoma		—	—	18	17	—	10	11
alveologenic bronchiolar neoplasm		—	3	—	—	—	—	—
FEMALE								
	N =	50	80	69	70	72	70	70
bronchiolar/alveolar adenoma		4	6	—	—	4	—	—
bronchiolar/alveolar carcinoma		12	3	—	—	—	—	—
alveolar type II carcinoma		—	—	21	27	—	7	12
bronchiolar carcinoma		—	—	1	—	—	—	—

Table 9

Historical Control Data in CD-1 Mice

	72020		81094		81003		81190		6100-104		Total	
	M	F	M	F	M	F	M	F	M	F	M	F
Tumor Type												
Lung												
M - alveolar carcinoma	11/64	15/67	10/110	3/108	2/49	0/49	8/57	5/57	1/60	1/60	32/340	24/341
X - malignant lymphoma	2/64	7/67	0/110	3/108	8/49	4/49	3/57	8/57	1/60	1/60	14/340	23/341
M - hepatocellular carcinoma	0/64	0/67	0/110	0/108	0/49	1/49	1/57	0/57	0/60	0/60	1/340	1/341
M - leiomyosarcoma	0/64	0/67	0/110	1/108	0/49	0/49	0/57	0/57	0/60	0/60	0/340	1/341
M - hemangiosarcoma	0/64	0/67	0/110	1/108	0/49	0/49	0/57	0/57	0/60	0/60	0/340	1/341
M - sarcoma, undiff.	0/64	0/67	1/110	1/108	0/49	0/49	0/57	0/57	0/60	0/60	1/340	0/341
B - alveolar/bronchiolar adenoma	0/64	0/67	0/110	0/108	1/49	2/49	0/57	0/57	2/60	2/60	3/340	4/341
Mesenteric LN												
X - malignant lymphoma	4/58	8/65	5/102	4/96	7/45	2/45	4/47	8/51	3/56	2/59	23/308	22/316
M - lymphosarcoma	1/58	0/65	0/102	0/96	0/45	0/45	0/47	0/51	0/56	0/59	1/308	0/316
Hemic/Lymphatic												
M - malignant lymphoma	-	-	0/110	10/100	0/1	-	9/58	16/54	4/60	3/60	21/229	29/222
Mesentery												
X - malignant lymphoma	5/5	0/2	-	1/5	0/3	-	-	-	3/3	1/1	8/11	2/8
M - endometrial stromal sarcoma	0/5	0/2	-	1/5	0/3	-	-	-	0/3	0/1	0/11	1/8
Thymus												
X - malignant lymphoma	2/27	4/36	1/82	8/97	5/41	4/40	5/51	11/50	3/57	2/55	16/258	29/278
Lymph Node, Other												
X - malignant lymphoma	2/2	5/6	2/2	-	1/1	-	-	-	-	-	5/5	5/6
Kidneys												
X - malignant lymphoma	5/64	5/66	4/110	4/108	8/64	3/64	2/58	7/55	4/60	1/60	23/356	20/353
Tubule cell carcinoma	0/64	0/66	1/110	0/108	0/64	0/64	0/58	0/55	0/60	0/60	1/356	0/353

JUN 1 5 1992

NDA: 19-982
Bisoprolol (Probeta™)
5 mg and 10 mg oral tablets
Lederle

SUBMISSION DATE: December 13, 1991.

REVIEWER: Lydia C. Kaus Boggs, M.S., Ph.D.

TYPE OF SUBMISSION: Response to Comments from Review of Original NDA.

RECOMMENDATION:
The firm has satisfactorily responded to comments raised by Dr. Mehul Mehta in his review of the original NDA 19-982. The Medical Officer's attention is drawn to the Conclusions #1 to 3 regarding labeling for this product. The dissolution specifications should be set as follows:

Apparatus type:	USP Method #2
Media:	Dearated Water, 900 mL
Speed of Rotation:	75 rpm
Sampling Time:	minutes
Q value:	%

Please note that the manufacturing name for bisoprolol was previously Monocor™ and is so referred in previous comments and correspondance. The firm now refers to bisoprolol product as Probeta™.

FDA Comment #1:
"The firm has provided no details on the standard breakfast that was used in report #42."

Firm's Response:
The breakfast provided in the study (Report #42 (page 1, vol. 1.46) was as follows:

200 mL orange juice
200 mL 2% milk
3 slices bacon
2 fried eggs
2 slices white toast
5 mL butter

Reviewer's comments:
The breakfast varies form the standard high fat breakfast. The firm has adequately responded to Comment #1.

FDA Comment #2:
"As validation of bisoprolol assay for report #26, the firm has submitted a publication (J. Chromatog., 382, 215, 1986) which describes methodology to quantify bisoprolol and metoprolol, atenolol and propranolol in plasma and urine using this does not provide validation of the method that was used to quantify bisoprolol in the samples from this specific study. If the firm intends to draw any conclusions on bisoprolol kinetics from this study, it should submit adequate assay validation."

Firm's Response:
Not applicable since we do not intend to draw any conclusions on bisoprolol kinetics from this study.

Reviewer's comments:
The firm's response is acceptable. The reviewer examined the annotated labeling for bisoprolol and no reference was made to report #26 in the labeling. Information on its metabolism was referred to in Report #8, Vol 1.38 and not to this particular report.

FDA Comment #3:
"For report #52, the publication submitted for hydrochlorothiazide assay validation is not adequate since there is no validation data for the method when it was used during the analysis of samples for this particular study. Therefore, hydrochlorothiazide results of this study are not evaluated. If the firm intends to draw any conclusions on the hydrochlorothiazide results from this study, it should submit adequate assay validation."

Firm's response:
The firm provided a report from E. Merck entitled "In use validation of the HCTZ assay in plasma". This is to be appended to the multiple dose interaction study of bisoprolol and hydrochlorothiazide entitled " Comparative bioavailability of a bisoprolol/HCTZ combination at steady-state in normal volunteers" (ZPD no. EMB 47378-27, E. Merck, Darmstadt). The firm then responded by also saying that they do not have similar "in-use" validation data for the HPTLC method used to measure HCTZ in the samples form the single dose interaction study (Report #52) that was reviewed in the single agent NDA. ...The firm also stated the following: "However, we believe that the HCTZ assay results presented in the report...provide adequate in-use validation of the method which was used during the analysis of samples in both the single dose interaction study (Report #52, NDA 19-982) and in the multiple dose interaction study subsequently filed in the combination NDA."

Reviewer's comments:
Study EMD 47 378 was a drug interaction study reviewed by Dr. Mehta, Division of Biopharmaceutics in the original NDA submission for bisoprolol. The following conclusions were made from Dr. Mehta's review:

1. Comparisons of the parameters showed that there was no significant difference ($p > 0.05$) between AUC, Cmax, Tmax, t1/2 and urinary recovery of bisoprolol when given with or without hydrochlorothiazide indicating that HCTZ does not significantly effect the kinetics of bisoprolol when the two are given together in single oral doses of 25 mg and 20 mg respectively.

2. As noted earlier, the firm has not submitted adequate validation for the HCTZ assay. Therefore, no conclusions will be made regarding the HCTZ results of this study."

In December 13, 1991 the firm submitted responses to comments raised in Dr. Mehta's review including the assay validation for HCTZ in plasma. The assay validation was as follows:

The assay range was from ng/mL.
Between-day precision for 50 ng/mL was less than 5% (%CV).
The calibration standard curves were linear with r values of >0.9995.

However many of the plasma concentrations in the multiple dose study were below the lowest calibration standard of 25 ng/mL. The assay is therefore not acceptable. No assay for HCTZ in urine was provided. This does not satisfy Dr. Mehta's comments as the assay validation was for a study other than the single dose interaction study he reviewed, although the method was purported to be the same by the firm.

The firm cannot make any statements in the labeling with regard to HCTZ's kinetics in the presence of bisoprolol on the basis of this response.

FDA Comment #4:
"For report #51, in terms of bisoprolol assay validation, the firm has cited the same

publication as discussed in comment #2 above. Therefore, for this study also, the assay is considered to be not adequately validated. If the firm intends to make any statements regarding the bisoprolol pharmacokinetics in hyperthyroidism in the proposed package insert, it should submit adequate assay validation."

Firm's Response:
Not applicable since we do not intend to make statements in the package insert regarding bisoprolol pharmacokinetics in hyperthyroidism.
Reviewer's comments:
The firm's response is acceptable. The labeling for bisoprolol does not have any statements so far describing its pharmacokinetics in hyperthyroidism.

FDA Comment #5:
"For report #54, in terms of bisoprolol assay validation, the firm has cited the same publication as discussed in comment #2 above. Therefore, for this study also, the assay is considered to be not adequately validated. If the firm intends to make any statements regarding the effect of trichlormethiazide on bisoprolol pharmacokinetics in the proposed package insert, it should submit adequate assay validation."

Firm's Response:
Not applicable since we do not intend to make any statements in the package insert regarding the effect of trichlormethiazide on bisoprolol pharmacokinetics.

Reviewer's comments:
The firm's response is acceptable. The labeling for bisoprolol does not have any statements so far describing its pharmacokinetics in the presence of trichlormethiazide.

FDA Comment #6:
"The Division does not agree with the following labeling statement "No clinically relevant adverse interactions have been observed with other agents given concomitantly, including thiazide diuretics, digoxin and cimetidine." This statement should be replaced with one that clearly reflects the findings that hydrochlorothiazide and cimetidine did not significantly affect bisoprolol pharmacokinetics when given concomitantly and that bisoprolol does not significantly affect plasma steady-state pharmacokinetics of digoxin."

Firm's Response:
The firm stated that they agreed with this comment and would provide statements which "clearly reflect the lack of significant pharmacokinetic interactions from the hydrochlorothiazide and cimetidine pharmacokinetic interaction studies with bisoprolol at the time of our labeling discussions".

Reviewer's comments:
The firm's response is acceptable. It is important that the Reviewing Medical Officer takes note about these responses concerning labeling issues.

FDA Comment #7:
"Regarding the dissolution data, the Division is of the opinion that the use of 100 rpm by the firm in this USP paddle method is unnecessarily high especially since the product is a salt and is therefore expected not to have any dissolution problems; this point is reflected by the above results which show that even at minutes, the lowest % dissolved individual value was %. Since the use of such high rpm can result in non-discriminatory dissolution conditions, the Division is of the opinion that the firm should obtain more data at lower rpm.

Therefore, the Division recommends that the firm obtain dissolution profiles, in water and simulated gastric fluid, on the bio lots (5 mg - formulation #11570, Batch #R1013-6; 10 mg - formulation #11571, batch #R1013-7) at 50 and 75 rpm and submit them, along with the 100 rpm results, for evaluation; these results should be submitted within 30 days post-approval of Monocor™. The Division will finalize the dissolution specifications after evaluating these data; until then, it is recommended that the specifications proposed by the firm (comment 1, page 64) be considered as Interim Specifications".

Firm's Response:
The firm provided the requested information. The firm described an artifact in dissolution at the lower speed of 50 rpm caused by the formation of a cone of material as the lower speed decreases contact between the medium and the tablet particles. At the higher agitation rate of 75 rpm the firm described the variation in dissolution being greater for the 10 mg formulation, although the release rate is equivalent to that seen at 100 rpm. These were the conclusions made when de-aerated water was used as the dissolution medium. In simulated gastric fluid without enzymes, the firm stated that dissolution was rapid for all agitation speeds and non-discriminatory.

The firm, based on the presented data, felt that their original dissolution specifications should stand.

Reviewer's comments:
The firm previously proposed the following dissolution specification.

Apparatus type:	USP Method #2
Media:	Dearated Water, 900 mL
Speed of Rotation:	100 rpm
Sampling Time:	minutes
Q value:	%

Based on the information provided by the firm (see attached Tables), the dissolution specification should be set as follows:

Apparatus type:	USP Method #2
Media:	Dearated Water, 900 mL
Speed of Rotation:	75 rpm

Sampling Time: minutes
Q value: %

JUN 1 5 1992

CONCLUSIONS:
The reviewing Medical Officer should take note of the following for the purpose of final labeling of this product:

1. The firm cannot make any statements in the labeling with regard to HCTZ's kinetics in the presence of bisoprolol on the basis of this response.

2. The firm stated that they would provide statements which "clearly reflect the lack of significant pharmacokinetic interactions from the hydrochlorothiazide and cimetidine pharmacokinetic interaction studies with bisoprolol at the time of our labeling discussions".

3. The firm stated that "we do not intend to make statements in the package insert regarding bisoprolol pharmacokinetics in hyperthyroidism."

4. The dissolution specification should be set as follows:

Apparatus type: USP Method #2
Media: Dearated Water, 900 mL
Speed of Rotation: 75 rpm
Sampling Time: minutes
Q value: %

/S/

3/18/92

Lydia C. Kaus Boggs, MS, PhD.
Reviewer, Division of Biopharmaceutics.

FT Signed by Nicholas Fleischer, Ph.D. /S/ 6/12/92
Branch Chief, Pharmacokinetic Evaluation

cc: NDA 19-982, HFD-110, HFD-426 (Kaus Boggs, Fleischer), Chron, Division, Drug, Review, FOI (HFD-19).PC:b:N19-982.3/16/92.

JUN 16 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 19-982 (Supplement S-005)
DRUG: bisoprolol fumarate tablets, 5 mg, 10 mg
SPONSOR: Wyeth Ayerst Research
TYPE OF SUBMISSION: Manufacturing Site Change
DATE OF SUBMISSION: 12/22/97 (to OCPB 6/15/98)
REVIEWER: Ameeta Parekh, Ph.D.

BACKGROUND: A manufacturing site change is being filed for the bisoprolol fumarate tablets (Zabeta®) from The other changes to be implemented include a reduction in batch size to one third the original sizes equipment change to those with the same operating principles, specification of the excipients to only USP/NF (instead of both USP/NF and BP/EP). It should be noted that the magnesium stearate used in has greater surface area than that used in The formulation remains exactly the same.

In support of this change, the sponsor has provided in-vitro data in accordance with SUPAC IR for a level 3 change in manufacturing site. Stability and validation data has been provided for the tablets manufactured at the 2 sites.

Dissolution profiles were generated for three lots each of Zabeta® 5 mg and 10 mg strengths using the approved method (USP 2, 75 rpm, 900 ml deaerated water, 37 C with specification of Q % in minutes) and compared to tablet batches manufactured at The time points for sampling were 5, 10, 20 and 30 minutes. Similarity factor (f2) was generated for the profile comparisons and were determined to be >50

RECOMMENDATION: A level 3 site change is being undertaken by the sponsor for Zabeta® tablets and supporting documentation based on the SUPAC IR Guidance has been provided. The data provided on in-vitro dissolution in support of this change is acceptable.

/S/ 6/16/98
Ameeta Parekh, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by Patrick Marroum, Ph.D. : 6/16/1998
cc: NDA 19-982, HFD-110 (McDonald, Cunningham), HFD-860 (Parekh), CDR (attn: Barbara Murphy), HFD-340 (Vish)

JUN 23 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 19-982 & NAD 20-189 **SUBMISSION DATES: JUNE 1998**
Zebeta® (bisoprolol fumarate) Tablets &
Ziac® (bisoprolol fumarate and hydrochlorothiazide) Tablets

WYETH-AYERST RESEARCH **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: NEW PROTOCOLS

SYNOPSIS:
Bisoprolol (Zebeta® Tablets), a β_1 adrenoceptor blocker, and its combination with hydrochlothothiazide (Ziac® tablets) are approved for the treament of hypertention (NDAs 19-982 & 20-189 respectively). The sponsor has submitted two protocols to obtain additional pediatric information on bisoprolol and bisoprolol hydrochlorothiazide that may produce health benefits in the pediatric population and therby receive the six months of market exclusivisity for these drugs according to FDA Modernization Act of 1997 (FDAMA).

SUMMARY:
The two proposed studies are:
(1) A double-blind, placebo-controlled, dose-escalation safety and efficacy study of Ziac® (bisoprolol fumarate and hydrochlorothiazide) in patients 8 to 18 years of age.
(2) An open-label, single-dose, randomized, crossover study to determine the pharmacokinetics profiles of Ziac® (bisoprolol fumarate and hydrochlorothiazide) and Zebeta® (bisoprolol fumarate) in patients, 8 to 18 years of age, with stage1- stage II essential hypertension.
The protocol synopses are attcahed.

COMMENTS CONVEYED TO THE SPONSOR:
An open-label, single-dose, randomized, crossover study to determine the pharmacokinetics profiles of Ziac® (bisoprolol fumarate and hydrochlorothiazide) and Zebeta® (bisoprolol fumarate) in patients, 8 to 18 years of age, with stage1- stage II essential hypertension.

(i) Sampling times: The proposed sampling times are at 0 (predose), 2, 3, 8, 22, and 24 hours post dose. The terminal half-life of bisoprolol is approximately 9 to 12 hours while that of hydrochlorothiazide is approximately 6 to 15 hours. In order to collect samples for about 3 half-lives for both drugs, the following sampling schedule is suggested: at 0 (predose), 1, 3, 8, 16, and 30 hours post dose.

(ii)The sponsor reported that no change has been observed in biovailability upon co-administration of bisoprolol with hydrochlorothiazide in adult population and therefore argues that the same should be observed in the pediatric population. Bisoprolol clearance is approximately 50% via metabolism to inactive metabolites and 50% excreted unchanged in

urine while hydrochlorothiazide is eliminated primarily (95%) unchanged in urine. It is therefore suggested that the sponsor analyze the samples (at least some if not all the subjects) from the subjects on the combination tablet for bisoprolol and compare these plasma levels with those on the monotherapy in order to rule out any possible interaction in this pediatric population.

CONCLUSION:

The Division of Pharmaceutical Evaluation I has reviewed the sponsor's protocols and has conveyed the comments above to the sponsor.

/S/ 6/18/98

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. ---/S/--- 6/23/98

cc: NDA 19-982, NDA 20-186, HFD-110, HFD-860 (Fadiran, CDR (Attn: Barbara Murphy).