CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-773

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-773
Drug Name:	[redacted] (exenatide injection)
Indication(s):	Type 2 Diabetes
Applicant:	Amylin
Date(s):	Received 6/29/04; user fee (10 months) 4/29/05
Review Priority:	Standard
Biometrics Division:	HFD-715
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Keywords: NDA review, clinical studies

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1. EXECUTIVE SUMMARY

Introduction and Background

The proposed indication for exenatide injection is to improve glycemic control in patients with type 2 diabetes mellitus, [redacted] as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea. [redacted]

Three 30-week placebo-controlled phase 3 combination studies evaluated exenatide 5 μg or 10 μg BID, administered SC in type 2 diabetes treated with metformin alone, a sulfonylurea alone, or metformin in combination with a sulfonylurea.

For the 3 phase 3 studies, patients randomized to exenatide began a 4 week initiation period with 5 μg bid to minimize nausea response to a 10 μg bid initiation dose. Table 1 summarizes the study results.

Table 1 Phase 3 Study Summary

Study	Metformin 112			SFU 113			Metformin +SFU 115		
Treatment	placebo	5 μg	10 μg	placebo	5 μg	10 μg	placebo	5 μg	10 μg
n[b]	113	110	113	123	125	129	247	245	241
Baseline Mean	8.20	8.26	8.18	8.69	8.49	8.61	8.49	8.46	8.50
LSM Change[a]	-0.00	-0.46	-0.86	0.06	-0.51	-0.91	0.12	-0.66	-0.88
Difference vs. Placebo		-0.46	-0.86		-0.57	-0.97		-0.78	-1.00
2-sided p-value[*]		0.0016	<0.0001		0.0002	<0.0001		<0.0001	<0.0001
Hypoglycemia	6 (5%)	5 (5%)	6 (5%)	4 (3%)	18 (14%)	46 (36%)	31 (13%)	47 (19%)	67 (28%)
Nausea	26(23%)	40(36%)	51 (45%)	9 (7%)	49 (39%)	66 (51%)	50 (21%)	96 (39%)	117 (49%)
anti-exenatide antibody	3 (3%)	44(40%)	51(46%)	2 (2%)	46 (38%)	51 (41%)	13 (5%)	120 (49%)	107 (45%)

[a] Least squared mean change based on an analysis of variance model with treatment, baseline HbA_{1c} strata, and site as fixed effects for 112 and 113 and with treatment, baseline HbA_{1c} strata, SFU management group, and site as fixed effects for 115

[b] ITT population for HbA_{1c} outcome

[*] Based on the Fisher's protected testing procedure.

Both the 5 μg bid and the 10 μg bid treatment groups showed a significant dose response difference from placebo in HbA_{1c} change from baseline to endpoint in the intent-to-treat (ITT) population.

There were several statistically significant treatment-by-subgroup interactions. However, there was no consistency in the findings among studies. Most of the significant interactions involved only the 5 mcg and placebo comparison. Additionally, the interactions were generally quantitative, not qualitative, in nature.

The dose dependent trend of the incidence of hypoglycemia was greater in the 2 sulfonylurea (SFU) studies than in the metformin alone study. In addition, the incidence of nausea was also dose related. The percentages of patients with anti-exenatide antibodies were significantly greater in the active treatment groups than placebo group; however, the HbA_{1c} change in general was similar with or without antibody. Further exploring of patients with antibody titer ≥125 showed a quantitative smaller reduction of HbA_{1c} than titer <125 patients.

2. INTRODUCTION

2.1 OVERVIEW

Exenatide belongs to a new therapeutic class called incretin mimetics. The postulated effect of incretin hormones is to enhance insulin secretion following their release into circulation from the gut in response to food intake.

2.2 DATA SOURCES

Data were provided electronically at \\Cdsesub1\evsprod\N021773\0000.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Please refer to the review of Medical Officer, Eddie K. Gabry, M.D. for Demographics and disposition of patients. All 3 combination studies were phase 3, randomized, double-blind, placebo controlled multicenter studies for 30 weeks to evaluate exenatide 5 μg bid and 10 μg bid in the treatment of type 2 diabetes. After a 4-week, single-blind placebo lead-in period, patients were stratified according to screening HbA_{1c} <9.0% or ≥9.0% and randomized to 4 treatment groups, A, B, C, or D in the ratios of 2:2:1:1 and began a 4-week, double-blind treatment initiation period with groups A and B receiving 5 μg exenatide and groups C and D an equivalent volume of placebo to minimize the occurrence of nausea during the introduction of the 10 μg dose. Subsequently, patients in group A continued at exenatide 5 μg bid and patients in group B increased from exenatide 5 μg to 10 μg bid for 26 weeks. To maintain the blind, patients randomized to C or D received dose volumes equivalent to the 5 μg (C) or 10 μg (D). The studies enrolled patients on a metformin dose≥1500 mg/day (Study 112, metformin alone), on the maximally effective dose of a SFU (Study 113, SFU alone) and on metformin ≥1500 mg/day and a maximally effect dose for that SFU (Study 115, metformin+SFU). The metformin+SFU study stratified patients at baseline to 2 SFU management approaches (1:1). Patients randomized to a minimum recommended SFU dose were required to reduce the maximally effective SFU dose and allowed an upward adjustment based on fasting plasma glucose. Patients randomized to continue on the maximally effective SFU dose were allowed an SFU dose reduction based on hypoglycemia events.

The inclusion criteria were males or females 16 to 72 years of age who have a screening HbA_{1c} ≥7.1% to ≤11.0% for the metformin alone study and 7.5% to 11.0%, inclusive for the metformin+SFU study and a body mass index in the range of 27 kg/m^2 to 45 kg/m^2.

The primary efficacy variable, HbA_{1c} change from baseline (Visit 3) to the last measurement was analyzed using analysis of variance method with treatment, center, screening HbA_{1c} stratum (≤9% or >9%) as fixed effects. Secondary efficacy variables included HbA_{1c} change from baseline to each of the intermediate visits, change in body weight from baseline, and the proportion of patients achieving HbA_{1c} target values by Week 30. The target values were HbA_{1c} ≤7% and 8%, as well as HbA_{1c} reductions of ≥0.5% and ≥1.0%.

The fixed factors in the analysis of variance model in all 3 studies were treatment, pooled center (by region), and stratification of screening HbA_{1c} <9% or ≥9% and in addition, the SFU stratum in the metformin+SFU study. Treatment-by center and/or treatment-by-stratum interaction was included in the model when the interaction test was significant (p≤0.1).

In the metformin add on study, Fisher's least significant test was significant in the overall test when all 3 treatment groups were in the analysis. This reviewer examined the treatment-by-baseline interaction; the overall treatment-by-stratum interaction was significant (p=0.056<0.1). The overall test for treatment difference including the interaction term was significant; however, the comparison between 5 μg and placebo was not significant (Table 2). The treatment-by-stratum interaction was significant between the 5 μg group and the placebo group and between the 5 μg group and the 10 μg group. The least squared mean difference in HbA_{1c} change from baseline between 5 μg group and placebo group was -0.61% in the HbA_{1c} <9% stratum but +0.07% for the ≥9% stratum in contrast to the -0.8% difference between 10 μg and placebo for both strata (Table 2). Figure 1 displays the median change from baseline for the 3 treatment groups and Figure 2 the mean HbA_{1c} change from baseline over time by strata and studies. Both of the figures showed that only in the ≥9% stratum of the metformin add on study (112) was the 5 μg group worse than placebo in HbA_{1c} change from baseline.

Table 2 Analysis of variance[a] in change from baseline HbA1c – Add on to metformin alone

All patients	Placebo (n=113)	5 µg (n=110)	10 µg (n=112)	5 µg vs. Plb Difference (95% C.I.)	10 µg vs. Plb Difference (95% C.I.)	10 vs. 5 µg Difference (95% C.I.)
Baseline	8.59 (0.08)	8.67 (0.08)	8.54 (0.08)			
Change	-0.02 (0.11)	-0.29 (0.12)	-0.84 (0.12)	-0.27 (-0.60, 0.05)	-0.82 (-1.13, -0.50)	-0.54 (-0.87, 0.22)
Stratum <9%	n=83	n=83	n=81			
Baseline	7.73 (0.08)	7.83 (0.09)	7.79 (0.09)			
Change	+0.26 (0.12)	-0.35 (0.12)	-0.55 (0.12)	-0.61 (-0.94, -0.29)	-0.81 (-1.14, -0.48)	-0.20 (-0.52, +0.13)
Stratum ≥ 9%	n=30	n=27	n=31			
Baseline	9.51 (0.14)	9.54 (0.15)	9.21 (0.14)			
Change	-0.30 (0.20)	-0.23 (0.21)	-1.13 (0.20)	+0.07 (-0.49, +0.63)	-0.82 (-1.37, -0.28)	-0.89 (-1.45, -0.34)

[a] ANOVA model included fixed effects for treatment, pooled site, screening HbA_{1c} stratum and treatment-by-HbA_{1c} stratum interaction. The interaction effect was not included in Table 1 for HbA_{1c} change from baseline.

In SFU add on study the overall comparison was statistically significant among treatment groups. All 3 pairwise comparisons were significant (Table 3). Treatment-by-stratum interaction was not significant (p=0.8).

Table 3 Analysis of variance in change from baseline HbA1c - Add on to Sulfonylurea

	Placebo (n=120)	5 µg (n=123)	10 µg (n=128)	5 µg vs. Plb Difference (95% C.I.)	10 µg vs. Plb Difference (95% C.I.)	10 vs. 5 µg Difference (95% C.I.)
Baseline	8.71 (0.08)	8.63 (0.08)	8.73 (0.08)			
Change	+0.09 (0.12)	-0.48 (0.12)	-0.87 (0.11)	-0.58 (-0.88, -0.28)	-0.96 (-1.26, -0.66)	-0.39 (-0.68, -0.09)

[a] Least squared mean change from baseline using ANOVA model with fixed effect of treatment, pooled site, screening HbA_{1c} stratum.

Table 4 ANOVA[a] results in change from baseline HbA_{1c} – Add on to Metformin+SFU

	Placebo (n=242)	5 µg (n=245)	10 µg (n=240)	5 µg vs. Plb Difference (95% C.I.)	10 µg vs. Plb Difference (95% C.I.)	10 vs. 5 µg Difference (95% C.I.)
Baseline	8.73 (0.06)	8.67 (0.06)	8.75 (0.07)			
Change	+0.19 (0.10)	-0.63 (0.10)	-0.90 (0.10)	-0.82 (-1.02, -0.61)	-1.09 (-1.30, -0.88)	-0.27 (-0.48, -0.06)
Stratum <9%	n=151	n=155	n=157			
Baseline	7.93 (0.07)	7.97 (0.07)	7.99 (0.07)			
	+0.28 (0.11)	-0.39 (0.11)	-0.52 (0.11)	-0.68 (-0.93, -0.43)	-0.80 (-1.05, -0.55)	-0.12 (-0.37, +0.12)
Stratum ≥ 9%	n=91	n=90	n=83			
	9.52 (0.09)	9.37 (0.90)	9.50 (0.09)			
	+0.10 (0.13)	-0.86 (0.14)	-1.28 (0.14)	-0.96 (-1.28, -0.63)	-1.38 (-1.71, -1.04)	-0.42 (-0.75, -0.08)

[a] Least squared mean change from baseline using ANOVA model with fixed effects for treatment, pooled site, screening HbA_{1c} stratum, SFU stratum and treatment-by-HbA_{1c} stratum interaction.

In the metformin + SFU study, HbA_{1c} change from baseline was significantly different among groups for the overall analysis of variance which included treatment, pooled sites, HbA_{1c} stratum, SFU stratum and treatment-by-HbA_{1c} stratum interaction as fixed effects. All 3 pairwise comparisons were all significant. The overall treatment-by-HbA_{1c} stratum was significant (p=0.03). Among the pairwise comparisons there has a quantitative interaction between the 10 µg group and the placebo group. The between treatment difference in HbA_{1c} change was -1.38% in the ≥9% stratum and -0.8% in the <9% stratum (Table 4). Figure 1 displays the median HbA_{1c} change from baseline and Figure 2 the mean HbA_{1c} change from baseline over time for the 3 studies.

Figure 1 Median HbA_{1c} change from baseline to endpoint by stratum – all studies

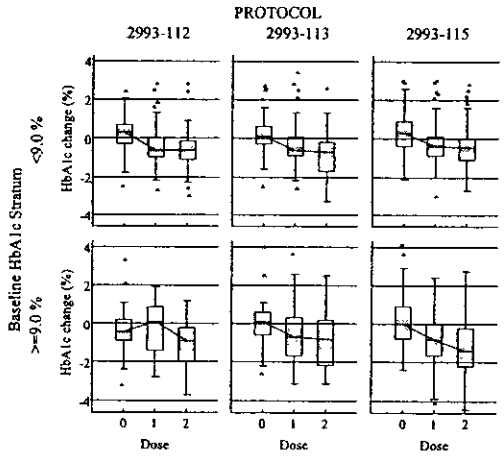
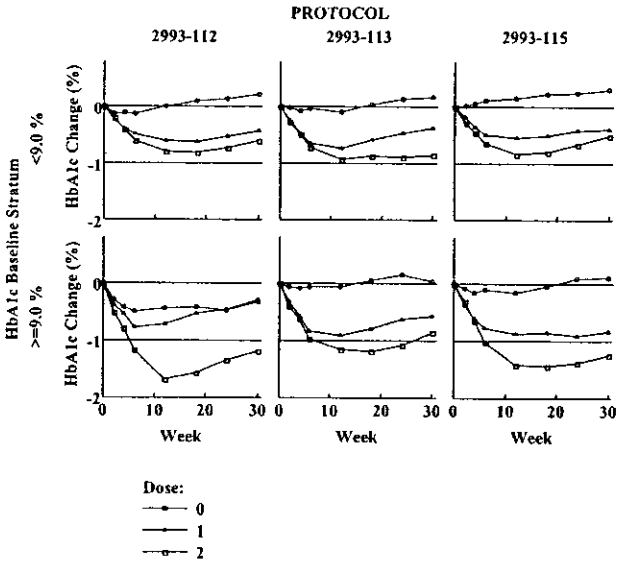


Figure 2 Mean HbA_{1c} change from baseline to endpoint over time by stratum – all studies



The sponsor terminated all the patients and excluded data from investigator Nath of New York (Site 87) due to concerns of GCPs (Good Clinical Practices). A total of 68 patients were excluded: 6 in metformin alone study, 3 in SFU alone study and 49 in metformin+SFU study. The pooled descriptive statistics for HbA_{1c} are displayed in the Appendix.

3.2 Evaluation of Safety

Nausea

The percent of patients with nausea during the study was significantly different among the treatment groups for all 3 studies (Table 5, & Fig3). 7 and Figure 4 display the percent of patients with nausea in early termination patients.

Table 5 Number and percent of patients with nausea during the study

Study	Placebo	5 µg	10 µg	p-value
Metformin	26/113 (23%)	42/110 (38%)	52/113 (46%)	0.0012
SFU	11/122 (9%)	49/124 (40%)	68/128 (53%)	<0.0001
Metformin+SFU	58/245 (24%)	100/245 (41%)	120/240 (50%)	<0.0001

Figure 3 Percent of patients with nausea by treatment group and study

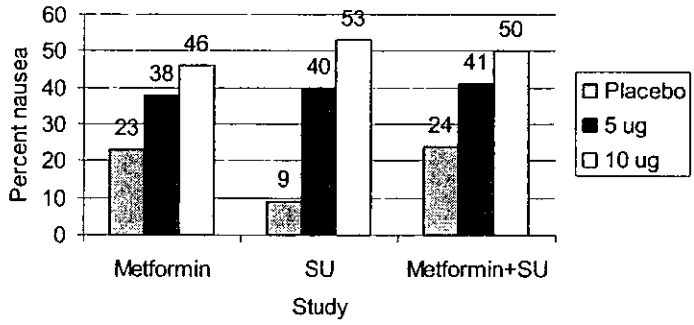
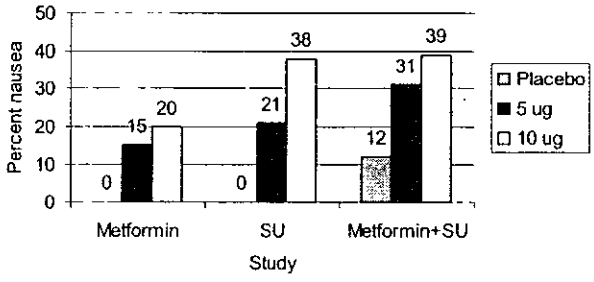


Table 6 and Figure 4 display the number (%) of patients with nausea in early termination patients.

Table 6 Analysis of nausea for early termination patients

Study	Placebo	5 µg	10 µg	p-value
Metformin	0/24	3/20 (15%)	4/20 (20%)	0.033
SFU	0/48	6/28 (21%)	14/37 (38%)	<0.0001
Metformin+SFU	7/59 (12%)	12/39 (31%)	16/41 (39%)	0.002

Figure 4 Percent of nausea in early termination patients



Hypoglycemia

The percentages of hypoglycemia events were not significantly different among treatment groups in the metformin alone study but were significantly different for the studies with SFU (Fig 5, Table 7).

Figure 5 Percent of patients with hyperglycemia

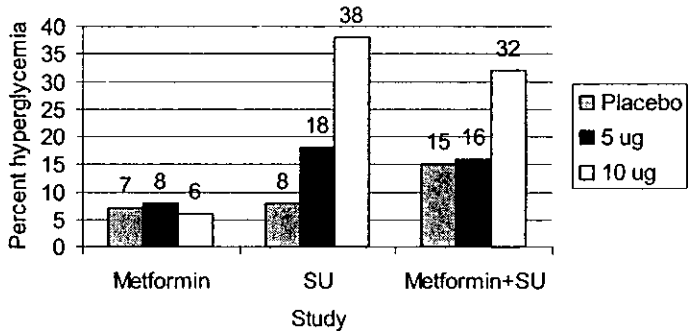


Table 7 Analysis of hyperglycemia

Study	Placebo	5 µg	10 µg	p-value
Metformin	8/113 (7%)	9/110 (8%)	7/113 (6%)	0.80
SFU	10/123 (8%)	23/125 (18%)	49/129 (38%)	<0.0001
Metformin+SFU	37/247 (15%)	63/245 (26%)	77/241 (32%)	<0.0001

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Gender

The treatment-by-gender interaction was significant for the metformin study (p=0.01) (Fig. 6). Female patients in the 5 µg and placebo groups experienced similar HbA_{1c} changes from baseline at endpoint. Table 8 displays the mean and standard deviation of HbA_{1c} change from baseline to endpoint by gender.

Figure 6 HbA_{1c} change from baseline by visit and gender

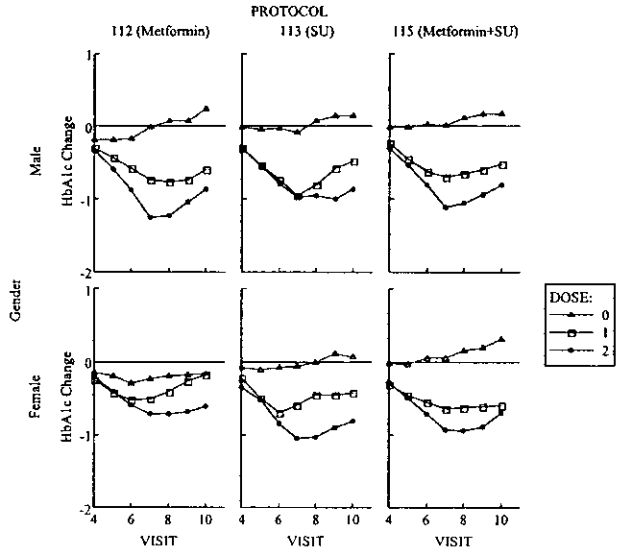


Table 8 Mean HbA_{1c} (%) change from baseline to endpoint by gender – Metformin

	Placebo		5 µg		10 µg	
	Male	Female	Male	Female	Male	Female
Metformin	n=67	n=42	n=57	n=53	n=68	n=45
baseline	8.06 (1.02)	8.41 (1.04)	8.23 (1.19)	8.29 (1.06)	8.26 (1.09)	8.06 (0.85)
change	+0.24 (1.06)	-0.17 (0.99)	-0.59 (1.17)	-0.18 (1.01)	-0.86 (1.04)	-0.61 (1.04)

Race

When 6 race categories were used in the model the overall treatment-by-race interaction was not significant in change from baseline HbA_{1c} for the 3 studies (p=0.9, 1.0, 0.2). However, when only 2 categories were used in the model (Caucasian and Black) the treatment-by-race interaction was significant for study 115 (p=0.07). Figure 7 displays the mean HbA_{1c} change from baseline over time and Figure 8 the median change at endpoint for the 3 races with the most patients, Caucasian, Black and Hispanic patients. Table 9 displays mean and median HbA_{1c} change from baseline for Caucasian and Black patients. The percentages of Caucasians, Blacks, and Hispanics were 68% (494), 11% (82) and 16% (117), respectively. From the descriptive statistics of HbA_{1c} change, the treatment effect is smaller in Black patients in the 5 µg bid group compared to Caucasian and Hispanic patients.

Figure 7 Mean HbA_{1c} change from baseline (%) over time by race

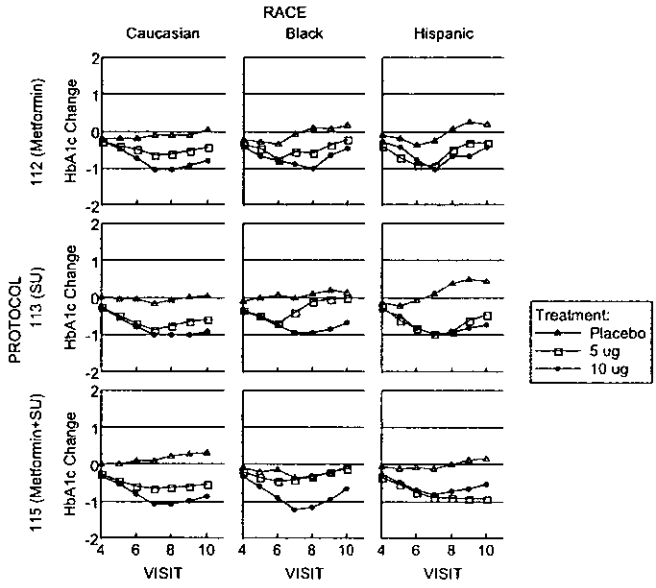


Figure 8 Median HbA_{1c} change from baseline at endpoint by race

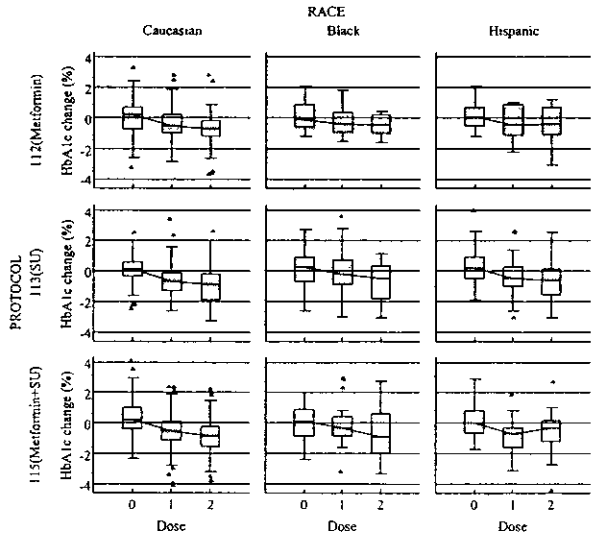


Table 9 Mean, Median of baseline HbA_{1c} & HbA_{1c} change (%) by race

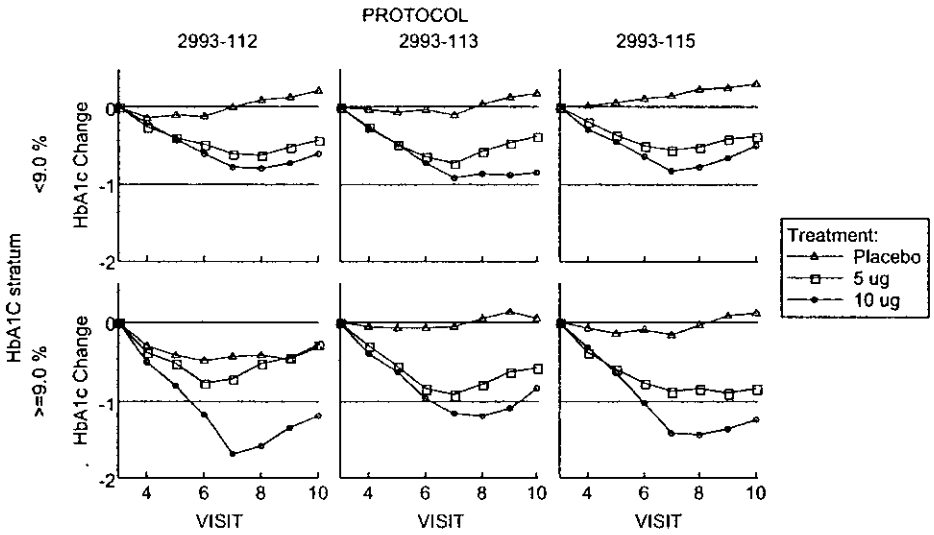
	Placebo				5 μg				10 μg			
	Caucasian		Black		Caucasian		Black		Caucasian		Black	
Metformin	n=82		n=15		n=85		n=12		n=89		n=10	
mean	8.07	+0.04	8.47	+0.18	8.20	-0.43	8.66	-0.21	8.12	-0.79	8.21	-0.45
median	7.85	+0.2	8.6	-0.1	8.0	-0.5	8.5	-0.4	8.0	-0.7	8.25	-0.45
SFU	n=80		n=12		n=75		n=21		n=77		n=21	
mean	8.56	+0.03	9.1	+0.13	8.32	-0.58	8.79	-0.02	8.38	-0.91	9.06	-0.67
median	8.2	+0.1	8.85	+0.25	8.1	-0.7	8.7	-0.2	8.3	-0.9	8.50	-0.5
Metformin+SFU	n=165		n=29		n=169		n=25		n=160		n=28	
mean	8.47	+0.31	8.57	-0.06	8.41	-0.53	8.5	-0.1	8.44	-0.85	8.42	-0.63
median	8.3	+0.2	8.5	+0.1	8.2	-0.5	8.7	-0.3	8.2	-0.85	8.3	-0.9

The treatment-by-age interaction was not significant.

4.2 Other Special/Subgroup Populations

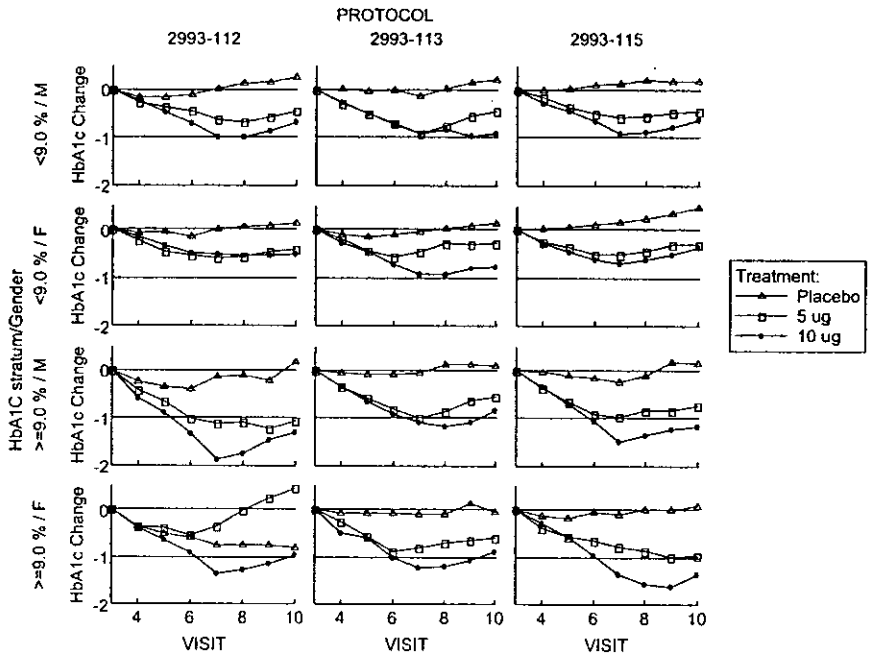
The overall treatment-by-HbA_{1c} stratum interaction was significant for the metformin study (p=0.056) and the metformin+SFU study (p=0.027) (Fig. 2 and 9). For the pairwise comparisons, the interaction was significant between the placebo group and the10 μg group and the 5 μg group and the10 μg group in the metformin study and between the placebo group and the 5 μg group in the metformin+SFU study. In the metformin study, the difference between 5 μg and placebo in HbA_{1c} change from baseline at endpoint was -0.61% and +0.07% for the HbA_{1c} <9% stratum and the ≥9% stratum respectively (Table 6). The difference between 10 μg and 5 μg was -0.2% and -0.89% for the 2 HbA_{1c} strata. In the metformin+SFU study the treatment difference between 10 μg and placebo was -0.8% and -1.37% for the 2 HbA_{1c} strata, respectively.

Figure 9 HbA_{1c} change from baseline over time by stratum and protocol



The treatment-by-stratum-by-gender interaction was significant for the metformin study (p=0.0003) and the metformin+SFU study (p=0.08). The qualitative interaction in the metformin alone study was caused by decreases in the placebo group (n=15) and increases in the 5 μg group (n=14) of HbA_{1c} in the female and HbA_{1c} ≥9% stratum subgroup (Fig 10, 18). There was a quantitative interaction involving the placebo and 10 μg groups for the metformin+SFU study (Fig 10). However, the sample size was small and gender and HbA_{1c} stratum might be confounded.

Figure 10 HbA_{1c} change from baseline (%) by HbA_{1c} stratum and gender

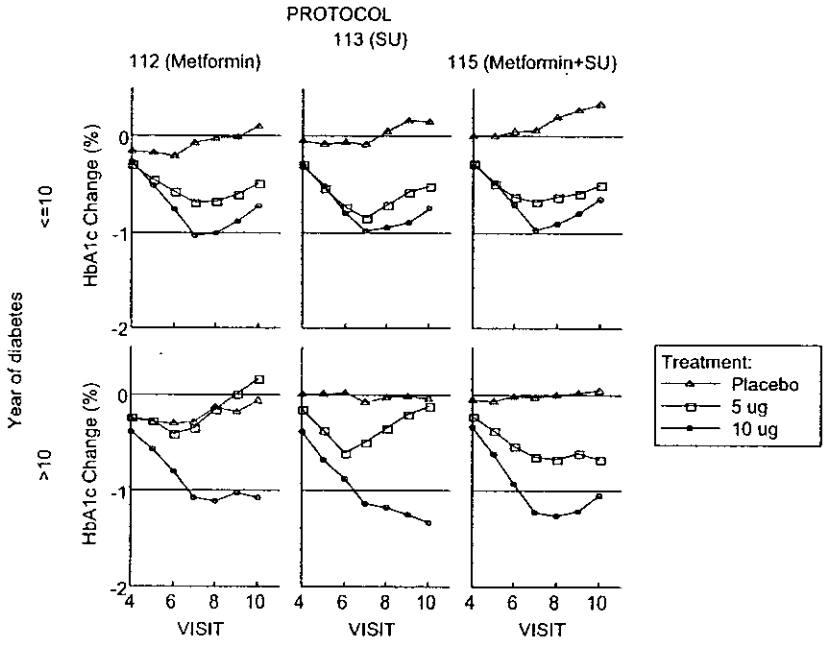


Treatment-by-years of diabetes (>10 or ≤10 yrs) interaction was significant for studies 112 and 113 (Fig 11). Patients in the 5μg group with >10 years of diabetes was similar to placebo at endpoint in HbA_{1c} change from baseline for studies 112 and 113. 15% of patients had >10 years of diabetes in studies 112 and 113, 31% in study 115 (Table 10).

Table 10 HbA_{1c} (%) in patients with >10 or ≤10 years of diabetes

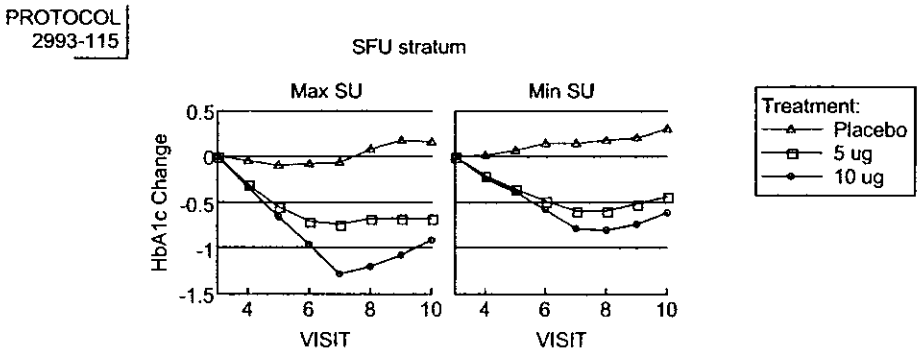
	Placebo		5 μg		10 μg	
	≤10	>10	≤10	>10	≤10	>10
Metformin	n=93	n=20	n=94	n=16	n=99	n=14
baseline	8.1	8.9	8.2	8.9	8.2	8.3
change	0.1	-0.1	-0.5	0.2	-0.7	-1.1
SFU	n=104	n=19	n=108	n=17	n=109	n=20
baseline	8.7	8.6	8.5	8.2	8.6	8.6
change	0.1	-0.04	-0.5	-0.1	-0.7	-1.3
Metformin+SFU	n=161	n=86	n=173	n=72	n=173	n=68
baseline	8.5	8.5	8.6	8.2	8.4	8.7
change	0.3	0.04	-0.5	-0.7	-0.6	-1.0

Figure 11 HbA_{1c} change from baseline by years of diabetes diagnosis



Patients in the metformin+SFU study were randomized to continue on to the maximum effective dose or reduce the SFU to the minimum recommended dose. The treatment-by-SFU (maximum or minimum dose) stratum interaction was not significant at endpoint in HbA_{1c} change from baseline (Fig 12).

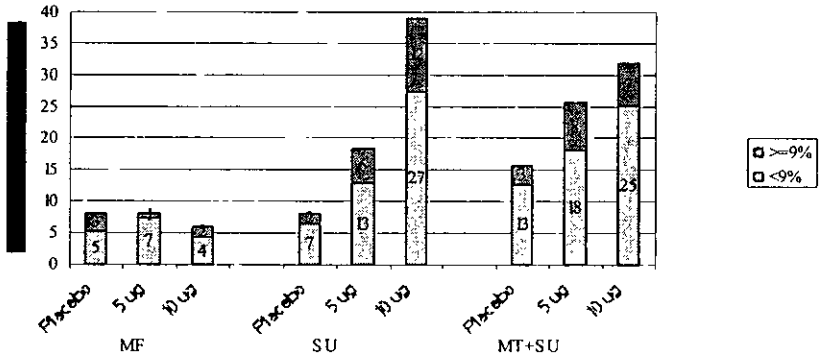
Figure 12 Mean HbA_{1c} change from baseline by visit and SFU stratum – metformin+SFU study



Hypoglycemia

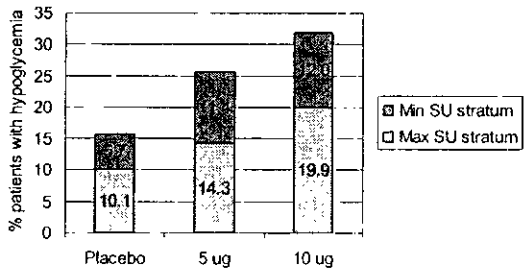
For all studies, there was a greater percentage of patients with hypoglycemia in the screening HbA_{1c} <9% stratum than in the ≥9% stratum (Fig 13).

Figure 13 Percent of patients with hypoglycemia by HbA_{1c} stratum – 3 studies



For the metformin+SFU study, there was a more pronounced dose response for hypoglycemia in patients randomized to the maximum effective dose SFU than patients randomized to the minimum recommended dose SFU (Figure 14).

Figure 14 Percent of patients with hypoglycemia by SFU stratum – Metformin+SFU study (#115)



Anti-exenatide antibody

At endpoint, the treatment groups were significantly different in percentage of patients with anti-exenatide antibodies (Table 11).

Table 11 Percent of patients with anti-exenatide antibodies at endpoint – All studies

	Placebo	5 µg	10 µg	p-value
Metformin alone	3/113 (3%)	44/109 (40%)	51/112 (46%)	<0.0001
SFU alone	2/120 (2%)	46/122 (38%)	51/125 (41%)	<0.0001
Metformin+SFU	13/242 (5%)	120/244 (49%)	107/240 (45%)	<0.0001

Table 12 displays mean and median HbA_{1c} change from baseline for 2 categories of antibody titer at endpoint (<125 or ≥125). Patients in the active treatment groups experienced reduction of HbA_{1c} in both antibody categories compared to placebo. However, the effect was smaller in the antibody titer ≥125 patients than in the antibody titer <125 patients. Note that antibody titer and HbA_{1c} were both outcome variables. Subgroups defined by antibody titer are not subgroups in the usual sense; therefore caution should be used in interpreting the results.

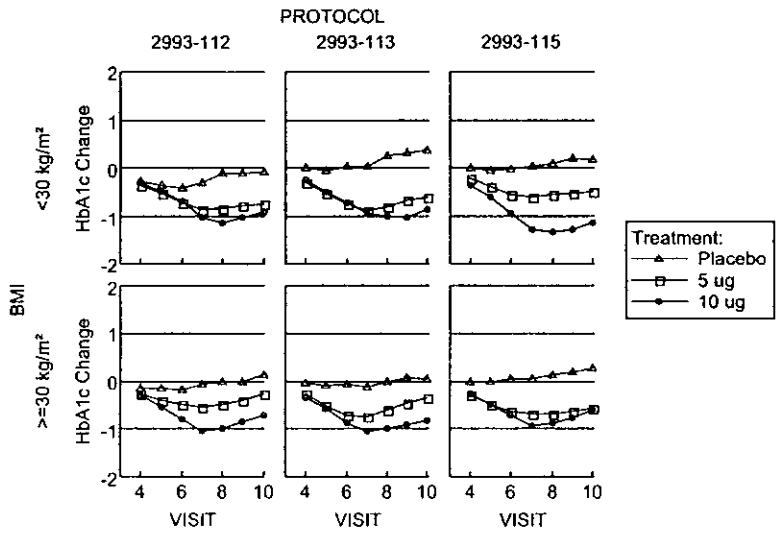
Table 12 Mean HbA_{1c} change (%) by antibody titer category – all studies

	Placebo		5 µg		10 µg	
	<125	≥125	<125	≥125	<125	≥125
Metformin alone	n=134	n=1	n=112	n=15	n=113	n=16
Mean (SD)	+0.1 (1.0)	+0.2	-0.4 (1.1)	-0.1 (0.7)	-0.7 (1.0)	-0.5 (1.1)
Median	+0.2	+0.2	-0.5	-0.3	-0.6	-0.3
SFU alone	n=156	n=5	n=131	n=15	n=131	n=27
Mean (SD)	+0.2 (1.0)	-0.8 (1.2)	-0.5 (1.2)	-0.5 (1.3)	-0.8 (1.2)	-0.5 (1.2)
Median	+0.2	-1.1	-0.5	-0.6	-0.7	-0.5
Metformin+SFU	n=290	n=2	n=233	n=48	n=227	n=47
Mean (SD)	+0.3 (1.1)	+0.5 (0.3)	-0.6 (1.1)	-0.2 (1.2)	-0.8 (1.1)	-0.3 (1.3)
Median	+0.2	+0.5	-0.5	-0.2	-0.8	-0.2

BMI

The treatment-by-BMI at screening (≥30, <30) interaction was significant in the metformin+SFU study (p=0.03). The interaction was significant between 10 µg and placebo and between 10 µg and 5 µg (Fig 15).

Figure 15 Mean HbA_{1c} change from baseline by screening BMI



In summary, treatment-by-subgroup analyses are exploratory without sufficient power. There were no consistent significant interaction findings in the subgroups among studies; however, the sample sizes of the studies vary. In general, the significant treatment-by-subgroup interactions were quantitative, not qualitative in nature and occurred mostly in the 5 µg group vs. placebo group. The label stated that "Based on clinical response, the dose of [redacted] can be increased to 10 mcg BID" after 1 month of 5 µg therapy. This may address the lack of efficacy for the 5 µg bid treatment observed in some subgroups.

Study 2993-120

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APPENDICES

Patients from investigator Nath – 6 from 2993-112, 11 from 2993-113 and 43 from 2993-115

Table 14 Descriptive statistics in HbA_{1c} change (%) from baseline – Nath

	Placebo	5 µg	10 µg
n	18	23	19
Mean (SD)	-0.006 (0.99)	-0.60 (0.96)	-0.63 (1.59)

Figure 17 Mean HbA_{1c} change (%) from baseline - Nath

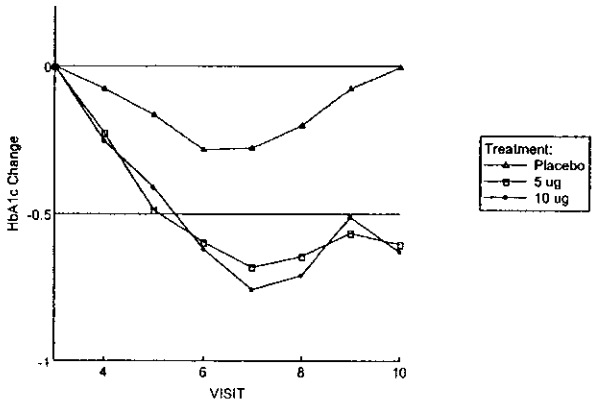
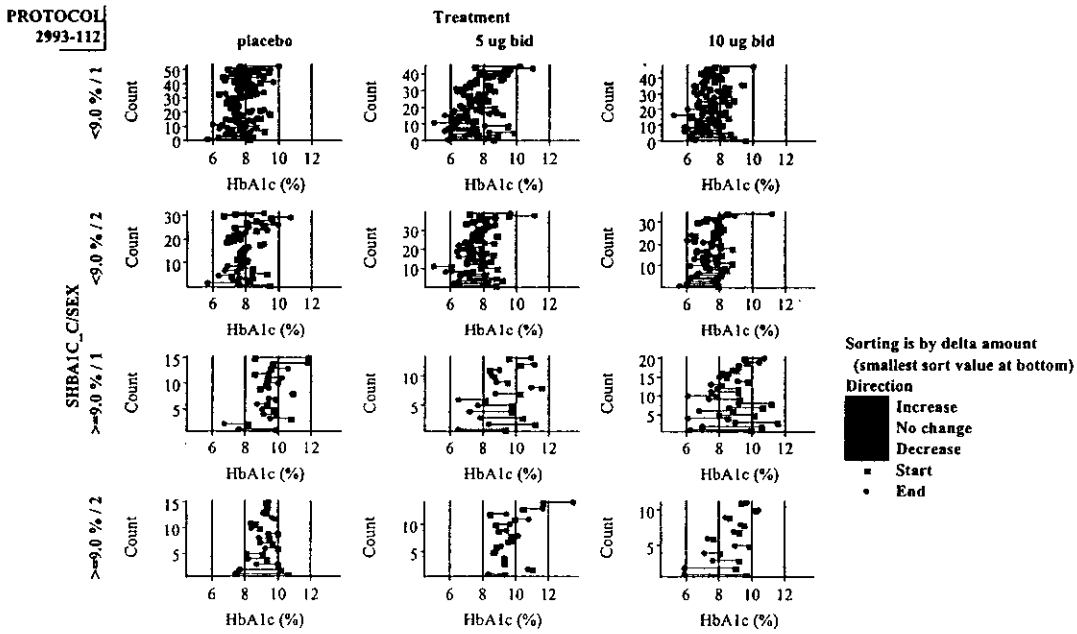


Figure 18 Note the subgroup female (2) and HbA_{1c} straum ≥9% response in 5 µg group compared to placebo (last row)



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S. Edward Nevius
3/18/05 06:56:44 PM
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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/Serial Number:	21-773/N-000
Drug Name:	[redacted] (exenatide) injection
Indication(s):	To improve glycemic control in patients with Type 2 diabetes mellitus [redacted] as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea
Applicant:	Amylin Pharmaceuticals, Inc.
Date(s):	Received 06/29/04; user fee (10 months) 04/30/05
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Cynthia Liu, MA
Concurring Reviewer(s):	Karl K. Lin, Ph.D., Expert Mathematical Statistician (Applications in Pharmacology and Toxicology)
Medical Division:	Div. of Metabolic and Endocrine Drug Products (HFD-510)
Pharmacology Team:	John Colerangle, Ph.D., Pharmacological Reviewer Karen Davis-Bruno, Ph.D., Team Leader
Project Manager:	Lina Aljuburi
Keywords:	NDA review, carcinogenicity studies, survival, neoplastic lesions

TABLE OF CONTENTS

Summary of Statistical Review

- Documents of two carcinogenicity studies (CD rat and CD-1 mouse) with two sexes each, submitted by the sponsor along with electronic data sets, were reviewed.

- Dose levels were 0, 18, 70, and 250 μg/kg/dose for both species. There were 2 identical controls in each study. Route of administration was subcutaneous.

- The rat and mouse studies were designed to be of 104 weeks. However, for the mouse study, due to reduced survival, treatment was discontinued after 98 weeks of dosing for the males and 96 weeks of dosing for the females, although scheduled in-life evaluations were continued through Week 104. As stated in the study report, this action was taken in accordance with the sponsor's agreement with the FDA.

- For the rat study, although survival rates in the 2 female control groups were down to 50% around Weeks 85-87, there were at least 63% of the animals in each of the other groups still surviving at the beginning of Week 90. For the mouse study, although survival rates of Groups 1 and 2 males and Groups 4 and 5 females were down to 38.5% (= 25/65) at Weeks 98 and 96, respectively, there were at least 50% of the animals in each group still surviving at the end of Week 88. Thus, both studies are considered to be valid in terms of adequacy of treatment exposure from the statistical point of view.

- In both the rat and mouse studies, the 2 controls behaved similarly in survival and almost all the neoplastic lesions. There were no significant positive trends or group comparisons in mortality in either sex of the two species, nor were there significant positive trends in tumor incidence rates. In fact, most findings were in a negative direction.

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

- This reviewer's findings of the survival and tumor analyses for both the rat and mouse studies generally agree with the sponsor's.

Introduction

The sponsor has submitted two carcinogenicity studies (rat and mouse) conducted by [redacted] for the new drug application (NDA 21-773) for [redacted] (exenatide) injection. There were two sexes in each species. The purpose of these studies was to evaluate the carcinogenic potential of AC2993 following once daily subcutaneous administration to rats and mice for at least 104 weeks.

This reviewer has performed her own independent statistical analyses on survival and neoplastic lesions, using the electronic data sets submitted by the sponsor on 6/29/2004. The data files and study reports this reviewer reviewed are located in \\Cdsesub1\evsprod\N021773\0000\m4\42-stud-rep\423-tox\4234-carcigen. In general, the file formats met the requirements specified in the electronic submission guidance. However, the data had some minor errors such as the same tumor code used for both benign and malignant tumors, time of death missing for some animals, etc.

Study Design

The group designation, dose level, and number of animals per group for the rat and mouse studies are provided below. The strains of rats and mice were CD® [redacted] CD® (SD) IGS BR] and CD® [redacted] CD-1® (ICR) BR], respectively. Note that the two controls were identical.

Group Number	Group Description	Rat			Mouse		
		Dose Level µg/kg/dose	Animals/group		Dose Level µg/kg/dose	Animals/group	
			Male	Female		Male	Female
1	Control I	0	65	65	0	65	65
2	Low	18	65	65	18	65	65
3	Mid	70	65	65	70	65	65
4	High	250	65	65	250	65	65
5	Control II	0	65	65	0	65	65

The sponsor stated that with the FDA's agreement, treatment was discontinued after 98 weeks of dosing for the male mice and 96 weeks of dosing for the female mice due to reduced survival, although scheduled in-life evaluations were continued through Week 104.

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. Two-sided tail probabilities for trend and group comparisons are evaluated at the 5% significance level.

Neoplastic Lesions. 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, which are based on the suggestions from National Toxicology Program (NTP). 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. There were no special cases of combining tumor types and/or organ types requested 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 trends and group comparisons in tumor incidences. The following table provides the criterion for determining the statistical significance according to the FDA's Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (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.

Common tumor is defined as a tumor type with background (control) rate >1% and rare tumor with background (control) rate ≤1%. The concurrent controls and historical controls (where applicable) were taken into consideration in determining commonality of a tumor.

Based on this reviewer's initial analyses, at the 2-sided 5% significance level, no survival differences between the two controls were observed for either sex of the rat and mouse

studies and the tumor incidence rates of the two controls were also similar in almost all the cases. Therefore, this reviewer used combined control (Groups 1+5) in all the statistical analyses. In the cases where a significant difference in tumor incidences between the 2 controls was observed, Groups 1 versus 2-4 and Groups 5 versus 2-4 were also analyzed.

For this reviewer's analyses, unless otherwise stated, arithmetic dose levels were used. This reviewer could not come up with the same p-values as the sponsor's, which might be due to some minor differences in the analysis methods, e.g., ordinal versus arithmetic doses, NTP versus FDA interval cut-off time points, exact versus asymptotic test, etc. Nevertheless, this reviewer's conclusions agree with the sponsor's.

Results and Discussion

In Tables 1-4, p-value under Group 1 is for trend analysis and p-values under Groups 2, 3, and 4 are for group comparisons. * = Significant at $p \leq 0.05$ and ** = Significant at $p \leq 0.01$.

The Rat Study

Survival. The mortality rates of the 18, 70, and 250 μg/kg/dose groups in each sex of the rat study were similar to each other, but were all significantly smaller than that of the combined control, as shown in Tables 1 and 2. In fact, in both sexes, the mid-dose group had the lowest mortality among all the study groups. Heterogeneity of survival functions across groups and significant departure from trends ($p < 0.01$ for all cases) were also observed in each sex, which were further confirmed by the Kaplan-Meier product limit survival curves, as depicted in Figures 1 (male) and 2 (female).

In the male study, there were at least 63% of the animals in each group still surviving at the beginning of Week 90, indicating that a sufficient number of male rats were exposed to the treatment adequately. In the female study, there were at least 67% of the animals in each of the low, mid, and high dose groups still surviving at the beginning of Week 90. However, the survival rates of the 2 controls in this sex were down to 50% around Weeks 85-87.

Neoplastic Lesions. There was a significant difference between the 2 controls in the incidences of benign pheochromocytoma of adrenal glands of the males (3/65 vs. 12/65, $p = 0.0129$). However, no significant positive trends were observed when each of the 2 controls as well as the combined control was analyzed with the other treatment groups (Groups 1 vs. 2-4 $p = 0.0689$, Groups 5 vs. 2-4 $p = 0.7077$, and Groups 1+5 vs. 2-4 $p = 0.6054$). 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 sex of the study. The summary incidences of neoplastic lesions can be found in Table 10 of rest01052.pdf, the sponsor's rat study report.

The Mouse Study

As mentioned in the Study Design section above, the sponsor discontinued the treatment (but not terminated the study) after 98 and 96 weeks of dosing for the males and females, respectively, because the survival rates of Groups 1 and 2 males and Groups 4 and 5 females were down to 25/65 (= 38.5%) at the end of those weeks. Therefore, this reviewer conducted 2 sets of analyses for both survival and neoplastic lesions. The 1st set of analyses treats all the male and female animals dying after Weeks 98 and 96, respectively, as the terminal sacrifice (censoring) animals. The 2nd set is the standard analysis, but ordinal dose levels (0, 1, 2, and 3) are used since there was about 6-8 weeks of no treatment period.

Survival. As shown in Tables 3 (male) and 4 (female), there were no significant positive trends or group comparisons in mortality in either of the two sexes. Since this is a mouse study and there were at least 50% of the animals in each group still surviving at the end of Week 88 in each sex, the study is considered to be valid in terms of adequacy of treatment exposure from the statistical point of view.

Neoplastic Lesions. Significant, but marginally differences between the 2 controls were found in the incidences of malignant lymphoma of urinary bladder, left flank injection site, and gallbladder of the females, and undifferentiated sarcoma of skin subcutis of the males. However, no significant positive trends were observed in these cases when each of the 2 controls as well as the combined control was analyzed with the other treatment groups. 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 sex of the study. The summary incidences of neoplastic lesions can be found in Table 10 of rest01053.pdf, the sponsor's mouse study report.

Conclusion

In both the rat and mouse studies, no significant positive findings in mortality or tumor incidence rates were observed in either sex. Based on examination of validity of the study designs, the majority of the rats and mice were exposed to the treatment adequately.

Prepared by Cynthia Liu, MA, Statistical Reviewer
Concurred by Karl K. Lin, Ph.D., Expert Mathematical Statistician
CC: HFD-510/LAljuburi, KDavisbruno, JColerangle
HFD-715/ENevius, KLin, TSahlroot, CLiu; HFD-700/CAnello

Table 1 – Results of Statistical Analyses of Mortality Data for Male Rats

Group	1	2	3	4	5
Dose (µg/kg/dose)	0	18	70	250	0
Number of Deaths ([a] = Including 1 animal with accidental death)					
Weeks 0-52	4 (6.2%)	3 (4.6%)	1[a] (1.5%)	6 (9.2%)	6[a] (9.2%)
Weeks 53-78	11 (16.9%)	5 (7.7%)	3 (4.6%)	5 (7.7%)	10 (15.4%)
Weeks 79-92	11 (16.9%)	12 (18.5%)	10[a] (15.4%)	11 (16.9%)	10 (15.4%)
Weeks 93-before term sac	15 (23.1%)	8 (12.3%)	14 (21.5%)	7 (10.8%)	16 (24.6%)
Terminal Sacrifice Weeks	24 (36.9%)	37 (56.9%)	37 (56.9%)	36 (55.4%)	23 (35.4%)
Unadjusted Mortality	41/65	28/65	26/65	29/65	41/65
Kaplan-Meier Estimate (Final)	0.631	0.431	0.412	0.466	0.640
Cox-Tarone Test (two-sided p)	0.0810 –	0.0178 – *	0.0027 – **	0.0308 – *	
Gehan-Breslow Test (two-sided p)	0.1135 –	0.0251 – *	0.0011 – **	0.0535 –	

Figure 1 – Kaplan-Meier Product Limit Survival Curves for Male Rats

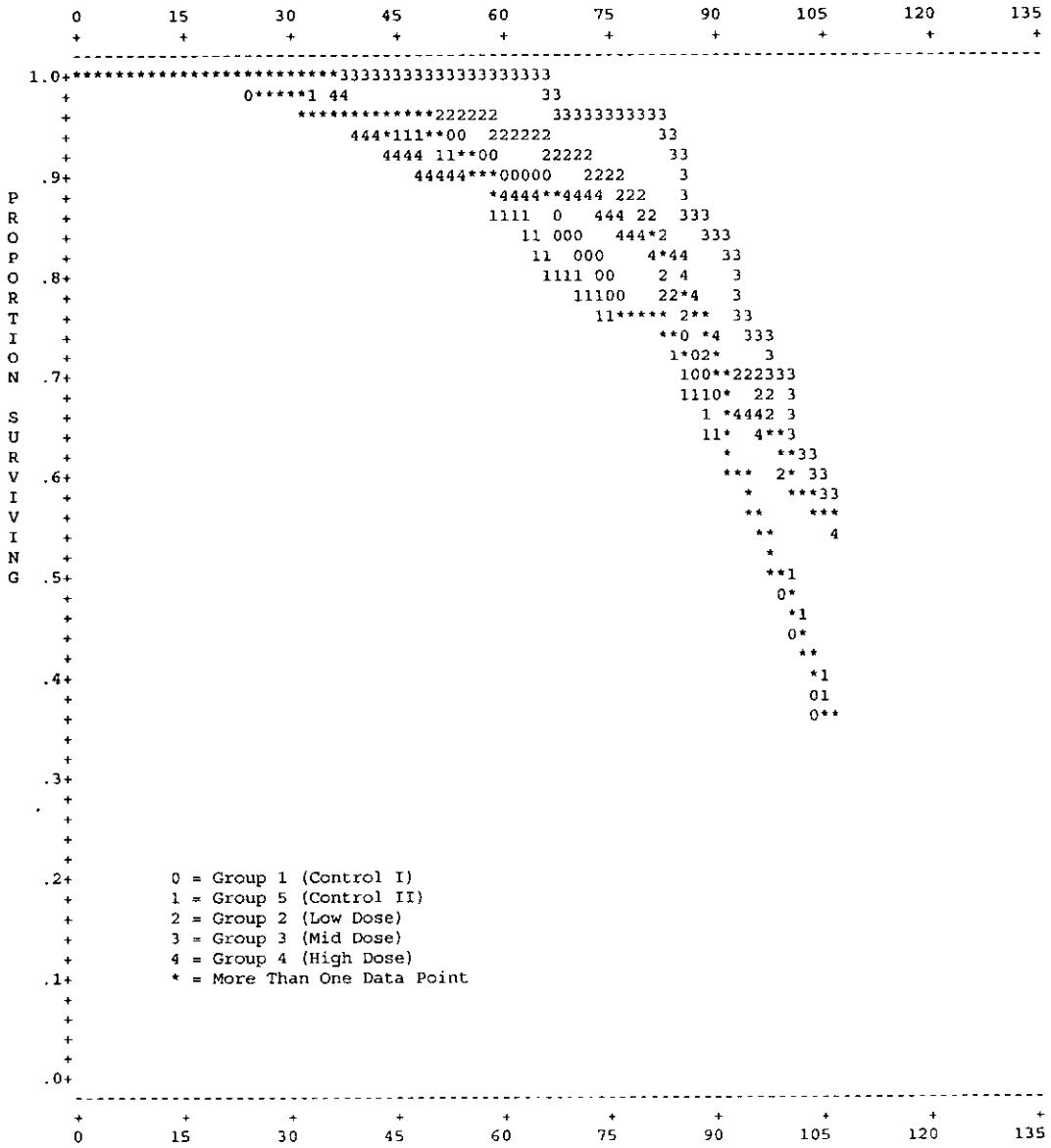

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Table 2 – Results of Statistical Analyses of Mortality Data for Female Rats

Group	1	2	3	4	5
Dose (µg/kg/dose)	0	18	70	250	0
Number of Deaths					
Weeks 0-52	6 (9.2%)	2 (3.1%)	1 (1.5%)	4 (6.2%)	7 (10.8%)
Weeks 53-78	13 (20.0%)	7 (10.8%)	7 (10.8%)	4 (6.2%)	13 (20.0%)
Weeks 79-92	21 (32.3%)	13 (20.0%)	7 (10.8%)	10 (15.4%)	16 (24.6%)
Weeks 93-before term sac	11 (16.9%)	13 (20.0%)	7 (10.8%)	12 (18.5%)	15 (23.1%)
Terminal Sacrifice Weeks	14 (21.5%)	30 (46.2%)	43 (66.2%)	35 (53.9%)	14 (21.5%)
Unadjusted Mortality	51/65	35/65	22/65	30/65	51/65
Kaplan-Meier Estimate (Final)	0.785	0.538	0.338	0.462	0.785
Cox-Tarone Test (two-sided p)	0.0001 – **	0.0003 – **	0.0000 – **	0.0000 – **	
Gehan-Breslow Test (two-sided p)	0.0001 – **	0.0002 – **	0.0000 – **	0.0000 – **	

Figure 2 – Kaplan-Meier Product Limit Survival Curves for Female Rats

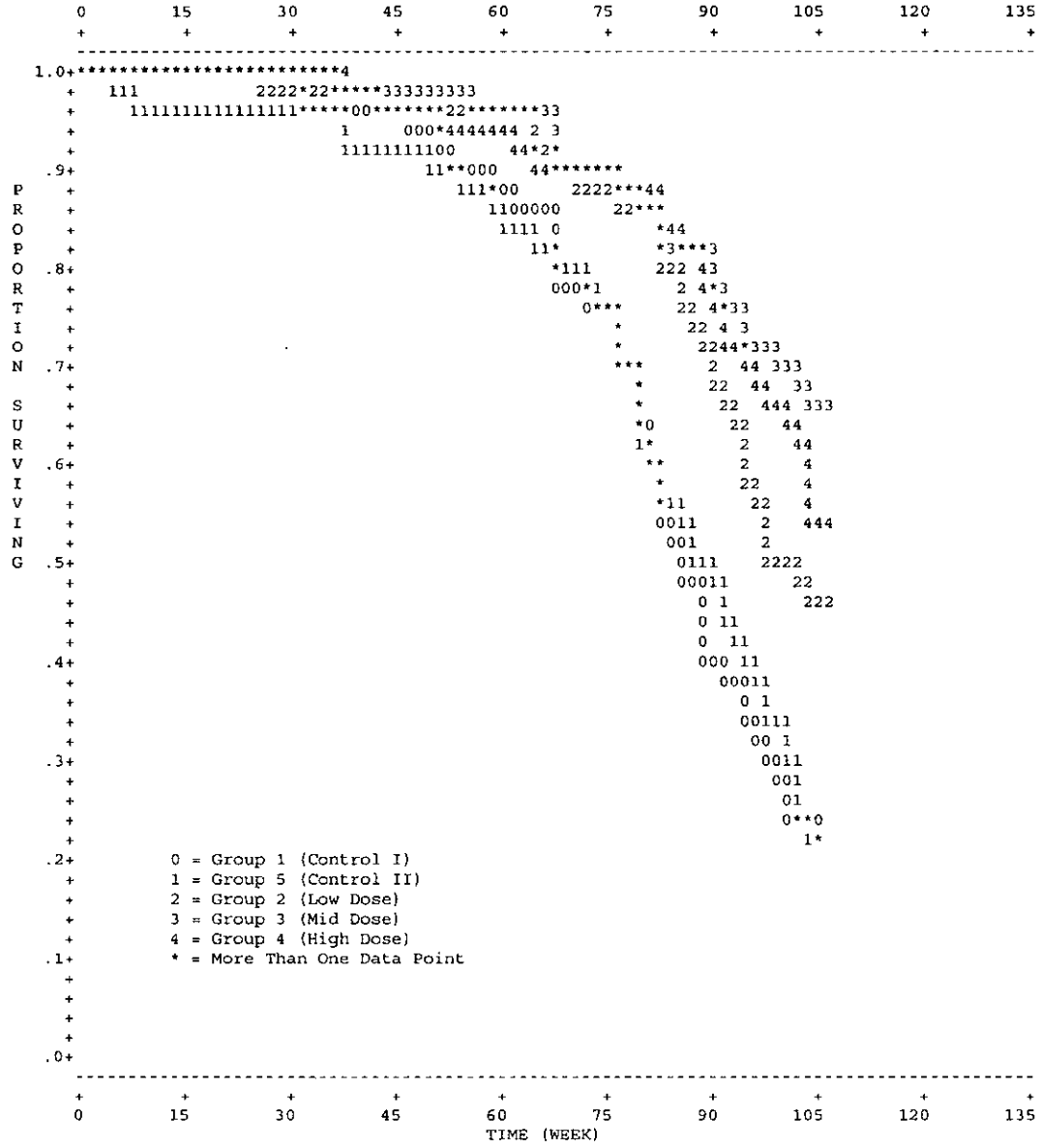

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Table 3 – Results of Statistical Analyses of Mortality Data for Male Mice

Group	1	2	3	4	5
Dose (μg/kg/dose)	0	18	70	250	0
Number of Deaths ([a] = Including 1 animal with accidental death)					
Weeks 0-52	8[a] (12.3%)	9 (13.8%)	6 (9.2%)	8 (12.3%)	3 (4.6%)
Weeks 53-78	12 (18.5%)	10 (15.4%)	12 (18.5%)	8 (12.3%)	18 (27.7%)
Weeks 79-92	14 (21.5%)	14 (21.5%)	10[a] (15.4%)	13 (20.0%)	11 (16.9%)
Weeks 93-98	6 (9.2%)	7 (10.8%)	7 (10.8%)	2 (3.1%)	7 (10.8%)
Weeks 99-before term sac	**8 (12.3%)**	**4 (6.2%)**	**5 (7.7%)**	**12 (18.5%)**	**6 (9.2%)**
Terminal Sacrifice Weeks	**17 (26.2%)**	**21 (32.3%)**	**25 (38.5%)**	**22 (33.8%)**	**20 (30.8%)**
Treating Weeks 99-105 as terminal sacrifice weeks (i.e., censoring any animals dying after Week 98) and using arithematic dose levels in the analysis					
Unadjusted Mortality	39/65	40/65	34/65	31/65	39/65
Kaplan-Meier Estimate (Final)	0.609	0.615	0.527	0.477	0.600
Cox-Tarone Test (two-sided p)	0.1320 –	0.9657 +	0.3598 –	0.1973 –	
Gehan-Breslow Test (two-sided p)	0.2421 –	0.9292 +	0.3618 –	0.2852 –	
Original study, but using ordinal dose levels (e.g., 0, 1, 2, and 3) in the analysis					
Unadjusted Mortality	47/65	44/65	39/65	43/65	45/65
Kaplan-Meier Estimate (Final)	0.734	0.677	0.606	0.662	0.692
Cox-Tarone Test (two-sided p)	0.2181 –	0.7828 –	0.2069 –	0.4115 –	
Gehan-Breslow Test (two-sided p)	0.2671 –	0.9010 –	0.2648 –	0.3932 –	

Figure 3 - Kaplan-Meier Product Limit Survival Curves for Male Mice

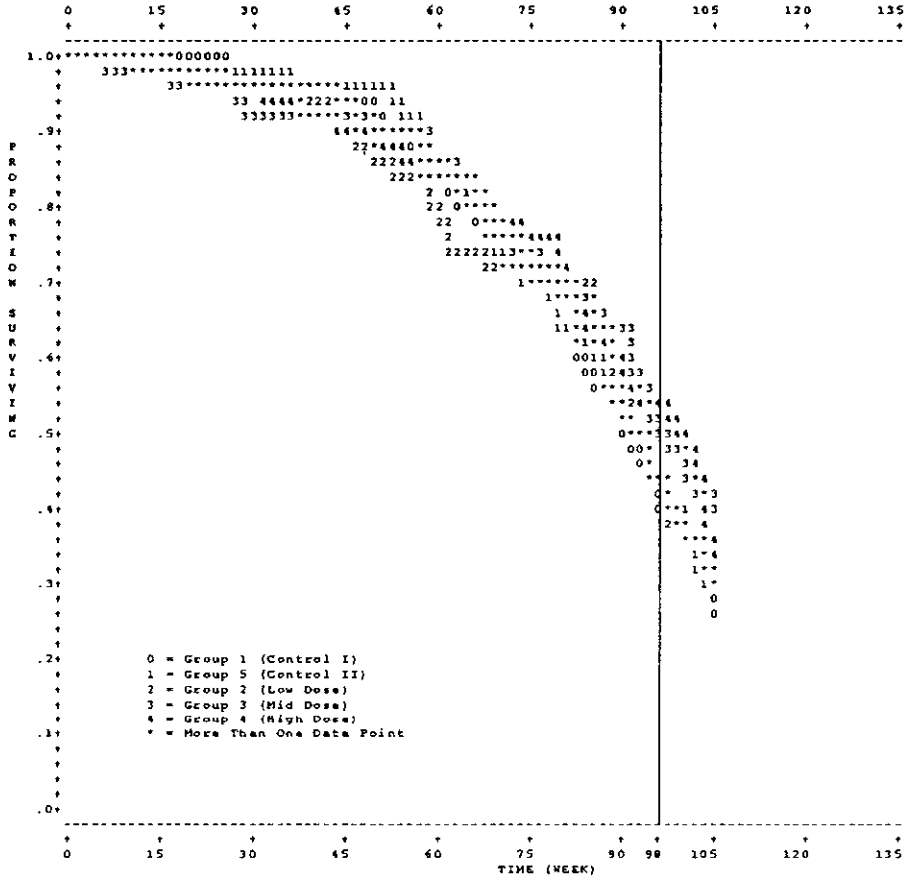
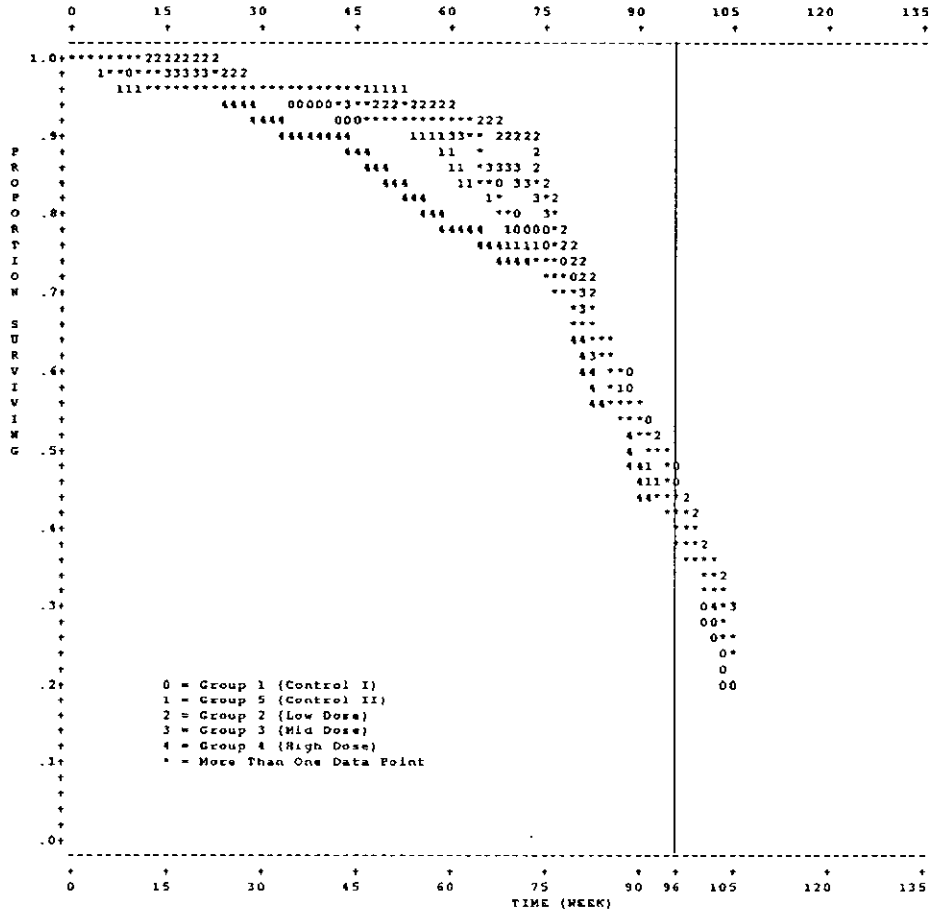


Table 4 – Results of Statistical Analyses of Mortality Data for Female Mice

Group	1	2	3	4	5
Dose (µg/kg/dose)	0	18	70	250	0
Number of Deaths					
Weeks 0-52	5 (7.7%)	4 (6.2%)	5 (7.7%)	11 (16.9%)	4 (6.2%)
Weeks 53-78	13 (20.0%)	12 (18.5%)	15 (23.1%)	8 (12.3%)	16 (24.6%)
Weeks 79-92	14 (21.5%)	15 (23.1%)	13 (20.0%)	18 (27.7%)	15 (23.1%)
Weeks 93-96	6 (9.2%)	6 (9.2%)	6 (9.2%)	3 (4.6%)	5 (7.7%)
Weeks 97-before term sac	**14 (21.5%)**	**12 (18.5%)**	**6 (9.2%)**	**10 (15.4%)**	**9 (13.8%)**
Terminal Sacrifice Weeks	**13 (20.0%)**	**16 (24.6%)**	**20 (30.8%)**	**15 (23.1%)**	**16 (24.6%)**
Treating Weeks 97-105 as terminal sacrifice weeks (i.e., censoring any animals dying after Week 96) and using arithematic dose levels in the analysis					
Unadjusted Mortality	38/65	37/65	39/65	40/65	40/65
Kaplan-Meier Estimate (Final)	0.585	0.569	0.600	0.615	0.615
Cox-Tarone Test (two-sided p)	0.4928 +	0.7263 –	0.9805 –	0.6695 +	
Gehan-Breslow Test (two-sided p)	0.3261 +	0.5765 –	0.9364 –	0.4276 +	
Original study, but using ordinal dose levels (e.g., 0, 1, 2, and 3) in the analysis					
Unadjusted Mortality	52/65	49/65	45/65	50/65	49/65
Kaplan-Meier Estimate (Final)	0.800	0.754	0.692	0.769	0.754
Cox-Tarone Test (two-sided p)	0.9802 –	0.6694 –	0.5158 –	0.8680 +	
Gehan-Breslow Test (two-sided p)	0.6644 +	0.5346 –	0.6944 –	0.5136 +	

Figure 4 - Kaplan-Meier Product Limit Survival Curves for Female Mice



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Cynthia Liu
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Karl Lin
12/8/04 02:51:54 PM
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Concur with review