CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-567 N000
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Applicant:	PGxHealth
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Keywords: Clinical studies; NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Vilazodone at a 40 mg/day was positive in the acute treatment of major depressive disorder, as measured by the change from baseline to week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score, based on two pivotal studies.

1.2 Brief Overview of Clinical Studies

This submission contains two pivotal, phase III studies to support the efficacy and safety of vilazodone in the acute treatment of major depressive disorder (MDD). Both studies were randomized, double-blind, placebo-controlled, parallel-group, multicenter, U.S. studies. Both studies investigated the efficacy and safety of vilazodone at a target dose of 40 mg/day. Patients went through a titration period to the target dose. The primary efficacy measure was the change from baseline to week 8 in the MADRS total score.

This NDA also contains five other studies that were either negative or failed and are not subject to this review.

1.3 Statistical Issues and Findings

Both pivotal studies were positive based on the primary efficacy variable pre-specified. None of the secondary efficacy measures were specified as key secondary efficacy measures or agreed upon a priori (b) (4)

(b) (4)

The long-term efficacy of vilazodone has not been adequately assessed. The current data are based on a one year open-label study (Study CLDA-07-DP-04). Because this was an open-label and there was no control group, the efficacy evaluation is limited and is subject to biases. (b) (4)

2. INTRODUCTION

2.1 Overview

This review provides a statistical evaluation of the efficacy of vilazodone as an acute treatment of major depressive disorder (MDD).

As defined in the DSM-IV-TR, major depressive disorder (MDD) is a mental illness characterized by one or more major depressive episodes. A major depressive episode implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning. MDD includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities,

significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

According to the sponsor, MDD is the leading cause of disability in the United States for people aged 15 to 44 years old and contributes to functional impairment and increases in morbidity and mortality.

According to the sponsor, vilazodone HCl (vilazodone), a dual-acting potent and selective serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist, is a new chemical entity belonging to the structural chemical group of the indolalkylamines.

Vilazodone is currently under development for the treatment of major depressive disorder (MDD). Vilazodone has been investigated in 5 phase II studies conducted in MDD patients where the safety of vilazodone was confirmed, but efficacy was not established. Two of these studies were negative and three were considered failed (b) (4)

Vilazodone was also studied in two phase III studies:

- Study CLDA-07-DP-02 was a U.S., randomized, double-blind, placebo-controlled, multicenter, 8-week study. The study consisted of three periods: a washout period, a screening period, and an 8-week double-blind treatment period. Patients were titrated to the target dose by Day 15. The primary efficacy variable was the change from baseline to week 8 in the MADRS total score.
- Study GNSC-04-DP-02 was a U.S., randomized, double-blind, placebo-controlled, multicenter, 8-week study. After an appropriate washout and screening, patients were randomly assigned to receive either placebo or vilazodone in a 1:1 ratio. Patients were titrated to the target dose by Day 15. The primary efficacy variable was the change from baseline to week 8 in the MADRS total score.

This review will focus on the efficacy evaluation of studies CLDA-07-DP-02 and GNSC-04-DP-02, with a brief summary of the primary efficacy results of other five phase II studies.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\Cdsesub1\evsprod\NDA022567\0000\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study CLDA-07-DP-02

3.1.1.1 Objectives

Primary: The primary objective of this study was to compare the efficacy between vilazodone and placebo using the change from baseline in the MADRS total score at week 8.

3.1.1.2 Study Design

This was a U.S., randomized, double-blind, placebo-controlled, multicenter, 8-week study. The study consisted of three periods: a washout period, a screening period, and an 8-week double-blind treatment period. Patients were titrated to their target dose by Day 15. The primary efficacy variable was the MADRS total score. The MADRS was evaluated at baseline, weeks 1, 2, 4, 6, and 8, or at early termination.

Eligible patients were male and female between the age of 18 and 70; diagnosed with MDD, single episode or recurrent, according to DSM-IV-TR; had a HAM-D score $\geq$ 22 on the first 17 items of the 21 item HAM-D at screening and baseline visits; and had a HAM-D item 1 (depressed mood) score $\geq$ 2 at screening and baseline visits.

The study was planned for 235 patients per arm to provide 90% power to detect an effect size of 0.3 on the change from baseline to week 8 in the MADRS total score.

3.1.1.3 Efficacy Endpoints and Analyses

Primary efficacy measure and analysis: The primary efficacy measure was the change from baseline to week 8 in the MADRS total score. Missing values were imputed by the Last Observation Carried Forward (LOCF) method. The primary analysis was an ANCOVA model with terms for treatment and center, and baseline MADRS total score as a covariate. Center was pooled as necessary for the analysis.

Sensitivity analyses on the primary efficacy variable include an ANCOVA model as above with the treatment-by-center interaction and a mixed-effects model for repeated measures (MMRM). For the MMRM analysis, the model included fixed categorical effect terms for treatment, center, visit, and treatment-by-visit interaction, as well as continuous fixed covariates for baseline MADRS and baseline-by-visit interaction.

3.1.1.4 Efficacy Results

3.1.1.4.1 Study Population

The disposition of patients is summarized in Table 1. A total of 481 subjects were randomized. Ninety three subjects (19.3%) discontinued from the study prematurely. The main reasons for dropping out were lost to follow-up (37%), consent withdrawal (24%), and adverse event (17%). There were about three times more dropouts due to adverse events in vilazodone arm than in the placebo arm. On the contrary, there were about twice more patients who dropped out due to lack of efficacy in the placebo arm than in vilazodone arm.

Table 1. Study CLDA-07-DP-02: Disposition of patients

	Placebo	Vilazodone	Total
Randomized	**241**	**240**	**481**
Discontinued study: n (%)	**46 (19.1)**	**47 (19.6)**	**93 (19.3)**
Adverse event	4 (8.7)	12 (25.5)	16 (17.2)
Withdrawal of consent	11 (23.9)	11 (23.4)	22 (23.7)
Lost to follow-up	17 (37.0)	17 (36.2)	34 (36.6)
Lack of therapeutic effect	7 (15.2)	3 (6.4)	10 (10.8)
Investigator decision	1 (2.2)	0 (0.0)	1 (1.1)
Non compliance	5 (10.9)	3 (6.4)	8 (8.6)
Other	1 (2.2)	1 (2.1)	2 (2.2)
Completed study: n (%)	**195 (80.9)**	**193 (80.4)**	**388 (80.7)**

Patients 2080-058 and 2020-173 were excluded because the same patients participated in two clinical sites.
(Source: CLDA-07-DP-02 Study Report; Table 6, page 51)

The demographic characteristics in the safety sample are presented in Table 2. The majority of the patients were white (80%). There were slightly more females than males. The average age was 42 years old and ranged from 18 to 70.

Table 2. Study CLDA-07-DP-02: Demographic characteristics (Safety sample)

	Placebo N = 233	Vilazodone N = 235	Total N = 468
Age at entry (yr) n			
Mean (SD)	42.4 (12.5)	41.1 (12.2)	41.7 (12.3)
Median (min-max)	43 (19 – 70)	42 (18 – 69)	42 (18 - 70)
Sex – n (%)			
Female	124 (53.2)	139 (59.2)	263 (56.2)
Male	109 (46.8)	96 (40.9)	205 (43.8)
Race – n (%)			
White	191 (82.0)	182 (77.5)	373 (79.7)
Black	31 (13.3)	35 (14.9)	66 (14.1)
Asian	8 (3.4)	8 (3.4)	16 (3.4)
Others	3 (1.3)	10 (4.3)	13 (2.8)

Patients 2080-058 and 2020-173 were excluded because the same patients participated in two clinical sites.
(Source: CLDA-07-DP-02 Study Report; Tables 9 & 10, pages 54 & 55)

3.1.1.4.2 Sponsor's Efficacy Results for Primary Efficacy Measure

The sponsor's primary efficacy analysis is summarized in Table 3. Vilazodone was superior to placebo on the change from baseline in the MADRS total score.

Table 3. Study CLDA-07-DP-02: Sponsor's primary efficacy results: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	231	232
Baseline MADRS total score		
Mean (Standard deviation)	32.0 (3.6)	31.9 (3.5)
Median (Min – Max)	32 (24 – 42)	32 (22 – 42)
Change from baseline		
LS Means	-10.8	-13.3
Difference from placebo (SE)		-2.5 (0.96)
(95% confidence interval)		(-4.4, -0.6)
P-value		0.009

The data for Patient IDs of 2080-058, 2020-173, and 2080-074 were excluded from analysis. Patient IDs 2020-016 (vilazodone) and 2080-058 (vilazodone) were the same patient enrolled at 2 different clinical sites and participation was consecutive. Patient IDs 2020-173 (placebo) and 2080-074 (vilazodone) were the same patient and participation was overlapping at 2 different clinical sites.
(Source: CLDA-07-DP-02 Study Report; Table 11, page 57)

3.1.1.4.3 Sponsor's Other Efficacy Results

Change from baseline in the CGI-Severity of Illness (LOCF):

An analysis of covariance on the change from baseline to week 8 in the CGI-S with missing values imputed by the LOCF method is summarized in Table 11. The results suggested the efficacy of vilazodone over placebo.

Table 4. Study CLDA-07-DP-02: Sponsor's efficacy results: change from baseline to week 8 in the CGI-S (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	231	231
LS Means	-1.1	-1.4
Difference from placebo		-0.4
(95% confidence interval)		(-0.6, -0.1)
Unadjusted p-value		0.004

(Source: CLDA-07-DP-02 Study Report; Table 18, page 70)

CGI-Improvement (LOCF):
An analysis of covariance on the CGI-I at week 8 with missing values imputed by the LOCF method is summarized in Table 5. The results suggested the efficacy of vilazodone over placebo.

Table 5. Study CLDA-07-DP-02: Sponsor's efficacy results: CGI-I at week 8 (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	231	231
LS Means	2.8	2.5
Difference from placebo		-0.3
(95% confidence interval)		(-0.5, -0.1)
Unadjusted p-value		0.004

(Source: CLDA-07-DP-02 Study Report; Table 19, page 71)

Change from baseline in the HAM-D17 total score (LOCF):
An analysis of covariance on the change from baseline to week 8 in the HAM-D17 total score with missing values imputed by the LOCF method is summarized in Table 6 The results supported the primary efficacy results.

Table 6. Study CLDA-07-DP-02: Sponsor's efficacy results: change from baseline to week 8 in the HAM-D17 (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	231	231
LS Means	-9.1	-10.7
Difference from placebo		-1.6
(95% confidence interval)		(-3.1, -0.2)
Unadjusted p-value		0.0256

(Source: CLDA-07-DP-02 Study Report; Table 17 page 69)

3.1.1.4.4 Reviewer's Results and Comments

This reviewer confirmed the findings based on the primary efficacy variable as presented in Table 3. Vilazodone was statistically significantly superior to placebo.

Sensitivity analysis on the primary efficacy variable: Table 7 summarizes an MMRM analysis of the treatment effects of vilazodone over the duration of the study. The model included baseline MADRS total score as a fixed covariate, a baseline-by-visit interaction, treatment group and visit as fixed factors, and treatment-by-visit interaction. Patients were treated as a random effect. An unstructured covariance matrix was used. It is noted that these results are slightly different from the sponsor's results reported on page 62 of the CLDA-07-DP-02 Study Report. However, the conclusion is the same and is supportive of the primary efficacy analysis.

Table 7. Study CLDA-07-DP-02: Reviewer's efficacy analysis: change from baseline in the MADRS total score (MMRM analysis) over time in the ITT sample

	Placebo		Vilazodone		Vilazodone - Placebo	
visit	N	Mean	N	Mean	Diff	P-value*
Week 1	231	-3.3	232	-3.7	-0.4	0.347
Week 2	223	-5.7	224	-6.7	-1.0	0.087
Week 4	216	-9.2	213	-10.8	-1.6	0.050
Week 6	207	-11.4	203	-13.7	-2.3	0.017
Week 8	196	-11.9	194	-14.8	-2.9	0.006

(Source: Reviewer's results).
Subjects 2080-058, 2020-173, and 2080-047 were excluded from this analysis.
*P-values are not adjusted for multiplicity

The sponsor stated that after the completion of the study, two sets of identical genotypes were noted during the DNA analysis. Further investigation found that two sets of patients were the same individuals. Patients 020-016 and 2080-058 were the same individual participating in two different, nearby sites, in a sequential manner. This individual was randomized to vilazodone both times. It was decided that only efficacy data from the first time to be included in the analysis. Patients 2020-173 and 2080-074 were the same individual participating in two different, nearby sites, during overlapping periods. This individual was randomized to placebo and vilazodone, respectively. This patient was excluded from all efficacy analysis.

Figure 1 captures the empirical cumulative distribution functions (CDFs) of the two arms of the study. The horizontal axis captures the range of the changes from baseline in the MADRS total score at the last visit (LOCF). The use of the LOCF approach to handle the premature dropouts appears sensible because of the relatively low dropouts in the study for this indication. This is further supported by the consistencies of the treatment effects across several sensitivity and secondary analyses. The vertical axis depicts the proportion of patients whose changes from baseline score were less than or equal to a given score on the horizontal axis. The CDF plots attempt to capture the entire distributions of the responses whereas the means (as in Table 3) capture the central tendency of the distributions only. It should be noted that the variations associated with the CDF curves were not captured and presented in Figure 1. Thus, these curves are mainly for descriptive purposes only. Separations between vilazodone and placebo were observed in these two curves.

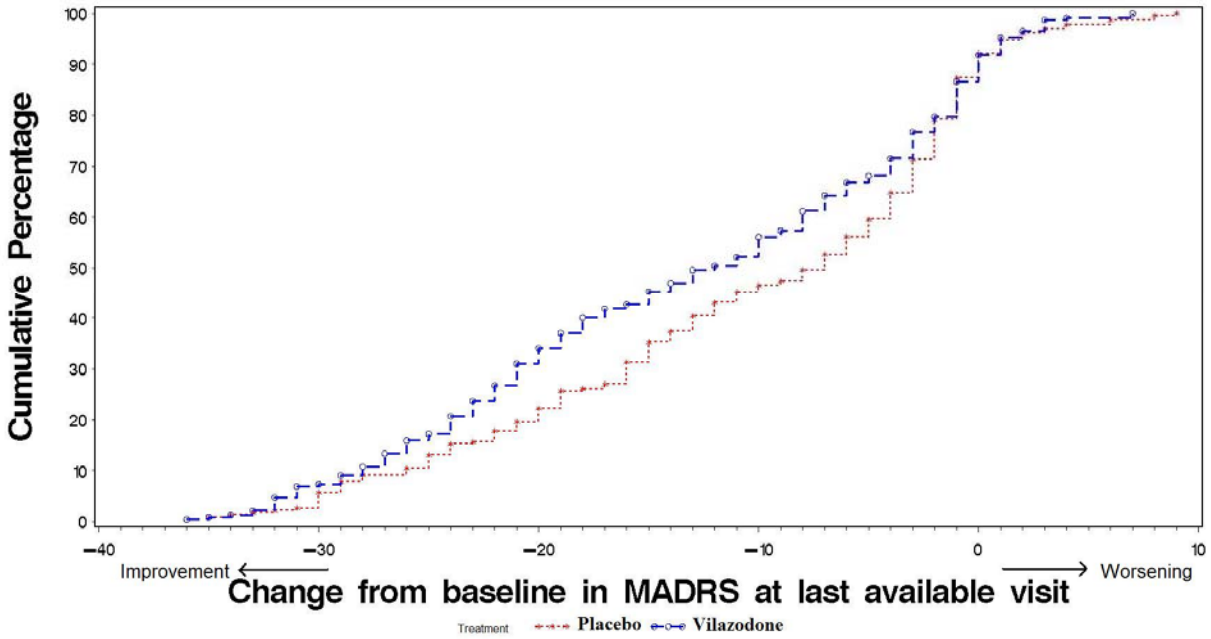

Figure 1. Study CLDA-07-DP-02: Cumulative distribution function

(Source: Reviewer's results)

3.1.2 Study GNSC-04-DP-02

3.1.2.1 Objective

Primary: The primary objective of this study was to compare the efficacy of vilazodone and placebo in the treatment of MDD, as measured by the mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score after 8 weeks of treatment.

3.1.2.2 Study Design

This was a U.S., randomized, double-blind, placebo-controlled, multicenter study. After an appropriate washout and screening, patients were randomly assigned to receive either placebo or vilazodone in a 1:1 ratio. Doses of vilazodone or matching placebo were titrated according to the following schedule: 10 mg/day for 7 days (Days 1-7), 20 mg/day for 7 days (Days 8-14), and 40 mg/day for 42 days (Days 15-56). Dose modification was permitted: patients experiencing intolerable adverse events (AEs) at 20 mg/day could remain at 20 mg/day if indicated, and patients who developed intolerable adverse events at 40 mg/day were permitted to reduce the dosage to 20 mg/day.

Patients were eligible to enroll if they were male or female between the age of 18-65 years; had a diagnosis of MDD, single episode or recurrent; had a HAM-D score ≥ 22 on the first 17 items of the 21-item HAM-D at screening and baseline visits; and had a HAM-D item 1 (depressed mood) score ≥ 2 at the screening and baseline visits.

The study was planned to enroll 408 patients with 266 patients randomized (133 per arm) to detect a 4.0 difference with a standard deviation of 10.

3.1.2.3 Efficacy Endpoints and Analyses

Primary efficacy measure and analysis: The primary efficacy measure was the change from baseline to week 8 in the MADRS total score, with dropout values imputed by the last observation carried forward (LOCF) method. The primary analysis model was ANCOVA with treatment and center factors, and baseline MADRS total score as a covariate. The primary efficacy measure was assessed at baseline, weeks 1, 2, 4, 6, and 8 or at early termination.

3.1.2.4 Efficacy Results

3.1.2.4.1 Study Population

A total of 561 patients were screened. Of these, 410 patients were randomized to either vilazodone or placebo (205 patients in each group). The disposition of patients is summarized in Table 8. Seventy five percent (75%) of the subjects completed the study. The main reasons for dropping out were lost to follow-up and adverse event. There were about twice more dropouts due to adverse events in the vilazodone arm than in the placebo arm. There were about twice more dropouts due to lack of efficacy and consent withdrawal in the placebo arm than in the vilazodone arm.

Table 8. Study GNSC-04-DP-02: Disposition of patients

	Placebo	Vilazodone	Total
Screened			**561**
Randomized	**205**	**205**	**410**
Discontinued study: n (%)	**51 (24.9)**	**53 (25.9)**	**104 (25.4)**
Adverse event	10 (19.6)	19 (35.9)	29 (27.9)
Lack of efficacy	9 (17.7)	4 (7.6)	13 (12.5)
Lost to follow-up	18 (35.3)	20 (37.7)	38 (36.5)
Non compliance	2 (3.9)	4 (7.6)	6 (5.8)
Withdrew consent	12 (23.5)	5 (9.4)	17 (16.4)
Investigator decision	0 (0.0)	1 (1.9)	1 (1.0)
Completed study: n (%)	**154 (75.1)**	**152 (74.1)**	**306 (74.6)**

(Source: GNSC-04-DP-02 Study Report; Figure 10-1, page 54)

The demographic characteristics of the safety sample are presented in Table 9. The average age was 40 years and ranged from 18 to 65 years. There were about twice more females and males. The majority of subjects were white, with more white patients in vilazodone group than in placebo group. On the contrary, there were more black/African American patients in the placebo arm than in the vilazodone arm.

Table 9. Study GNSC-04-DP-02: Demographic characteristics (Safety sample)

	Placebo N = 204	Vilazodone N = 205	Total N = 409
Age at entry (yr) n			
Mean (SD)	39.8 (12.7)	40.0 (12.1)	39.9 (12.4)
Median (Min – Max)	39 (18 – 65)	40 (18 – 63)	40 (18 – 65)
Sex – n (%)			
Male	74 (36.3%)	78 (38.0%)	152 (37.2%)
Female	130 (63.7%)	127 (62.0%)	257 (62.8%)
Race – n (%)			
White	157 (77.0%)	181 (88.3%)	338 (82.6%)
Black/African American	36 (17.7%)	20 (9.8%)	56 (13.7%)
Others	11 (5.4%)	4 (2.0%)	15 (3.7%)

(Source: GNSC-04-DP-02 Study Report; Table 11-3, page 59)

3.1.2.4.2 Sponsor's Efficacy Results for the Primary Efficacy Measure

The sponsor's primary analysis is summarized in Table 10. Vilazodone was statistically significantly superior to placebo.

Table 10. Study GNSC-04-DP-02: Sponsor's primary analysis: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	199	198
Baseline MADRS total score		
Mean (Standard deviation)	30.7 (3.9)	30.8 (3.9)
Median (Min – Max)	31 (20 – 41)	31 (21 – 43)
Change from baseline		
LS Means	-9.7	-12.9
Difference from placebo (SE)		-3.2 (0.99)
(95% confidence interval)		(-5.1, -1.2)
P-value		0.001

(Source: GNSC-04-DP-02 Study Report; Tables 11-6 & 11-7, page 66)

3.1.1.4.3 Sponsor's Other Efficacy Results

Change from baseline in the CGI-Severity of Illness (LOCF):

An analysis of covariance on the change from baseline to week 8 in the CGI-S with missing values imputed by the LOCF method is summarized in Table 11. The results suggested an efficacy of vilazodone over placebo.

Table 11. Study GNSC-04-DP-02: Sponsor's efficacy results: change from baseline to week 8 in the CGI-S (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	199	198
LS Means	-1.0	-1.4
Difference from placebo		-0.4
(95% confidence interval)		(-0.7, -0.2)
Unadjusted p-value		0.001

(Source: GNSC-04-DP-02 Study Report; Table 11-24, page 84)

CGI-Improvement (LOCF):

An analysis of covariance on the CGI-I at week 8 with missing values imputed by the LOCF method is summarized in Table 12. The results also suggested an efficacy of vilazodone over placebo.

Table 12. Study GNSC-04-DP-02: Sponsor's efficacy results: CGI-I at week 8 (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	199	198
LS Means	3.0	2.6
Difference from placebo		-0.4
(95% confidence interval)		(-0.6, -0.2)
Unadjusted p-value		0.001

(Source: GNSC-04-DP-02 Study Report; Table 11-26, page 85)

Change from baseline in the HAM-D 17-item total score (LOCF):

An analysis of covariance on the change from baseline to week 8 in the HAM-D17 total score with missing values imputed by the LOCF method is summarized in Table 13. The results supported the primary efficacy results.

Table 13. Study GNSC-04-DP-02: Sponsor's efficacy results: change from baseline to week 8 in the HAM-D17 total score (LOCF) in the ITT sample

	Placebo	Vilazodone
Sample size	199	198
LS Means	-8.6	-10.4
Difference from placebo		-1.7
(95% confidence interval)		(-3.2, -0.2)
Unadjusted p-value		0.022

(Source: GNSC-04-DP-02 Study Report; Table 11-20, page 81)

3.1.2.4.4 Reviewer's Results and Comments

This reviewer confirmed the results based on the primary efficacy measure as presented in Table 10. Vilazodone was statistically superior to placebo on the change from baseline to week 8 in the MADRS total score.

Study GNSC-04-DP-02 stipulated three main secondary efficacy measures (the MADRS response, the MADRS remission, and the HAM-A total score) (b) (4)

[redacted]

Sensitivity analysis on the primary efficacy variable: Table 14 summarizes an MMRM analysis of the treatment effects of vilazodone over the duration of the study. The model included baseline MADRS total score as a fixed covariate, treatment group and visit as fixed factors, and treatment-by-visit interaction. Patients were treated as random effect. An unstructured covariance matrix was used. It is noted that these results are slightly different from the sponsor's results reported on pages 160-162 of the GNSC-04-DP-02 Study Report. However, the conclusion is the same and is supportive of the primary efficacy analysis.

Table 14. Study GNSC-04-DP-02: Reviewer's efficacy analysis: change from baseline in the MADRS total score (MMRM analysis) over time in the ITT sample

	Placebo		Vilazodone		Vilazodone - Placebo	
visit	N	Mean	N	Mean	Diff	P-value*
Week 1	194	-2.3	192	-4.0	-1.7	0.0001
Week 2	190	-4.8	179	-6.6	-1.7	0.0063
Week 4	178	-7.6	163	-10.4	-2.9	0.0005
Week 6	162	-9.3	160	-13.3	-4.1	<0.0001
Week 8	154	-10.8	152	-14.4	-3.6	0.0007

(Source: Reviewer's results).
*P-values are not adjusted for multiplicity

This study was powered for 133 subjects per arm. However, due to the study's genetic objective, approximately 200 subjects per arm were randomized. It was of interest to see if the efficacy benefit was still maintained for the first 266 randomized subjects (based on the baseline evaluation date). This analysis is summarized in Table 15 below. It appears that the treatment benefit was still observed.

Table 15. Study GNSC-04-DP-02: Reviewer's analysis: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample for the first 266 subjects

	Placebo	Vilazodone
Sample size	130	136
Baseline MADRS total score		
Mean (Standard deviation)	30.9 (3.8)	30.8 (4.1)
Median (Min – Max)	31 (23 – 41)	31 (21 – 43)
Change from baseline		
LS Means	-9.1	-12.6
Difference from placebo		-3.5
(95% confidence interval)		(-5.9, -1.1)
P-value		0.005

(Source: Reviewer's results)

It appears that when the Statistical Analysis Plan was submitted to the FDA, the primary efficacy analysis was proposed using center as a factor in the model. However, the current analysis utilizes pooled centers instead of centers. It was stated that the pooling approach would be determined and documented prior to the breaking of the blind. This reviewer performed some additional analyses using centers (instead of pooled centers) and without centers in the model. The results are consistent with the sponsor's results on Table 10.

Figure 2 captures the empirical cumulative distribution functions (CDFs) of the two arms of the study. The horizontal axis captures the range of the changes from baseline in the MADRS total score at the last visit (LOCF). The use of the LOCF approach to handle the premature dropouts appears sensible because of the consistencies of the treatment effects across several sensitivity and secondary analyses. The vertical axis depicts the proportion of patients whose changes from baseline score were less than or equal to a given score on the horizontal axis. The CDF plots attempt to capture the entire distributions of the responses whereas the means (as in Table 10) capture the central tendency of the distributions only. It should be noted that the variations associated with the CDF curves were not captured and presented in Figure 2. Thus, these curves are mainly for descriptive purposes only. Separations between vilazodone and placebo were observed in the two curves.

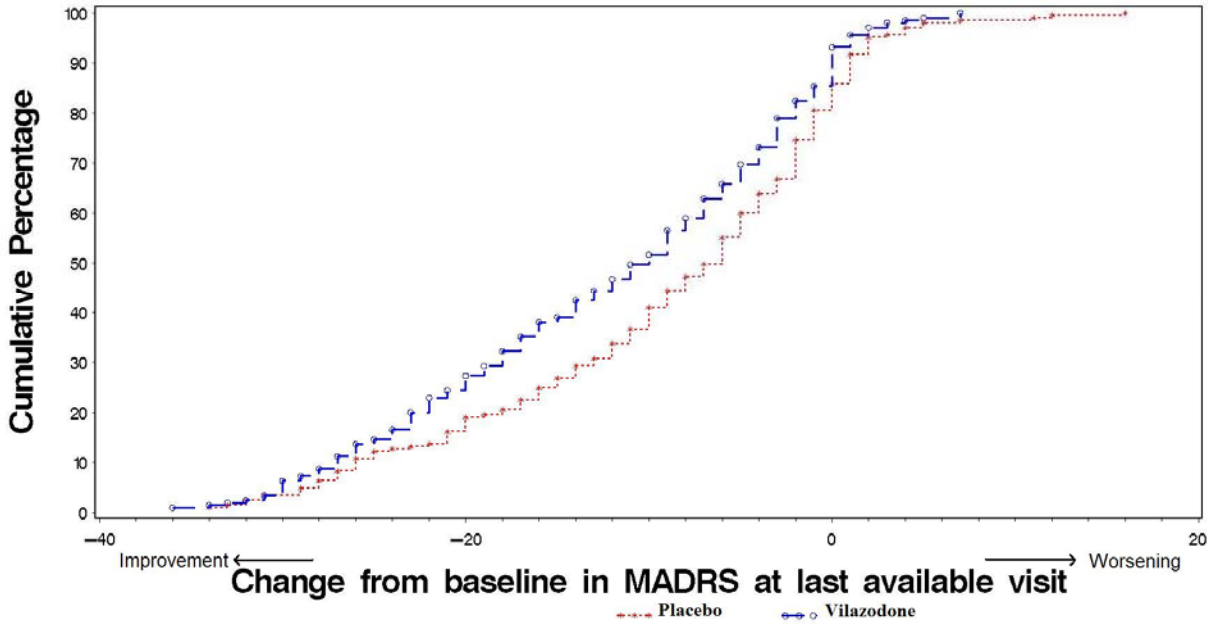

Figure 2. Study GNSC-04-DP-02: Cumulative distribution function

(Source: Reviewer's results)

3.1.3 Summary of primary efficacy results of phase II studies

Vilazodone was also studied in five other phase II studies. The dosages in these five studies ranged from 5 mg/day to 100 mg/day. Three of these five had an active control for assay sensitivity. The primary efficacy measure for these studies was the change from baseline to the end visit in the HAM-D-17 total score. The primary efficacy results of these five studies are summarized in Table 16. Three studies that had an active control were considered failed (b) (4) The remaining two studies were negative.

Table 16. Summary of results on the primary efficacy variables of phase II studies

Report Number (Protocol Number)	Dose/Size	Efficacy results				
		N	Baseline (SD)	LS Means Change from baseline (SE)	Diff from placebo	Unadjusted P-value[§]
*244	Vilazodone (20-100 mg)	86	23.4 (2.9)	-8.9 (0.8)[†]	0.76[†]	0.4938[†]
(EMD 68 843-009)	Fluoxetine 20 mg	89	24.4 (3.2)	-9.5 (0.8)[†]	0.15[†]	0.8924[†]
	Placebo	95	24.0 (3.1)	-9.6 (0.8)[†]		
*245	Vilazodone 10-20 mg	104	23.8 (3.0)	-9.7 (0.7)[†]	0.5[†]	0.6479[†]
(EMD 68 843-010)	Vilazodone 40-60 mg	97	23.9 (3.1)	-10.5 (0.8)[†]	-0.3[†]	0.7527[†]
	Vilazodone 80-100 mg	93	23.5 (3.0)	-8.6 (0.8)[†]	1.6[†]	0.1310[†]
	Fluoxetine 20 mg	92	23.5 (2.3)	-11.1 (0.8)[†]	-0.9[†]	0.3866[†]
	Placebo	99	23.4 (2.8)	-10.2 (0.8)[†]		
*246	Vilazodone 10 mg	120	23.8 (3.1)	-10.8 (0.7)	-0.5	0.5852[†]
(SB 659746-003)	Vilazodone 20 mg	123	23.7 (3.1)	-11.1 (0.7)	-0.8	0.4069[†]
	Citalopram 20 mg	117	23.1 (2.6)	-10.9 (0.7)	-0.7	0.5111[†]
	Placebo	129	23.3 (2.8)	-10.2 (0.7)		
*247	Vilazodone (5-20 mg)	109	23.3 (2.7)	-10.7 (0.7)	-1.0	0.2723
(SB 659746-014)	Placebo	111	23.5 (2.5)	-9.7 (0.7)		
*248	Vilazodone 5mg	140	24.0 (3.0)	-11.0 (0.6)	0.5	0.5654
(SB 659746-002)	Vilazodone 10mg	133	24.5 (3.3)	-12.8 (0.6)	-1.2	0.1770
	Vilazodone 20mg	132	24.3 (3.0)	-11.7 (0.6)	-0.2	0.8019
	Placebo	128	23.7 (2.9)	-11.5 (0.7)		

*All reports begin with GPP-007-CLN-CP2-2003-xxx.
§ P-values are based on respective ANCOVA analyses.
† Reviewer's results. These results are for informational purposes only because they do not strictly conform to the statistical analysis plan. For example, the active controls were not part of the primary contrast so they were not included in the primary analysis model. In study 245, the high dose group was excluded from the primary confirmatory hypotheses. There was also lack of details in term of how centers were pooled. Thus, the results presented in this table are only approximate and are different from the sponsor's results reported in the study reports. However, the results do not change the conclusions of the studies.
(Sources: Study 244: pages 142-143/1543; Study 245: pages 160-161/3600; Study 246: pages 75, 85/1724; Study 247: pages 71, 81/1234; Study 248: pages 73, 84/1624)

3.2 Evaluation of Safety

The evaluation of safety was not performed and reported here. Please refer to the clinical review for the safety evaluation and report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Study CLDA-07-DP-02

4.1.1.1 Gender

The primary analysis stratified by gender is presented in Table 17. Treatment effects appeared numerically greater for female patients than for male patients; however, numerical improvements were seen in both groups.

Table 17. Study CLDA-07-DP-02: Reviewer's primary efficacy results by gender: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
Females		
Sample size	122	138
LS Means	-11.0	-13.9
Difference from placebo		-2.9
(95% confidence interval)		(-5.3, -0.4)
Males		
Sample size	109	94
LS Means	-9.7	-11.6
Difference from placebo		-1.9
(95% confidence interval)		(-5.0, 1,2)

(Source: Reviewer's results)

4.1.1.2 Race

The primary analysis stratified by race is presented in Table 18. Treatment effects were observed in both race groups.

Table 18. Study CLDA-07-DP-02: Reviewer's primary efficacy results by race: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
White		
Sample size	189	180
LS Means	-11.1	-13.4
Difference from placebo		-2.3
(95% confidence interval)		(-4.4, -0.2)
Others		
Sample size	42	52
LS Means	-10.7	-12.5
Difference from placebo		-1.7
(95% confidence interval)		(-6.1, 2.6)

(Source: Reviewer's results)

4.1.1.3 Age

Only 1% of the subjects were over the age of 65 years. Age is dichotomized into ≤ *40* years versus > 40 years. The primary analysis stratified by age is presented in Table 19. Numerical improvements were observed in both age groups with higher numerical improvement seen in patients > 40 years old.

Table 19. Study CLDA-07-DP-02: Reviewer's primary efficacy results by age: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
Age ≤ 40 years		
Sample size	100	108
LS Means	-9.3	-10.5
Difference from placebo		-1.1
(95% confidence interval)		(-3.8, 1.6)
Age > 40 years		
Sample size	131	124
LS Means	-11.5	-15.3
Difference from placebo		-3.8
(95% confidence interval)		(-6.4, -1.1)

(Source: Reviewer's results)

4.1.1.4 Baseline disease severity

Patients in this study had either moderate (baseline MADRS < 30) or severe (baseline MADRS ≥ 30) disease at baseline. The primary analysis stratified by baseline disease severity is presented in Table 20. Numerical improvements were observed in both groups with higher numerical improvement seen in patients with severe baseline disease.

Table 20. Study CLDA-07-DP-02: Reviewer's primary efficacy results by baseline disease severity: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
Moderate		
Sample size	163	172
LS Means	-12.0	-14.1
Difference from placebo		-2.1
(95% confidence interval)		(-4.2, 0.1)
Severe		
Sample size	67	60
LS Means	-4.8	-9.4
Difference from placebo		-4.7
(95% confidence interval)		(-8.7, -0.6)

(Source: Reviewer's results)

4.1.1.5 Disease history

Disease history is classified according to whether the current MDD episode was the first lifetime episode of MDD. The primary analysis stratified by disease history is presented in Table 21. Numerical improvements were observed in both groups.

Table 21. Study CLDA-07-DP-02: Reviewer's primary efficacy results by disease history: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
First episode		
Sample size	67	65
LS Means	-12.7	-16.6
Difference from placebo		-3.9
(95% confidence interval)		(-7.7, -0.2)
Not a first episode		
Sample size	163	167
LS Means	-9.7	-12.0
Difference from placebo		-2.3
(95% confidence interval)		(-4.6, -0.1)

(Source: Reviewer's results)

4.1.2 Study GNSC-04-DP-02

4.1.2.1 Gender

The primary analysis stratified by gender is summarized below. Numerical improvements were observed in both females and males.

Table 22. Study GNSC-04-DP-02: Reviewer's primary efficacy results by gender: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
Females		
Sample size	126	125
LS Means	-10.1	-13.0
Difference from placebo		-2.9
(95% confidence interval)		(-5.5, -0.4)
Males		
Sample size	73	73
LS Means	-9.6	-13.0
Difference from placebo		-3.4
(95% confidence interval)		(-6.6, -0.3)

(Source: Reviewer's results)

4.1.2.2 Race

Due to small sample sizes, race was dichotomized into white versus non-white. The primary analysis stratified by race is summarized below. Numerical improvement was seen for white patients. For other races, the treatment effect appears null. However, it is noted that the majority of patients in this study were white.

Table 23. Study GNSC-04-DP-02: Reviewer's primary efficacy results by race: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
White		
Sample size	154	176
LS Means	-8.9	-12.9
Difference from placebo		-3.9
(95% confidence interval)		(-6.0, -1.9)
Others		
Sample size	45	22
LS Means	-11.5	-11.3
Difference from placebo		0.2
(95% confidence interval)		(-6.4, 6.8)

(Source: Reviewer's results)

4.1.2.3 Age

The primary analysis stratified by age (≤ 40 years versus > 40 years) is summarized below. Improvements were observed in both age groups.

Table 24. Study GNSC-04-DP-02: Reviewer's primary efficacy results by age: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
Age ≤ 40 years		
Sample size	102	99
LS Means	-10.1	-12.1
Difference from placebo		-2.0
(95% confidence interval)		(-4.7, 0.8)
Age > 40 years		
Sample size	97	99
LS Means	-9.4	-13.5
Difference from placebo		-4.1
(95% confidence interval)		(-7.0, -1.2)

(Source: Reviewer's results)

4.1.2.4 Baseline disease severity

Patients in this study had either moderate (baseline MADRS < 30) or severe (baseline MADRS ≥ 30) disease at baseline. The primary analysis stratified by baseline disease severity is presented in Table 25. Numerical improvements were observed in both groups with higher numerical improvement seen in patients with severe baseline disease.

Table 25. Study GNSC-04-DP-02: Reviewer's primary efficacy results by baseline disease severity: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
Moderate		
Sample size	142	142
LS Means	-10.0	-12.5
Difference from placebo		-2.6
(95% confidence interval)		(-4.8, -0.3)
Severe		
Sample size	57	56
LS Means	-8.1	-13.5
Difference from placebo		-5.4
(95% confidence interval)		(-9.6, -1.3)

(Source: Reviewer's results)

4.1.2.5 Disease history

Disease history was classified according to whether the current MDD episode was the first lifetime episode of MDD. The primary analysis stratified by disease history is presented in Table 26. Numerical improvements were observed in both groups.

Table 26. Study GNSC-04-DP-02: Reviewer's primary efficacy results by disease history: change from baseline to week 8 in the MADRS total score (LOCF) in the ITT sample

	Placebo	Vilazodone
First episode		
Sample size	75	69
LS Means	-10.5	-12.4
Difference from placebo		-2.0
(95% confidence interval)		(-5.1, 1.2)
Not a first episode		
Sample size	124	129
LS Means	-9.6	-13.4
Difference from placebo		-3.7
(95% confidence interval)		(-6.2, -1.2)

(Source: Reviewer's results)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Both pivotal studies were positive based on the primary efficacy variable pre-specified. None of the secondary efficacy measures were specified as key secondary efficacy measures or agreed upon a priori. (b) (4)

(b) (4)

The long-term efficacy of vilazodone has not been adequately assessed. The current data are based on a one year open-label study (Study CLDA-07-DP-04). Because this was an open-label and there was no control group, the efficacy evaluation is limited and is subject to biases. (b) (4)

5.2 Conclusions and Recommendations

Vilazodone at a 40 mg/day was positive in the acute treatment of major depressive disorder, as measured by the change from baseline to week 8 in the MADRS total score, based on two pivotal studies

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/s/

PHILLIP V DINH
11/30/2010

PEILING YANG
11/30/2010
I concur.

HSIEN MING J J HUNG
11/30/2010

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

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 22-567
Drug Name:	EMD-68843
Indication(s):	104 Week Carcinogenicity in Rats and Mice
Applicant:	Sponsor: PGxHealtb, LLC 5 Science Park, New Haven, CT 06511
Documents Reviewed:	Electronic submission, Dated: May, 19, 2010 Electronic data submitted on June 30, 2007
Review Priority:	Priority
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad Nagem, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Psychiatry Products
Reviewing Pharmacologist:	Violetta Klimek , Ph.D., Linda H. Fossom, Ph.D.
Project Manager:	William Bender
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of EMD-68843 in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Klimek.

2. Rat Study

The Rats studies consisted of two phase studies. In the first phase each of the Male and Female groups were assigned to either one of three active treatment groups or a control group. Five hundred HsdCpb:WU Wistar rats were randomly allocated to treated and control groups (250 hundreds Males and 250 for Females). The control group has 100 rats per sex. The dose levels for treated groups were 7.5, 25 and 75 mg/kg/day and each group has 50 rats per sex. In this review these dose groups would be referred to as the low, medium and high dose group, respectively. The controls received the vehicle (0. 25% aqueous hydroxypropyl methylcellulose (Methocel® K4M Premium), and served to generate concurrent control data.

In a second phase and 6 months after the start of the first phase of the study, two groups were added to the study, one control and one active. The control has 50 rats in each sex group and each animal in this group received the vehicle (0. 25% aqueous hydroxypropyl methylcellulose (Methocel® K4M Premium). The active treatment group has 50 rats per sex and each received a dose of 150 mg/kg/day. In this review these dose groups would be referred to as the new control and new high dose group, respectively.

In this review three datasets were analyzed by this reviewer:

- Combined datasets: datasets from the two phases were combined; the control groups were combined into one control group. The dose levels 7.5, 25, 75 and 150 mg/kg/day would be referred to as the low, mid, mid-high and the high dose group respectively.

- First phase dataset: consisting of the original control group, and the dose levels 7.5, 25 and 75 mg/kg/day.

- Second phase dataset: consisting of the new control group and the new high dose 150 mg/kg/day.

During the administration period all animals were observed for physical and clinical signs three times everyday on normal week days and twice on weekends and holidays. In addition, palpation was performed once a week to detect superficial masses. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

2.1. Sponsor's analyses

2.1.1. Survival analysis

Survival function of each treatment group was estimated using the Kaplan-Meier product limit method. The dose response relationship[1] in mortality was tested using similar method as was suggested by Tarone. Pairwise comparisons of control and each treated group were performed using the Log-Rank test. All tests were conducted at one-tailed significance level of 0.05.

Sponsor's findings: Sponsor's analysis showed survival rates of 69.3%, 82.0%, 74.0%, 48.0% and 72.0% in combined control, low, medium, medium-high and high dose groups, respectively in males and 67.3%, 80.0%, 70.0%, 66.0%, and 52.0%, respectively in females. Sponsor concluded that there was no statistically significant treatment related effect on the survival in either sex.

2.1.2. Tumor data analysis

The analysis for positive dose response relationship for tumor incidences among control, low, medium, medium- high, and high dose groups and pairwise comparisons of control and treated groups were performed using the methods outlined in the paper of Peto et al. (1982). For incidental tumors, the analysis intervals were: weeks 0 - 52, 53 - 78, 79 - 92, 92 – 104, and 105 till termination of the live phase. Exact permutation test were used for tumors with less than 10 incidences.

The analysis for dose response relationship was conducted at the significance levels of 0.005 (one tailed-level) for common tumors and 0.025 (one tailed-level) for rare tumors. Pairwise comparisons were conducted at the significance levels of 0.01 (one tailed-level) for common tumors and 0.05 (one tailed-level) for rare tumors.
Common tumors were defined as those with a historical incidence in controls of 1% or more and rare tumors as less than 1%.

Reviewer's comment: *The above significance levels for dose response relationship test were suggested by Lin and Rahman (1998) and those for pairwise comparisons were suggested by Haseman (1983) to adjust for multiple testing (to keep the false-positive rate at the nominal level of approximately 10%).*

Sponsor's findings: Sponsor's analyses showed no statistically significant positive dose response relationship or pairwise difference between control and any of the treated groups in any of the tested tumor types.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses on the combined phases' dataset as well as the separate analysis for each phase's dataset. Data used in this reviewer's analyses were provided by the sponsor electronically.

[1] In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

2.2.1. Survival analysis

The survival distributions of animals in all four treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship was tested using the likelihood ratio test and homogeneity of survival distributions was tested using the log-rank test. The intercurrent mortality data are given in Tables 1A, 1A1, 1A2 for the combined, first phase and second phase respectively for the male rats. For the female rats the intercurrent mortality data are given in Tables 1B, 1B1 and 1B2 for the combined, first phase and second phase respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively for the combined dataset. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for males and females, respectively.

Reviewer's findings: The tests showed no statistically significant dose response relationship or differences between the control and any of the treated groups in survivals across treatment groups in male rats for the combined dataset. However, the dose response in mortality in female rats is statistically significant ($p=0.0325$). For the original study, the trend test was statistically significant in the male group ($p=0.0123$), but not statistically significant in the female group ($p=0.3849$). For the second phase dataset, no statistically significant differences between the new control and the new high dose group were observed.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationship and pairwise comparisons of control group with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of $k=3$ is suggested in the literature. Hence, this reviewer used $k=3$ for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in the appendix. For male rats in tables 3A, 3A1 and 3A2 for the combined, first phase and second phase respectively, for female rats in tables 3B, 3B1 and 3B2 for the combined, first phase and second phase respectively.

Multiple testing adjustment: The adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998), which recommend the use of a significance level $\alpha=0.025$ for rare tumors and $\alpha=0.005$ for common tumors for a submission with two species, and the use of a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. The adjustment for multiple pairwise comparisons was done using the criteria developed by Haseman (1983), which recommend the use of a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by the same authors (Rahman and Lin, 2008) indicated similar usefulness of their recommendation for Poly-3 analysis also.

As suggested by the reviewing pharmacologist Dr. Klimek, this reviewer did the analysis of the following tumor/organ combinations:

Hemangioma and Hemangiosarcoma (across organs in both sexes)

Male Rats:

HEMOLYMPHORET. SYS/ Lymphoblastic malignant lymphoma/Lymphocytic malignant lymphoma,
PANCREAS SAMPLE 1/ Islet cell adenoma/Islet cell carcinoma,
SKIN/SUBCUTIS /Basal cell carcinoma/Benign Schwannoma/Fibroma/ Fibrous histiocytoma /Inverted papilloma/Keratoacanthoma/Malignant Schwannoma/Sarcoma (not otherwise specified)/ Squamous cell carcinoma/Squamous cell papilloma
THYROID GLANDS/C-cell adenoma/C-cell carcinoma
ZYMBAL'S GLANDS /Anaplastic carcinoma/Squamous cell papilloma.

Female Rats:

MAMMARY GLAND/Adenocarcinoma/Adenoma/Fibroadenoma/Fibrosarcoma/Sarcoma (not otherwise specified)
OVARIES/Benign thecoma/Malignant thecoma
SKIN/SUBCUTIS /Basal cell carcinoma/Keratoacanthoma/Squamous cell carcinoma/Squamous cell papilloma
THYROID GLANDS/C-cell adenoma/C-cell carcinoma

Reviewer's findings: Combined phases' dataset:
The following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of control and treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons Combined phases' Dataset: Female Rats

Organ Name	Tumor Name	0 mg Cont N=150	7.5 mg Low N=50	25 mg Med N=50	75 mg MidHi N=50	150 mg High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. MIDHI	P_Value C vs. H
HEMOLYMPHORET.	Histiocytic sarcoma	2	0	0	0	3	0.0298	0.4493	0.4298	0.4429	0.0944

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman the incidence of none of the above or any other tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. Also based on the criteria by Haseman, none of the pair-wise comparisons of treated groups with the control was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

Reviewer's findings: First phase's dataset: The following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of control and treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons
First Phase Dataset: Female Rats

Organ Name	Tumor Name	0 mg Cont N=100	7.5 mg Low N=50	25 mg Med N=50	75 mg High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
MAMMARY GLAND	Adeno-carcinoma+	1	4	1	5	0.0291	**0.0471***	0.5435	**0.0181***
	Adenocarcinoma	1	3	0	4	0.0471	0.1167	1.0000	**0.0471***

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman the incidence of none of the above or any other tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. However, based on the criteria by Haseman, the pair-wise comparisons of the high dose group with the control was considered to be statistically significant in the female group for the increased tumor incidence in Mammary Gland /Adenocarcinoma. In addition the pair-wise comparisons of low dose group dose with the control and high dose with control were also statistically significant in the female group for the increased tumor when the Adenocarcinoma and Carcinoma in Mammary Gland were combined.

Reviewer's findings: Second phase's dataset:
Based on the criteria by Haseman, none of the pair-wise comparisons of treated group (new high dose) with the new control was considered to be statistically significant in either sex.

3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Three hundred B6 C3 F1 mice of each sex were randomly allocated to treated and control groups. The control group with 120 mice received received the vehicle of [Aqueous 0.25% hydroxypropyl – methylcellulose (b) (4) 56340 ~ 4000 mPa.s, 2% in water, 25°C)]. The treated groups received dose levels of 15, 45, and 135 mg/kg/day were in equal size of 60 animals per sex. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively.

During the administration period all animals were observed for physical and clinical signs (palpable mass observation, body weight, food consumption and clinical pathology) and post mortem (gross pathology and histology). A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data from the mouse study were analyzed using the same statistical methodologies as those that were used to analyze the survival data from the rat study.

Sponsor's findings: The sponsor's analysis showed survival rates of 86.7%, 90.0%, 81.7%, and 78.3%, in control, low, medium, and high dose groups, respectively in males and 79.2%, 75.0%, 85.0%, and 70.0%, respectively in females. Sponsor concluded that a trend towards an increase in mortality, compared to controls, was noted in both sexes at the highest dose. No relevant differences from controls were found at the low and medium doses.

3.1.2. Tumor data analysis

Tumor data from the mouse study were also analyzed using the same statistical methodologies as were used to analyze the tumor data from the rat study.

Sponsor's findings: The sponsor's analysis showed a statistically significant positive dose response relationship in the incidence of the thyroid, mammary gland and liver in both sexes. Pairwise comparisons showed statistically significant increased incidence of hepatocellular adenoma in high dose group of male and medium and high dose groups of females compared to their respective control.

3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses from the mouse study. For the mouse data analyses this reviewer used similar methodologies as those he used to analyze the data from the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for males and females, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for males and females, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for males and females, respectively.

Reviewer's findings: The tests showed no statistically significant dose response relationship or differences between the control and any of the treated groups in survivals across treatment groups in female mice. However, the dose response in mortality in male mice is statistically significant (p=0.0440).

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of control and treated groups are given in Table 6A and 6B in the appendix for males and females, respectively.

As requested by the reviewing Pharmacologist Dr. Klimek, this reviewer did the analysis of the following tumor/organ combinations:

Hemangioma and Hemangiosarcoma (across organs in both sexes)

Male Mouse: Lacrimal gl.-Harder /adenocarcinoma/ adenoma
Liver/ hepatocellular, adenoma/ hepatocellular, carcinoma

Lungs/ bronchiolar/alveolar adenoma/ bronchiolar/alveolar carcinoma/ carcinoma
Multiple organs/ fibrosarcoma/ histiocytic sarcoma/ lymphosarcoma
Pancreas/ islets, adenoma/ islets, carcinoma
Pituitary/ anterior (pars distalis), adenoma/ pars intermedia, carcinom

Female Mouse: Lacrimal gl.-Harder /adenocarcinoma/ adenoma
Liver/ hepatocellular, adenoma/ hepatocellular, carcinoma
Lungs/ bronchiolar -alveolar adenoma/ bronchiolar -alveolar carcinoma/ carcinoma
Mammary gland/ adenoacanthoma/ adenocarcinoma
Multiple organs/ fibrosarcoma/ histiocytic sarcoma/ lymphosarcoma/ stromal cell sarcoma
Pancreas/ islets, adenoma/ islets, carcinoma
Pituitary/ anterior (pars distalis), adenoma/ pars intermedia, carcinom
Thyroid glands/ follicle(s), adenoma/ parafollicular cells carcinoma

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

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons

Organ Name	Tumor Name	0 mg Cont N=120	15 mg Low N=60	45 mg Med N=60	135 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male									
Liver	**hepatocellular x(ad.**	**36**	**32**	**20**	**40**	**<0.001***	**0.0034***	**0.3848**	**<0.001***
	hepatocellular, aden	22	23	14	27	<0.001*	0.0045*	0.2635	<0.001*
	hepatocellular, carc	15	11	10	19	0.0012*	0.2227	0.2842	0.0016*
Pituitary	**Anterior-Others**	**1**	**4**	**1**	**0**	**0.8377**	**0.0457***	**0.5543**	**1.0000**
	anterior (pars dista	0	4	1	0	0.7537	0.0123*	0.3314	.
Testes	Leydig cell tumor	0	3	0	1	0.4054	0.0377*	.	0.3195
Thyroid glands	follicle(s), adenoma	3	1	7	4	0.0650	0.8126	0.0161	0.1480
Female									
Liver	hepatocellular, aden	13	4	12	13	0.0121	0.8931	0.1010	0.0456
	hepatocellular/(ad.+	**21**	**13**	**18**	**20**	**0.0084**	**0.3237**	**0.0582**	**0.0128**
Lungs	carcinoma	1	2	3	7	0.0011*	0.2633	0.1193	0.0021*
Mammary gland	adenocarcinoma	3	1	6	7	0.0050*	0.8108	0.0482	0.0166
	adenoacanthoma+adeno	3	1	6	8	0.0017*	0.8108	0.0482	0.0069*
Thyroid glands	follicle(s), adenoma	10	3	7	9	0.0498	0.8779	0.3601	0.1319
	follicles +Others	10	3	8	9	0.0499	0.8779	0.2466	0.1319

Based on the criteria of Lin and Rahman, the incidences of hepatocellular adenoma, hepatocellular carcinoma, hepatocellular adenoma+carcinoma in liver in male; and of carcinoma in lung, adenocarcinoma, adenocarcinoma+adenoacathoma in mammary gland, in female were considered to have statistically significant positive dose response relationships.

Also based on the males analsyses results, the increased incidences of hepatocellular adenoma, and hepatocellular adenoma+carcinoma in low and high dose groups, hepatocellular carcinoma in high dose group, pituitary anterior (pars dista), pituitary anterior-other, and testes Leydig cell tumor in low dose group were considered to be statistically significant. For the female group, the incidences of lungs carcinoma in the high dose and Mammary gland adenocarcinoma+ adenoacanthoma in high dose group were considered to be statistically significant compared to their respective control.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of EMD-68843 in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks.

In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

Rat Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two control groups. Two sperate phase of the study were considered as follows:

In the first phase each of the Male and Female groups were assigned either one of three active treatment groups or a control group. Five hundred HsdCpb:WU Wistar rats were randomly allocated to treated and control groups (250 hundreds Males and 250 for Females). The control group has 100 rats per sex. The dose levels for treated groups were 7.5, 25 and 75 mg/kg/day and each group has 50 rats per sex. In this review these dose groups would be referred to as the low, medium and high dose group, respectively. The controls received the vehicle (0. 25% aqueous hydroxypropyl methylcellulose (Methocel® K4M Premium), and served to generate concurrent control data.

In a second phase and 6 months after the start of the first phase of the study, two groups were added to the study, one control and one active. The control has 50 rats for each sex group and each animal in this group received the vehicle (0. 25% aqueous hydroxypropyl methylcellulose (Methocel® K4M Premium). The active treatment has 50 rats per sex group and each received a dose of 150 mg/kg/day. In this review these doses groups would be referred to as the new control and new high dose group, respectively.

In this review three datasets were analyzed by this reviewer:

- Combined datasets: datasets from the two phases were combined; the control groups were combined into one control group. The dose levels 7.5, 25, 75 and 150 mg/kg/day would be referred to as the low, mid, mid-high and the high dose group respectively.

- First phase dataset: consisting of the original control group, and the dose levels 7.5, 25 and 75 mg/kg/day.

- Second phase dataset: consisting of the new control group and the new dose 150 mg/kg/day.

In the combined phases' study, the tests showed no statistically significant dose response relationship or differences between the control and any of the treated groups in survivals across treatment groups in male rats for the combined analyses. However, the dose response in mortality in female rats is statistically significant (p=0.0325).

For the original study, the trend test was statistically significant in the male group (p=0.0123), but not statistically significant in the female group (p=0.3849). The pair-wise comparison of the high dose group with the control was statistically significant in the female group for the increased tumor incidence in Mammary Gland /Adenocarcinoma. In addition the pair-wise comparisons of the low dose group with the control and the

high dose with control were also statistically significant in the female group for the increased tumor when the Adenocarcinoma and Carcinoma in Mammary Gland were combined.

For the second phase dataset, no statistically significant difference between the new control and the new high dose group was observed.

Mouse Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one control group. Three hundred B6 C3 F1 mice of each sex were randomly allocated to treated and control groups. The control group with 120 mice received the vehicle of [Aqueous 0.25% hydroxypropyl – methylcellulose (b) (4) 56340 ~ 4000 mPa.s, 2% in water,25°C)]). The treated groups received dose levels of 15, 45, and 135 mg/kg/day and were in equal size of 60 animals per sex. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively.

The tests showed no statistically significant dose response relationship or differences in survival across treatment groups in female mice. However, the dose response in mortality in male mice is statistically significant (p=0.0440)

Test results showed that the incidences of hepatocellular adenoma, hepatocellular carcinoma, hepatocellular adenoma+carcinoma in liver in male; and of carcinoma in lung, adenocarcinoma, adenocarcinoma+adenoacathoma in mammary gland, in female were considered to have statistically significant positive dose response relationships.

Also based on the males analsyses results, the increased incidences of hepatocellular adenoma, and hepatocellular adenoma+carcinoma in low and high dose groups, hepatocellular carcinoma in high dose group, pituitary anterior (pars dista), pituitary anterior-other, and testes Leydig cell tumor in low dose group were considered to be statistically significant. For the female group, the incidences of lungs carcinoma in the high dose and Mammary gland adenocarcinoma+ adenoacanthoma in high dose group were considered to be statistically significant compared to their respective control.

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5. Appendix

Table 1A: Intercurrent Mortality Rate
Combined Dataset: Male Rats

	0mg|kg|day		7.5mg|kg|day		25mg|kg|day		75mg|kg|day		150mg|kg|day	
	No. of		No. of		No. of		No. of		No. of	
Week	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %
0 - 52	3	2.00	1	2.00	.	.	1	2.00	.	.
53 - 78	9	8.00	3	8.00	2	4.00	5	12.00	4	8.00
79 - 91	18	20.00	1	10.00	1	6.00	5	22.00	5	18.00
92 - 104	16	30.67	4	18.00	9	24.00	14	50.00	5	28.00
Ter. Sac.	104	69.33	41	82.00	38	76.00	25	50.00	36	72.00

Table 1A1: Intercurrent Mortality Rate
First phase Dataset: Male Rats

	0 mg|kg|day		7.5 mg|kg|day		25 mg|kg|day		75 mg|kg|day	
	No. of		No. of		No. of		No. of	
Week	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %
0 - 52	3	3.00	1	2.00	.	.	1	2.00
53 - 78	6	9.00	3	8.00	2	4.00	5	12.00
79 - 91	13	22.00	1	10.00	1	6.00	5	22.00
92 - 104	13	35.00	4	18.00	9	24.00	14	50.00
Ter. Sac.	65	65.00	41	82.00	38	76.00	25	50.00

Table 1A2: Intercurrent Mortality Rate
Second phase Dataset: Male Rats

	0 mg|kg|day		150 mg|kg|day	
	No. of		No. of	
Week	Death	Cum. %	Death	Cum. %
53 - 78	3	6.00	4	8.00
79 - 91	5	16.00	5	18.00
92 - 104	3	22.00	5	28.00
Ter. Sac.	39	78.00	36	72.00

Table 1B: Intercurrent Mortality Rate
Combined Dataset: Female Rats

	0mg|kg|day		7.5mg|kg|day		25mg|kg|day		75mg|kg|day		150mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	2	1.33	2	4.00	3	6.00	.	.	1	2.00
53 - 78	11	8.67	2	8.00	1	8.00	2	4.00	5	12.00
79 - 91	14	18.00	3	14.00	6	20.00	4	12.00	6	24.00
92 - 104	21	32.00	3	20.00	5	30.00	11	34.00	12	48.00
Ter. Sac.	102	68.00	40	80.00	35	70.00	33	66.00	26	52.00

Table 1B1: Intercurrent Mortality Rate
First phase Dataset: Female Rats

	0 mg|kg|day		7.5 mg|kg|day		25 mg|kg|day		75 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	2	2.00	2	4.00	3	6.00	.	.
53 - 78	5	7.00	2	8.00	1	8.00	2	4.00
79 - 91	9	16.00	3	14.00	6	20.00	4	12.00
92 - 104	13	29.00	3	20.00	5	30.00	11	34.00
Ter. Sac.	71	71.00	40	80.00	35	70.00	33	66.00

Table 1B2: Intercurrent Mortality Rate
Second phase Dataset: Female Rats

	0 mg|kg|day		150 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	.	.	1	2.00
53 - 78	6	12.00	5	12.00
79 - 91	5	22.00	6	24.00
92 - 104	8	38.00	12	48.00
Ter. Sac.	31	62.00	26	52.00

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	P-Value		
	Combined Dataset	**First phase Dataset**	**Second phase Dataset**
Dose Response	0.3257	0.0123	0.5110
Homogeneity	0.0034	0.0018	0.5092

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	P-Value		
	Combined Dataset	**First phase Dataset**	**Second phase Dataset**
Dose Response	0.0325	0.3849	0.4979
Homogeneity	0.0850	0.5278	0.4958

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Combined Dataset: Male Rats

Organ Name	Tumor Name	0 mg Cont N=150	7.5 mg Low N=50	25 mg Med N=50	75 mg MidHi N=50	150 mg High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. MIDHI	P_Value C vs. H
ABDOMINAL CAVIT	Hemangiosarcoma	0	0	0	1	0	0.2769	.	.	0.2398	.
	Malignant mesothelio	1	0	0	0	0	0.5752	0.2614	0.2614	0.2353	0.2529
ADRENAL GLANDS	Adenoma:Cortex	0	0	0	1	1	0.0580	.	.	0.2353	0.2529
	Pheochromocytoma	20	8	9	5	9	0.3347	0.4481	0.3416	0.5799	0.3002
BONE	Sarcoma (not otherwi	0	0	1	0	0	0.2745	.	0.2614	.	.
BRAIN	Astrocytoma	0	0	0	0	1	0.1466	.	.	.	0.2571
	Mixed glioma	1	0	0	0	0	0.5752	0.2614	0.2614	0.2353	0.2529
	Oligodendroglioma	1	0	0	0	0	0.5752	0.2614	0.2614	0.2353	0.2529
DUODENUM	Sarcoma (not otherwi	0	0	0	0	1	0.1438	.	.	.	0.2529
EYES	Meningeal sarcoma	1	0	0	0	0	0.5752	0.2614	0.2614	0.2353	0.2529
HEART	Malignant endocardia	2	0	0	0	0	0.8203	0.4555	0.4555	0.4163	0.4429
HEMOLYMPHORET.	Histiocytic sarcoma	7	1	1	1	0	0.9506	0.6627	0.6727	0.6085	0.8736
	Lymphoblastic malign	1	1	0	0	0	0.6914	0.4617	0.2614	0.2353	0.2529
	Lymphoblastic_ML	5	1	0	0	1	0.7329	0.5012	0.7824	0.7409	0.4712
	Lymphocytic malignan	4	0	0	0	1	0.5830	0.7036	0.7036	0.6593	0.3702
	Malignant fibrous hi	3	0	0	0	0	0.9243	0.5995	0.5995	0.5553	0.5854
KIDNEYS	Fibrosarcoma	0	0	0	1	0	0.2745	.	.	0.2353	.
	Liposarcoma	0	0	1	0	1	0.1014	.	0.2614	.	0.2529
LIVER	Cholangiocellular ca	2	0	0	1	0	0.5513	0.4555	0.4555	0.5631	0.4429
	Cholangioma:cystic	0	0	0	1	0	0.2769	.	.	0.2398	.
LUNGS	Alveolar/bronchiolar	1	0	0	0	0	0.5752	0.2614	0.2614	0.2353	0.2529
	Squamous cell carcin	0	0	0	1	0	0.2745	.	.	0.2353	.
MAMMARY GLAND	Sarcoma (not otherwi	1	0	0	0	0	0.5733	0.2599	0.2599	0.2339	0.2514
MANDIB.LYMPH NO	Hemangioma	0	0	0	1	0	0.2745	.	.	0.2353	.
MESENT. LYMPH N	Hemangioma	1	1	1	0	0	0.6714	0.4555	0.4555	0.2353	0.2529
	Hemangiosarcoma	1	0	0	0	0	0.5752	0.2614	0.2614	0.2353	0.2529
MESENTERIC TISS	Hemangioma	1	0	0	0	0	0.5752	0.2614	0.2614	0.2353	0.2529
Multiple organs	Hemangioma+Hemangios	3	2	1	2	0	0.7184	0.3914	0.2800	0.3453	0.5854
PANCREAS	Acinar cell adenoma	2	1	0	0	0	0.8428	0.5995	0.4555	0.4163	0.4429
PANCREAS SAMPLE	Islet cell adenoma	1	1	1	1	2	0.0796	0.4555	0.4555	0.4163	0.1579
	Islet cell carcinoma	0	0	1	1	0	0.3235	.	0.2614	0.2353	.
	Islet-cell(adenoma+c	1	1	2	2	2	0.0818	0.4555	0.1676	0.1383	0.1579
PARATHYROID GLA	Adenoma	1	0	0	0	0	0.5752	0.2614	0.2614	0.2353	0.2529
PITUITARY GLAND	Adenoma of pars dist	33	10	4	9	4	0.9800	0.6367	0.9904	0.5867	0.9849
SKIN/SUBCUTIS	BCc+Others	8	2	4	1	3	0.4935	0.5068	0.3807	0.6662	0.5539
	Basal cell carcinoma	1	1	0	0	0	0.6922	0.4555	0.2614	0.2353	0.2529
	Benign Schwannoma	1	0	0	0	0	0.5752	0.2614	0.2614	0.2353	0.2529
	Fibroma	2	0	0	0	0	0.8203	0.4555	0.4555	0.4163	0.4429
	Fibrous histiocytoma	0	0	1	1	0	0.3235	.	0.2614	0.2353	.
	Hemangioma	0	1	0	0	0	0.4248	0.2614	.	.	.
	Inverted papilloma	0	1	0	0	0	0.4248	0.2614	.	.	.
	Keratoacanthoma	0	0	0	0	1	0.1438	.	.	.	0.2529
	Malignant Schwannoma	0	0	2	0	0	0.4743	.	0.0672	.	.

	Sarcoma (not otherwi	1	0	0	0	0	0.5752	0.2614	0.2614	0.2353	0.2529
	Squamous cell carcin	1	0	0	0	2	0.0625	0.2614	0.2614	0.2353	0.1579
	Squamous cell papill	2	0	1	0	0	0.7295	0.4555	0.5995	0.4163	0.4429
TESTES	Benign Leydig cell t	2	1	3	2	2	0.1608	0.5995	0.1128	0.2357	0.2654
THYMUS	Lymphocytic thymoma	1	0	1	0	0	0.5418	0.2614	0.4555	0.2353	0.2529
THYROID GLANDS	C-cell adenoma	8	3	5	1	1	0.9041	0.5849	0.2401	0.6699	0.7137
	C-cell carcinoma	4	1	1	2	1	0.4717	0.3914	0.3914	0.4321	0.3733
	C-cell(adenoma+carci	12	4	6	3	2	0.8491	0.4100	0.3321	0.4882	0.7380
	Follicular cell aden	4	2	0	0	4	0.0755	0.4949	0.7060	0.6618	0.1127
ZYMBAL'S GLANDS	Anaplastic carcinoma	1	0	0	0	1	0.2887	0.2614	0.2614	0.2353	0.4493
	Anaplastic carcinoma	1	0	0	0	0	0.5752	0.2614	0.2614	0.2353	0.2529
	Squamous cell papill	0	0	0	0	1	0.1466	.	.	.	0.2571

Table 3A1: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
First Phase Dataset: Male Rats

		0 mg	7.5 mg	25 mg	75 mg	P_Value			
		Cont	Low	Med	High	Dos	P_Value	P_Value	P_Value
Organ Name	Tumor Name	N=100	N=50	N=50	N=50	Resp	C vs. L	C vs. M	C vs. H
ABDOMINAL CAVIT	Hemangiosarcoma	0	0	0	1	0.1881	.	.	0.3254
ADRENAL GLANDS	Adenoma:Cortex	0	0	0	1	0.1843	.	.	0.3200
	Pheochromocytoma	13	8	9	5	0.6879	0.4682	0.3675	0.7657
BONE	Sarcoma (not otherwi	0	0	1	0	0.3963	.	0.3511	.
BRAIN	Mixed glioma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Oligodendroglioma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
EYES	Meningeal sarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
HEMOLYMPHORET.	Histiocytic sarcoma	6	1	1	1	0.8481	0.9544	0.9568	0.9399
	Lymphoblastic malign	1	1	0	0	0.8491	0.5871	1.0000	1.0000
	Lymphoblastic_ML	4	1	0	0	0.9913	0.8916	1.0000	1.0000
	Lymphocytic malignan	3	0	0	0	1.0000	1.0000	1.0000	1.0000
	Malignant fibrous hi	2	0	0	0	1.0000	1.0000	1.0000	1.0000
KIDNEYS	Fibrosarcoma	0	0	0	1	0.1843	.	.	0.3200
	Liposarcoma	0	0	1	0	0.3963	.	0.3511	.
LIVER	Cholangiocellular ca	2	0	0	1	0.4754	1.0000	1.0000	0.6966
	Cholangioma:cystic	0	0	0	1	0.1881	.	.	0.3254
LUNGS	Squamous cell carcin	0	0	0	1	0.1843	.	.	0.3200
MAMMARY GLAND	Sarcoma (not otherwi	1	0	0	0	1.0000	1.0000	1.0000	1.0000
MANDIB.LYMPH NO	Hemangioma	0	0	0	1	0.1843	.	.	0.3200
MESENT. LYMPH N	Hemangioma	1	1	1	0	0.6842	0.5807	0.5807	1.0000
	Hemangiosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
MESENTERIC TISS	Hemangioma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Multiple organs	Hemangioma+Hemangios	3	2	1	2	0.3856	0.5768	0.8272	0.5258
PANCREAS	Acinar cell adenoma	1	1	0	0	0.8477	0.5807	1.0000	1.0000
PANCREAS SAMPLE	Islet cell adenoma	1	1	1	1	0.3241	0.5807	0.5807	0.5394
	Islet cell carcinoma	0	0	1	1	0.1118	.	0.3511	0.3200
	Islet-cell(adenoma+c	1	1	2	2	0.1197	0.5807	0.2817	0.2397
PARATHYROID GLA	Adenoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
PITUITARY GLAND	Adenoma of pars dist	19	10	4	9	0.5679	0.6373	0.9906	0.6044
SKIN/SUBCUTIS	BCc+Others	5	2	4	1	0.7288	0.7709	0.3852	0.9045
	Basal cell carcinoma	0	1	0	0	0.6083	0.3511	.	.
	Benign Schwannoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
SKIN/SUBCUTIS	Fibrous histiocytoma	0	0	1	1	0.1118	.	0.3511	0.3200
	Hemangioma	0	1	0	0	0.6083	0.3511	.	.
	Inverted papilloma	0	1	0	0	0.6083	0.3511	.	.
	Malignant Schwannoma	0	0	2	0	0.3795	.	0.1216	.
	Sarcoma (not otherwi	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Squamous cell carcin	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Squamous cell papill	2	0	1	0	0.7820	1.0000	0.7302	1.0000
TESTES	Benign Leydig cell t	1	1	3	2	0.1326	0.5807	0.1241	0.2397
THYMUS	Lymphocytic thymoma	1	0	1	0	0.6367	1.0000	0.5807	1.0000

THYROID GLANDS	C-cell adenoma	6	3	5	1	0.8079	0.6729	0.3429	0.9381
	C-cell carcinoma	3	1	1	2	0.3157	0.8272	0.8272	0.5148
	C-cell(adenoma+carci	9	4	6	3	0.6559	0.7370	0.4553	0.8055
	Follicular cell aden	2	2	0	0	0.9269	0.4394	1.0000	1.0000

Table 3A2: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Second Phase Dataset: Male Rats

Organ Name	Tumor Name	0 mg Cont N=50	150 mg High N=50	P_Value C vs. H
ABDOMINAL CAVIT	Malignant mesothelio	1	0	1.0000
ADRENAL GLANDS	Adenoma:Cortex	0	1	0.4944
	Pheochromocytoma	7	9	0.3733
BONE	Sarcoma (not otherwi	0	0	.
BRAIN	Astrocytoma	0	1	0.5000
DUODENUM	Sarcoma (not otherwi	0	1	0.4944
HEART	Malignant endocardia	2	0	1.0000
HEMOLYMPHORET.	Histiocytic sarcoma	1	0	1.0000
	Lymphoblastic malign	0	0	.
	Lymphoblastic_ML	1	1	0.7472
	Lymphocytic malignan	1	1	0.7472
	Malignant fibrous hi	1	0	1.0000
KIDNEYS	Liposarcoma	0	1	0.4944
LUNGS	Alveolar/bronchiolar	1	0	1.0000
MESENT. LYMPH N	Hemangioma	0	0	.
Multiple organs	Hemangioma+Hemangios	0	0	.
PANCREAS	Acinar cell adenoma	1	0	1.0000
PANCREAS SAMPLE	Islet cell adenoma	0	2	0.2416
	Islet cell carcinoma	0	0	.
	Islet-cell(adenoma+c	0	2	0.2416
PITUITARY GLAND	Adenoma of pars dist	14	4	0.9983
SKIN/SUBCUTIS	BCc+Others	3	3	0.6509
	Basal cell carcinoma	1	0	1.0000
	Fibroma	2	0	1.0000
	Fibrous histiocytoma	0	0	.
	Hemangioma	0	0	.
	Inverted papilloma	0	0	.
	Keratoacanthoma	0	1	0.4944
	Malignant Schwannoma	0	0	.
	Squamous cell carcin	0	2	0.2416
	Squamous cell papill	0	0	.
TESTES	Benign Leydig cell t	1	2	0.4915
THYMUS	Lymphocytic thymoma	0	0	.
THYROID GLANDS	C-cell adenoma	2	1	0.8750
	C-cell carcinoma	1	1	0.7472
	C-cell(adenoma+carci	3	2	0.8126
	Follicular cell aden	2	4	0.3275
ZYMBAL GLANDS	Anaplastic carcinoma	1	1	0.7473
ZYMBAL'S GLANDS	Anaplastic carcinoma	1	0	1.0000
	Squamous cell papill	0	1	0.5000

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Combined Dataset: Female Rats

Organ Name	Tumor Name	0 mg Cont N=150	7.5 mg Low N=50	25 mg Med N=50	75 mg MidHi N=50	150 mg High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. MIDHI	P_Value C vs. H
ADRENAL GLANDS	Adenoma:Cortex	2	0	0	0	0	0.8155	0.4493	0.4298	0.4429	0.4231
	Pheochromocytoma	3	0	0	0	0	0.9213	0.5925	0.5707	0.5854	0.5631
	pheochromocytoma benign	2	0	.	.	1	0.4890	0.5925	0.3641	0.5854	0.6697
CERVIX	Squamous cell papill	0	0	1	0	0	0.2815	.	0.2442	.	.
HEMOLYMPHORET.	Histiocytic sarcoma	2	0	0	0	3	0.0298	0.4493	0.4298	0.4429	0.0944
	Lymphocytic malignan	0	0	0	1	0	0.2838	.	.	0.2571	.
KIDNEYS	Liposarcoma	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398
LIVER	Cholangioma:cystic	5	1	1	2	0	0.8029	0.4849	0.4538	0.5659	0.7508
MAMMARY GLAND	Adenocarcinoma	2	3	0	4	1	0.2462	0.1128	0.4298	0.0411	0.5631
	Adenoma	2	1	1	1	0	0.6619	0.5925	0.5707	0.5854	0.4231
	Fibroadenoma	24	8	5	9	8	0.3438	0.4500	0.7749	0.4714	0.5050
	Fibrosarcoma	0	1	0	0	0	0.4205	0.2571	.	.	.
	Sarcoma (not otherwi	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398
OVARIES	Benign thecoma	1	1	0	1	0	0.4927	0.4493	0.2442	0.4429	0.2398
	Malignant thecoma	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398
	Sertoliform tubular	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398
PANCREAS	Acinar cell adenocar	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398
PANCREAS SAMPLE	Islet cell adenoma	0	0	1	1	0	0.3150	.	0.2442	0.2529	.
PITUITARY GLAND	Adenoma of pars dist	44	15	14	14	11	0.7793	0.4580	0.4956	0.5307	0.7200
SALIVARY GLANDS	Adenocarcinoma	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398
SKIN/SUBCUTIS	Basal cell carcinoma	1	0	1	0	0	0.5449	0.2571	0.4298	0.2529	0.2398
	Hemangioma	0	0	0	0	1	0.1358	.	.	.	0.2398
	Keratoacanthoma	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398
	Squamous cell carcin	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398
	Squamous cell papill	0	1	0	0	0	0.4205	0.2571	.	.	.
THYMUS	Lymphocytic thymoma	4	1	1	1	1	0.5275	0.3824	0.3548	0.3733	0.3453
THYROID GLANDS	C-cell adenoma	1	2	2	1	0	0.7061	0.1627	0.1481	0.4429	0.2398
	C-cell carcinoma	3	2	1	0	1	0.6170	0.3914	0.6774	0.5854	0.6697
	Follicular cell aden	1	1	0	1	0	0.4927	0.4493	0.2442	0.4429	0.2398
URINARY BLADDER	Papilloma	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398
UTERUS	Adenocarcinoma	19	2	0	0	2	0.9895	0.9373	0.9958	0.9967	0.9193
	Adenosquamous Carcin	0	1	0	0	0	0.4205	0.2571	.	.	.
	Leiomyoma	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398
	Polyp	22	5	6	3	6	0.7077	0.7320	0.5307	0.9177	0.5070
	Sarcoma endometrial	2	1	1	1	0	0.6582	0.5970	0.5757	0.5830	0.4210
UTERUS	Squamous cell carcin	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398
VAGINA	Polyp	1	0	0	0	0	0.5695	0.2571	0.2442	0.2529	0.2398

Table 3B1: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
First Phase Dataset: Female Rats

Organ Name	Tumor Name	0 mg Cont N=100	7.5 mg Low N=50	25 mg Med N=50	75 mg High N=50	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL GLANDS	Adenoma:Cortex	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Pheochromocytoma	2	0	0	0	1.0000	1.0000	1.0000	1.0000
				2	0	0.6953	1.0000	0.3982	1.0000
CERVIX	Squamous cell papill	0	0	1	0	0.3927	.	0.3231	.
HEMOLYMPHORET.	Histiocytic sarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Lymphocytic malignan	0	0	0	1	0.2045	.	.	0.3383
KIDNEYS	Liposarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
LIVER	Cholangioma:cystic	4	1	1	2	0.4482	0.8781	0.8631	0.6540
MAMMARY GLAND	Adeno-carcinoma+	1	4	1	5	0.0291	0.0471*	0.5435	0.0181*
	Adenocarcinoma	1	3	0	4	0.0471	0.1167	1.0000	0.0471*
	Adenocarcinoma+Other	22	13	6	13	0.3776	0.4156	0.9505	0.3882
	Adenoma	0	1	1	1	0.1737	0.3383	0.3231	0.3333
	Fibro-sarcoma+	20	9	5	9	0.6213	0.7153	0.9597	0.6940
	Fibroadenoma	20	8	5	9	0.5888	0.8104	0.9597	0.6940
	Fibrosarcoma	0	1	0	0	0.5982	0.3383	.	.
	Sarcoma (not otherwi	1	0	0	0	1.0000	1.0000	1.0000	1.0000
OVARIES	Benign thecoma	1	1	0	1	0.3940	0.5639	1.0000	0.5573
	Benign+Malignant	2	1	0	1	0.5501	0.7137	1.0000	0.7071
	Malignant thecoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	Sertoliform tubular	1	0	0	0	1.0000	1.0000	1.0000	1.0000
PANCREAS SAMPLE	Islet cell adenoma	0	0	1	1	0.1170	.	0.3231	0.3333
PITUITARY GLAND	Adenoma of pars dist	32	15	14	14	0.6917	0.7144	0.7448	0.7708
SALIVARY GLANDS	Adenocarcinoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
SKIN/SUBCUTIS	BCc+Others	1	1	1	0	0.6849	0.5639	0.5435	1.0000
	Basal cell carcinoma	1	0	1	0	0.6323	1.0000	0.5435	1.0000
	Squamous cell papill	0	1	0	0	0.5982	0.3383	.	.
THYMUS	Lymphocytic thymoma	1	1	1	1	0.3383	0.5639	0.5435	0.5573
THYROID GLANDS	C-cell adenoma	1	2	2	1	0.4096	0.2643	0.2439	0.5573
	C-cell carcinoma	1	2	1	0	0.7384	0.2710	0.5435	1.0000
	C-cell/(adenoma + ca	2	4	3	1	0.6423	0.1051	0.1909	0.7071
	Follicular cell aden	1	1	0	1	0.3940	0.5639	1.0000	0.5573
URINARY BLADDER	Papilloma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
UTERUS	Adenocarcinoma	5	2	0	0	0.9929	0.7529	1.0000	1.0000
	Adenosquamous Carcin	0	1	0	0	0.5982	0.3383	.	.
	Polyp	11	5	6	3	0.8171	0.6815	0.4789	0.9039
	Sarcoma endometrial	2	1	1	1	0.4883	0.7168	0.6969	0.7037
UTERUS	Squamous cell carcin	1	0	0	0	1.0000	1.0000	1.0000	1.0000
VAGINA	Polyp	1	0	0	0	1.0000	1.0000	1.0000	1.0000

Table 3B1: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Second Phase Dataset: Female Rats

Organ Name	Tumor Name	0 mg Cont N=50	150 mg High N=50	P_Value C vs. H
ADRENAL GLANDS	Adenoma:Cortex	1	0	1.0000
	Pheochromocytoma	1	0	1.0000
			1	0.7470
CERVIX	Squamous cell papill	0	0	.
HEMOLYMPHORET.	Histiocytic sarcoma	1	3	0.3079
LIVER	Cholangioma:cystic	1	0	1.0000
MAMMARY GLAND	Adeno-carcinoma+	3	1	0.9360
	Adenocarcinoma	1	1	0.7410
	Adenocarcinoma+Other	7	9	0.3319
	Adenoma	2	0	1.0000
	Fibro-sarcoma+	4	8	0.1634
	Fibroadenoma	4	8	0.1634
	Fibrosarcoma	0	0	.
OVARIES	Benign thecoma	0	0	.
	Benign+Malignant	0	0	.
PANCREAS	Acinar cell adenocar	1	0	1.0000
PANCREAS SAMPLE	Islet cell adenoma	0	0	.
PITUITARY GLAND	Adenoma of pars dist	12	11	0.6389
SKIN/SUBCUTIS	BCc+Others	2	0	1.0000
	Basal cell carcinoma	0	0	.
	Hemangioma	0	1	0.4940
	Keratoacanthoma	1	0	1.0000
	Squamous cell carcin	1	0	1.0000
	Squamous cell papill	0	0	.
THYMUS	Lymphocytic thymoma	3	1	0.9391
THYROID GLANDS	C-cell adenoma	0	0	.
	C-cell carcinoma	2	1	0.8751
	C-cell/(adenoma + ca	2	1	0.8751
	Follicular cell aden	0	0	.
UTERUS	Adenocarcinoma	14	2	0.9998
	Adenosquamous Carcin	0	0	.
	Leiomyoma	1	0	1.0000
	Polyp	11	6	0.9296
	Sarcoma endometrial	0	0	.

Table 4A: Intercurrent Mortality Rate in Male Mice

	CONTROL		LOW		MEDIUM		High	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
53 - 78	2	1.67	.	.	2	3.33	5	8.33
79 - 91	5	5.83	2	3.33	1	5.00	3	13.33
92 - 104	9	13.33	4	10.00	8	18.33	5	21.67
Ter. Sac.	104	86.67	54	90.00	49	81.67	47	78.33

Table 4B: Intercurrent Mortality Rate Female Mice

	CONTROL		LOW		MEDIUM		High	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
53 - 78	2	1.67	.	.	2	3.33	5	8.33
79 - 91	5	5.83	2	3.33	1	5.00	3	13.33
92 - 104	9	13.33	4	10.00	8	18.33	5	21.67
Ter. Sac.	104	86.67	54	90.00	49	81.67	47	78.33

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	P-Value
Dose Response	0.0440
Homogeneity	0.1260

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	P-Value
Dose Response	0.1609
Homogeneity	0.1471

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice

Organ Name	Tumor Name	0 mg Cont N=120	15 mg Low N=60	45 mg Med N=60	135 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Adrenals	cortex, adenoma	0	1	0	0	0.5965	0.3391	.	.
	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	pheochromocytoma ben	2	0	0	1	0.4765	1.0000	1.0000	0.6876
	subcapsular cells, a	7	2	1	0	0.9921	0.8716	0.9633	1.0000
Cecum	leiomyoma	0	0	0	1	0.1895	.	.	0.3195
Duodenum	lymphosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Femur	hemangiosarcoma	0	1	0	0	0.5965	0.3391	.	.
Gallbladder	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Heart	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	thymoma	0	0	1	0	0.3895	.	0.3314	.
Kidneys	hepatocholangiocarci	1	0	2	0	0.5492	1.0000	0.2554	1.0000
	mast cell tumor	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	tubule(s), adenoma	0	0	1	1	0.1114	.	0.3314	0.3195
Lacrimal gl.-Ha	adenocarcinoma	2	3	1	1	0.6018	0.2156	0.7037	0.6876
	adenoma	18	7	11	6	0.7205	0.8156	0.3453	0.8476
	adenoma+adenocarcino	20	10	12	7	0.7656	0.6066	0.3502	0.8420
Liver	hemangioma	0	2	0	0	0.6704	0.1137	.	.
	hemangiosarcoma	2	1	2	1	0.4354	0.7139	0.4039	0.6876
	hepatocellular x(ad.	36	32	20	40	<0.001*	0.0034*	0.3848	<0.001*
	hepatocellular, aden	22	23	14	27	<0.001*	0.0045*	0.2635	<0.001*
	hepatocellular, carc	15	11	10	19	0.0012*	0.2227	0.2842	0.0016*
	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Lungs	bronchiolar-al./(ad.	29	14	15	8	0.9351	0.6525	0.5330	0.9608
	bronchiolar/alveolar	12	2	7	1	0.9508	0.9793	0.4492	0.9947
	bronchiolar/alveolar adenoma	19	12	8	7	0.7938	0.3354	0.7513	0.7937
	carcinoma	4	5	3	2	0.5988	0.1478	0.4248	0.6247
	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	thymoma	0	0	1	0	0.3895	.	0.3314	.
Mandibular lymp	thymoma	0	0	1	0	0.3895	.	0.3314	.
Mediastinal lym	carcinoma	0	0	1	0	0.3895	.	0.3314	.
Mediastinal tis	adenocarcinoma	0	0	0	1	0.1895	.	.	0.3195
	carcinoma	0	0	1	0	0.3895	.	0.3314	.
	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Mesenteric lymp	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	lymphosarcoma	0	0	1	0	0.3895	.	0.3314	.
	neuroendocrine tumor	0	0	1	0	0.3895	.	0.3314	.
Mesenteric tiss	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	thymoma	0	0	1	0	0.3895	.	0.3314	.
Multiple organs	fibrosarcoma	0	0	1	1	0.1114	.	0.3314	0.3195
	fibrosarcoma+Others	10	6	8	5	0.4599	0.4667	0.2118	0.5629
	hemangioma+hemangios	6	7	4	2	0.7815	0.1033	0.4353	0.7880
	hemangiosarcoma	2	0	1	0	0.7825	1.0000	0.7037	1.0000
	histiocytic sarcoma	3	2	2	0	0.8670	0.5486	0.5410	1.0000
	lymphosarcoma	7	4	5	4	0.3832	0.5471	0.3598	0.5013
	mast cell tumor	0	1	0	0	0.5965	0.3391	.	.
Pancreas	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	islets x(ad.+carc.)	1	0	0	1	0.3436	1.0000	1.0000	0.5383
	islets, adenoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	islets, carcinoma	0	0	0	1	0.1895	.	.	0.3195
Penis	papilloma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Pituitary	Anterior-Others	1	4	1	0	0.8377	0.0457*	0.5543	1.0000
	anterior (pars dista	0	4	1	0	0.7537	0.0123*	0.3314	.
	pars intermedia, car	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Salivary g.-Par	hemangioma	0	0	1	0	0.3895	.	0.3314	.
Seminal vesicle	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000

	leiomyosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Skin	subcutaneous, hemang	0	0	0	1	0.1895	.	.	0.3195
Spleen	hemangioma	1	2	0	0	0.8340	0.2657	1.0000	1.0000
	hemangiosarcoma	1	1	0	0	0.8380	0.5645	1.0000	1.0000
Sternum with bo	lipomatous (ITO cell	0	0	1	0	0.3895	.	0.3314	.
Stomach	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	neuroendocrine tumor	0	0	1	0	0.3895	.	0.3314	.
	nonglandular, mucosa	0	1	0	0	0.5965	0.3391	.	.
Subcutaneous	fibrosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	lipoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Testes	Leydig cell tumor	0	3	0	1	0.4054	0.0377*	.	0.3195
Thymus	hepatocholangiocarci	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	thymoma	0	0	1	0	0.3895	.	0.3314	.
Thyroid glands	follicle(s), adenoma	3	1	7	4	0.0650	0.8126	0.0161	0.1480

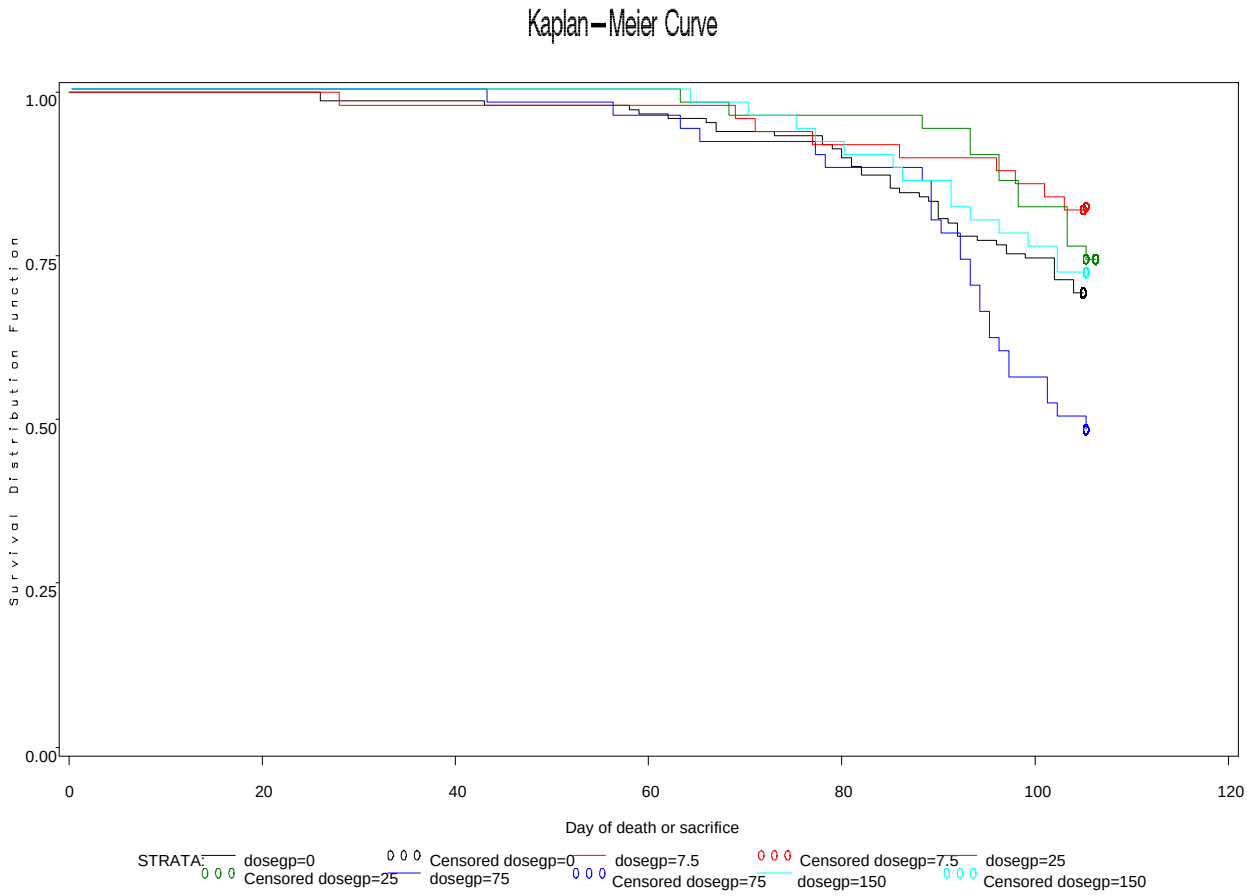
Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Female Mice

Organ Name	Tumor Name	0 mg Cont N=120	15 mg Low N=60	45 mg Med N=60	135 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Adrenals	cortex, adenoma	0	1	0	0	0.6079	0.3394	.	.
	pheochromocytoma ben	0	0	2	1	0.1266	.	0.1193	0.3354
	subcapsular cells, a	0	0	2	1	0.1266	.	0.1193	0.3354
Cerebrum	carcinoma	2	1	0	0	0.9397	0.7117	1.0000	1.0000
Cervix	leiomyoma	0	0	1	0	0.4065	.	0.3473	.
	mucosa, stromal cell	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Colon	leiomyosarcoma	0	0	0	1	0.1978	.	.	0.3354
Femur	hemangiosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Heart	bronchiolar/alveolar	0	0	1	0	0.4086	.	0.3512	.
	undifferentiated sar	0	0	0	1	0.1978	.	.	0.3354
Jejunum	adenocarcinoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Kidneys	lipoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Lacrimal gl.-Ha	adenocarcinoma	2	2	0	2	0.3080	0.4183	1.0000	0.4110
	adenoma	9	4	4	5	0.4006	0.6975	0.7187	0.5279
	adenoma+adenocarcino	11	6	4	7	0.3161	0.5410	0.8295	0.3875
	undifferentiated sar	0	0	0	1	0.1978	.	.	0.3354
Liver	hemangioma	1	0	0	2	0.1009	1.0000	1.0000	0.2606
	hemangiosarcoma	0	1	0	1	0.2014	0.3394	.	0.3354
	hepatocellular, aden	13	4	12	13	0.0121	0.8931	0.1010	0.0456
	hepatocellular, carc	8	9	7	9	0.0877	0.0672	0.2179	0.0623
	hepatocellular/(ad.+	21	13	18	20	0.0084	0.3237	0.0582	0.0128
Lungs	adenocarcinoma	0	0	1	0	0.4065	.	0.3473	.
	bronchiolar-al./(ad.	9	8	8	4	0.6676	0.1690	0.1989	0.6863
	bronchiolar/alveolar	4	3	4	3	0.3265	0.4388	0.2880	0.4293
	bronchiolar/alveolar adenoma	5	5	4	1	0.8556	0.2151	0.3773	0.9162
	carcinoma	1	2	3	7	0.0011*	0.2633	0.1193	0.0021*
	osteosarcoma	0	1	0	1	0.2014	0.3394	.	0.3354
	undifferentiated sar	0	0	0	1	0.1978	.	.	0.3354
Mammary gland	adenoacanthoma	0	0	0	1	0.1978	.	.	0.3354
	adenoacanthoma+adeno	3	1	6	8	0.0017*	0.8108	0.0482	0.0069*
	adenocarcinoma	3	1	6	7	0.0050*	0.8108	0.0482	0.0166
	hemangioma	0	0	1	0	0.4065	.	0.3473	.
Mandibular lymp	undifferentiated sar	0	0	0	1	0.1978	.	.	0.3354
Mediastinal lym	undifferentiated sar	0	0	0	1	0.1978	.	.	0.3354
Mediastinal tis	leiomyosarcoma	0	1	0	0	0.6079	0.3394	.	.

Mesenteric tiss	bronchiolar/alveolar	0	0	1	1	0.1220	.	0.3512	0.3354
	hemangiosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Multiple organs	fibrosarcoma	0	0	0	1	0.1978	.	.	0.3354
	fibrosarcoma+Others	21	16	18	10	0.6520	0.1365	0.0657	0.6420
	hemangioma+hemangios	15	5	4	4	0.8932	0.8730	0.9465	0.9381
	hemangiosarcoma	6	1	1	1	0.8672	0.9475	0.9518	0.9452
	histiocytic sarcoma	4	4	3	2	0.5891	0.2628	0.4663	0.6529
	lymphosarcoma	17	12	14	7	0.7351	0.2349	0.1270	0.7621
	stromal cell sarcoma	0	0	1	0	0.4065	.	0.3473	.
Ovaries	Sertoli-like cell tu	0	0	1	0	0.4065	.	0.3473	.
	hemangioma	0	1	0	0	0.6079	0.3394	.	.
Pancreas	islets, adenoma	2	0	1	1	0.4302	1.0000	0.7246	0.7091
	islets, carcinoma	0	1	0	0	0.6079	0.3394	.	.
	islets/(ad.+carci.)	2	1	1	1	0.5016	0.7144	0.7246	0.7091
Pituitary	Anterior-Others	35	15	18	15	0.6698	0.7905	0.6196	0.7699
	anterior (pars dista	2	1	0	0	0.9397	0.7117	1.0000	1.0000
anterior (pars distalis), adenoma		33	14	18	15	0.5814	0.8039	0.5398	0.7050
	pars intermedia, ade	0	0	0	1	0.1978	.	.	0.3354
Rib	osteosarcoma	0	0	0	1	0.1978	.	.	0.3354
Salivary g.-man	undifferentiated sar	0	0	0	1	0.1978	.	.	0.3354
Skeletal muscle	hemangiosarcoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
Spleen	hemangioma	2	0	1	0	0.8003	1.0000	0.7246	1.0000
	hemangiosarcoma	1	0	1	0	0.6486	1.0000	0.5754	1.0000
	lymphosarcoma	0	0	1	0	0.4065	.	0.3473	.
Stomach	adenocarcinoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	nonglandular, mucosa	0	1	0	0	0.6079	0.3394	.	.
Subcutaneous	hemangioma	1	2	0	0	0.8477	0.2660	1.0000	1.0000
	undifferentiated sar	0	0	0	1	0.1978	.	.	0.3354
Thyroid glands	follicle(s), adenoma	10	3	7	9	0.0498	0.8779	0.3601	0.1319
	follicles +Others	10	3	8	9	0.0499	0.8779	0.2466	0.1319
	parafollicular cells	0	0	1	0	0.4065	.	0.3473	.
Uterus	endometrial stromal	2	0	1	1	0.4302	1.0000	0.7246	0.7091
	hemangioma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	leiomyoma	1	0	0	0	1.0000	1.0000	1.0000	1.0000
	mucosa, stromal cell	0	1	0	0	0.6079	0.3394	.	.

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

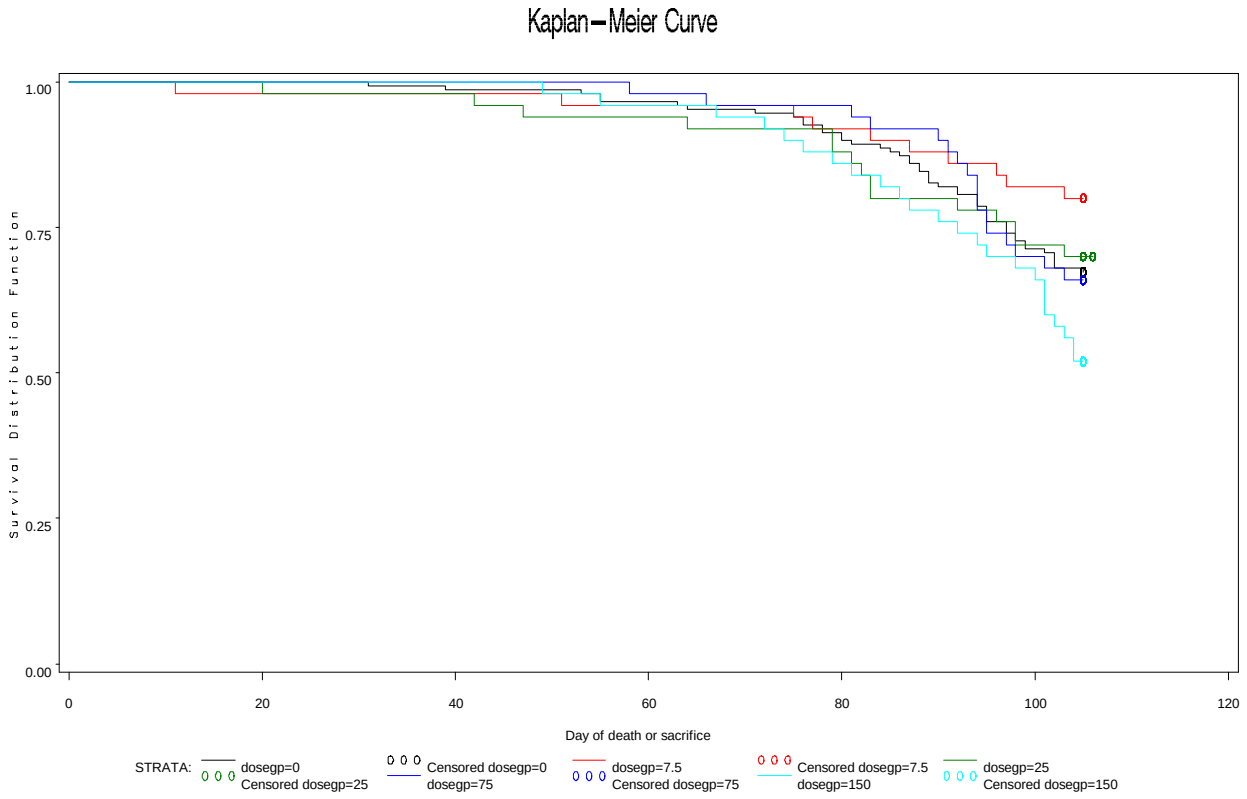
Combined dataset: Male Rats



X-Axis: Weeks, Y-Axis: Survival rates

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

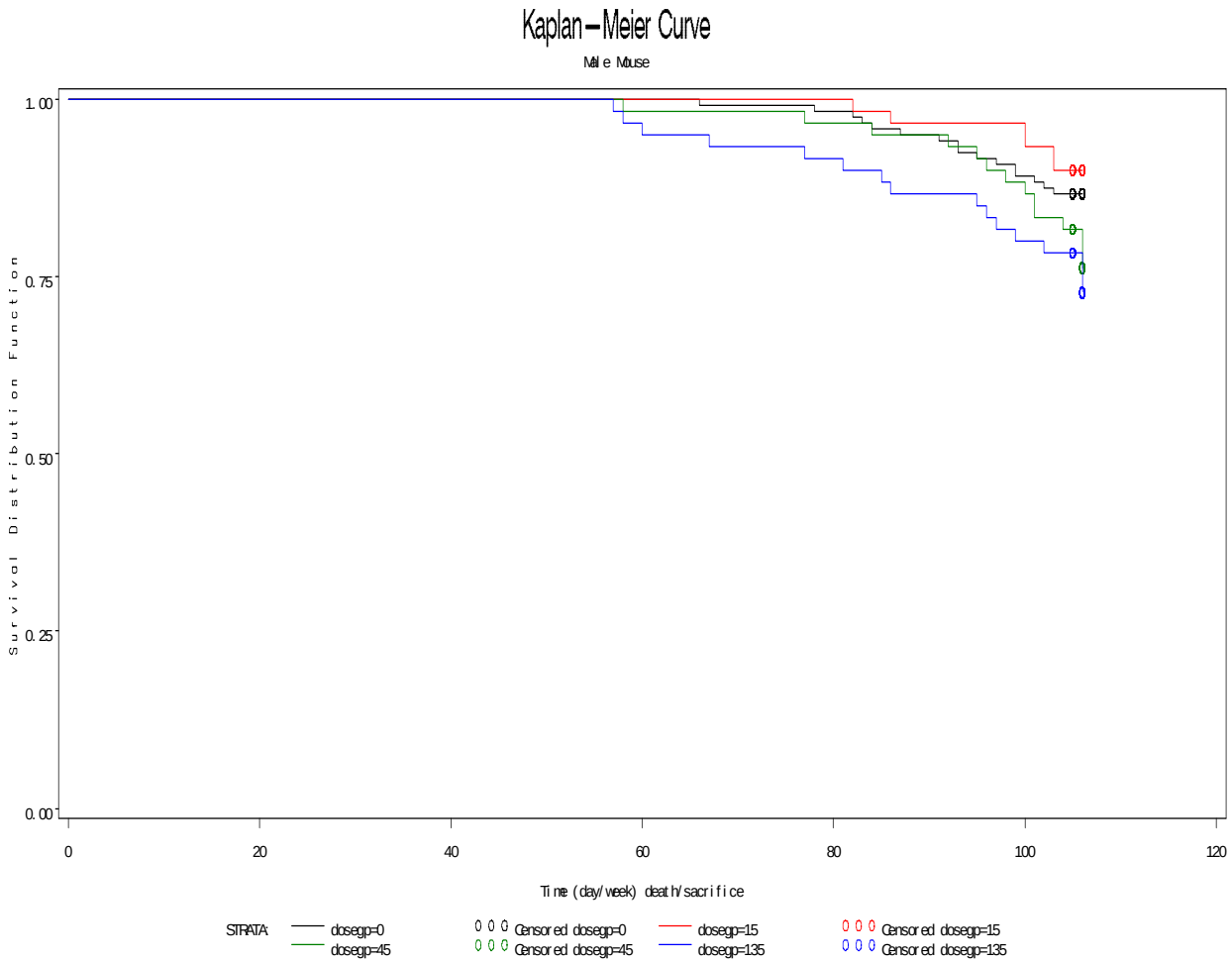
Combined dataset: Female Rats



X-Axis: Weeks, Y-Axis: Survival rates

Figure 2A: Kaplan-Meier Survival Functions for Male Mice

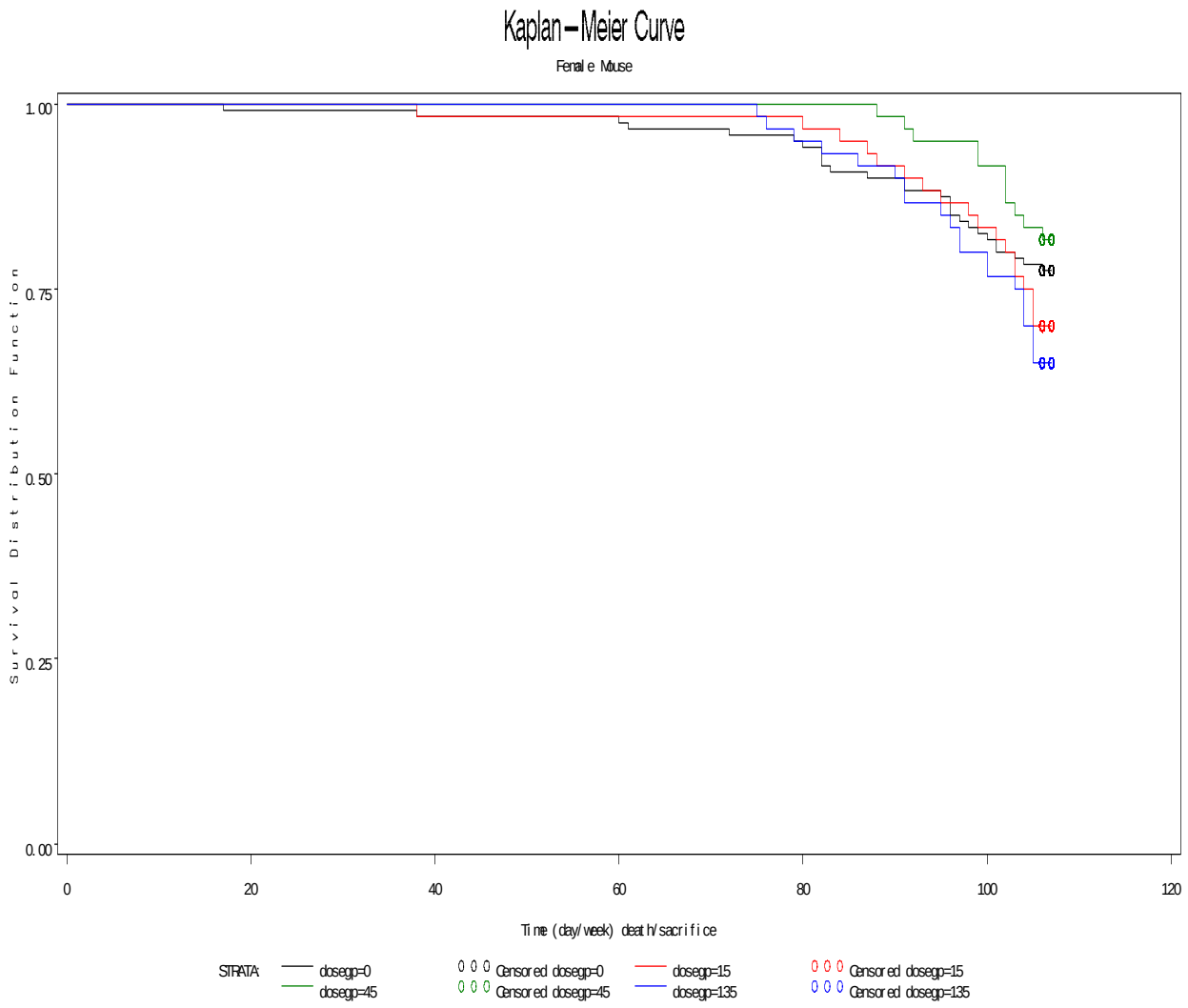
Male Mice



X-Axis: Weeks, Y-Axis: Survival rates

Figure 2B: Kaplan-Meier Survival Functions for Female Mice

Female Mice



X-Axis: Weeks, Y-Axis: Survival rates

6. References:

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/s/

MOHAMED O NAGEM
11/05/2010

KARL K LIN
11/09/2010
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-567 **Applicant: PGxHealth** **Stamp Date: 3/22/2010**

Drug Name: Vilazodone **NDA/BLA Type: NDA (Standard)**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			For pooled data based on 2 pivotal studies
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes___

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			√	
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			√	**No safety data reviewed**
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			**MMRM analyses**

File name: 5_Statistics Filing Checklist for a New NDA_ (b) (4)

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Phillip Dinh, Ph.D.	5/11/2010
Reviewing Statistician	Date
Peiling Yang, Ph.D.	5/11/2010
Supervisor/Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22567	ORIG-1	PGXHEALTH LLC	VILAZODONE HCL

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/s/

PHILLIP V DINH
05/11/2010

PEILING YANG
05/11/2010