CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-250s000

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22,250
Drug Name:	Fampridine-SR Tablets
Indication(s):	Multiple Sclerosis
Applicant:	Acorda Therapeutics
Date(s):	Document Date: January 30, 2009
	PDUFA Date: September 22, 2009
Review Priority:	Priority Review
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Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Fampridine-SR is proposed as a treatment for patients with multiple sclerosis (MS) for improvement of walking ability. The primary efficacy variable for both pivotal studies F203 and F204 is response rate, which is based on timed 25-foot walking test. In both studies response rate for Fampridine-SR group is statistically significantly higher than the response rate for placebo group. Statistical significance is also achieved in the 3-step analysis that comprises the primary analysis for Study F203. Although both studies have achieved statistical significance in all 3 steps, the treatment difference is very small. Given that the global measure SGI did not show significant treatment difference, the clinical meaning and value of such small treatment difference is an issue that needs to be addressed.

1.2 Brief Overview of Clinical Studies

Fampridine-SR is proposed as a treatment for patients with multiple sclerosis (MS) for improvement of walking ability. The clinical development program for Fampridine-SR consists of 3 clinical studies MS-F202, MS-F203, and MS-F204, in which MS-F203 and MS-F204 are pivotal studies and are covered in this review.

The two pivotal Phase 3 studies (MS-F203 and MS-F204) were parallel group, randomized, double-blind study comparing Fampridine-SR 10 mg b.i.d. with placebo. The primary efficacy variable was Timed-Walk Response, defined as consistent improvement in walking speed based on the T25FW (T25FW Responder Analysis) where at least three of the four on-treatment efficacy visits had walking speeds faster than the fastest walking speed achieved among five off-treatment visits (i.e. the four pre-treatment visits and the post-treatment visit two weeks after drug withdrawal). The 12- item Multiple Sclerosis Walking Scale and the Subject Global Impression and Clinician Global Impression were used to validate the clinical meaningfulness of the Timed-Walk response criterion. The duration of the double-blind period was 14 weeks for F-203 and 8 weeks for F-204.

1.3 Statistical Issues and Findings

In Study F203, 301 subjects were randomized and 283 completed the study. A significantly greater proportion of patients taking Fampridine-SR had a consistent improvement in walking speed, the study's primary outcome, compared to patients taking placebo (34.8% vs. 8.3%) as measured by the Timed 25-Foot Walk ($p < 0.001$). In addition, the effect was maintained throughout the 14-week treatment period in an analysis of change from baseline to Week 14 in walking speed, comparing Fampridine-SR responders and placebo group ($p < 0.001$). There was a statistically significant improvement in the 12-Item MS Walking Scale (MSWS-12) for walking responders vs. non-responders ($p < 0.001$). Thus, all three components of the pre-specified primary endpoint were achieved.

In MS-F204, a total of 239 patients with MS were randomized and 227 completed this study. The primary efficacy endpoint for this study was met: the percentage of patients who met the Timed-Walk Responder criterion was 42.9% in the Fampridine-SR-treated group compared with 9.3% in the placebo-treated group ($p<0.001$).

The primary efficacy endpoint, the responder status based on timed 25-foot walking test, was not a conventional or validated endpoint. In order to validate this endpoint, a 3-step analysis was defined and statistical significance needed to be achieved in all 3 steps for Study F203. Although both studies have achieved statistical significance in all 3 steps, the treatment difference is very small. Given that the global measure SGI did not show significant treatment difference, the clinical meaning and value of such small treatment difference is an issue that needs to be addressed.

2. INTRODUCTION

2.1 Overview

Fampridine-SR was proposed as a treatment for patients with multiple sclerosis (MS) for improvement of walking ability. The clinical development program for Fampridine-SR included 2 pivotal studies, MS-F203 and MS-F204.

The two pivotal Phase 3 studies (MS-F203 and MS-F204) were parallel group, randomized, double-blind study comparing Fampridine-SR 10 mg b.i.d. with placebo. The primary efficacy variable was Timed-Walk Response, defined as consistent improvement in walking speed based on the T25FW (T25FW Responder Analysis) where at least three of the four on-treatment efficacy visits had walking speeds faster than the fastest walking speed achieved among five off-treatment visits (i.e. the four pre-treatment visits and the post-treatment visit two weeks after drug withdrawal). The 12- item Multiple Sclerosis Walking Scale and the Subject Global Impression and Clinician Global Impression were used to validate the clinical meaningfulness of the Timed-Walk response criterion. The duration of the double-blind period was 14 weeks for F-203 and 8 weeks for F-204.

Both studies were conducted in centers in US and Canada. A total of 301 subjects were randomized in F203, and 239 subjects were randomized in F204.

2.2 Data Sources

All document reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for the submission is listed below:

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study F203

3.1.1.1 Description of the Study

The objectives of this study were to assess the safety and efficacy of Fampridine-SR in patients diagnosed with MS. The study was to evaluate the efficacy of Fampridine-SR in walking speed, as measured by the Timed 25-Foot Walk and performed in a response analysis, to determine numbers of patients who showed a consistent improvement while on drug.

This was a Phase 3, double-blind, placebo-controlled, parallel group, 21-week study (one week post screening, two weeks of single-blinded placebo run-in, 14 weeks of double-blind treatment, and four weeks of no treatment as follow-up) in patients diagnosed with MS.

A total of 240 patients from approximately 30 centers in the U.S. and Canada were planned to be randomized to one of two treatment groups, 10 mg b.i.d. Fampridine-SR or placebo, in a ratio of 3:1 (three patients in the active treatment group to every one patient in the placebo treatment group).

Upon meeting the eligibility criteria through assessments at Visit -1 (screening visit), subjects returned to clinic after one week for assessments at Visit 0, which represented the beginning of a single-blind two-week placebo run-in period. Subjects returned for another assessment at Visit 1 after one week. Immediately following the placebo run-in, patients were randomized at Visit 2 to one of two treatment arms (Fampridine-SR or placebo) to begin 14 weeks of treatment.

Visit 6 marked the end of the 14-week randomized treatment period. At this visit, patients began a four-week follow-up period during which no study medication was to be taken. Patients returned to the clinic after two weeks and after 4 weeks for follow-up assessments at Visit 7 and Visit 8.

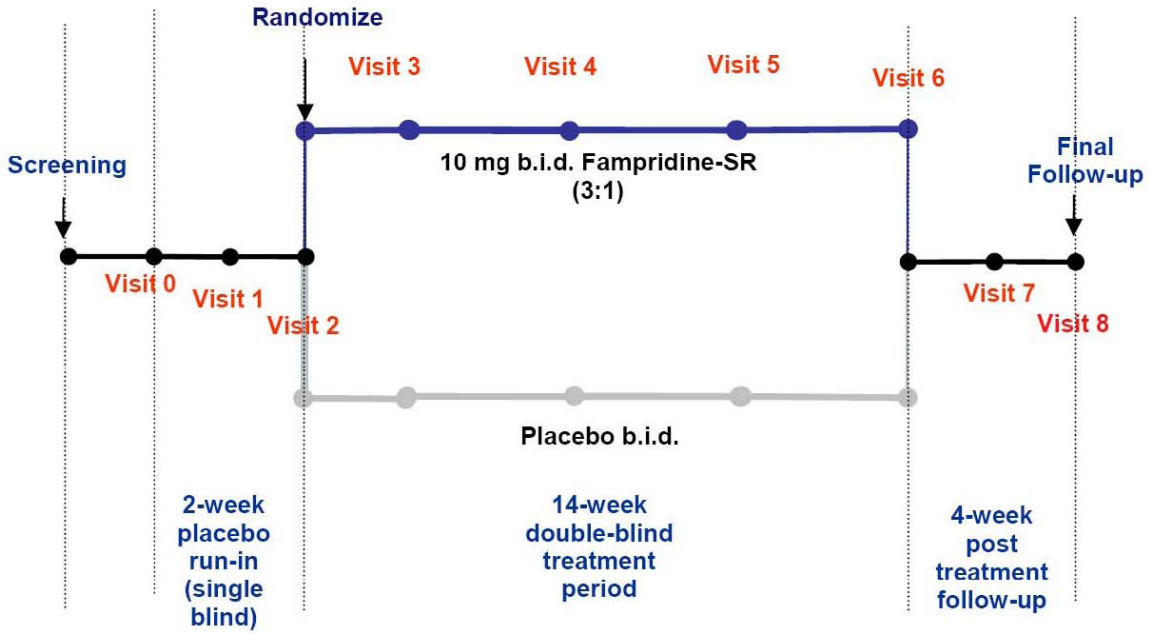

Figure 1 General Scheme of the Overall Study Design (Source: Figure 1 of Sponsor's Study Report)

3.1.1.2 Efficacy Evaluation

Background

In Acorda's previous phase II study MS-F202, the primary efficacy analysis of the percent change from baseline in average walking speed on the T25FW failed to show treatment effect of Fampridine-SR. In a post hoc analysis, a response criterion was defined based on consistently faster walking speeds while on drug than when not on drug. This criterion was met by 36.7% of patients in the combined Fampridine-SR group versus 8.5% of the patients in the placebo group.

This response variable was applied prospectively in the current study as the first step in a three stage, stepwise analysis that defined the primary endpoint.

The Primary Efficacy Variable

The primary efficacy variable was responder status, based on consistency of response in walking speed on the Timed 25-Foot Walk. A three stage, stepwise analysis based on this variable was to be used to establish a positive outcome on the primary endpoint and to define a successful trial.

The first step was to show a significantly greater proportion of responders in the Fampridine-SR group as compared to the placebo group. The second step was to provide validation of the clinical meaningfulness of this primary efficacy variable by testing whether the responders register a significant improvement in MSWS-12 score, when compared to non-responders,

regardless of treatment group. The third step was to confirm maintenance of effect by testing whether those patients who responded to Fampridine-SR would still register a significant improvement in walking speed relative to placebo-treated patients at the last observed double-blind visit.

Responder Criteria and Data Handling

At each study visit, there were to be two trials of the Timed 25-Foot Walk. Time was recorded in seconds using a stopwatch. The walking speed for a particular study visit was to be derived by calculating the average of the walking speeds for Trial 1 and Trial 2 of that visit. If either trial was missed, then the walking speed for that visit was to be the walking speed from the completed trial. If both trials were missed, the walking speed for the visit was to be considered slower than the maximum speed recorded during the non-double-blind period.

A responder was defined as a patient with a faster walking speed for at least three visits during the double-blind treatment period (Visits 3 through 6) as compared to the maximum speed for any of the pre-treatment visits (Screening Visit, Visits 0, 1 and 2) and the first post-treatment visit (Visit 7). The last follow-up visit (Visit 8) was to be primarily a safety visit and was not to be used as part of the responder criterion. Patients with fewer than three on-treatment walking speed measurements were to be categorized as non-responders.

The MSWS-12 is a 12-question questionnaire that asks patients to rate limitations of their mobility due to MS during the preceding two weeks on a 5-point scale (from 1= not at all to 5 = extremely). For a visit in which at least 50% of the component questions were answered but at least one was not, scores from unanswered component questions were to be imputed using the respondent-specific mean score. For a visit in which at least 50% of the component questions were not answered, the MSWS-12 score was to be considered missing. For a particular visit the MSWS-12 Score was to be calculated by summing the 12 components and transforming to a scale with a range of 0 to 100.

Analysis of Efficacy Variables

The principal analysis of efficacy was to be based on the intent-to-treat (ITT) population. The ITT population was to consist of all randomized patients to whom double-blind study medication was dispensed and who had at least one efficacy (Timed 25-Foot Walk and MSWS-12) evaluation during the treatment period.

For this study to be considered a positive study, all three of the conditions listed below must have been met in the following stepwise order:

1. Fampridine-SR had to be statistically superior to placebo with respect to the primary efficacy variable – the proportion of responders
2. The responders had to be statistically superior to the non-responders with respect to the average change from baseline in the MSWS-12 (i.e., it had to be demonstrated that primary efficacy variable was clinically meaningful)

3. Fampridine-SR responders had to be statistically superior to the placebo group with respect to the endpoint change from baseline (i.e., it had to be demonstrated that among patients who responded to Fampridine-SR, the response was maintained).

The overall significance level of the above was to be no greater than 0.05.

Step 1: Responder Analysis

Treatment differences in the proportion of responders between Fampridine-SR-treated and placebo-treated groups were to be analyzed by the Cochran-Mantel-Haenszel (CMH) test, controlling for center.

A sensitivity analysis of the responder criterion was to be performed to determine whether missing data on the follow-up visit might have affected the overall outcome. A modified responder was defined in the same manner with the following restriction: any patient treated with Fampridine-SR who was considered a responder for the primary analysis but who was missing the first post-treatment visit (Visit 7) was to be considered a non-responder for the purpose of the sensitivity analysis. This restriction was not to be applied to placebo patients. That is, if a placebo patient was a responder for the primary analysis, the patient would still be a modified responder for the sensitivity analysis, regardless of whether or not the patient missed the first post-treatment visit (Visit 7).

Step 2: Validation Procedure

Validation of the clinical meaningfulness of the responder variable (based on consistently improved double-blind walking speeds) was to be performed by testing whether responders perceived improvement in their walking disability, as registered by the MSWS-12 score, when compared to non-responders. The average change from baseline in the MSWS-12 score over the double-blind treatment period was to be analyzed with respect to responder status (responders vs. non-responders) by an analysis of variance model, with effects for responder status and center.

Step 3: Change from Baseline in Walking Speed

For the walking speed endpoint change from baseline, differences between the three responder analysis groups (placebo, Fampridine-SR non-responders, and Fampridine-SR responders) were to be analyzed by t-tests of the least-squares means using the mean square error via an ANOVA model with effects for responder analysis group and center. The primary efficacy comparison of interest was the Fampridine-SR responders versus placebo.

For walking speed only, the endpoint in walking speed was to be derived based on the last observed (non-missing) double-blind visit walking speed.

If assumptions of normality were grossly violated, nonparametric analysis via the CMH test controlling for center, using the row mean score statistic and standardized midranks (i.e., in SAS, scores=modridit) was to be employed.

Analysis for Secondary Efficacy Variables

A number of secondary efficacy variables were proposed. In order to maintain the overall alpha level less than or equal to 0.05, a prospectively defined stepwise procedure was to be performed for the secondary variables. If statistical significance was not achieved at a particular step, no subsequent step would be eligible to be declared statistical significant. Provided that the significance of primary endpoint was achieved, eligibility for the secondary objective variables was to be determined in the following stepwise order:

1. the Fampridine-SR responders must be statistically superior to the placebo group with respect to the average change from baseline in LEMMT during the double- blind period;
2. the Fampridine-SR non-responders must be statistically superior to the placebo group with respect to the average change from baseline in LEMMT during the double-blind period;
3. Fampridine-SR must be statistically superior to placebo with respect to the percentage of patients with consistent improvements in LEMMT;
4. the clinical significance of the consistent improvement in LEMMT must be validated by demonstrating patients who have consistent improvements significantly perceive this improvement (via the average SGI score during the double-blind) versus those who do not;
5. the Fampridine-SR responders must be statistically superior to the placebo group with respect to the average change from baseline in Ashworth score during the double-blind period;
6. the Fampridine-SR non-responders must be statistically superior to the placebo group with respect to the average change from baseline in Ashworth score during the double-blind period.

For the endpoint change from baseline and each of the secondary objective variables, differences between the three responder analysis groups (placebo, Fampridine-SR non-responders, and Fampridine-SR responders) were to be analyzed by t-tests of the least-squares means using the mean square error via an ANOVA model, with effects for responder analysis group and center.

If assumptions of normality were grossly violated, nonparametric analysis via the CMH test controlling for center, using the row mean score statistic and standardized midranks (i.e., in SAS, scores=modridit) was to be employed.

3.1.1.3 Study Population Results

A total of 301 subjects were randomized: 72 to the placebo group and 229 to the Fampridine-SR group. One subject was “unable to digest the study medication” during the placebo run-in period and was excluded from the safety population. The subject was randomized to Fampridine-SR group, but did not take any double-blind medication. A total of 18 subjects discontinued study prematurely. Among the 17 subjects discontinued from the study in Fampridine-SR group, 11 were due to AEs, 4 withdrew consent, and 2 were due to other reasons. One placebo-treated subject discontinued due to lost of follow-up. A total of 5 subjects, all randomized to

Fampridine-SR (including one subject who did not take any double-blind medication), discontinued study prior to completing any of the scheduled double-blind walking speed and MSWS-12 assessments, and therefore were excluded from the ITT patient population. The primary efficacy analysis was based on the ITT population which was comprised of 296 patients (72 patients randomized to placebo and 224 to Fampridine-SR).

The safety population consisted of 68.3% females and 31.7% males. There were more males in the placebo group than in the Fampridine-SR group (40.3% vs. 28.9%). The majority of the patients were Caucasian (92.7%). The mean age of the patients was 51.4 years (range: 26-70 years). Most of the patients (53.3%) had a diagnosis type of secondary progressive followed by relapsing remitting (27.7%), primary progressive (15.0%) and progressive-relapsing (4.0%). The mean duration of disease was 13.3 years (range: 0.4- 41.7 years), while the mean Expanded Disability Status Scale (EDSS) score at screening was 5.8 (range: 2.5-7.0).

3.1.1.4 Efficacy Results

The efficacy results presented in this section represent the analyses performed by the sponsor and confirmed by the reviewer. Additional analyses performed by the reviewer are noted where they are presented.

3.1.1.4.1 Analysis of Primary Efficacy Variable

The first step of the primary analysis was to compare the response rate between the placebo group and the Fampridine-SR group. A total of 78 (34.82%) of the 224 Fampridine-SR-treated subjects and 6 (8.33%) of the 72 placebo-treated subjects were responders. The treatment difference was statistically significant with a p-value of <.0001.

A prospectively planned sensitivity analysis was performed. In this analysis, Fampridine-SR responders who missed first post-treatment visit (Visit 7) were re-categorized as non-responders. Responder status for the placebo-treated subjects was not changed. Two such Fampridine-SR-treated subjects had their status changed from responders to non-responders, resulting in 76 responders in the Fampridine-SR group compared to 6 responders in the placebo group. The treatment difference in this modified responder analysis was still statistically significant with a p-value of < .0001.

To validate the clinical meaningfulness of the responder variable, the 84 responders (78 in the Fampridine-SR group and 6 in the placebo group) were compared against the 212 non-responders (146 in the Fampridine-SR group and 66 in the placebo group) on the average change from baseline in MSWS-12 to determine if patients with consistently improved walking speeds could perceive benefit relative to those patients without consistent improvement. The mean reduction from baseline in average MSWS-12 over the double-blind period was 6.84 among the responders, compared to an increase of 0.05 among the non-responders. The difference was statistically significant with a p-value of 0.0002.

The last step of the primary analysis was to compare between the Fampridine-SR responders and placebo patients in the maintenance of walking speed evaluated by the change from baseline to endpoint. The mean changes in walking speed from baseline to the end of the double-blind were 0.10 ft/sec, 0.17 ft/sec, and 0.52 ft/sec for the placebo group, Fampridine-SR non-responder group and Fampridine-SR responder group, respectively. The treatment difference between Fampridine-SR responder group and the placebo group was statistically significant with a p-value of < .001. The treatment difference between Fampridine-SR non-responder group and placebo group was not significant (p=0.483) and the treatment difference between Fampridine-SR responder group and Fampridine-SR non-responder group was statistically significant (p <.001).

By achieving the statistical significance in the above 3 steps, the study has achieved statistical significance in the primary efficacy analysis.

Additional analyses are performed by the reviewer in order to shed some light in interpreting the complex of the study results.

In addition to the comparisons between Fampridine-SR responders and placebo group in the change from baseline in 25-foot walking speed, Fampridine-SR group and placebo group are also compared to assess the treatment difference without regarding to responder status. From Visit 2 to Visit 6, the mean walking speed for Fampridine-SR group increased by 0.21 ft/sec, representing 1.05 second improvement for the 25-foot walk, compared to an increase of walking speed for placebo group of 0.05 ft/sec, representing 0.27 second improvement in time. The difference of 0.16 ft/sec in change of walking speed is statistically significant with a p-value of 0.0342.

Table 1 Mean Change from Visit 2 to End of Treatment Period in Walking Speed by Treatment Group - F203 (Source: Reviewer's Analysis)

Mean (SD) in Walking Speed (ft/sec)	**Placebo N=71**	**Fampridine-SR N=222**
Visit 2	2.11 (.79)	2.13 (.84)
Visit 6 (LOCF)	2.16 (.81)	2.34 (1.05)
Change	.05 (.45)	.21 (.56)
Difference in Time (sec)	.27	1.05
Nominal p-value		.0342

Mean walking speed at each visit by treatment group and response status were calculated and presented in the following table.

Table 2 Average Walking Speed (ft/sec) by Visit and Response Status (Observed Cases) (Source: Reviewer's Analysis)

	Pre-Treatment Visit				Double-blind Treatment				Follow-up
	Visit -1	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Placebo									
N	72	72	72	71	72	71	70	70	
Mean	2.02	2.03	2.09	2.12	2.11	2.23	2.20	2.17	2.19
# Non-resp	66	66	66	65	66	65	64	64	64
Mean	2.04	2.03	2.09	2.11	2.09	2.20	2.17	2.14	2.19
#Resp	6	6	6	6	6	6	6	6	6
Mean	1.82	2.06	2.09	2.18	2.32	2.60	2.52	2.58	2.23
Fampridine									
N	224	222	221	222	223	218	214	213	
Mean	2.00	2.00	2.07	2.14	2.34	2.34	2.35	2.37	2.05
# Non-resp	146	145	145	144	146	140	137	136	141
Mean	2.01	1.96	2.06	2.10	2.22	2.20	2.20	2.23	2.04
#Resp	78	77	76	78	77	78	77	77	76
Mean	1.98	2.08	2.10	2.21	2.57	2.59	2.61	2.60	2.07
Non Resp									
N	212	211	211	209	212	205	201	200	205
Mean	2.02	1.98	2.07	2.11	2.18	2.20	2.19	2.20	2.08
Responder									
N	84	83	82	84	83	84	83	83	82
Mean	1.97	2.08	2.10	2.21	2.55	2.59	2.61	2.60	2.08

The average walking speed was comparable between the two treatment groups during the pre-treatment visits. The average speed was below 2.05 ft/sec before placebo run-in period (Visits -1 and 0), and went up slightly to above 2.10 ft/sec after the placebo run-in period. By the end of the double-blind treatment period, the walking speed can be summarized as follows:

1. Subjects improved their walking speed during the pre-treatment period and double-blind treatment period regardless of treatment group or responder status.
2. At Visit 2 assessment (the last visit before randomization), the mean walking speed for placebo group was 2.12 ft/sec, represented 11.79 seconds used in the 25 feet walking test. The mean walking speed for Fampridine-SR group at the visit was 2.14 ft/sec, represented 11.68 seconds for the test. At the Visit 6 (the end of the treatment visit), the mean walking speed of 2.17 ft/sec for placebo-treated patients represented a time of 11.52 seconds on the 25-feet walking test and the mean walking speed of 2.37 ft/sec for Fampridine-SR-treated patients represented a time of 10.55 seconds on the same test. The treatment difference in walking speed represented a difference of about 1 second in time spent on the walking test.
3. The walking speed achieved during the double-blind period was generally maintained through the end of the double-period.
4. There was little treatment difference among the non-responders, and there was little treatment difference among the responders at the end of the double-blind treatment period. When combining the treatment groups, the responders improved walking speed

quite significantly from the beginning of the treatment group, and maintained so through the end of the treatment period.

5. At the end of the double-blind treatment period, the walking speed between the non-responders and responders represented a difference of 1.75 seconds in time spent on the 25-feet walking test. For the placebo-treated patients, non-responders spent 1.99 seconds more than the responders. The difference for Fampridine-SR-treated patients was 1.60 seconds.

Analysis of MSWS-12 scores was also performed. The mean change from baseline to Visit 6 in MSWS-12 scores was -1.56 for Fampridine-SR group and 3.59 for placebo group. The difference yielded a nominal p-value of 0.0633. Means of MSWS-12 scores were calculated by treatment group and response status at each visit. The MSWS-12 score ranges 0 to 100 with 100 indicating extreme illness.

Table 3 Mean MSWS-12 Scores by Treatment Group and Response Status (Observed Cases) (Source: Reviewer's Analysis)

	Pre-treatment		**Double-blind**				**Follow-up**
	Visit 0	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Placebo							
N	72	72	72	70	70	70	71
Mean	69.93	67.03	67.61	67.56	68.44	72.05	73.42
# Non-resp	66	66	66	64	64	64	65
Mean	70.67	67.85	68.45	69.08	70.17	74.12	75.00
# Resp	6	6	6	6	5	6	6
Mean	61.81	57.99	58.33	51.39	50.00	50.00	56.25
Fampridine							
N	222	223	222	219	215	213	220
Mean	72.31	68.98	66.57	68.11	68.85	69.28	75.89
# Non-resp	145	146	144	141	137	136	143
Mean	71.50	69.56	67.43	71.09	71.06	72.11	74.81
# Resp	77	77	78	78	78	77	77
Mean	73.84	67.86	64.98	62.71	64.96	64.29	77.90
Non-resp							
N	211	212	210	205	201	200	208
Msws	71.24	69.03	67.75	70.46	70.78	72.75	74.87
Responder							
N	83	83	84	84	84	83	83
Msws	72.97	67.15	64.51	61.90	63.89	63.25	76.33

Overall, placebo group had an average of about 2 points increase and Fampridine-SR group had an average of about 3 points reduction in MSWS-12 scores from Visit 0 to Visit 6. There was little change in MSWS-12 scores among the non-responders while the responders had an average of 9.7 point decrease. However, most f the 9.7 points decrease among the responders occurred from Visit 0 to Visit 2 during the pre-treatment period. Breaking down to the treatment, placebo

responders had 3.82 points decrease during the pre-treatment period and 7.99 points decrease during the treatment period. Fampridine-SR responders had 5.98 points decrease during the pre-treatment period and 3.57 points decrease during the treatment period.

3.1.1.4.2 Analysis of Secondary Efficacy Variables

Average change from baseline in LEMMT and Ashworth scores were analyzed. In the analyses, the average change was obtained by averaging all double-blind available scores minus the average of all pre-treatment scores. The following table presents the results from comparisons between treatment groups and between responder groups in LEMMT and Ashworth scores. The nominal p-values were obtained from comparisons of Fampridine-SR group versus placebo group.

Table 4 Average Change from Baseline in LEMMT and Ashworth Scores - F203 (Source: Reviewer's Analysis)

Study F203	Placebo	Fampridine-SR	Fampridine-SR	
			Responders	Non-Responders
LEMMT				
Mean (SD)	0.04 (.22)	0.13 (.21)	0.18 (.19)	0.11 (.21)
Nominal p-value		.0029	.0002	.0207
Ashworth				
Mean (SD)	-0.07 (.28)	-0.16 (.34)	-0.13 (0.36)	-0.17 (.33)
Nominal p-value		.0210	.0899	.0240

For the Ashworth scores, Fampridine-SR non-responders had larger improvement than Fampridine-SR responders in average. Based on the closed testing procedure, statistical significance for LEMMT has been reached in the comparisons of Fampridine-SR versus placebo, Fampridine-SR responders versus placebo, and Fampridine-SR non-responders versus placebo.

Change from baseline to endpoint in SGI scores was calculated. The average change of SGI was -0.1967 for the placebo group and -0.0045 for the Fampridine-SR group (nominal p=.1227).

3.1.2 Study F204

3.1.2.1 Description of the Study

The primary efficacy objective was to assess whether the proportion of patients who experienced consistent improvements in walking speed while on drug would be greater in the Fampridine-SR-treated group compared to the placebo-treated group. This “response to drug” criterion was considered validated as a clinically meaningful measure in study F203.

The design of this study was similar to that of F203 except that the double-blind treatment period was shorter in this study. This was a Phase 3, multi-center, double-blind, placebo-controlled, parallel group, 14-week study (one week post screening, two weeks of single-blind placebo run-in, nine weeks of double-blind treatment, and two weeks of no-treatment follow-up). The treatment group comparisons with respect to efficacy were based on the first eight weeks of double-blind treatment; end of dosing interval activity (pharmacokinetics and pharmacodynamics of drug) was evaluated at the end of the final week of double-blind treatment. Approximately 200 patients were planned to be randomized in a ratio of 1:1 to one of two treatment groups, 10 mg b.i.d. Fampridine-SR or placebo. The following figure displays the general scheme.

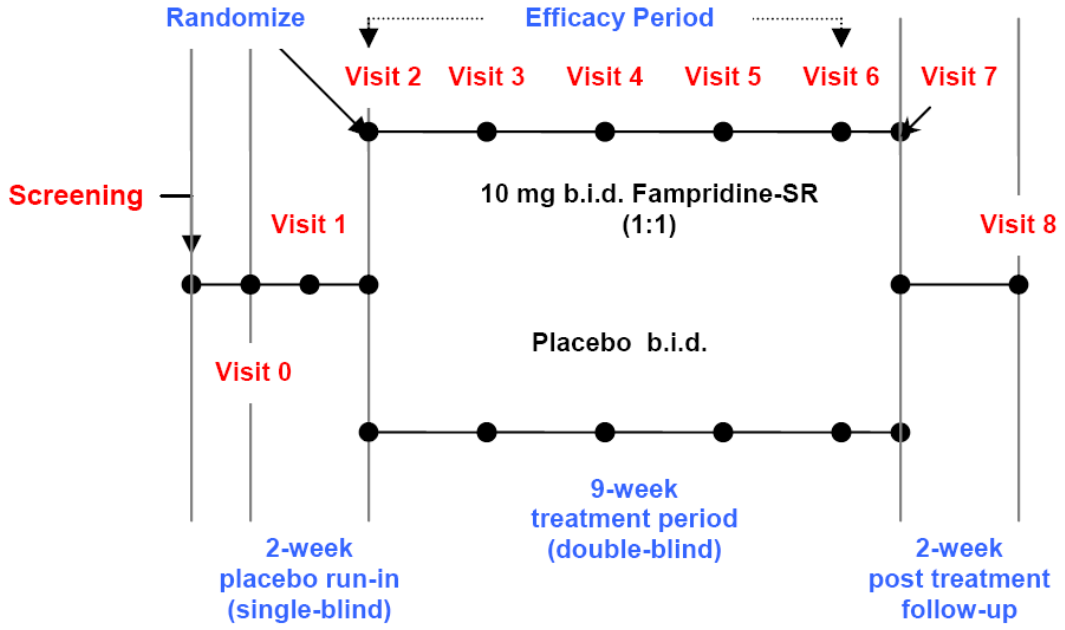

Figure 2 General Scheme of the Overall Study Design – F204 (Source: Figure 1 of Sponsor's Study Report)

The target population consisted of patients diagnosed with clinically definite MS. Patients were to be enrolled at approximately 35 investigational centers in the U.S. and Canada, with each site enrolling approximately 6 patients until a minimum of 200 patients had been randomized.

3.1.2.2 Efficacy Evaluation

The Primary Efficacy Variable

The primary goal of this study was to confirm the efficacy results obtained in study F-203. The primary efficacy variable was responder status defined similarly as in F-203. However, this efficacy variable was considered validated by study F-203, and thus the validation and

maintenance of the walking speed were not part of the primary analysis in this study. However, to be consistent with study MS-F203, the additional measurements (Ashworth assessment of spasticity, MSWS-12, SGI, and CGI) collected in Study F-203 were also assessed in the MS-F204 study.

The primary efficacy variable was responder status, based on consistency of response in walking speed on the Timed 25-Foot Walk.

A Timed Walk Responder was defined as a patient with a faster walking speed for at least three of the first four double-blind visits (Visits 3 through 6) as compared to the maximum walking speed for any of the pre-treatment visits (Screening Visit, Visits 0, 1 and 2) and the post-treatment visit (Visit 8). The purpose of the last double-blind visit (Visit 7) was to obtain data on efficacy and drug plasma concentration near the end of the normal 12-hour dosing interval. As such, this visit (Visit 7) was not part of the responder criterion.

For the calculation of the patient's responder status, if a walking speed for an eligible double-blind visit (Visits 3 through 6) was missing, the walking speed for that double-blind visit was considered slower than the maximum walking speed during the non-double-blind period. Patients with walking speeds at fewer than three of the eligible double-blind treatment visits therefore were automatically categorized as non-responders.

Secondary Efficacy Variable

The secondary efficacy variable was the average change from baseline in LEMMT during the eight-week, double-blind treatment period.

Analysis of Efficacy Variables

Treatment difference between Fampridine-SR-treated and placebo-treated patients in the proportion of Timed Walk Responders was to be analyzed by the Cochran-Mantel-Haenszel (CMH) test, controlling for center.

A sensitivity analysis of the responder criterion was to be performed on the modified responder variable. A modified responder variable was defined in the same manner as a responder with the following restriction: Any patient treated with Fampridine-SR who was considered a Responder for the primary analysis but who was missing the post-treatment visit (Visit 8) was considered a Non-responder for the modified responder variable. This restriction was not to be applied to placebo patients. That is, if a placebo patient was a Responder for the primary analysis, the patient was also a modified Responder for the sensitivity analysis, regardless of whether or not the patient missed the post-treatment visit (Visit 8).

With respect to the secondary efficacy variable (average change from baseline LEMMT score), it was hypothesized that in addition to patients who experienced a consistent improvement in walking speed with treatment, Fampridine-SR may also have benefits for patients who did not experience a consistent improvement in walking speed. In order to maintain the overall alpha level less than or equal to 0.05, a prospectively defined, stepwise procedure was to be performed

for the secondary efficacy variable. If statistical significance was not achieved at the first step, the second step would not be eligible to be declared statistical significant. Provided that there was a statistically significant difference between the two treatments on the primary endpoint, eligibility for the secondary variable was to be determined in the following stepwise order:

1. the Fampridine-SR Timed Walk Responders had to be statistically superior to the placebo group with respect to the average change from baseline in LEMMT during the eight-week double-blind period;
2. the Fampridine-SR Timed Walk Non-responders had to be statistically superior to the placebo group with respect to the average change from baseline in LEMMT during the eight-week double-blind period.

Differences in the average change from baseline in LEMMT between the three walking speed responder analysis groups (placebo, Fampridine-SR non-responders, and Fampridine-SR responders) were to be analyzed by t-tests of the least-squares means using the mean square error via an ANOVA model with effects for responder analysis group and center. The normality assumption was to be assessed via the Shapiro-Wilk test. Should the normality assumption be grossly violated, nonparametric analysis via the CMH test, controlling for center: using the row mean score statistic and standardized midranks (i.e., in SAS, scores=modridit) was to be employed to analyze each of the three pairwise responder group comparisons.

3.1.2.3 Population Results

A total of 239 patients were randomized into the study at 39 centers in the U.S. and Canada: 119 were assigned to placebo and 120 to 10 mg b.i.d. Fampridine-SR. All 239 patients took at least one dose of investigational drug and were included in the safety population. A total of 12 patients, 5 in the placebo group and 7 in the Fampridine-SR group, discontinued study prematurely. Two patients, one for each treatment group, discontinued from the study prior to completing any scheduled assessments and were excluded from the (modified) ITT population, which included 237 patients (118 placebo/119 Fampridine-SR).

The safety population consisted of 67.8% females and 32.2% males. There were more males in the placebo group than in the Fampridine-SR group (37.8% vs. 26.7%). The majority of the patients were White (91.2%). The mean age of the patients was 51.7 years (range: 24-73 years). Almost half of the patients (49.4%) had a diagnosis type of secondary progressive followed by relapsing remitting (34.7%), primary progressive (13.0%) and progressive-relapsing (2.9%). The mean duration of disease was 13.76 years (range: 0.1-45.6 years). The mean EDSS score at baseline was 5.55 for the placebo group and 5.83 for the Fampridine-SR group, and more patients in the Fampridine-SR group than in the placebo group (94 versus 83) had baseline EDSS scores in the 8 to 10 range, resulting in a significant difference with a p-value of 0.024.

3.1.2.4 Efficacy Results

3.1.2.4.1 Analysis of Primary Efficacy Variable

The primary efficacy variable was responder status. There were 51 (42.9%) responders and 68 non-responders in the Fampridine-SR group compared to 11 (9.3%) responders and 107 non-responders in the placebo group. This difference was statistically significant with a p-value of <.001.

No Fampridine-SR responders had missed post-treatment visit 8. Therefore, the prospectively planned sensitivity analysis was identical to the primary analysis.

In order to exam the consistency and robustness of the efficacy results, the reviewer performed same 3-step analysis as was done in Study F203, although the validation procedure and endpoint analysis for walking speed were not required for this study.

Among the 175 non-responders, the average MSWS-12 score over the double-blind treatment period increased by 0.85, compared to a decrease of 6.04 among the responders. This difference was statistically significant ($p < .001$).

In the endpoint analysis, mean change in walking speed from baseline to Visit 6 (the end of Week 8) reduced by 0.19 ft/sec, 0.56 ft/sec, and 0.10 ft/sec for the placebo group, Fampridine-SR responder group, and Fampridine-SR non-responder group, respectively. The difference in the walking speed between Fampridine-SR responder group and the placebo group was statistically significant ($p<.001$). The difference between Fampridine-SR responders and Fampridine-SR non-responders was also statistically significant ($p<.001$). The difference between Fampridine-SR non-responder group and the placebo group was not statistically significant.

Thus, the study has achieved statistical significance in the same 3-step analysis defined in F-203.

In addition to the comparisons by responder group, traditional comparison by treatment groups in the walking speed at the end of the treatment period was also performed. Note that in the above analysis of maintenance of efficacy in walking speed, baseline was defined as the average of all pre-treatment values. Because of large difference in walking speed during the pre-treatment period (see Table 6), the following table used Visit 2 (the last visit before double-blind treatment) value as baseline. At the end of the double-blind treatment period, the change from Visit 2 in walking speed was 0.11 for the placebo group and 0.22 for the Fampridine-SR group. The difference in speed translated to a time improvement of 0.50 second for the placebo group and 1.02 second for the Fampridine-SR group. The nominal p-value for the treatment difference of 0.11 ft/sec in change of walking speed was 0.0425.

Table 5 Mean Change from Visit 2 to End of Treatment in Walking Speed by Treatment Group – F204 (Source: Reviewer's Analysis)

Mean (SD) in Walking Speed (ft/sec)	**Placebo N=118**	**Fampridine-SR N=117**
Visit 2	2.28 (.73)	2.22 (.80)
Visit 6 (LOCF)	2.39 (.84)	2.44 (.93)
Change	.11 (.40)	.22 (.43)
Difference in Time (sec)	.50	1.02
Nominal p-value		.0425

The following table presents the average walking speed by treatment group and responder status at each visit using observed cases.

Table 6 Average Walking Speed (ft/sec) by Visit and Response Status (Observed Cases) - F204 (Source: Reviewer's Analysis)

	Pre-Treatment Visit				**Double-blind Treatment**				**Follow-up**
	Visit -1	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Placebo									
N	118	118	117	117	116	114	113	113	116
Mean	2.11	2.16	2.26	2.28	2.36	2.36	2.41	2.40	2.38
# Non-resp	107	107	106	106	105	103	102	102	106
Mean	2.11	2.16	2.26	2.28	2.33	2.31	2.38	2.36	2.38
#Resp	11	11	11	11	11	11	11	11	10
Mean	2.09	2.16	2.28	2.25	2.69	2.77	2.74	2.76	2.36
Fampridine									
N	119	119	119	118	116	116	114	113	116
Mean	2.05	2.06	2.15	2.21	2.39	2.45	2.41	2.44	2.21
# Non-resp	68	68	68	67	66	65	63	62	64
Mean	2.06	2.04	2.09	2.14	2.20	2.27	2.20	2.21	2.19
#Resp	51	51	51	51	50	51	51	51	51
Mean	2.05	2.09	2.21	2.30	2.63	2.68	2.67	2.73	2.25
Non Resp									
N	175	175	174	173	171	168	165	164	170
Mean	2.09	2.12	2.19	2.23	2.28	2.30	2.31	2.30	2.31
Responder									
N	62	62	62	62	61	62	62	62	61
Mean	2.06	2.10	2.23	2.29	2.64	2.70	2.68	2.73	2.27

The data above can be summarized as follows:

1. Subjects improved their walking speed during the pre-treatment period regardless of treatment group or responder status.
2. At the Visit 2 assessment (the last visit before randomization), the mean walking speed for placebo group was 2.28 ft/sec, represented 10.96 seconds to complete the 25 feet walking test. The mean walking speed for Fampridine-SR group was 2.21 ft/sec, represented 11.31 seconds for the test. At the Visit 6 (end of treatment visit), the mean walking speed of 2.40 ft/sec for placebo-treated subjects translated to 10.42 seconds for the 25-feet walking, an improvement of about a half second. The mean walking speed of 2.44 ft/sec for Fampridine-SR-treated subjects translated to 10.25 seconds for the same test at the Visit 6, an improvement of about 1 second.

3. The walking speed achieved during the double-blind period was generally maintained through the end of the double-period.
4. The non-responders had little changes from Visit 2 through the end of the treatment period while responders improved walking speed quite significantly, and maintained so through the end of the treatment period.
5. At the end of the treatment period, non-responders used 10.87 seconds to complete the 25 feet walking test, and responders used 9.16 seconds for the same test. The difference in time spent was 1.71 seconds. Breaking down the treatment group, the difference in time between the responders and non-responder among placebo-treated subjects was 1.54 seconds, and the same difference for the Fampridine-SR-treated subjects was 2.15 seconds.

The above findings are consistent to the findings from Study F203.

Traditional comparison in the treatment difference of MSWS-12 scores was also performed. The mean change from baseline to Visit 6 in MSWS-12 scores was -3.12 for Fampridine-SR group and 0.72 for placebo group. The difference yielded a nominal p-value of 0.0264. Means of MSWS-12 scores were also calculated by treatment group and response status at each visit using observed cases. The MSWS-12 score ranges 0 to 100 with 100 indicating extreme illness.

Table 7 Mean MSWS-12 Score by Visit and Response Status (Observes Cases) - F204 (Source: Reviewer's Analysis)

	Pre-treatment		**Double-blind**				**Follow-up**
	Visit 0	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Placebo							
N	118	117	117	116	116	113	116
Mean	67.79	67.53	68.33	68.37	68.62	68.38	70.85
# Non-resp	107	106	106	105	105	102	106
Mean	66.90	66.72	68.16	68.05	68.47	67.85	70.52
# Resp	11	11	11	11	11	11	10
Mean	76.45	75.38	69.97	71.40	70.08	73.30	74.38
Fampridine							
N	118	119	118	118	116	114	116
Mean	75.59	73.27	70.63	71.03	72.09	70.23	76.24
# Non-resp	67	68	68	67	65	63	66
Mean	75.68	74.94	74.93	74.97	76.43	73.91	76.99
# Resp	51	51	50	51	51	51	50
Mean	73.16	71.04	64.78	65.85	66.56	65.69	75.25
Non-resp							
N	174	174	174	172	170	165	172
Msws	70.28	69.93	70.81	70.75	71.52	70.16	73.00
Responder							
N	62	62	61	62	62	62	60
Msws	73.74	71.81	65.72	66.83	67.18	67.04	75.10

3.1.2.4.2 Analysis of Secondary Efficacy Variables

Average change from baseline in LEMMT scores was analyzed. In this analysis, the average change was obtained by averaging all double-blind available scores minus the average of all pre-treatment scores. The following table presents the results from comparisons between treatment groups and between responder groups in LEMMT scores. The nominal p-values were obtained from comparisons of each group versus placebo group.

Table 8 Average Change of LEMMT and Ashworth Scores - F204 (Source: Reviewer's Analysis)

Study F204	Placebo	Fampridine	Fampridine-SR	
			Responders	Non-Responders
LEMMT				
Mean (SD)	0.04 (.25)	0.09 (.22)	0.14 (.21)	0.05 (.22)
Nominal p-value		.1059	.0278	.5998

Based on the closed testing procedure, statistical significance for LEMMT has been reached in the comparisons of Fampridine-SR responders versus placebo. Statistical significance in the comparison of Fampridine-SR group versus placebo group and Fampridine-SR non-responders versus placebo group were not reached based on the order of the testing.

Change from baseline to endpoint in SGI scores was calculated. The average change of SGI was -0.04 for the placebo group and 0.09 for the Fampridine-SR group (nominal p=.1939).

3.2 Evaluation of Safety

Please refer to Clinical Review by Dr. Illoh and Safety Review by Dr. Boehm for evaluation of safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Response rate and mean walking speed are summarized by gender and age group and presented in Table 9 for Study F203 and in Table 10 for Study F204. No gender or age discrepancies were found in response rate. The mean walking speeds were similar between males and females and between older age group and younger age group.

Table 9 Response Rate and Change from Baseline in Walking Speed by Gender and Age - F203 (Source: Reviewer's Analysis)

Study F-203	Placebo	Fampridine-SR
Responder		
Gender		
Male		
N	29	66
# (%) of Responders	3 (10.34%)	19 (28.79%)
Female		
N	43	158
# (%) of Responders	3 (6.98%)	59 (37.34%)
Age		
≤ 50 (years)		
N	36	97
# (%) of Responders	4 (11.11%)	36 (37.11%)
> 50 years		
N	36	127
# (%) of Responders	2 (5.56%)	42 (33.07%)
Change in Walking Speed		
Gender		
Male		
N	29	66
Mean (SD)	0.10 (.26)	0.29 (.40)
Female		
N	43	158
Mean (SD)	0.10 (.32)	0.28 (.39)
Age		
≤ 50 years		
N	36	97
Mean (SD)	0.11 (.36)	0.29 (.45)
> 50 years		
N	36	127
Mean (SD)	0.08 (.22)	0.28 (.35)

Table 10 Response Rate and Change from Baseline in Walking Speed by Gender and Age - F204 (Source: Reviewer's Analysis)

Study F-204	Placebo	Fampridine-SR
Responder		
Gender		
Male		
N	44	31
# (%) of Responders	2 (4.55%)	13 (41.94%)
Female		
N	74	88
# (%) of Responders	9 (12.16%)	38 (43.18%)
Age		
≤ 50 (years)		
N	55	44
# (%) of Responders	4 (7.27%)	16 (36.36%)
> 50 years		
N	63	75
# (%) of Responders	7 (11.11%)	35 (46.67%)
Change in Walking Speed		
Gender		

Male		
N	44	31
Mean (SD)	0.20 (.31)	0.38 (.38)
Female		
N	74	88
Mean (SD)	0.15 (.38)	0.26 (.33)
Age		
≤ 50 years		
N	55	44
Mean (SD)	0.17 (.34)	0.28 (.38)
> 50 years		
N	63	75
Mean (SD)	0.16 (.38)	0.29 (.33)

4.2 Other Special/Subgroup Populations

In order to exam the efficacy of Fampridine-SR in sub-type of MS, mean walking speed is summarized by sub-type MS in the following table. Analysis of responder status was not performed due to the small number of responders in the placebo group. Because of the large difference in walking speed during the pre-treatment period, subject's Visit 2 walking speed was used as baseline.

Table 11 Mean Walking Speed by MS Type (Source: Reviewer's Analysis)

	Placebo	**Fampridine**	**Fampridine-SR**	
			Responders	**Non-Responders**
Study F203				
Primary Progressive				
N	14	30	12	18
Mean (SD)	-0.04 (.41)	0.14 (.47)	0.26 (.51)	0.06 (.43)
Progressive Relapsing				
N	2	10	4	6
Mean	-0.32 (.09)	0.32 (.28)	0.49 (.24)	0.21 (.26)
Relapsing Remitting				
N	21	61	15	46
Mean	0.08 (.59)	0.32 (.76)	0.60 (1.16)	0.23 (.57)
Secondary Progressive				
N	34	121	47	74
Mean	0.09 (.38)	0.16 (.48)	0.37 (.43)	0.04 (.46)
Study F204				
Primary Progressive				
N	19	10	5	5

Mean	0.17 (.30)	0.24 (.46)	0.45 (.53)	0.03 (.29)
Progressive Relapsing				
N	2	5	2	3
Mean	-0.16 (.49)	0.25 (.53)	0.64 (.75)	-0.01 (.18)
Relapsng Remitting				
N	40	42	16	26
Mean	0.05 (.39)	0.17 (.49)	0.42 (.39)	0.02 (.49)
Secondary Progressive				
N	56	61	28	33
Mean	0.14 (.43)	0.24 (.38)	0.41 (.37)	0.09 (.34)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The main issues of this submission are the unconventional approach in establishing efficacy and the small treatment difference in walking speed. The walking speed improvement from Visit 2 to Visit 6 was 0.05 (F203) and 0.11 (F204) ft/sec for placebo group and 0.21 (F203) and 0.22 (F204) ft/sec for Famrpidine-SR group. The improvement translated to up to 0.5 second for placebo group and 1 second for Fampridine-SR group in the time improvement for the 25-foot walking test.

5.2 Conclusions and Recommendations

The two pivotal studies have met the primary objectives by achieving statistically significant difference in the 3-step primary analysis. The traditional analysis of change from baseline in walking speed has also showed treatment difference between the Fampridine-SR group and the placebo group. However, the treatment difference, although in favor of Fampridine-SR treatment, is so small. Given the safety concern, (discussed in Dr. Boehm's and Dr. Illoh's reviews) the clinical value of such difference becomes a question.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS

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/s/

XIAORONG YAN
10/06/2009

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10/06/2009

HSIEN MING J J HUNG
10/06/2009

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 22-250
Drug Name:	Fampridine
Indication(s):	104 Week Carcinogenicity in Rats and Mice
Applicant:	Sponsor: Elan Corporation PLC, Monksland, Athlone County, Westmeath, Republic of Ireland Sponsor's Representative: David T. Drees D.V.M., Ph.D., 10234 Russell, Overland Park, KS 66212 Test Facility: (b) (4)
Documents Reviewed:	Electronic submission: Dated: January 30, 2009 Electronic data submitted on January 30, 2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Neurology Products
Reviewing Pharmacologist:	Richard Houghtling, Ph.D.
Project Manager:	James H. Reese
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 Fampridine in rats and mice when administered orally through dietary mixture at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Houghtting.

2. 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 identical control groups. Three hundred Charles River Crl: CD®BR (VAF/Plus) rats of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The dose levels for treated groups were 2, 6, and 18 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively. The two controls will be referred to as Control 1 and Control 2. The controls received the untreated diet only.

During the administration period all rats were observed twice daily for morbidity and mortality. The rats were observed for signs of toxicity at the time of morbidity/mortality checks. Detailed observations of physical conditions and existence of palpable masses were done once a week. Microscopical examinations were performed on all females from all groups for uterus and cervix. All other tissues were microscopically examined for rats in Control 1 and high dose group, and rats from all other groups in males and females dying or euthanized in extremis during the course of study. Body weights of individual animals were obtained prior to the initiation, weekly, and at study termination.

The sponsor submitted the data twice. In the first submission the sponsor collected and submitted the data following the protocol. Therefore, in the first submission the data showed the results of microscopical examinations of all females from all groups for uterus and cervix only, and for all other tissues of males and females results of microscopical examination for rats in Control 1 and high dose group, and rats from all other groups dying or euthanized in extremis during the course of study. However, since the submitted body weight data along with the first submission of tumor data showed a significant decrement in bodyweight gain in the high dose group, the agency had a concern that the rats in the high dose group might not have eaten enough food and might not have enough challenge for tumor occurrence. Therefore, the agency advised the sponsor to examine the tumor slides of all rats form low and medium dose groups as well. Consequently, the sponsor submitted a second set of data which included results of microscopic examination of all rats form all treatment groups. In following, this reviewer has presented the statistical analyses of these two sets of tumor data separately and compared the results.

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 pairwise comparisons of survivals between control and each of the treated groups 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 27 (45%), 27 (45%), 28 (47%), 26 (43%), and 21 (35%) in Control 1, Control 2, low, medium, and high dose groups respectively, in male rats and 25 (42%), 20 (33%), 25 (42%), 27 (45%), and 28 (47%) in Control 1, Control 2, low, medium, and high dose groups respectively, in female rats. Sponsor concluded that there was no statistically significant treatment related

effect on the survival in either sex.

2.1.2. Tumor data analysis from the first submission (Original data)

Tumor incidence data were analyzed using both age unadjusted and age adjusted tests. The age unadjusted tests were performed using the Cochran-Armitage test for dose response relationships and Fisher exact test for pairwise comparisons of control with the treated groups. The age adjusted tests were performed using the methods outlined in the paper of Peto et al. (1982) for dose response relationships. Analyses were only performed on a tumor types having an incidence difference of 2 or more between any two groups.

Sponsor's findings: The sponsor's analysis showed incidence rates of 1/60, 2/60, 4/60, 1/60, and 9/60 for uterus/polyp in Control 1, Control 2, low, medium, and high dose group, respectively. The sponsor's both age unadjusted test (Cochran-Armitage test. p-value=0.0014 using Control 1 and p-value=0.0039 using Control 2) and age adjusted tests (p-value<0.005 Peto test) showed a positive dose response relationship p-values of less than 0.005 for the incidence of uterine polyp using either control group. The pairwise comparison of high dose group with Control 1 showed a p-value of less than 0.005 and less than 0.05 compared to Control 2. The sponsor concludes that all neoplasms seen in the study rats were of the usual types that occur in aging rats of this strain.

2.1.3. Tumor data analysis from the second submission (Amended data)

Tumor incidence data were analyzed using the same statistical methodologies as the sponsor used to analyze the tumor data for the first submission.

Sponsor's findings: The sponsor's analysis showed incidence rates of 1/60, 2/60, 4/60, 1/60, and 9/60 for uterus/benign polyp in Control 1, Control 2, low, medium, high dose group, respectively. For dose response analysis the age unadjusted p-value was 0.008 (Cochran-Armitage test. p-value=0.008 using Control 1) and age adjusted p-value was 0.011 (Peto test p-value=0.011 using Control 1). The sponsor did not report the corresponding p-values using Control 2.

Reviewer's comments:

1) *The sponsor did not explicitly draw any conclusion regarding the statistical significance of the positive dose response of uterus/benign polyp found in the amended data set. However, considering this as a common tumor type and using the multiple testing adjustment procedure suggested in the FDA guidance, this dose response relationship can not be considered as statistically significant.*
2) *The sponsor's analyses showed the same incidence rates of uterine polyp in both the original and the amended data i.e. 1/60, 2/60, 4/60, 1/60, and 9/60 for uterus/benign polyp in Control 1, Control 2, low, medium, high dose group, respectively, yet the calculated p-values for dose response relationship were different. As a result the dose response test for uterine polyp in the original data was found to be statistically significant, while that in the amended data was not found to be significant. The sponsor did not provide much detail of their calculation procedures to explain these discrepancies. Some calculations of this reviewer indicates that the sponsor used the asymptotic permutation test in the original data set, while used exact Cochran-Armitage test in the amended data set. The Cochran-Armitage test for dose response relationship is the same as the permutation test with arithmetic score of 0, 1, 2, and 3 for control, low, medium, and high dose group. Since, for tumor data analysis the use of actual dose as the score is recommended, a permutation test is preferred over Cochran-Armitage test. Moreover, an exact test is preferred over asymptotic test, especially if the number of tumor bearing animals is small. With these in mind, the calculated p-values from the amended data set using the exact Cochran-Armitage test are not preferable. This reviewer's calculations showed that for positive dose response test, the age unadjusted exact permutation test p-values were 0.0027 using Control 1, 0.0063*

using Control 2, and 0.0016 using the pooled control. These p-values show statistically significant positive dose response in the incidence of uterine polyp.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all five treatment groups were estimated by the Kaplan-Meier product limit method. Since the two controls were identical, for the inferential statistical tests this reviewer pooled the two control groups to form a single control group. This type of pooling increases the statistical power of the tests. The dose response relationship and homogeneity of survival distributions were tested for combined control (pooling Control 1 and Control 2), low, medium and high dose groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings: The tests showed no statistically significant dose response relationship across treatment groups or differences between the combined control and any of the treated groups in survivals in either sex.

2.2.2. Tumor data analysis from first submission (original data)

Since the sponsor microscopically examined all animals from all treatment groups only for uterus and cervix tumors, and animals from Control 1 and high dose group for tumors in all other organs, in this reviewer's analysis dose response relationship tests and pairwise comparisons of control with each of the treated groups for uterus and cervix tumors were performed using the combined control (pooling Control 1 and Control 2). For tumor types observed in all other organs only pairwise comparisons of Control 1 with each of the treated groups were performed. Both these dose response tests and pairwise comparisons 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 Tables 3A (From First Submission) and 3B (From First Submission) in the appendix for males and females, respectively.

Multiple testing adjustment: For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of test levels α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two species, and a significance level α=0.01 for common tumors and α=0.05 for rare tumors for a submission with 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%. For multiple pairwise comparisons of treated group with control the FDA guidance suggests the use of test levels α=0.01 for common tumors and α=0.05 for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one submission.

In any carcinogenicity study review by this agency, the above test levels are generally used for the final interpretation of the statistical findings. However, it should be noted that the above suggestions were made for studies in which all organs of all animals from all treatment groups are microscopically examined for the existence any tumor. In the present study, since only two organs were microscopically examined, the above rule can not be applied. Noting that the multiplicity was minimal, this reviewer decided to use α=0.05 for all tests. This reviewer believes that the use of α=0.05 for all test in this study, should also keep the overall false positive rate less than 10%.

Reviewer's findings: 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.

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

Sex	Organ Name	Tumor Name	Pooled Cont. N=120	Low N=60	Med N=60	High N=60	Dos Resp	C 1 vs. L	C 1 vs. M	C 1 vs. H
Female	Uterus	Polyp	3	4	1	9	0.0027*	0.1876	0.4305	0.0050*

Using α=0.05, the incidence of benign polyps in uterus in female rats was considered to have statistically significant positive dose response relationship. Also, the increased incidence of benign polyps in uterus in high dose group was considered to be statistically significant compared to combined control.

2.2.3. Tumor data analysis from second submission

To analyze the tumor data from the second submission, this reviewer used the same statistical methodologies as he used to analyze the tumor data for the first submission. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A (From Second Submission) and 3B 3A (From Second Submission) in the appendix for males and females, respectively.

Reviewer's findings: 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

Sex	Organ Name	Tumor Name	Cont. N=60	Low N=60	Med N=60	High N=60	Dos Resp	Cont 1 vs. L	C 1 vs. M	C 1 vs. H
Male	skin, subcutis	fibroma, benign	2	5	1	7	0.0333	0.2172	0.5082	0.0546
Female	uterus#	polyp, benign	3	4	1	9	0.0027*	0.1876	0.4305	0.0050*

#All tests for uterus tumors were performed using the combined control (Pooling Control 1 and Control 2, N=120).

Using α=0.05, the incidences of benign fibroma of skin subcutis in male rats and of benign polyps of uterus in female rats were considered to have statistically significant positive dose response relationships. Also, the increased incidence of benign polyps in uterus in high dose group was considered to be statistically significant compared to combined control.

Reviewer's comment:

1. *The original data showed a group size of 60 for each treatment group.*
2. *The amended data showed a group size of 60 for Control 1, Control 2, medium and high dose group, but a group size of 65 for low dose group (2 mg/kg/day) in male rats.*

3. *The extra 5 animals in low dose group which were in amended data but not in the original data were Animal Numbers 7009, 7010, 7011, 7012, and 7013.*
4. *Assuming that these extra animals were included in the data set by mistake, this reviewer excluded these 5 animals from his analysis.*
5. *The original data set showed a total of 114 organ/tumor types in male rats (shown in Table 3A (First submission)), while the amended data showed 59 organ/tumor types (shown in Table 3A (Second submission)).*
6. *The original data set showed a total of 77 organ/tumor types in female rats (shown in Table 3B (First submission)), while the amended data showed 57 organ/tumor types (shown in Table 3B (Second submission)).*
7. *The organ names, organ codes in the original and amended data sets were not consistent. As a result it was hard to compare the consistency of the two data sets. For example, the following were tumors types observed in adrenal gland, medulla.*

Original Data

Organ name	*Organ code*	*Tumor name*	*Tumor code*
AdrenalGgland, Medulla	*3.0*	*Pheochromocytoma, benign*	*667.0*
AdrenalGgland, Medulla	*3.0*	*Pheochromocytoma, complex*	*668.0*
AdrenalGgland, Medulla	*3.0*	*Pheochromocytoma, malignant*	*669.0*

Amended Data

Organ name	*Organ code*	*Tumor name*	*Tumor code*
adrenal gland, medulla	*889*	*pheochromocytoma, benign*	*PCT*
adrenal gland, medulla	*889*	*pheochromocytoma, malignant*	*PCT*
adrenal gland, medulla	*889*	*pheochromocytoma, complex, benign*	*PHC*

Note that the organ names, organ codes, tumor names, and tumor codes are all different (including differences in cases of the letters) between the original and amended data sets. Moreover, since the analyses programs work with the organ and tumor codes, instead of organ and tumor names, the original data showed there were three different tumor types with codes 667.0, 668.0 and 669.0, while the amended data showed there were two different tumor types with codes PCT, and PHC. Also note that in the amended data set both benign and malignant pheochromocytoma has the same tumor code (PCT).

8. *Besides all these deficiencies of the original and amended data sets, the overall conclusion was consistent.*

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 two identical control groups. Three hundred Crl:CD-1®(ICR) BR VAF/Plus™ mice of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The dose levels for treated groups were 2, 12.5, and 80 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively. The two controls will be referred to as Control 1 and Control 2. The controls received the untreated diet only.

During the administration period all mice were observed twice daily for morbidity and mortality. The mice were observed for signs of toxicity at the time of morbidity/mortality checks. Detailed observations of physical conditions and existence of palpable masses were done once a week. Microscopical examinations were performed on all males from all groups for liver only. All other tissues were microscopically examined for mice in Control 1 and high dose group, and mice from all other groups dying or euthanized in extremis during the course of study. Body weights of individual animals were obtained prior to the initiation, weekly, and at study termination.

3.1. Sponsor's analyses

3.1.1. Survival analysis

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

Sponsor's findings: Sponsor's analysis showed survival rates of 26 (43%), 29 (48%), 34 (57%), 24 (40%), and 16 (27%) in Control 1, Control 2, low, medium, and high dose groups respectively, in male mice and 27 (45%), 24 (40%), 18 (30%), 24 (40%), and 20 (23%) in Control 1, Control 2, low, medium, and high dose groups respectively, in female mice. The sponsor concluded that there were decreased survivals in males and females high dose groups. Due to this reduced survival, all surviving females at high dose group were euthanized prematurely during study week 100. Sponsor further concluded that the survivals in the other treatment groups were similar to controls during most of the study period.

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: Sponsor's age adjusted trend test using the Peto method for hepatocellular carcinoma in males showed the p-values of 0.0470 and 0.0482 using Control 1 and Control 2, respectively. For this tumor type, the survival unadjusted test using the Cochran-Armitage test showed the p-values of 0.0447 and 0.09955 using Control 1 and Control 2, respectively. Because of these statistical findings, histologic sections of livers from males of the 2 and 12.5 mg/kg/day dose groups were also microscopically examined and no treatment related effects were evident in the liver. The pairwise comparison using the Fisher exact test showed p-values of 0.2479, 0.1218, and 0.1218 in the 2, 12.5, and 80 mg/kg/day doge groups, respectively compared to Control 1. When compared to Control 2, the p-values were 0.6907, 0.5000, and 0.5000 in the 2, 12.5, and 80 mg/kg/day doge groups, respectively. The sponsor concluded that the incidence of hepatocellular carcinoma in the 80 mg/kg/day dose group of males was within the normal range of occurrence in untreated control mice of this strain in the historical data from this test facility. Therefore, the sponsor did not consider the hepatocellular carcinoma in males in the high dose group to be a treatment induced change. The sponsor further concluded that all microscopic changes seen in the study mice were spontaneous or age-related origin and there were no treatment related gross or microscopic changes suggestive of a carcinogenic effect of the test article in study mice.

Reviewer's comment: Since there were statistically significant differences in survivals among treatment groups, an age unadjusted test not be valid.

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 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

Similar to the rat study, the dose response relationship and homogeneity of survival distributions were tested for combined control (pooling Control 1 and Control 2), low, medium and high dose groups using the Likelihood Ratio test and the Log-Rank test. 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 statistically significant dose response relationship in mortality in both sexes. Also in both sexes, the pairwise comparisons showed statistically significant increased death in high dose group compared to combined control.

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.

Reviewer's findings: None of the tested tumor types in male or female mice was considered to have a statistically significant positive dose response relationship. Also, none of the pairwise comparisons of Control 1 with any of the treated groups was considered to be statistically significant.

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 Fampridine in rats and mice when administered orally through dietary mixture 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 identical control groups. Three hundred Charles River Crl: CD®BR (VAF/Plus) rats of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The dose levels for treated groups were 2, 6, and 18 mg/kg/day. The controls received the untreated diet only. Microscopical examinations were performed on all females from all groups for uterus and cervix. The sponsor submitted the data twice. In the first submission the sponsor collected and submitted the data following the protocol, where the data showed the results of microscopical examinations of all females from all groups for uterus and cervix only, and for all other tissues of males and females results of microscopical examination for rats in Control 1 and high dose group, and rats from all other groups dying or euthanized in extremis during the course of study. However, since the submitted body weight data along with the first submission of tumor data showed a significant decrement in bodyweight gain in the high dose group, the agency had a concern that the rats in the high dose group might not have eaten enough food and might not have enough challenge for tumor occurrence. Therefore, the agency advised the sponsor to examine the tumor slides of all rats form low and medium dose groups as well. Consequently, the sponsor submitted a second set of data (referred to as the amended data) which included results of microscopic examination of all rats form all treatment groups.

The tests showed no statistically significant dose response relationship or differences between the combined control and any of the treated groups in survivals across treatment groups in either sex. The tests showed

statistically significant positive dose response relationships the incidence of benign fibroma of skin subcutis in male rats and of benign polyps of uterus in female rats. Also, the increased incidence of benign polyps in uterus in high dose group was found to be statistically significant compared to combined control.

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 two identical control groups. Three hundred Crl:CD-1®(ICR) BR VAF/Plus™ mice of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The dose levels for treated groups were 2, 12.5, and 80 mg/kg/day. The controls received the untreated diet only. Microscopical examinations were performed on all males from all groups for liver only. All other tissues were microscopically examined for mice in Control 1 and high dose group, and mice from all other groups dying or euthanized in extremis during the course of study.

The tests showed statistically significant dose response relationship in mortality in both sexes. Also in both sexes the pairwise comparisons showed statistically significant increased death rates in high dose group compared to Control 1. The tests did not showed statistically significant positive dose response relationship in the incidence of any of the tested tumor types in either sex. The tests also did not show statistically significant pairwise comparisons of Control 1 (or combined controls for male mouse liver tumor) with any of the treated groups.

Mohammad Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
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cc:
Archival NDA 22-250 Fampridine
Dr. Houghtling
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5. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

	Control 1		Control 2		2.0 mg|kg|day		6.0 mg|kg|day		18.0 mg|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	3	5.00	1	1.67	5	8.33	1	1.67	9	15.00
53 - 78	8	18.33	15	26.67	6	18.33	7	13.33	9	30.00
79 - 91	7	30.00	8	40.00	6	28.33	10	30.00	8	43.33
92 - 104	15	55.00	9	55.00	15	53.33	16	56.67	13	65.00
Ter. Sac.	27	45.00	27	45.00	28	46.67	26	43.33	21	35.00

Table 1B: Intercurrent Mortality Rate
Female Rats

	Control 1		Control 2		2.0 mg|kg|day		6.0 mg|kg|day		18.0 mg|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	1	1.67	2	3.33	2	3.33	2	3.33	1	1.67
53 - 78	11	20.00	11	21.67	11	21.67	9	18.33	12	21.67
79 - 91	12	40.00	15	46.67	11	40.00	12	38.33	5	30.00
92 - 104	11	58.33	12	66.67	11	58.33	10	55.00	14	53.33
Ter. Sac.	25	41.67	20	33.33	25	41.67	27	45.00	28	46.67

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	Statistic	P_Value
Dose-Response#	Likelihood Ratio	0.1148
Homogeneity#	Log-Rank	0.5438

#Dose response and homogeneity tests were performed using the combined control (Pooling Control 1 and Control 2)

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	Statistic	P_Value
Dose-Response#	Likelihood Ratio	0.1942
Homogeneity#	Log-Rank	0.4761

#Dose response and homogeneity tests were performed using the combined control (Pooling Control 1 and Control 2)

Table 3A: Tumor Rates and P-Values for Pairwise Comparisons of Control 1 and High Dose Group
Male Rats
(Original Data)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Cont. 1 vs. H
Adipose Tissue	Sarcoma, histiocytic	0	0	0	1	0.4706
Adrenal Gland, Cortex	Sarcoma, histiocytic	0	0	0	1	0.4706
Adrenal Gland, Medulla	Pheochromocytoma, benign	5	4	1	1	0.8635
	Pheochromocytoma, complex	0	0	0	1	0.4706
	Pheochromocytoma, malignant	1	0	0	0	0.4706
Bone Marrow, Femur	Leukemia, granulocytic	0	1	0	0	.
	Lymphoma, lymphoblastic, malig	0	1	1	1	0.4767
	Sarcoma, histiocytic	1	1	0	0	0.4651
Bone Marrow, Sternum	Leukemia, granulocytic	0	1	0	0	.
	Lymphoma, lymphoblastic, malig	0	1	1	1	0.4767
	Sarcoma, histiocytic	1	1	0	0	0.4651
Bone, Sternum	Leukemia, granulocytic	0	1	0	0	.
Brain	Astrocytoma, benign	0	1	0	0	.
	Glioma, benign	0	0	1	0	.
	Granular cell tumor, benign	1	0	0	0	0.4706
	Lymphoma, lymphoblastic, malig	0	0	1	1	0.4767
	Meningioma, malignant	1	0	0	0	0.4651
	Pinealoma	1	0	0	0	0.4706
	Sarcoma, histiocytic	0	1	0	1	0.4706
Cavity, Pericardial	Sarcoma, histiocytic	1	0	0	0	0.4651
Epididymis	Sarcoma, histiocytic	1	0	1	1	0.7168
Esophagus	Sarcoma, histiocytic	1	0	0	0	0.4706

(Continued)

Table 3A: Tumor Rates and P-Values for Pairwise Comparisons of Control 1 and High Dose Group
Male Rats
(Original Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Cont. 1 vs. H
Eye	Leukemia, granulocytic	0	1	0	0	.
	Lymphoma, lymphoblastic, malig	0	0	0	1	0.4767
Foot	Sarcoma, undifferentiated	0	0	0	1	0.4767
Harderian Gland	Leukemia, granulocytic	0	1	0	0	.
Heart	Hemangioma	0	0	1	0	.
	Mesothelioma, malignant	0	0	1	0	.
	Sarcoma, histiocytic	1	0	0	0	0.4651
	Schwannoma, malignant	1	0	0	0	0.4651
Hemolymphoreticular Syste	Hemangiosarcoma	2	0	2	0	0.7168
	Leukemia, granulocytic	0	1	0	0	.
	Leukemia, mononuclear cell	1	0	0	0	0.4706
	Lymphoma, lymphoblastic, malig	0	1	1	1	0.4767
	Sarcoma, histiocytic	3	1	1	2	0.4332
Joint, Tibiofemoral	Sarcoma, histiocytic	1	0	0	0	0.4651
Kidney	Leukemia, granulocytic	0	1	0	0	.
	Lymphoma, lymphoblastic, malig	0	0	0	1	0.4767
	Sarcoma, histiocytic	1	1	0	2	0.4554
Large Intestine, Cecum	Sarcoma, histiocytic	0	0	0	1	0.4706
Large Intestine, Colon	Sarcoma, histiocytic	1	0	0	0	0.4706
Larynx	Leukemia, granulocytic	0	1	0	0	.
Lip	Papilloma	0	1	0	0	.
	Rhabdomyosarcoma	0	0	0	1	0.4706

(Continued)

Table 3A: Tumor Rates and P-Values for Pairwise Comparisons of Control 1 and High Dose Group
Male Rats
(Original Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Cont. 1 vs. H
Liver	Adenoma, hepatocellular	4	1	0	0	0.9232
	Carcinoma, hepatocellular	0	1	0	0	.
	Leukemia, granulocytic	0	1	0	0	.
	Leukemia, mononuclear cell	1	0	0	0	0.4706
	Lymphoma, lymphoblastic, malig	0	1	1	1	0.4767
	Sarcoma, histiocytic	3	1	1	2	0.4332
	Schwannoma, malignant	0	0	1	0	.
Lung	Leukemia, granulocytic	0	1	0	0	.
	Sarcoma, histiocytic	3	1	1	1	0.6372
Lymph Node, Axillary	Lymphoma, lymphoblastic, malig	0	0	0	1	0.4767
	Sarcoma, histiocytic	0	1	0	0	.
Lymph Node, Iliac	Sarcoma, histiocytic	1	0	0	0	0.4651
Lymph Node, Mandibular	Leukemia, granulocytic	0	1	0	0	.
	Lymphoma, lymphoblastic, malig	0	0	1	1	0.4767
Lymph Node, Mediastinal	Leukemia, granulocytic	0	1	0	0	.
	Lymphoma, lymphoblastic, malig	0	0	0	1	0.4767
	Sarcoma, histiocytic	1	0	1	0	0.4706
Lymph Node, Mesenteric	Hemangiosarcoma	1	0	2	0	0.4651
	Leukemia, granulocytic	0	1	0	0	.
	Lymphoma, lymphoblastic, malig	0	0	0	1	0.4767
	Sarcoma, histiocytic	1	0	1	1	0.7168
Lymph Node, Renal	Leukemia, granulocytic	0	1	0	0	.
	Sarcoma, histiocytic	1	0	0	0	0.4651
Mammary Gland	Adenocarcinoma	1	0	0	0	0.4651

(Continued)

Table 3A: Tumor Rates and P-Values for Pairwise Comparisons of Control 1 and High Dose Group
Male Rats
(Original Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Cont. 1 vs. H
Mammary Gland	Adenoma	0	1	0	0	.
	Fibroadenoma	0	1	0	0	.
Mesentery	Sarcoma, histiocytic	1	0	0	0	0.4706
Nerve, Sciatic	Leukemia, granulocytic	0	1	0	0	.
Pancreas	Adenoma	1	0	0	0	0.4651
	Adenoma, islet cell	4	1	7	2	0.5927
	Sarcoma, histiocytic	2	0	1	1	0.4471
Pituitary Gland	Adenoma	27	23	25	16	0.9056
	Lymphoma, lymphoblastic, malig	0	0	1	0	.
Prostate Gland	Leukemia, granulocytic	0	1	0	0	.
	Sarcoma, histiocytic	2	0	1	0	0.7168
Seminal Vesicle	Sarcoma, histiocytic	1	0	0	0	0.4706
Skeletal Muscle	Rhabdomyosarcoma	2	1	0	0	0.7168
	Sarcoma, histiocytic	0	0	0	1	0.4706
Skeletal Muscle, Diaphrag	Sarcoma, histiocytic	1	0	0	0	0.4651
Skin	Adenoma, sebaceous	2	2	2	0	0.7168
	Carcinoma, sebaceous	1	0	0	1	0.7291
	Carcinoma, squamous cell	0	0	0	1	0.4767
	Fibroma	1	0	1	0	0.4651
	Keratoacanthoma	2	2	0	2	0.6461
Skin, Subcutis	Fibroma	2	5	1	7	0.0546
	Lipoma	1	2	1	0	0.4706

(Continued)

Table 3A: Tumor Rates and P-Values for Pairwise Comparisons of Control 1 and High Dose Group
Male Rats
(Original Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Cont. 1 vs. H
Skin, Subcutis	Sarcoma, histiocytic	1	1	0	0	0.4651
	Sarcoma, undifferentiated	0	0	0	1	0.4767
	Schwannoma, malignant	3	0	0	0	0.8517
Small Intestine, Duodenum	Sarcoma, histiocytic	1	0	0	0	0.4706
Small Intestine, Ileum	Sarcoma, histiocytic	1	0	0	0	0.4706
Small Intestine, Jejunum	Adenocarcinoma	0	0	1	0	.
	Sarcoma, histiocytic	1	0	0	0	0.4706
Soft Tissue, Abdomen	Fibrosarcoma	1	0	0	0	0.4651
	Osteosarcoma	0	0	0	1	0.4706
	Sarcoma, histiocytic	1	0	0	1	0.7168
	Sarcoma, undifferentiated	1	0	0	0	0.4651
	Schwannoma, malignant	0	0	1	0	.
Spleen	Hemangioma	0	0	1	0	.
	Hemangiosarcoma	1	0	0	0	0.4706
	Leukemia, granulocytic	0	1	0	0	.
	Leukemia, mononuclear cell	1	0	0	0	0.4706
	Lymphoma, lymphoblastic, malig	0	1	0	1	0.4767
	Sarcoma, histiocytic	1	0	1	1	0.7168
Stomach, Glandular	Sarcoma, histiocytic	2	0	0	1	0.4471
Testis	Interstitial cell tumor, benig	1	2	1	0	0.4651
	Mesothelioma, benign	0	0	1	0	.
	Sarcoma, histiocytic	1	0	0	0	0.4651
Thymus Gland	Leukemia, granulocytic	0	1	0	0	.
	Sarcoma, histiocytic	2	0	0	1	0.4471

(Continued)

Table 3A: Tumor Rates and P-Values for Pairwise Comparisons of Control 1 and High Dose Group
Male Rats
(Original Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Cont. 1 vs. H
Thymus Gland	Thymoma	0	1	0	0	.
Thyroid Gland	Adenoma, C-cell	5	0	1	2	0.7213
	Adenoma, follicular	2	0	1	0	0.7227
Tongue	Papilloma	0	1	0	0	.

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Rats
(Original Data)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Dos Resp	P_Value C 1 vs. L	P_Value C 1 vs. M	P_Value C 1 vs. H
Adipose Tissue	Lipoma	1	0	0	0	.	.	.	0.5111
Adrenal Gland, Cortex	Adenocarcinoma	3	0	1	0	.	.	.	0.8873
	Leukemia, granulocytic	0	0	1	0	.	.	.	.
Adrenal Gland, Medulla	Pheochromocytoma, benign	1	1	0	0	.	.	.	0.5169
	Pheochromocytoma, malignant	0	1	1	0	.	.	.	.
Bone Marrow, Femur	Leukemia, granulocytic	0	0	1	0	.	.	.	.
	Lymphoma, lymphoblastic, malig	0	1	0	0	.	.	.	.
Bone Marrow, Sternum	Leukemia, granulocytic	0	0	1	0	.	.	.	.
	Lymphoma, lymphoblastic, malig	0	1	0	0	.	.	.	.
Bone, Vertebra	Osteosarcoma	0	0	1	0	.	.	.	.
Brain	Astrocytoma, benign	1	0	0	0	.	.	.	0.5169
Ear	Basal cell tumor, benign	0	1	0	0	.	.	.	.
Eye	Leukemia, granulocytic	0	0	1	0	.	.	.	.
Harderian Gland	Leukemia, granulocytic	0	0	1	0	.	.	.	.
Heart	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5169
Hemolymphoreticular Syste	Hemangiosarcoma	0	0	0	1	.	.	.	0.5222
	Leukemia, granulocytic	0	0	1	0	.	.	.	.
	Leukemia, mononuclear cell	0	0	1	0	.	.	.	.
	Lymphoma, lymphoblastic, malig	0	1	1	1	.	.	.	0.5169
	Sarcoma, histiocytic	2	0	1	0	.	.	.	0.7638

(Continued)

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Rats
(Original Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Dos Resp	P_Value C 1 vs. L	P_Value C 1 vs. M	P_Value C 1 vs. H
Kidney	Leukemia, granulocytic	0	0	1	0	.	.	.	.
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5169
	Sarcoma, undifferentiated	1	0	0	0	.	.	.	0.5111
Large Intestine, Colon	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5169
Liver	Adenoma, hepatocellular	0	0	0	1	.	.	.	0.5169
	Leukemia, granulocytic	0	0	1	0	.	.	.	.
	Leukemia, mononuclear cell	0	0	1	0	.	.	.	.
	Lymphoma, lymphoblastic, malig	0	1	0	0	.	.	.	.
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5111
Lung	Adenoma, alveolar bronchiolar	0	0	0	1	.	.	.	0.5169
	Leukemia, granulocytic	0	0	1	0	.	.	.	.
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5169
Lymph Node, Iliac	Sarcoma, histiocytic	0	0	1	0	.	.	.	.
Lymph Node, Mandibular	Leukemia, granulocytic	0	0	1	0	.	.	.	.
Lymph Node, Mediastinal	Leukemia, granulocytic	0	0	1	0	.	.	.	.
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5169
Lymph Node, Mesenteric	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5169
Lymph Node, Popliteal	Leukemia, granulocytic	0	0	1	0	.	.	.	.
Mammary Gland	Adenocarcinoma	13	8	4	7	.	.	.	0.8972
	Adenoma	6	7	4	3	.	.	.	0.7796
	Fibroadenoma	26	31	25	34	.	.	.	0.1431
Meninges	Lymphoma, lymphoblastic, malig	0	1	0	0	.	.	.	.

(Continued)

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Rats
(Original Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Dos Resp	P_Value C 1 vs. L	P_Value C 1 vs. M	P_Value C 1 vs. H
Mesentery	Mesothelioma, malignant	0	1	0	0	.	.	.	.
Ovary	Granulosa cell tumor, benign	0	0	0	1	.	.	.	0.5169
	Granulosa cell tumor, malignan	0	0	0	1	.	.	.	0.5169
Pancreas	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5169
Parathyroid Gland	Adenoma	1	0	0	1	.	.	.	0.2584
Pituitary Gland	Adenocarcinoma	0	0	1	0	.	.	.	.
	Adenoma	47	40	41	39	.	.	.	0.8955
Skin	Basal cell tumor, benign	0	0	0	1	.	.	.	0.5169
	Carcinoma, sebaceous	0	0	1	0	.	.	.	.
	Carcinoma, squamous cell	1	1	0	1	.	.	.	0.2584
	Keratoacanthoma	0	0	1	0	.	.	.	.
Skin, Subcutis	Fibroma	2	2	4	1	.	.	.	0.5169
	Lipoma	0	1	0	0	.	.	.	.
	Sarcoma, histiocytic	0	0	1	0	.	.	.	.
	Schwannoma, malignant	0	0	0	1	.	.	.	0.5169
Soft Tissue, Abdomen	Mesothelioma, malignant	0	0	1	0	.	.	.	.
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5169
Spleen	Leukemia, granulocytic	0	0	1	0	.	.	.	.
	Leukemia, mononuclear cell	0	0	1	0	.	.	.	.
	Lymphoma, lymphoblastic, malig	0	1	0	0	.	.	.	.
Stomach, Glandular	Leukemia, granulocytic	0	0	1	0	.	.	.	.
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5169

(Continued)

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Rats
(Original Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Dos Resp	P_Value C 1 vs. L	P_Value C 1 vs. M	P_Value C 1 vs. H
Stomach, Nonglandular	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5169
Thymus Gland	Leukemia, granulocytic	0	0	1	0	.	.	.	.
	Lymphoma, lymphoblastic, malig	0	0	1	1	.	.	.	0.5169
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.5169
Thyroid Gland	Adenoma, C-cell	5	1	1	3	.	.	.	0.6555
	Adenoma, follicular	0	0	0	1	.	.	.	0.5169
Trachea	Leukemia, granulocytic	0	0	1	0	.	.	.	.
Uterus#	Adenocarcinoma	0	1	0	1	0.2129	0.3411	.	0.3511
	Adenoma	0	1	0	0	0.4136	0.3411	.	.
	Polyp	3	4	1	9	0.0027*	0.1876	0.4305	0.0050*
Uterus, Cervix#	Fibroma	0	0	1	0	0.4136	.	0.3462	.
	Hemangiosarcoma	0	0	0	1	0.2127	.	.	0.3561
	Polyp	0	0	1	0	0.4136	.	0.3462	.
	Sarcoma, stromal cell	0	1	0	0	0.4136	0.3411	.	.

#All tests for uterus and uterus, Cervix tumors were performed using the combined control (Pooling Control 1 and Control 2).

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats
(Amended Data)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
All Organs	Hemangioma + Hemangiosarcoma	2	1	4	0	0.8132	0.5000	0.3592	0.7168
	Mesothelioma_malignant	0	0	2	0	0.3999	.	0.2582	.
	Rhabdomyosarcoma	3	1	0	2	0.4803	0.7000	0.8870	0.4554
adrenal gland, cortex	adenoma, benign	0	1	0	0	0.4888	0.5055	.	.
	osteosarcoma, malignant	0	0	0	1	0.2247	.	.	0.4706
adrenal gland, medulla	pheochromocytoma, benign	6	8	6	1	0.9812	0.3863	0.3947	0.9203
	pheochromocytoma, complex, ben	0	0	0	1	0.2247	.	.	0.4706
	Pheochromocytoma_benign + complex	0	0	0	1	0.2247	.	.	0.4706
brain	astrocytoma, malignant	0	2	0	0	0.7400	0.2527	.	.
	glioma, benign	0	0	1	0	0.2235	.	0.5161	.
	granular cell tumor, benign	1	0	0	0	0.7472	0.5055	0.5109	0.4706
	meningioma, malignant	1	0	0	0	0.7430	0.5000	0.5054	0.4651
	pinealoma, benign	1	0	0	0	0.7472	0.5055	0.5109	0.4706
	Astrocytoma_malig + Glioma_benign	0	2	1	0	0.6616	0.2527	0.5161	.
cavity, thoracic	ganglioneuroma, malignant	0	1	0	0	0.4888	0.5055	.	.
epididymides	mesothelioma, malignant	0	0	1	0	0.2247	.	0.5109	.
foot/feet	sarcoma, undifferentiated, mal	0	0	0	1	0.2291	.	.	0.4767
heart	mesothelioma, malignant	0	0	1	0	0.2247	.	0.5109	.
	schwannoma, malignant	1	0	0	0	0.7430	0.5000	0.5054	0.4651
joint, tibiofemoral	schwannoma, malignant	1	0	0	0	0.7472	0.5055	0.5109	0.4706

(Continued)

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats
(Amended Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
lip	papilloma, benign	0	1	0	0	0.4888	0.5055	.	.
	rhabdomyosarcoma, malignant	0	0	0	1	0.2247	.	.	0.4706
liver	adenoma, hepatocellular, benig	4	1	0	0	0.9939	0.8195	0.9441	0.9232
	carcinoma, hepatocellular, mal	0	1	0	0	0.4888	0.5055	.	.
	schwannoma, malignant	1	0	1	0	0.6058	0.5055	0.2582	0.4706
lung	osteosarcoma, malignant	0	0	0	1	0.2247	.	.	0.4706
	sarcoma, undifferentiated, mal	0	0	0	1	0.2247	.	.	0.4706
	schwannoma, malignant	1	0	0	0	0.7430	0.5000	0.5054	0.4651
lymph node, inguinal	sarcoma, undifferentiated, mal	0	0	0	1	0.2291	.	.	0.4767
mammary gland	adenocarcinoma, malignant	1	0	0	0	0.7430	0.5000	0.5054	0.4651
	adenoma, benign	0	1	0	0	0.4888	0.5055	.	.
	fibroadenoma, benign	0	1	0	0	0.4888	0.5055	.	.
multicentric neoplasm	hemangioma, benign	0	0	2	0	0.3999	.	0.2582	.
	hemangiosarcoma, malignant	2	1	2	0	0.8284	0.5000	0.3166	0.7168
	leukemia, granulocytic, malign	0	1	0	0	0.4860	0.5109	.	.
	leukemia, mononuclear cell, ma	1	0	0	0	0.7472	0.5055	0.5109	0.4706
	lymphoma, lymphoblastic, malig	0	1	1	1	0.2659	0.5109	0.5109	0.4706
	sarcoma, histiocytic, malignan	3	1	1	2	0.4770	0.6998	0.6998	0.4332
pancreas	adenoma, benign	1	0	0	0	0.7430	0.5000	0.5054	0.4651
	adenoma, islet cell, benign	4	2	8	2	0.6196	0.6616	0.2099	0.5927
parathyroid glands	adenoma, benign	0	1	0	0	0.4888	0.5055	.	.
pituitary gland	adenoma, benign	27	29	31	16	0.9658	0.4645	0.3972	0.9056
skeletal muscle	rhabdomyosarcoma, malignant	2	1	0	0	0.9354	0.5083	0.7635	0.7227

(Continued)

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats
(Amended Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
skin	adenoma, sebaceous cell, benig	2	2	2	0	0.8782	0.6917	0.3166	0.7168
	carcinoma, sebaceous cell, mal	1	0	0	1	0.4066	0.5055	0.5109	0.7291
	carcinoma, squamous cell, mali	0	0	0	1	0.2247	.	.	0.4706
	fibroma, benign	1	0	1	0	0.6015	0.5000	0.2527	0.4651
	keratoacanthoma, benign	2	2	0	2	0.4247	0.3166	0.7635	0.6461
	Carcinoma_squa_cell + Keratoacen	2	2	0	3	0.2170	0.3166	0.7635	0.4554
skin, subcutis	fibroma, benign	2	5	1	7	0.0333	0.2172	0.5082	0.0546
	lipoma, benign	1	2	1	0	0.8103	0.5083	0.2582	0.4706
	sarcoma, undifferentiated, mal	0	0	0	1	0.2247	.	.	0.4706
	schwannoma, malignant	3	0	0	0	0.9838	0.8791	0.8830	0.8517
small intestine, jejunum	adenocarcinoma, malignant	0	0	1	0	0.2247	.	0.5109	.
soft tissue, abdomen	fibrosarcoma, malignant	1	0	0	0	0.7430	0.5000	0.5054	0.4651
	osteosarcoma, malignant	0	0	0	1	0.2247	.	.	0.4706
	sarcoma, undifferentiated, mal	1	0	0	0	0.7430	0.5000	0.5054	0.4651
	schwannoma, malignant	0	0	1	0	0.2235	.	0.5161	.
tail	schwannoma, malignant	1	0	0	0	0.7472	0.5055	0.5109	0.4706
testes	interstitial cell tumor, benig	1	3	1	0	0.8722	0.3166	0.2582	0.4706
	mesothelioma, malignant	0	0	1	0	0.2247	.	0.5109	.
thymus gland	thymoma, benign	0	1	0	0	0.4888	0.5055	.	.
thyroid gland	adenoma, c-cell, benign	5	5	4	2	0.8484	0.6303	0.5138	0.7213
	adenoma, follicular cell, beni	2	0	1	0	0.8182	0.7582	0.5165	0.7227
tongue	papilloma, benign	0	1	0	0	0.4888	0.5055	.	.

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Rats
(Amended Data)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
All Organs	Basal_Cell_Tumor_benign + carcinoma_sebaceous	0	1	1	1	0.3121	0.5057	0.5114	0.5169
	Basal_Cell_Tumor_Benign	0	1	0	1	0.3256	0.5057	.	0.5169
	Leukemia_Granuloc + Mononuclea	0	0	2	0	0.4490	.	0.2643	.
	Mesothelioma_Malignant	0	1	1	0	0.5140	0.5057	0.5114	.
	Osteosarcoma_Malignant	0	0	1	0	0.2584	.	0.5114	.
adipose tissue	lipoma, benign	1	0	0	0	0.7542	0.5000	0.5056	0.5111
adrenal gland, cortex	adenocarcinoma, malignant	2	0	1	0	0.8413	0.7586	0.5172	0.7694
	adenoma, benign	1	0	0	0	0.7542	0.5000	0.5056	0.5111
	mesothelioma, malignant	0	1	0	0	0.5112	0.5057	.	.
adrenal gland, medulla	pheochromocytoma, benign	1	3	2	0	0.8902	0.3168	0.5172	0.5169
bone, vertebra	osteosarcoma, malignant	0	0	1	0	0.2584	.	0.5114	.
brain	astrocytoma, malignant	1	0	0	0	0.7584	0.5057	0.5114	0.5169
ears	basal cell tumor, benign	0	1	0	0	0.5112	0.5057	.	.
kidneys	sarcoma, undifferentiated, mal	1	0	0	0	0.7542	0.5000	0.5056	0.5111
liver	adenocarcinoma, malignant	2	0	1	1	0.5294	0.7529	0.5085	0.5169
	adenoma, hepatocellular, benig	0	0	0	1	0.2584	.	.	0.5169
	carcinoma (primary site unknow	0	0	1	0	0.2584	.	0.5114	.
lung	adenocarcinoma, malignant	4	1	1	0	0.9808	0.8198	0.8267	0.9469
	adenoma, bronchiolar alveolar,	0	0	0	1	0.2584	.	.	0.5169

(Continued)

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Rats
(Amended Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
lymph node, iliac	adenocarcinoma, malignant	1	0	0	0	0.7542	0.5000	0.5056	0.5111
	osteosarcoma, malignant	0	0	1	0	0.2584	.	0.5114	.
lymph node, mandibular	adenocarcinoma, malignant	0	0	0	1	0.2584	.	.	0.5169
	carcinoma, squamous cell, mali	0	0	0	1	0.2584	.	.	0.5169
lymph node, mediastinal	osteosarcoma, malignant	0	0	1	0	0.2584	.	0.5114	.
mammary gland	adenocarcinoma, malignant	13	9	4	7	0.8953	0.7680	0.9834	0.8972
	adenoma, benign	6	7	4	3	0.9080	0.5177	0.6450	0.7796
	fibroadenoma, benign	26	31	26	34	0.1370	0.2807	0.5811	0.1431
	Adenoma + Fibroadenoma	28	36	28	35	0.3198	0.1436	0.5819	0.2354
mesentery/peritoneum	mesothelioma, malignant	0	1	0	0	0.5112	0.5057	.	.
multicentric neoplasm	hemangiosarcoma, malignant	0	0	0	1	0.2626	.	.	0.5222
	leukemia, granulocytic, malign	0	0	1	0	0.2584	.	0.5114	.
	leukemia, mononuclear cell, ma	0	0	1	0	0.2584	.	0.5114	.
	lymphoma, lymphoblastic, malig	0	1	1	1	0.3102	0.5114	0.5114	0.5169
	sarcoma, histiocytic, malignan	2	0	1	0	0.8413	0.7586	0.5172	0.7694
ovaries	adenocarcinoma, malignant	0	0	0	1	0.2584	.	.	0.5169
	granulosa cell tumor, benign	0	0	1	2	0.0668	.	0.5114	0.2643
	mesothelioma, malignant	0	1	0	0	0.5112	0.5057	.	.
pancreas	adenoma, islet cell, benign	0	2	0	0	0.7625	0.2529	.	.
	osteosarcoma, malignant	0	0	1	0	0.2584	.	0.5114	.
parathyroid glands	adenoma, benign	1	0	1	1	0.4049	0.5000	0.2528	0.2584
pituitary gland	adenocarcinoma, malignant	0	0	1	0	0.2584	.	0.5114	.
	adenoma, benign	47	44	47	39	0.9445	0.5350	0.6012	0.8955

(Continued)

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Rats
(Amended Data)

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	6 mg Med N=60	18 mg High N=60	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
skin	basal cell tumor, benign	0	0	0	1	0.2584	.	.	0.5169
	carcinoma, sebaceous cell, mal	0	0	1	0	0.2584	.	0.5114	.
	carcinoma, squamous cell, mali	1	1	0	1	0.5459	0.7529	0.5056	0.2584
	keratoacanthoma, benign	0	0	1	0	0.2584	.	0.5114	.
skin, subcutis	fibroma, benign	2	2	4	1	0.7184	0.6919	0.3491	0.5169
	lipoma, benign	0	1	0	0	0.5112	0.5057	.	.
	schwannoma, malignant	0	0	0	1	0.2584	.	.	0.5169
soft tissue, abdomen	adenocarcinoma, malignant	1	0	0	1	0.4490	0.5000	0.5056	0.2584
	mesothelioma, malignant	0	0	1	0	0.2584	.	0.5114	.
	osteosarcoma, malignant	0	0	1	0	0.2584	.	0.5114	.
thymus gland	osteosarcoma, malignant	0	0	1	0	0.2584	.	0.5114	.
thyroid gland	adenoma, c-cell, benign	5	2	4	3	0.6372	0.7832	0.5145	0.6680
	adenoma, follicular cell, beni	0	1	0	1	0.3256	0.5057	.	0.5169
	carcinoma, follicular cell, ma	0	1	0	0	0.5112	0.5057	.	.
	Adenoma + Carcinoma_Follicular	0	2	0	1	0.4555	0.2529	.	0.5169
uterus#	adenocarcinoma, malignant	0	1	0	1	0.2149	0.3437	.	0.3538
	adenoma, benign	0	1	0	0	0.4155	0.3437	.	.
	osteosarcoma, malignant	0	0	1	0	0.4155	.	0.3488	.
	polyp, benign	3	4	1	9	0.0027*	0.1876	0.4305	0.0050*
uterus, cervix#	fibroma, benign	0	0	1	0	0.4155	.	0.3488	.
	polyp, benign	0	0	1	0	0.4155	.	0.3488	.
	sarcoma, stromal, malignant	0	1	0	0	0.4155	0.3437	.	.

#All tests for uterus and uterus, Cervix tumors were performed using the combined control (Pooling Control 1 and Control 2).

Table 4A: Intercurrent Mortality Rate in Male Mice

	__Control 1__		__Control 2__		2.0 mg|kg|day		13.0 mg|kg|day		80.0 mg|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	9	15.00	4	6.67	3	5.00	7	11.67	17	28.33
53 - 78	9	30.00	11	25.00	4	11.67	8	25.00	13	50.00
79 - 91	7	41.67	6	35.00	6	21.67	10	41.67	7	61.67
92 - 104	9	56.67	10	51.67	13	43.33	11	60.00	7	73.33
Ter. Sac.	26	43.33	29	48.33	34	56.67	24	40.00	16	26.67

Table 4B: Intercurrent Mortality Rate Female Mice

	__Control 1__		__Control 2__		2.0 mg|kg|day		13.0 mg|kg|day		80.0 mg|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	4	6.67	3	5.00	8	13.33	9	15.00	11	18.33
53 - 78	10	23.33	7	16.67	8	26.67	7	26.67	17	46.67
79 - 91	10	40.00	15	41.67	10	43.33	7	38.33	12	66.67
92 - 104	9	55.00	11	60.00	16	70.00	13	60.00	6	76.67
Ter. Sac.	27	45.00	24	40.00	18	30.00	24	40.00	14	23.33

*** The high dose group was sacrificed on Week 99. The six animals in high dose group shown in interval 92-104 are actually in interval Week 92-98, and the 14 animals shown in Ter. Sac. interval were terminally sacrificed on Week 99.**

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	Statistic	P_Value
Dose-Response#	Likelihood Ratio	0.0017
Homogeneity#	Log-Rank	<.0001

#Dose response and homogeneity tests were performed using the combined control (Pooling Control 1 and Control 2)

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	Statistic	P_Value
Dose-Response#	Likelihood Ratio	<.0001
Homogeneity#	Log-Rank	0.0005

#Dose response and homogeneity tests were performed using the combined control (Pooling Control 1 and Control 2)

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

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	13 mg Med N=60	80 mg High N=60	P_Value Dos Resp	P_Value C 1 vs. L	P_Value C 1 vs. M	P_Value C 1 vs. H
Artery, Aorta	Lymphoma, lymphoblastic, malig	0	2	1	0	.	.	.	.
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085
Bone Marrow, Sternum	Hemangiosarcoma	1	0	0	0	.	.	.	0.4085
	Lymphoma, lymphoblastic, malig	1	0	0	0	.	.	.	0.4085
Bone, Sternum	Lymphoma, lymphoblastic, malig	1	0	1	0	.	.	.	0.4085
Brain	Lymphoma, lymphoblastic, malig	2	0	0	0	.	.	.	0.6467
Epididymis	Lymphoma, lymphoblastic, malig	1	0	0	0	.	.	.	0.4085
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085
Eye	Lymphoma, lymphoblastic, malig	1	0	0	0	.	.	.	0.4085
Eye, Optic Nerve	Lymphoma, lymphoblastic, malig	1	0	0	0	.	.	.	0.4085
Harderian Gland	Adenoma	5	3	0	0	.	.	.	0.9347
Heart	Lymphoma, lymphoblastic, malig	1	2	0	0	.	.	.	0.4085
Hemolymphoreticular Syste	Hemangiosarcoma	4	3	1	3	.	.	.	0.6110
	Lymphoma, lymphoblastic, malig	3	3	6	1	.	.	.	0.5465
	Sarcoma, histiocytic	2	0	1	1	.	.	.	0.3744
Kidney	Lymphoma, lymphoblastic, malig	3	1	2	0	.	.	.	0.7931
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085
Liver#	Adenoma, hepatocellular	19	10	7	2	0.9754	0.5099	0.6692	0.9512
	Carcinoma, hepatocellular	2	2	3	3	0.0554	0.4689	0.1982	0.1081
	Hemangioma	2	1	0	0	0.8014	0.3047	0.5432	0.4424
	Hemangiosarcoma	4	2	1	3	0.1317	0.3876	0.5312	0.2574
	Leukemia, granulocytic	1	0	0	0	0.5825	0.3676	0.3228	0.2522
	Lymphoma, lymphoblastic, malig	7	2	2	0	0.9407	0.7026	0.5967	0.8693
	Sarcoma, histiocytic	2	0	0	0	0.8269	0.6019	0.5432	0.4424

#All tests for liver tumors were performed using the combined control (Pooling Control 1 and Control 2).

(Continued)

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

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	13 mg Med N=60	80 mg High N=60	P_Value Dos Resp	P_Value C 1 vs. L	P_Value C 1 vs. M	P_Value C 1 vs. H
Lung	Adenoma, alveolar bronchiolar	10	11	4	6	.	.	.	0.5344
	Carcinoma, alveolar bronchiola	4	1	2	0	.	.	.	0.8800
	Lymphoma, lymphoblastic, malig	3	2	4	0	.	.	.	0.7931
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085
Lymph Node, Axillary	Lymphoma, lymphoblastic, malig	0	0	2	0	.	.	.	.
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085
Lymph Node, Hepatic	Lymphoma, lymphoblastic, malig	1	0	1	0	.	.	.	0.4085
Lymph Node, Iliac	Lymphoma, lymphoblastic, malig	1	2	0	0	.	.	.	0.4085
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085
Lymph Node, Inguinal	Lymphoma, lymphoblastic, malig	0	1	0	0	.	.	.	.
Lymph Node, Mandibular	Lymphoma, lymphoblastic, malig	2	0	1	0	.	.	.	0.6535
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085
Lymph Node, Mediastinal	Lymphoma, lymphoblastic, malig	1	0	2	0	.	.	.	0.4085
Lymph Node, Mesenteric	Hemangioma	1	0	1	0	.	.	.	0.4143
	Lymphoma, lymphoblastic, malig	3	3	3	0	.	.	.	0.7931
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085
	Sarcoma, undifferentiated	0	0	1	0	.	.	.	.
Lymph Node, Renal	Lymphoma, lymphoblastic, malig	2	3	0	0	.	.	.	0.6535
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085
Pancreas	Lymphoma, lymphoblastic, malig	1	0	2	0	.	.	.	0.4085

(Continued)

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

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	13 mg Med N=60	80 mg High N=60	P_Value Dos Resp	P_Value C 1 vs. L	P_Value C 1 vs. M	P_Value C 1 vs. H
Pituitary Gland	Adenoma	0	0	1	0	.	.	.	.
	Lymphoma, lymphoblastic, malig	1	0	0	0	.	.	.	0.4085
Prostate Gland	Lymphoma, lymphoblastic, malig	1	0	1	0	.	.	.	0.4085
	Sarcoma, histiocytic	2	0	0	0	.	.	.	0.6535
Salivary Gland, Mandibula	Lymphoma, lymphoblastic, malig	1	0	1	0	.	.	.	0.4085
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085
Seminal Vesicle	Adenoma	0	0	1	0	.	.	.	.
	Lymphoma, lymphoblastic, malig	1	0	2	0	.	.	.	0.4085
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085
Skin, Subcutis	Hemangiosarcoma	1	0	0	0	.	.	.	0.4085
	Lymphoma, lymphoblastic, malig	0	0	1	0	.	.	.	.
	Sarcoma, histiocytic	0	0	1	0	.	.	.	.
Soft Tissue, Abdomen	Lipoma	0	0	0	1	.	.	.	0.4225
Soft Tissue, Head	Lymphoma, lymphoblastic, malig	0	0	1	0	.	.	.	.
Spleen	Hemangiosarcoma	2	2	0	0	.	.	.	0.6535
	Lymphoma, lymphoblastic, malig	2	3	3	0	.	.	.	0.6535
	Sarcoma, histiocytic	1	0	0	1	.	.	.	0.6631
Stomach, Glandular	Lymphoma, lymphoblastic, malig	2	0	2	0	.	.	.	0.6535
Testis	Interstitial cell tumor, benig	1	0	0	0	.	.	.	0.4085
Thymus Gland	Lymphoma, lymphoblastic, malig	3	3	1	1	.	.	.	0.5465
	Sarcoma, histiocytic	1	0	0	0	.	.	.	0.4085

(Continued)

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

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	13 mg Med N=60	80 mg High N=60	P_Value Dos Resp	P_Value C 1 vs. L	P_Value C 1 vs. M	P_Value C 1 vs. H
Thyroid Gland	Adenoma, C-cell	0	1	0	0	.	.	.	.
	Adenoma, follicular	1	0	1	0	.	.	.	0.4143
	Lymphoma, lymphoblastic, malig	1	0	0	0	.	.	.	0.4085
Urinary Bladder	Lymphoma, lymphoblastic, malig	1	0	0	0	.	.	.	0.4085

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

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	13 mg Med N=60	80 mg High N=60	P_Value Cont. 1 vs. H
Adipose Tissue	Lymphoma, lymphoblastic, malig	0	0	1	0	.
	Sarcoma, histiocytic	1	0	0	0	0.4177
Adrenal Gland, Cortex	Adenoma, A cell	0	1	0	0	.
	Lymphoma, lymphoblastic, malig	1	5	6	1	0.6641
Adrenal Gland, Medulla	Lymphoma, lymphoblastic, malig	0	0	0	1	0.4177
	Pheochromocytoma, benign	1	0	0	0	0.4177
All Organs	Lymph_Lymph_Malig + Leuke_Granu	5	14	16	6	0.3286
	Lymphoma_Lymphoblastic_Maligna	5	14	15	6	0.3286
Artery, Aorta	Lymphoma, lymphoblastic, malig	0	5	1	1	0.4177
	Sarcoma, histiocytic	0	1	1	0	.
Bone	Osteosarcoma	0	0	0	1	0.4250
Bone Marrow, Femur	Lymphoma, lymphoblastic, malig	0	0	1	0	.
	Sarcoma, histiocytic	0	1	0	0	.
Bone Marrow, Sternum	Lymphoma, lymphoblastic, malig	0	0	2	0	.
	Sarcoma, histiocytic	0	1	0	0	.
Bone, Skull	Osteoma	1	0	0	0	0.4177
Bone, Sternum	Lymphoma, lymphoblastic, malig	0	2	3	0	.
	Sarcoma, histiocytic	0	0	1	0	.
Brain	Lymphoma, lymphoblastic, malig	0	0	1	0	.
Esophagus	Lymphoma, lymphoblastic, malig	1	5	1	1	0.6641
	Sarcoma, histiocytic	0	0	1	0	.

(Continued)

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

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	13 mg Med N=60	80 mg High N=60	P_Value Cont. 1 vs. H
Eye	Lymphoma, lymphoblastic, malig	0	2	1	0	.
Eye, Optic Nerve	Lymphoma, lymphoblastic, malig	0	2	1	0	.
Gallbladder	Lymphoma, lymphoblastic, malig	1	2	2	1	0.6641
	Sarcoma, histiocytic	0	1	0	0	.
Harderian Gland	Adenoma	5	1	0	0	0.9362
	Lymphoma, lymphoblastic, malig	0	0	2	2	0.1775
Heart	Leukemia, granulocytic	0	0	1	0	.
	Lymphoma, lymphoblastic, malig	3	9	5	3	0.5091
	Sarcoma, histiocytic	0	0	1	0	.
Hemolymphoreticular Syste	Hemangiosarcoma	2	2	1	0	0.6641
	Leukemia, granulocytic	0	0	1	0	.
	Lymphoma, lymphoblastic, malig	5	14	15	6	0.3286
	Sarcoma, histiocytic	4	6	2	0	0.8914
Kidney	Lymphoma, lymphoblastic, malig	4	12	11	5	0.3454
	Sarcoma, histiocytic	1	3	2	0	0.4177
Large Intestine, Cecum	Lymphoma, lymphoblastic, malig	2	2	1	0	0.6641
Large Intestine, Rectum	Lymphoma, lymphoblastic, malig	1	0	0	0	0.4177
Larynx	Lymphoma, lymphoblastic, malig	0	4	1	1	0.4177
Liver	Adenoma, hepatocellular	1	2	1	0	0.4177
	Carcinoma, hepatocellular	0	1	0	0	.
	Hemangioma	1	0	1	1	0.6579
	Hemangiosarcoma	1	1	1	0	0.4177

(Continued)

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

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	13 mg Med N=60	80 mg High N=60	P_Value Cont. 1 vs. H
Liver	Leukemia, granulocytic	0	0	1	0	.
	Lymphoma, lymphoblastic, malig	1	5	13	3	0.2034
	Sarcoma, histiocytic	3	5	2	0	0.8080
Lung	Adenoma, alveolar bronchiolar	16	15	9	7	0.8786
	Carcinoma, alveolar bronchiola	5	1	0	3	0.4333
	Leukemia, granulocytic	0	0	1	0	.
	Lymphoma, lymphoblastic, malig	3	11	5	6	0.1354
	Mesothelioma, benign	1	0	0	0	0.4177
	Sarcoma, histiocytic	2	2	0	0	0.6641
Lymph Node, Axillary	Lymphoma, lymphoblastic, malig	0	1	3	0	.
Lymph Node, Hepatic	Lymphoma, lymphoblastic, malig	1	4	1	0	0.4177
Lymph Node, Iliac	Leukemia, granulocytic	0	0	1	0	.
	Lymphoma, lymphoblastic, malig	2	1	6	1	0.3761
	Sarcoma, histiocytic	1	2	1	0	0.4177
Lymph Node, Inguinal	Lymphoma, lymphoblastic, malig	1	4	4	1	0.6641
Lymph Node, Mandibular	Lymphoma, lymphoblastic, malig	2	6	9	3	0.3579
	Sarcoma, histiocytic	0	1	0	0	.
Lymph Node, Mediastinal	Lymphoma, lymphoblastic, malig	0	3	8	2	0.1775
	Sarcoma, histiocytic	1	1	0	0	0.4177
Lymph Node, Mesenteric	Lymphoma, lymphoblastic, malig	3	11	12	2	0.3579
	Sarcoma, histiocytic	1	1	1	0	0.4177
Lymph Node, Renal	Lymphoma, lymphoblastic, malig	3	3	3	2	0.3579
	Sarcoma, histiocytic	0	2	1	0	.

(Continued)

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

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	13 mg Med N=60	80 mg High N=60	P_Value Cont. 1 vs. H
Mammary Gland	Adenocarcinoma	5	3	4	0	0.9362
	Adenoma	0	1	1	1	0.4250
	Lymphoma, lymphoblastic, malig	1	7	4	3	0.2034
	Sarcoma, histiocytic	0	0	1	0	.
Nerve, Sciatic	Lymphoma, lymphoblastic, malig	0	4	6	1	0.4177
Ovary	Adenoma	3	2	0	1	0.5580
	Leiomyoma	1	0	0	0	0.4177
	Leukemia, granulocytic	0	0	1	0	.
	Lymphoma, lymphoblastic, malig	3	8	9	4	0.3486
	Sarcoma, histiocytic	1	2	2	0	0.4177
Pancreas	Lymphoma, lymphoblastic, malig	2	6	6	3	0.3711
	Sarcoma, histiocytic	0	1	0	0	.
Pituitary Gland	Adenoma	4	2	2	0	0.8914
	Lymphoma, lymphoblastic, malig	0	1	4	0	.
Salivary Gland, Mandibula	Lymphoma, lymphoblastic, malig	0	2	4	3	0.0728
Salivary Gland, Sublingua	Lymphoma, lymphoblastic, malig	0	0	6	0	.
	Sarcoma, histiocytic	0	1	0	0	.
Skeletal Muscle	Rhabdomyosarcoma	0	1	0	0	.
Skeletal Muscle, Abdomina	Rhabdomyosarcoma	1	0	0	0	0.4177
Skeletal Muscle, Quadrice	Lymphoma, lymphoblastic, malig	0	2	3	0	.
	Sarcoma, histiocytic	0	0	1	0	.
Skeletal Muscle, Thoracic	Lymphoma, lymphoblastic, malig	0	1	0	0	.

(Continued)

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

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	13 mg Med N=60	80 mg High N=60	P_Value Cont. 1 vs. H
Skin	Basal cell tumor, malignant	1	0	0	0	0.4177
	Papilloma	0	1	0	0	.
Skin, Subcutis	Lymphoma, lymphoblastic, malig	0	0	2	1	0.4177
	Sarcoma, histiocytic	0	1	0	0	.
	Sarcoma, undifferentiated	1	0	0	0	0.4177
Small Intestine, Duodenum	Lymphoma, lymphoblastic, malig	0	1	1	0	.
Small Intestine, Ileum	Lymphoma, lymphoblastic, malig	1	0	0	0	0.4177
Small Intestine, Jejunum	Lymphoma, lymphoblastic, malig	1	1	0	0	0.4177
	Osteosarcoma	0	0	1	0	.
Soft Tissue, Abdomen	Lymphoma, lymphoblastic, malig	1	4	1	0	0.4177
	Neurofibrosarcoma	0	1	0	0	.
Soft Tissue, Thorax	Leukemia, granulocytic	0	0	1	0	.
	Lymphoma, lymphoblastic, malig	0	0	1	0	.
Spleen	Hemangiosarcoma	0	1	1	0	.
	Leukemia, granulocytic	0	0	1	0	.
	Lymphoma, lymphoblastic, malig	3	7	10	3	0.5241
	Sarcoma, histiocytic	2	1	1	0	0.6641
Stomach, Glandular	Lymphoma, lymphoblastic, malig	3	8	6	3	0.5091
Stomach, Nonglandular	Lymphoma, lymphoblastic, malig	0	1	0	0	.
Thymus Gland	Lymphoma, lymphoblastic, malig	3	12	11	5	0.2158
	Sarcoma, histiocytic	0	2	1	0	.

(Continued)

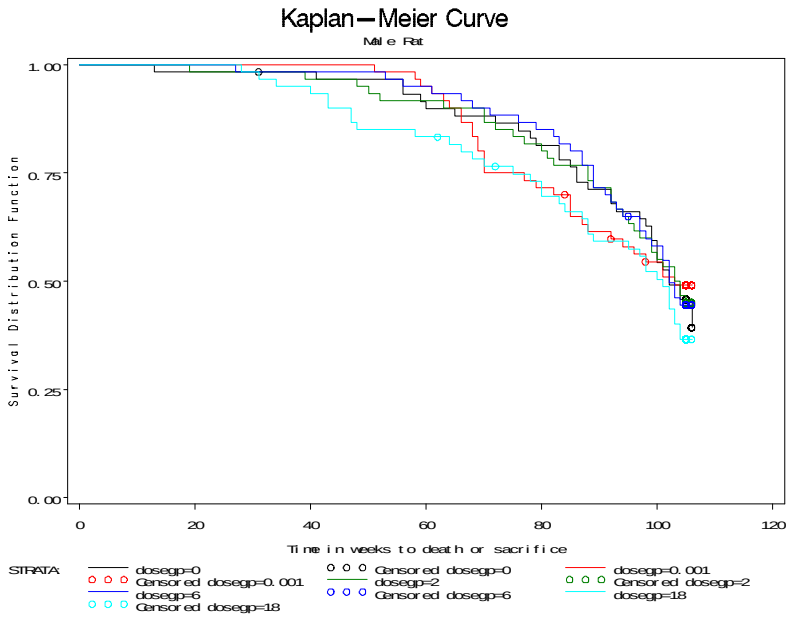
Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

(Continued)

Organ Name	Tumor Name	0 mg Cont N=60	2 mg Low N=60	13 mg Med N=60	80 mg High N=60	P_Value Cont. 1 vs. H
Thyroid Gland	Adenoma, follicular	1	0	0	0	0.4177
	Lymphoma, lymphoblastic, malig	0	3	1	0	.
Tongue	Papilloma	1	1	0	0	0.4177
Trachea	Lymphoma, lymphoblastic, malig	0	2	1	0	.
Urinary Bladder	Lymphoma, lymphoblastic, malig	4	5	5	4	0.4814
Uterus	Hemangiosarcoma	1	0	0	0	0.4177
	Leiomyoma	4	5	1	2	0.4936
	Lymphoma, lymphoblastic, malig	1	0	2	0	0.4177
	Polyp	7	1	2	0	0.9815
	Sarcoma, histiocytic	0	4	2	0	.
	Sarcoma, undifferentiated	0	0	1	0	.
Uterus, Cervix	Leiomyoma	1	0	0	3	0.2034
	Leukemia, granulocytic	0	0	1	0	.
	Lymphoma, lymphoblastic, malig	0	3	2	0	.
	Polyp	1	0	0	0	0.4177
	Sarcoma, histiocytic	1	0	1	0	0.4177
Vagina	Lymphoma, lymphoblastic, malig	0	1	1	1	0.4177

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

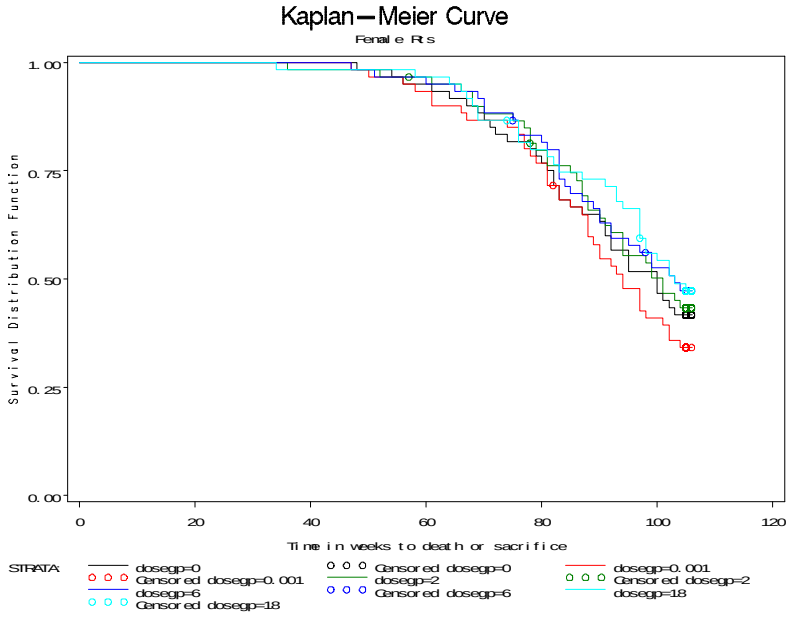
Male Rats



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

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

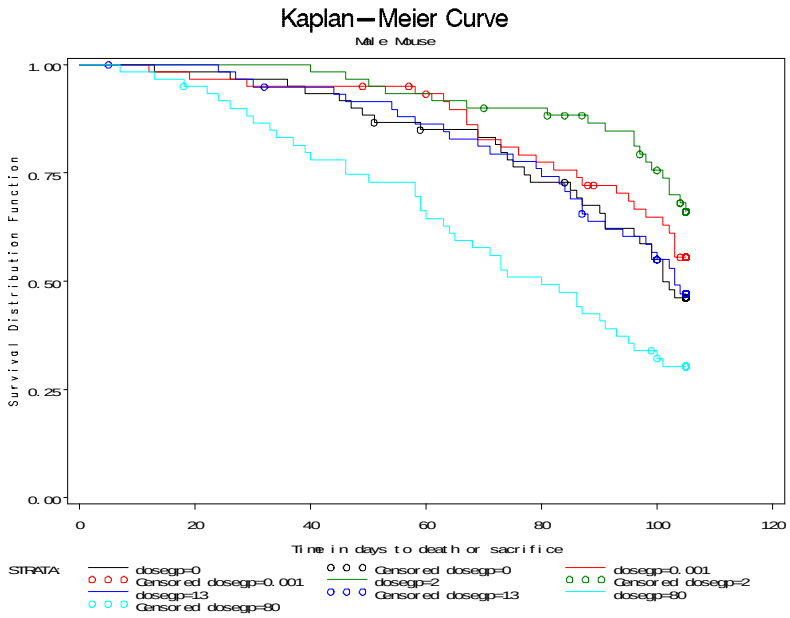
Female Rats



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

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

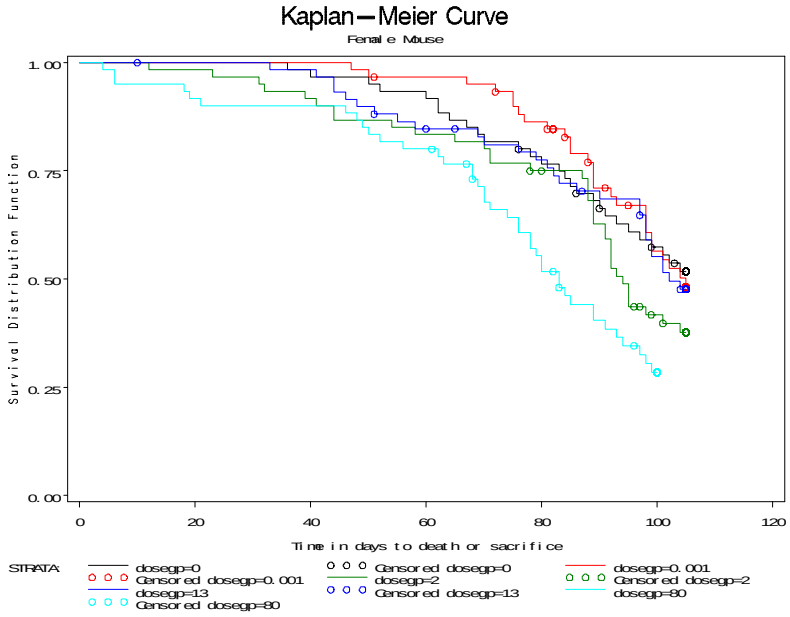
Male Mice



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

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22250	ORIG 1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS

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KARL K LIN
07/30/2009
Concur with review