CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

The pivotal study A2304 was designed to assess a population of patients with secondary progressive multiple sclerosis (SPMS). The primary efficacy analysis demonstrated a statistically significant reduction of the risk of 3-month confirmed disability progression (CDP) in the siponimod group compared to the placebo group (HR =0.79, p =0.0134). However, the clinical distinctions between relapsing-remitting multiple sclerosis (RRMS) and SPMS can be difficult. For this study to be able to claim for SPMS indication, it seems necessary to evaluate whether the population actually enrolled was the intended population and whether the treatment effect on CDP is independent of an effect on relapses. In this study, there appeared to be a nominally highly significant effect of siponimod on the annualized relapse rate, suggesting that the effect on disability progression could be partially due to the siponimod's effect on relapses. Sensitivity/supportive analyses of the effect on 3-month CDP independent of an effect on relapses or in the subgroup of non-relapsing patients suggested a hazard ratio or relative risk in the range of 0.82-0.87, which was smaller and did not reach nominal statistical significance.

The blinding for the study may not be adequately maintained throughout the course of the trial. The analysis of 3-month CDP after removing the potentially unblinded subjects yielded a relative risk reduction of 17%, which was numerically smaller compared to 21% for FAS. The smaller treatment effect may be unlikely to occur by chance, based on the simulation using a bootstrap type process.

The analysis of the first key secondary endpoint (time to 3-month confirmed worsening in T25W of at least 20% from baseline) showed a risk reduction of 6.2%, which did not reach statistical significance. Benefits in favor of siponimod were observed on T2 lesion volume (the second key secondary endpoint; nominal p <0.0001) and annualized relapse rate (exploratory endpoint; nominal p <0.0001). The potential unblinding did not affect the results for T2 lesion volume or annualized relapse rate.

For the Phase 2 supportive study A2201, the primary efficacy endpoint was met. A dose-response relationship was demonstrated among the five doses of siponimod and placebo during 3 months of treatment in patients with relapsing-remitting multiple sclerosis (RRMS), measured by the number of combined unique active lesions (CUAL, p =0.0001 for the Emax model).

In conclusion, the data overall provided statistical evidence to support the efficacy of siponimod in treating patients with relapsing forms of MS. However, the Study A2304 did not appear to provide sufficient evidence that siponimod slows progression independent of relapses to support a claim for SPMS.

2 INTRODUCTION

2.1 Overview

Siponimod (BAF312) is being developed under IND 76122 as a treatment for multiple sclerosis (MS). The Phase 3 Study A2304 was designed to demonstrate the efficacy of siponimod for patients with secondary progressive multiple sclerosis (SPMS). Additional supportive efficacy data were collect in the Phase 2 study A2201 in patients with relapsing-remitting MS (RRMS).

Study A2304 was a multicenter, randomized, double-blind, parallel-group, placebo-controlled Phase 3 study in 1651 patients (1105 in siponimod 2 mg once daily group, 546 in placebo group). The median duration of double-blind treatment was 18 months. The study was intended to enroll patients with SPMS, defined as patients with a progressive increase in disability of at least 6 months duration independent of concurrent relapses. The entry criteria included an Expanded Disability Status Scale (EDSS) of 3.0 to 6.5 (inclusive), attestation by the investigator in a written statement that the disease had entered the progressive stage at least 6 months prior to enrollment, and evidence of progression as measured by EDSS in the prior 2 years, or centrally adjudicated clinical evidence if documented EDSS scores were not available (however, the attestations of SPMS stage and the central adjudication of disease progression were not properly conducted; see clinical review for additional details). Patients had to have no evidence of relapse or corticosteroid treatment within 3 months prior to randomization. The primary endpoint was time to 3-month confirmed disability progression (CDP).

Study A2201 was an adaptive dose-ranging Phase 2 study evaluating the dose response for the MRI-based efficacy in 297 RRMS patients. Patients had to have either at least 2 relapses in the past 2 years or 1 relapse in past 1 year or a positive Gd-enhanced MRI scan at screening MRI and an EDSS score at screening of 0 to 5.0, inclusive.

Table 1: Completed clinical studies in MS patients

Study	Population	Design	Patients randomized	Treatment duration	Key endpoints
A2304	Intended for SPMS	Randomized, double-blind, multi-center, placebo- controlled	N=1651 Placebo or 2 mg (1:2 randomization)	Variable, up to 37 months	3mCDP, time to 3m confirmed 20% worsening on T25W, T2 lesion volume
A2201	RRMS	Randomized, double-blind, multi-center, placebo- controlled, adaptive dose ranging	N=297 Period 1: Placebo, 0.5 mg, 2 mg, 10 mg Period 2: Placebo, 0.25 mg, 1.25 mg	Period 1: 6 months Period 2: 3 months	Number of CUAL

3mCDP: 3-month confirmed disability progression; 6mCDP: 6-month confirmed disability progression; T25W: timed 25-foot walk; ARR: annualized relapse rate; CUAL: combined unique active lesions on monthly brain MRIs.

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, which are in the following directories:

\\CDSESUB1\evsprod\NDA209884\0000
\\CDSESUB1\evsprod\NDA209884\0005\m5\datasets
\\CDSESUB1\evsprod\NDA209884\0029\m5\datasets\baf312a2201\analysis\legacy\programs

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This reviewer could trace how the primary endpoint was derived from the raw data. Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

The blinding for Study A2304 may not be adequately maintained throughout the course of the trial. As a measure to minimize the potential unblinding due to heart rate reductions after the first dose, the sponsor utilized a first dose team and a First Dose database that were separate from the treating and evaluating neurologists and the Main study database. However, 34 users of the Main database and 3 EDSS raters had inappropriate access to the First Dose database, which potentially compromised the treatment blinding for over 100 subjects.

3.2 Evaluation of Efficacy

3.2.1 Study A2304

3.2.1.1 Study Design and Endpoints

Study A2304 was initiated on 20 December 2012, and the Core Part of the study was completed on 29 April 2016. The original protocol was dated 12 July 2012. There were 4 amendments and the final protocol was dated 23 March 2016. An additional requirement was added at the time of Amendment 3 (dated 06 October 2015, which was after the interim futility analysis) so that more than 95% of patients would have been randomized 1 year before the Core Part of the study was stopped. Other changes were considered minor and had minimal impact on the study results. The original SAP was documented prior to study initiation. There were 4 amendments dated after the unblinded interim futility analysis and prior to database lock, which included additional exploratory analyses and subgroup analyses.

Study Design

The Core Part of this study was a randomized, multicenter, double-blind, placebo-controlled parallel-group study in patients with SPMS. This study was conducted in a total of 294 centers in 31 countries. Approximately 1530 eligible patients were to be randomized in a 2:1 ratio to receive either siponimod or placebo, stratified by country. Evaluations were performed at screening and every 3 months and at the time of relapse. MRI evaluations were performed at screening and every 12 months. Patients who experienced 6-month CDP during the treatment period had the following options:

- Continue on the blinded study treatment assignment;
- Discontinue the blinded study treatment and switch to open-label siponimod, continuing the regularly scheduled visits;

- Discontinue the blinded study treatment and start any other MS treatment, continuing under the abbreviated visit schedule.

This was an event-driven study that was to terminate when the required number of 374 3-month CDP would be observed. The protocol was updated after the interim analysis to additionally require that more than 95% of patients would have been randomized for 1 year or more. Furthermore, an Extension Part was added, in which eligible patients were to receive open-label siponimod.

Interim analysis

A futility interim analysis (IA) was to be performed when at least 50% of the required numbers of 3-month CDP were available. The DMC recommended on 14 July 2015 that the study would continue and not be stopped for futility, based on more than 60% of the total planned events available then.

Originally the protocol allowed an assessment for stopping the trial early for efficacy at the interim analysis, using an O'Brien-Fleming boundary. However, prior to the futility interim analysis being performed it was decided that even if this stopping boundary was reached the study was to continue to allow the collection of sufficient long-term safety and efficacy data. Nevertheless, the alpha level for the final analysis was calculated considering the alpha level spent at IA to achieve an overall type I error rate smaller than 5%.

A blinded sample size review was performed prior to the unblinded futility interim analysis, and it was decided to proceed as planned in the protocol. However, after the interim analysis, the protocol was amended to extend the duration of the study which essentially increased the number of events. Reviewer's comment: In principle, the type I error rate might be compromised without proper statistical adjustment for such an increase of the number of events.

Efficacy Endpoints

The primary efficacy endpoint was time to 3-month CDP based on Expanded Disability Status Scale (EDSS) which ranges from 0 (normal) to 10 (death due to MS). Disability progression was defined as an increase of 1 point in patients with a baseline EDSS score of 3.0 to 5.0, or 0.5 point in patients with a baseline EDSS score of 5.5 to 6.5. Sustained disability progression for 3-month CDP was determined by confirming that the criteria were also met at visits 3 months (i.e., ≥76 days) later, with any intervening EDSS values also meeting the criteria for change. EDSS was assessed by an independent EDSS rater every 3 months and at the time of suspected relapse. Only the EDSS assessments obtained at scheduled visits (including follow-up visits) and in the absence of relapse (confirmed or unconfirmed) were to be used for confirmation of progression. MS relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. A confirmed MS relapse was defined as accompanied by a clinically-relevant change in the EDSS performed by the independent EDSS rater.

There were two key secondary endpoints: time to 3-month confirmed worsening of at least 20% from baseline in timed 25-foot walk (T25W); and change from baseline in T2 lesion volume, averaged over Month 12 and Month 24.

3.2.1.2 Statistical Methodologies

Efficacy analyses were conducted on Full Analysis Set (FAS), consisting of all randomized patients who took at least one dose of study medication.

A hierarchical testing procedure was implemented for the primary and key secondary endpoints. The primary endpoint was to be tested at a significance level (two sided) adjusted according to the O'Brien-Fleming alpha spending function, which was calculated to be 0.0434. The key secondary endpoints were to be tested in the order listed in the previous section at a two-sided significance level of 0.05 (Reviewer's note: in principle, the type I error rate of the key secondary endpoints might be compromised without proper statistical adjustment of alpha level for testing these endpoints).

The primary endpoint of 3-months CDP was analyzed using a Cox proportional hazards model with treatment, country, baseline EDSS and SPMS group (with/without superimposed relapses in the 2 years prior to screening) as covariates. The time to 3-month confirmed worsening in T25W was analyzed similarly using a Cox model, with an additional covariate of baseline T25W. The change from baseline in T2 lesion volume was tested using a mixed model for repeated measures (MMRM) with an unstructured covariance matrix. The model included the following terms: treatment, visit (categorical), country, age, SPMS group, T2 volume at baseline, and number of T1 Gd-enhancing lesions at baseline (continuous).

Sensitivity Analyses

In the primary analysis, data for patients receiving open-label therapy after discontinuing study treatment were included. Sensitivity analyses assessing the impact of study/treatment discontinuations were specified as follows:

- Assuming that patients with a start of a tentative disability progression, who discontinued the Core Part prematurely within the 3-month confirmation interval, had confirmed progression.
- Assuming that patients who discontinued the Core Part prematurely without reaching the endpoint had confirmed progression at the time they stopped study participation.
- Assuming that all patients who discontinued the Core Part prematurely for reasons related to lack of efficacy without reaching the endpoint had confirmed progression.
- Using Modified Full Analysis Set (MFAS), in which onset of disability progression could not have occurred after the first dose of MS disease modifying therapy (DMT) or open-label siponimod treatment.

Subgroups Analyses

Subgroup analyses were performed to examine whether the treatment difference was consistent

in patients with different demographic/baseline or post-treatment disease characteristics. Cox models were used with the subgroup covariate and a treatment by subgroup interaction term in addition to the terms in the primary analysis. The following subgroups of patients were defined:

- SPMS patients with or without superimposed relapses in the 2 years prior to the screening visit. This was noted as "baseline definition" of relapsing or non-relapsing.
- Patients with or without at least one confirmed relapse at any time on or after Day 1. This was noted as “post-treatment definition” of relapsing or non-relapsing.
- Treatment history: previous interferon beta-1b treatment, previous MS-DMT treatment, (previous interferon treatment was added as a post-hoc analysis).
- Rapidly evolving patients (an EDSS change ≥1.5 in the 2 years prior to or at study start).
- Disease course: moderate/severe subgroup with Global MSSS ≥4.
- Number of T1 Gd-enhancing lesions at baseline (0; ≥1).
- Baseline demographic factors.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 1651 patients were randomized in a 2:1 ratio to receive either siponimod 2mg (n=1105) or placebo (n=546). Six patients randomized to siponimod were excluded from efficacy analyses, including 5 patients who never received study drug, and 1 patient who did not sign informed consent before starting study procedures. A total of 903 siponimod patients (82%) and 424 placebo patients (78%) completed the study. The most common reasons for discontinuation in each group were subject/guardian decision, adverse event, and lack of efficacy (Table 2).

The proportions of patients who completed the treatment on study drug were 67% in siponimod arm and 59% in placebo arm. After prematurely discontinuing double-blind study drug, 11% siponimod and 17% placebo patients continued in the study on open-label siponimod; 12% siponimod and 10% placebo patients continued on other MS treatment with abbreviated visit schedule. The most common reasons for discontinuing double-blind study drug were subject/guardian decision, disease progression, and adverse event (Table 2).

Table 2: Study A2304: Subject disposition

	BAF312 N=1105 n (%)	Placebo N=546 n (%)	Total N=1651 n (%)
Received study drug	**1100 (99.5)**	**546 (100)**	**1646 (99.7)**
Did not receive study drug	**5 (0.5)**	**0**	**5 (0.3)**
Completed Study Core Part	**903 (81.7)**	**424 (77.7)**	**1327 (80.4)**
Discontinued Study Core Part	**202 (18.3)**	**122 (22.3)**	**324 (19.6)**
Primary reason for not completing Study Core Part			
Subject/guardian decision	96 (8.7)	77 (14.1)	173 (10.5)
Adverse event	45 (4.1)	18 (3.3)	63 (3.8)
Lack of efficacy	16 (1.4)	11 (2.0)	27 (1.6)
Physician decision	13 (1.2)	1 (0.2)	14 (0.8)
Lost to follow-up	9 (0.8)	8 (1.5)	17 (1.0)

	BAF312 N=1105 n (%)	Placebo N=546 n (%)	Total N=1651 n (%)
Progressive disease	8 (0.7)	4 (0.7)	12 (0.7)
Non-compliance with study treatment	5 (0.5)	0	5 (0.3)
Protocol deviation	3 (0.3)	1 (0.2)	4 (0.2)
Death	3 (0.3)	1 (0.2)	4 (0.2)
Technical problems	2 (0.2)	0	2 (0.1)
New therapy for study indication	2 (0.2)	1 (0.2)	3 (0.2)
Completed Treatment of study drug	**737 (66.7)**	**322 (59.0)**	**1059 (64.1)**
Prematurely discontinued study drug	**363 (32.9)**	**224 (41.0)**	**587 (35.6)**
Continued on open-label siponimod	116 (10.5)	94 (17.2)	210 (12.7)
Completed Study Core Part	102 (9.2)	77 (14.1)	179 (10.8)
Discontinued Study Core Part	14 (1.3)	17 (3.1)	31 (1.9)
Continued on abbreviated visit schedule	135 (12.2)	57 (10.4)	192 (11.6)
Completed Study Core Part	64 (5.8)	25 (4.6)	89 (5.4)
Discontinued Study Core Part	71 (6.4)	32 (5.9)	103 (6.2)
Primary reason for premature discontinuation from study drug			
Subject/guardian decision	114 (10.3)	71 (13.0)	185 (11.2)
Disease progression	101 (9.1)	81 (14.8)	182 (11.0)
Adverse event	94 (8.5)	28 (5.1)	122 (7.4)
Lack of efficacy	36 (3.3)	27 (4.9)	63 (3.8)
Physician decision	12 (1.1)	13 (2.4)	25 (1.5)
As Per Protocol	3 (0.3)	2 (0.4)	5 (0.3)
Protocol deviation	3 (0.3)	0	3 (0.2)
Dosing error	0	1 (0.2)	1 (0.1)
Technical problems	0	1 (0.2)	1 (0.1)

Source: CSR Table 10-1&10-2.

Overall, the 2 treatment groups were comparable regarding demographic characteristics (Table 3). The study population had a median age of 49 years and were mostly female (60%) and White (95%).

Table 3: Study A2304: Demographics

Demographic variable	BAF312 N=1105	Placebo N=546	Total N=1651
Age groups - n (%)			
18-30	26 (2.4)	12 (2.2)	38 (2.3)
31-40	162 (14.7)	91 (16.7)	253 (15.3)
41-55	716 (64.8)	331 (60.6)	1047 (63.4)
>55	201 (18.2)	112 (20.5)	313 (19.0)
Age (years)			
n	1105	546	1651
Mean (SD)	48.0 (7.84)	48.1 (7.94)	48.0 (7.87)
Median	49.0	49.0	49.0

Demographic variable	BAF312 N=1105	Placebo N=546	Total N=1651
Min - Max	22 - 61	21 - 61	21 - 61
Sex - n (%)			
Female	669 (60.5)	323 (59.2)	992 (60.1)
Male	436 (39.5)	223 (40.8)	659 (39.9)
Race - n (%)			
Asian	31 (2.8)	18 (3.3)	49 (3.0)
Black or African American	7 (0.6)	3 (0.5)	10 (0.6)
Other	12 (1.1)	7 (1.3)	19 (1.2)
Unknown	5 (0.5)	5 (0.9)	10 (0.6)
White	1050 (95.0)	513 (94.0)	1563 (94.7)

Source: CSR Table 11-2.

Overall, the 2 treatment groups were comparable regarding baseline disease characteristic (Table 4). Patients had a median disease duration of about 16 years, and a median EDSS score of 6.0. Most patients (64%) had no relapses in the 2 years prior to screening.

Table 4: Study A2304: Disease baseline characteristics

	BAF312 N=1105	Placebo N=546	Total N=1651
Duration of MS since first symptom (years)			
N	1103	545	1648
Mean (SD)	17.12 (8.39)	16.23 (8.23)	16.83 (8.34)
Median	16.35	15.40	16.04
Min – Max	1.4 - 45.0	1.3 - 43.0	1.3 - 45.0
Time since conversion to SPMS (years)			
N	1103	546	1649
Mean (SD)	3.85 (3.61)	3.56 (3.28)	3.76 (3.51)
Median	2.57	2.52	2.55
Min – Max	0.1 - 24.2	0.1 - 21.7	0.1 - 24.2
Number of relapses in the last 2 years prior to screening			
N	1102	545	1647
Mean (SD)	0.7 (1.20)	0.7 (1.16)	0.7 (1.19)
Median	0.0	0.0	0.0
Min – Max	0 - 12	0 - 8	0 - 12
Number of relapses in the last 2 years prior to screening (categories) - n (%)			
0	712 (64.4)	343 (62.8)	1055 (63.9)
1	199 (18.0)	104 (19.0)	303 (18.4)
2-3	158 (14.3)	81 (14.8)	239 (14.5)
4-5	26 (2.4)	13 (2.4)	39 (2.4)
>5	7 (0.6)	4 (0.7)	11 (0.7)
EDSS			
N	1105	546	1651
Mean (SD)	5.43 (1.076)	5.41 (1.026)	5.42 (1.059)
Median	6.00	6.00	6.00
Min – Max	2.0 - 7.0	2.5 - 7.0	2.0 - 7.0

	BAF312 N=1105	Placebo N=546	Total N=1651
EDSS (categories) - n (%)			
<3.0	6 (0.5)	2 (0.4)	8 (0.5)
3.0-4.5	312 (28.2)	148 (27.1)	460 (27.9)
5.0-5.5	165 (14.9)	100 (18.3)	265 (16.1)
6.0-6.5	620 (56.1)	295 (54.0)	915 (55.4)
>6.5	2 (0.2)	1 (0.2)	3 (0.2)

Source: CSR Table 11-3 &11-4.

3.2.1.4 Results and Conclusions

3.2.1.4.1 Analyses of the Primary Endpoint

Siponimod showed a significant risk reduction of 21% compared to placebo for time to 3-month CDP as measured by EDSS (HR =0.79, p =0.0134; Table 5).

Table 5: Study A2304: Primary analysis of time to 3-month CDP

Treatment	n/N' (%)	Risk reduction	Hazard ratio (95% CI)	p-value
BAF312(N=1099)	288/1096(26.3)	21.2%	0.79 (0.65; 0.95)	0.0134
Placebo (N=546)	173/545 (31.7)			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (with non-missing covariates).
Using a Cox model with treatment, country/region, baseline EDSS, and SPMS group as covariates.
Source: CSR Table 11-7, confirmed by this reviewer.

3.2.1.4.1.1 Assessment of the impact of relapses on the effect of BAF312 on disability progression

Per findings from FDA inspection, some of the key entry criteria were not conducted properly, including attestation by the investigator in a written statement that the disease had entered the progressive stage at least 6 months prior to enrollment, and central adjudication of disease progression in the absence of prior EDSS scores (see clinical review for additional details). Therefore, the claim that the subjects in the study population actually had SPMS may be questionable.

SPMS is defined by a progressive increase in disability in the absence of relapses or independent of relapses (i.e., at a similar rate irrespective of individual relapse frequency).Unlike in RRMS, where relapse lead typically to incomplete recovery/remnant disability, they do not appear to have a major impact on disability in progressive MS. In Study A2304, however, the onset of disease progression could be triggered by a relapse, and the proportion of patients with CDP almost doubled for patients with on-study relapse compared to patients without relapse (Table 6). This further supported the concern that the enrolled study population may not be the intended SPMS population.

Table 6: Study A2304: Proportion of patients with 3-month CDP by relapse status

	Patient without confirmed relapse n/N' (%)	Patient with confirmed relapse n/N' (%)
BAF312	237/983 (24)	51/113 (45)
Placebo	122/443 (28)	51/102 (50)
Total	359/1426 (25)	102/215 (47)

N'= number of patients with or without confirmed relapse in each arm.
Source: FDA reviewer.

Although treatment with siponimod in Study A2304 resulted in significant reduction in risk of disability progression in the overall population, siponimod also demonstrated a strong effect on annualized relapse rate (ARR ratio =0.445, nominal p <0.0001; Table 7). This raised the question of siponimod's ability to delay CDP unrelated to its effect on relapses.

Table 7: Study A2304: ARR for confirmed relapses

Treatment	Estimated ARR (95% CI)	ARR ratio (95% CI)	Nominal p-value
BAF312 (N=1099)	0.071 (0.055; 0.092)	0.445 (0.337; 0.587)	<0.0001
Placebo (N=546)	0.160 (0.123; 0.207)		

Obtained from a negative binomial regression model adjusted for treatment, country/region, baseline EDSS, baseline number of T1 Gd-enhancing lesions, and SPMS group.
Source: CSR Table 11-12, confirmed by this reviewer.

The following analyses were conducted to evaluate the evidence of the treatment effect on slowing disability progression independent of an effect on relapses or in the subgroup of non-relapsing patients.

Treatment effect on 3-month CDP in non-relapsing patients

Subgroups based on pre-study and on-study relapses were specified in the SAP. The subgroup of patients without on-study relapse was defined based on post-randomization criteria. The result for this subgroup may not be interpretable due to confounding factors as both relapse and disability progression may have been impacted by treatment. For the subgroup of patients without relapse in the 2 years prior to study, the analysis showed a hazard ratio of 0.86 (Table 8), suggesting a smaller treatment effect on CDP compared to the overall population. Additionally, there was still a nominally highly significant treatment effect on relapse in this subgroup (p<0.0001, result not shown in table). Therefore, the criterion of no relapse in the 2 years prior to study may not be sufficient to properly identify non-relapsing patients.

Additionally, the applicant performed post-hoc principal stratum (PS) analyses. The principal stratum of interest was a subgroup of patients that would not relapse within a given period of time, whether they receive placebo or siponimod. Subsequently, the principal stratum membership is not affected by treatment and can thus be regarded as a pre-treatment (baseline) characteristic. However, the stratum membership is missing for some subjects and need to be predicted. For example, subjects in siponimod group who had no relapse during the study may or may not belong to the PS of non-relapsing patients. The applicant used Bayesian framework to

predict the missing stratum membership and estimate the treatment effect within the PS. To perform the analyses, the following assumptions are required:

1. Monotonicity assumption that a patient who would not have relapsed if untreated (receiving placebo) would not experience a relapse if assigned to the siponimod arm.
2. Assumptions about missing data and covariates as not all patients had available data for the period of time being considered due to variable follow-up time. Specifically, it was assumed that
    a. principal stratum membership is independent of missingness conditional on the covariates; and
    b. disability is independent of missingness conditional on stratum membership, covariates and treatment.
3. Assumption of a probabilistic model that captures the data-generating distributions and prior distributions for each parameter (including probability for stratum membership and stratum-specific probability of disability progression for each treatment group) for the Bayesian analyses.

Reviewer's note: the above assumptions are strong. Furthermore, the median follow-up time in this study was 18 months and the maximum follow-up time was 37 months. Therefore, the PS of subjects who would not relapse within a period of time being considered (12 months, 18 months, or 24 months) does not guarantee that all subjects in the PS would not experience relapse for the entire duration of this study. For example, about 25% of the first relapse occurred after 12 months in the placebo group. Therefore, 12-month PS may not be a true subgroup of non-relapsing patients for this study.

The results of principal stratum analyses were presented in Table 8. In this study, 87% patients did not experience on-study relapse, including those who might have relapse had them not been treated with siponimod. Based on the PS analysis, the estimated percentages of patients who would not relapse in 18 months (median follow-up time) regardless of treatment was 84%. The proportions of patients with 3-month CDP were much smaller (16% for siponimod and 18% for placebo) in the principle stratum of non-relapsing patients, compared to the overall study population (26% for siponimod and 32% for placebo). For the principal stratum of non-relapsing patients within 18 months, the relative risk for 3-month CDP was 0.86, with 95% CI of (0.57, 1.24), indicating a possible 14% risk reduction by siponimod treatment not driven by an effect on relapses. The 24-month PS included fewer patients, subsequently the estimate of hazard ratio was associated with broader 95% CI. The applicant also conducted the PS analyses without the monotonicity assumption. The estimated relative risk was 0.86 for 18-months PS and 0.85 for 24-months PS.

Table 8: Study A2304: Exploratory analyses of the 3-month CDP in non-relapsing patients

	BAF312 %	Placebo %	Estimate of Treatment effect*	95% CI
Subgroups (observed proportion of the subgroup)				
Patients without relapse in the 2 years prior to study (64%)	27	29	0.87	(0.68; 1.11)
Patients without on-study relapse (87%)	24	28	0.85	(0.69; 1.06)
Principal stratum of non-relapsing patients (estimated proportion of the PS)				
Patients who would not relapse in 12 months (87%)	16	19	0.80	(0.56; 1.08)
Patients who would not relapse in 18 months (84%)	16	18	0.86	(0.57; 1.24)
Patients who would not relapse in 24 months (80%)	17	20	0.82	(0.48; 1.32)
Principal stratum without monotonicity assumption				
Patients who would not relapse in 18 months			0.86	(0.52; 1.37)
Patients who would not relapse in 24 months			0.85	(0.48; 1.45)

*For subgroup analyses, Cox model was performed, and the estimates are hazard ratio. For principal stratum analyses, the estimation was carried out with Bayesian logistic regression for the disability progression rate at 12, 18 and 24 months and the estimates are relative risk.
Source: CSS Statistical Overview Table 2-2, Table 2-3, Table 4-11 and FDA reviewer.

Treatment effect on disability progression independent of an effect on relapses in the overall study population

The first analysis performed to evaluate the effect on CDP and not related to relapse in the overall population was to reset baseline after a relapse. For this analysis, the onset of progression could not occur during a relapse and, if the EDSS values did not return to baseline after a relapse, the new EDSS value after resolution of the relapse was used to establish a new baseline value. Accordingly, the EDSS score at the time of a subsequent tentative progression was to be compared to the new baseline EDSS score established after relapse rather than to the EDSS score measured at the original baseline visit. If the tentative progression was before the relapse, the original baseline value was used. Based on this definition, the percentage of patient with 3-month CDP (not related to relapse) was 24% for siponimod and 26% for placebo. The hazard ratio was 0.89 (Table 9), indicating a risk reduction of 11%. However, this analysis may be biased as both relapse and disability progression may have been impacted by treatment. There was a higher percentage of placebo patients with on study relapse, for whom there was less time to observe a CDP after relapse. Additionally, patients may switch to alternative medication after a relapse-related CDP, which further limited the possibility to show a treatment effect.

The second analysis examined the hypothetical scenarios where no relapse would be observed in the study and was performed using a Cox model with censoring at the time of first relapse. The estimated hazard ratio based on this analysis was 0.88 (Table 9). Similar to the analysis of 'reset baseline after a relapse', this estimate may be biased as the censoring at time of relapse was related to the treatment received and was therefore likely informative.

To correct for such potential bias, the applicant conducted a Cox model with Inverse Probability Censoring Weight (IPCW). Essentially, the IPCW method intended to compensate informatively censored patients by patients with similar characteristics who were not censored. It computed weights as the inverse of the probability of not observing a relapse via modelling. The applicant's analysis used MRI covariates in the computing of the weights which subsequently excluded 3% patients with missing MRI data. The resulting Cox model with IPCW indicated a hazard ratio of 0.86 (Table 9). The reviewer conducted an analysis without the MRI covariates so more patients were included. The results were similar.

The last analysis used simulations from empirical distribution to generate a hypothetical scenario where relapse rate would be similar between the two arms. In the applicant's analysis, a larger weight was given to patients with confirmed relapses in the siponimod arm so that the relapse rate was similar between siponimod and placebo. Similarly, this reviewer conducted an analysis in which a larger weight was given to placebo patient without confirmed relapses. The results of the two analyses were comparable, with a hazard ratio of 0.82~0.83. In this approach, however, the weights were computed based on a post-randomization outcome (presence of a relapse) therefore could lead to bias. Although the applicant attempted to address the potential bias using stratified simulations, it was not clear if such bias could be completed corrected as post-randomization outcomes were still utilized to compute the weights in the stratified simulations.

Table 9: Study A2304: Estimation of effect of BAF312 on CDP independent of treatment effect on relapses

Analysis	BAF312 %	Placebo %	Hazard ratio	95% CI
Reset baseline after a relapse (N'=1641)	24	26	0.89	(0.72, 1.10)
Censoring at time of first relapse (N'=1641)	23	24	0.88	(0.71, 1.09)
IPCW* (applicant's analysis) (N'=1584)	22	24	0.86	(0.70, 1.04)
IPCW* (reviewer's analysis) (N'=1638)	22	24	0.87	(0.72, 1.06)
Simulations based on empirical distribution (applicant's analysis)			0.82	(0.68, 0.99)
Simulations based on empirical distribution (reviewer's analysis)			0.83	(0.68, 1.004)

*Inverse Probability Censoring Weight to correct for informative censoring.
Source: CSS Statistical Overview Table 2-4, Table 4-5 and FDA reviewer.

Summary of Treatment effect of BAF312 on disability progression

The analyses of 'resetting baseline after a relapse' and 'censoring at time of first relapse' may be biased in favor of placebo, and the resulting treatment effects (hazard ratio of 0.88~0.89) were potentially under-estimated. Other sensitivity/supportive analyses yielded a hazard ratio or relative risk in the range of 0.82-0.87 for 3-month CDP, smaller than the treatment effect for the overall population. These analyses may suggest the possibility of a treatment effect on disability progression independent of relapse. However, these analyses in general required many assumptions and did not reach nominal statistical significance, therefore were not statistically conclusive.

3.2.1.4.1.2 Assessment of the impact of potential unblinding

The blinding for the study may not be adequately maintained throughout the course of the trial. As a measure to minimize the potential unblinding due to heart rate reductions after the first dose, the sponsor utilized a first dose team and a First Dose database that were separate from the treating (investigator) and evaluating (EDSS rater) neurologists and the Main study database. However, 34 users of the Main database had access to the First Dose database, which compromised the treatment blinding for 101 subjects. Additionally, 3 EDSS raters had inappropriate access to the First Dose database, potentially compromising the blinding for 13 subjects. Taking into account the duplicate counting of 2 subjects, the treatment blinding was potentially compromised for a total of 112 subjects.

To assess the potential impact of the improper dual database access on the efficacy result, the reviewer compared the results without the affected subject to the results for FAS. If removing the affected subjects results in a smaller treatment effect compared to that of FAS, it may raise concerns about the study integrity; if the results are similar, then the potential unblinding may be less of a concern. Table 10 showed that the analysis of 3-month CDP after removing the affected subjects (either 101 or 112 subjects as mentioned above) yielded a relative risk reduction of 17%, which was numerically smaller compared to 21% for FAS.

Table 10: Study A2304: Analyses of time to 3-month CDP after removing potentially unblinded subjects

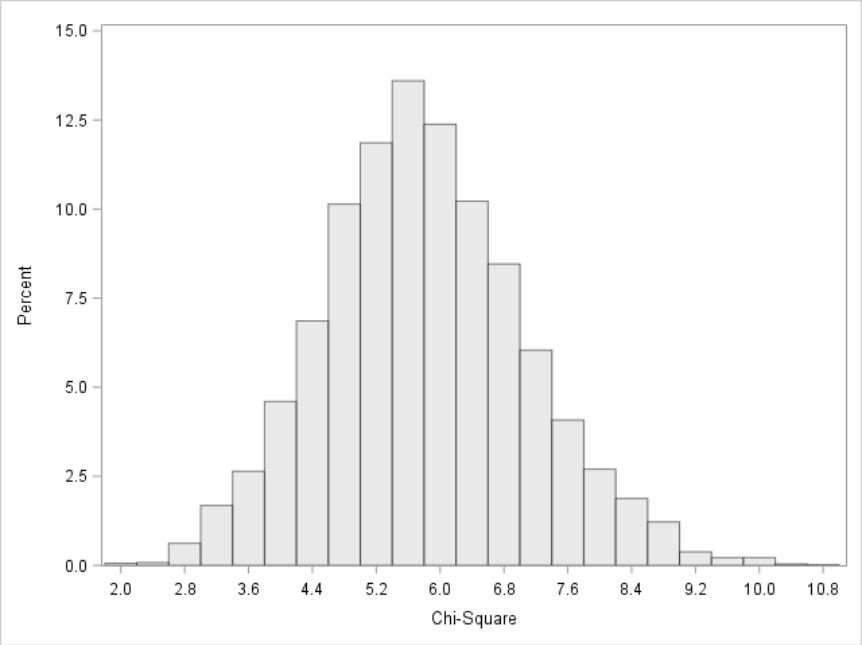
Treatment	n/N' (%)	Risk reduction	Hazard ratio (95% CI)	Chi-Square / p-value
Removing 101 subjects				
BAF312	274/1031(26.6)	17%	0.83 (0.68; 1.01)	3.4825 / 0.062
Placebo	157/509 (30.8)			
Removing 112 subjects				
BAF312	272/1024(26.6)	17%	0.83 (0.68; 1.01)	3.5146 / 0.061
Placebo	156/505 (30.9)			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (with non-missing covariates).
Source: FDA reviewer.

This reviewer further performed a simulation using a bootstrap type process that repeatedly removed 101 or 112 random subjects from the overall population and conducted the analysis of 3-month CDP. Based on the empirical distributions of the Chi-Square test statistic from 5000 repeats, illustrated in Figure 1 and Figure 2, we calculated the probability of observing a more extreme test statistic, that is, the p-value for testing if the treatment effect is the same for the population without the affected subjects and for the population after randomly removing the same number of subjects. The probability of observing a Chi-Square test statistic <3.4825 when randomly removing 101 subjects from FAS is 0.028, and the probability of observing a Chi-Square test statistic <3.5146 when randomly removing 112 subjects from FAS is 0.037, approaching to the 1-sided significance level of 0.025. Therefore, it is of concern that the smaller

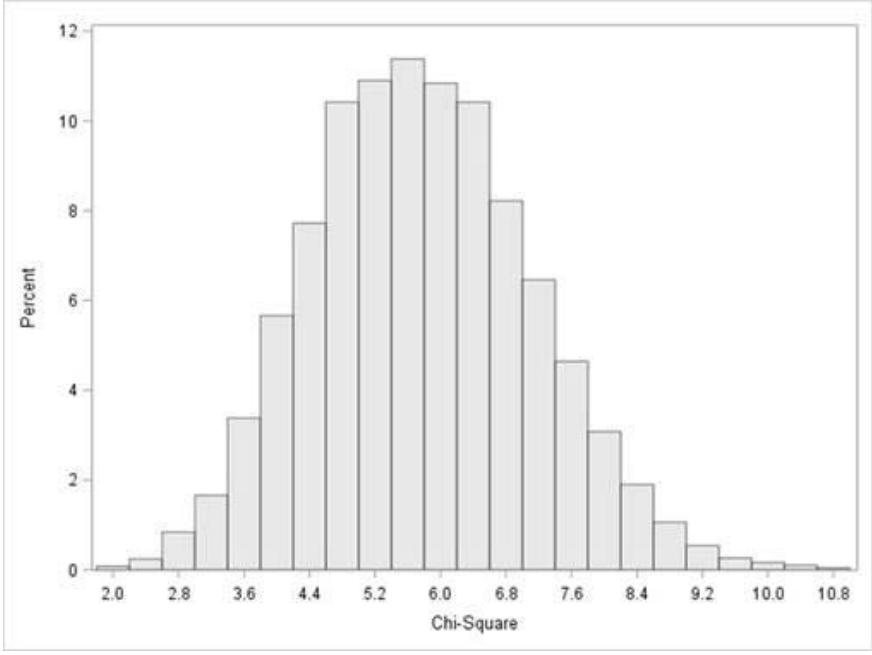
treatment effect on CDP after removing the potentially unblinded subjects may be unlikely to occur by chance.

Figure 1. Study A2304: Empirical distribution of Chi-square test statistic when randomly removing 101 subjects from the FAS



Source: FDA reviewer.

Figure 2. Study A2304: Empirical distribution of Chi-square test statistic when randomly removing 112 subjects from the FAS



Source: FDA reviewer.

3.2.1.4.1.3 Additional sensitivity analyses

Sensitivity analyses for handling study/treatment discontinuation confirmed the primary analysis, showing nominally statistically significant differences favoring siponimod, regardless of how the discontinuations were handled (Table 11).

Table 11: Study A2304: Sensitivity analyses for handling study/treatment discontinuation

Analysis	BAF312 %	Placebo %	Hazard ratio (95% CI)	Nominal p-value
Tentative progression at the end of the Core Part was categorized as CDP	28	35	0.76 (0.63; 0.91)	0.0028
Discontinuation for any reason was categorized as CDP	41	48	0.82 (0.70; 0.96)	0.0123
Discontinuation for lack of efficacy or progressive disease was categorized as CDP	28	33	0.81 (0.68; 0.98)	0.0282
CDP could not occur after starting MS-DMT or open-label siponimod treatment	26	32	0.79 (0.65; 0.95)	0.0153

Source: CSR Table 14.2-1.7, Table 14.2-1.9, Table 14.2-1.11, Table 14.2-1.17.

Supportive analyses based on more strict definition of sustained CDP were conducted. The 6-month CDP required that the tentative disease progression was confirmed at 6 months later. The 3-month CDP sustained until end of Core Part required that progression was confirmed at a scheduled visit performed at least 3 months later and every EDSS score obtained after onset of the tentative progression until the end of Core Part met the progression criteria. The analyses showed a risk reduction of about 25% to 26% for siponimod relative to placebo (Table 12), supporting the results obtained for the primary analysis.

An additional supportive analysis was performed for the time period from study start to date of the 374th 3-month CDP event according to the original protocol assumptions (i.e. prior to protocol amendment 3 extending the duration of the study). This analysis showed a risk reduction of 24% for siponimod (Table 12), consistent with the primary analysis.

Table 12: Study A2304: Supportive analyses for sustained CDP

Analysis	BAF312 %	Placebo %	Hazard ratio (95% CI)	Nominal p-value
6-month CDP	20	26	0.74 (0.60; 0.92)	0.0058
3-month CDP sustained until end of Core Part	21	27	0.75 (0.61; 0.92)	0.0060
Only the first 374 3mCDP were included	21	26	0.76 (0.61; 0.93)	0.0093

Source: CSR Table 14.2-1.19, Table 14.2-1.18 & Table 14.2-4.1.

The primary analysis using Cox model did not include 4 patients whose data on the number of relapses in the 2 years prior to screening was not available. A log rank test, which was essentially a Cox model without covariates, included these 4 patients and yielded similar results (nominal p =0.0129, results not shown in the table), suggesting that covariates and exclusion of the 4 patients did not affect the efficacy conclusion.

3.2.1.4.2 Analyses of the Key Secondary Endpoints

The first key secondary endpoint of time to 3-month confirmed worsening in T25W did not reach statistical significance. The hazard ratio was 0.94 in favor of the siponimod group (p =0.4398; Table 13).

Table 13: Study A2304: Time to 3-month confirmed worsening in T25W of at least 20% from baseline

Treatment	n/N'	(%)	Hazard ratio (95% CI)	p-value
BAF312 (N=1099)	432/1087	(39.7)	0.94 (0.80; 1.10)	0.4398
Placebo (N=546)	225/543	(41.4)		

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates).
Using a Cox model with treatment, country/region, baseline EDSS, baseline T25W, and SPMS group as covariates.
Source: CSR Table 11-9, confirmed by this reviewer.

As the first key secondary endpoint failed to show statistical significance, the testing procedure stopped and the analysis of change from baseline in T2 lesion volume was considered descriptive. The average increase over Month 12 and 24 in T2 lesion volume was numerically smaller in the siponimod, with nominal p <0.0001 (Table 14).

Table 14: Study A2304: Change from baseline in T2 lesion volume

Treatment	N'	LSmeans (SE)	Difference (95% CI)	Nominal p-value
BAF312 (N=1099)	995	183.9 (66.33)	-695.3 (-877.3; -513.3)	<0.0001
Placebo(N=546)	495	879.2 (85.43)		

N'=number of subjects included in the analysis (i.e. with post-baseline MRI scan and non- missing covariates)
Obtained from a repeated measures model.
Source: CSR Table 11-10, confirmed by this reviewer.

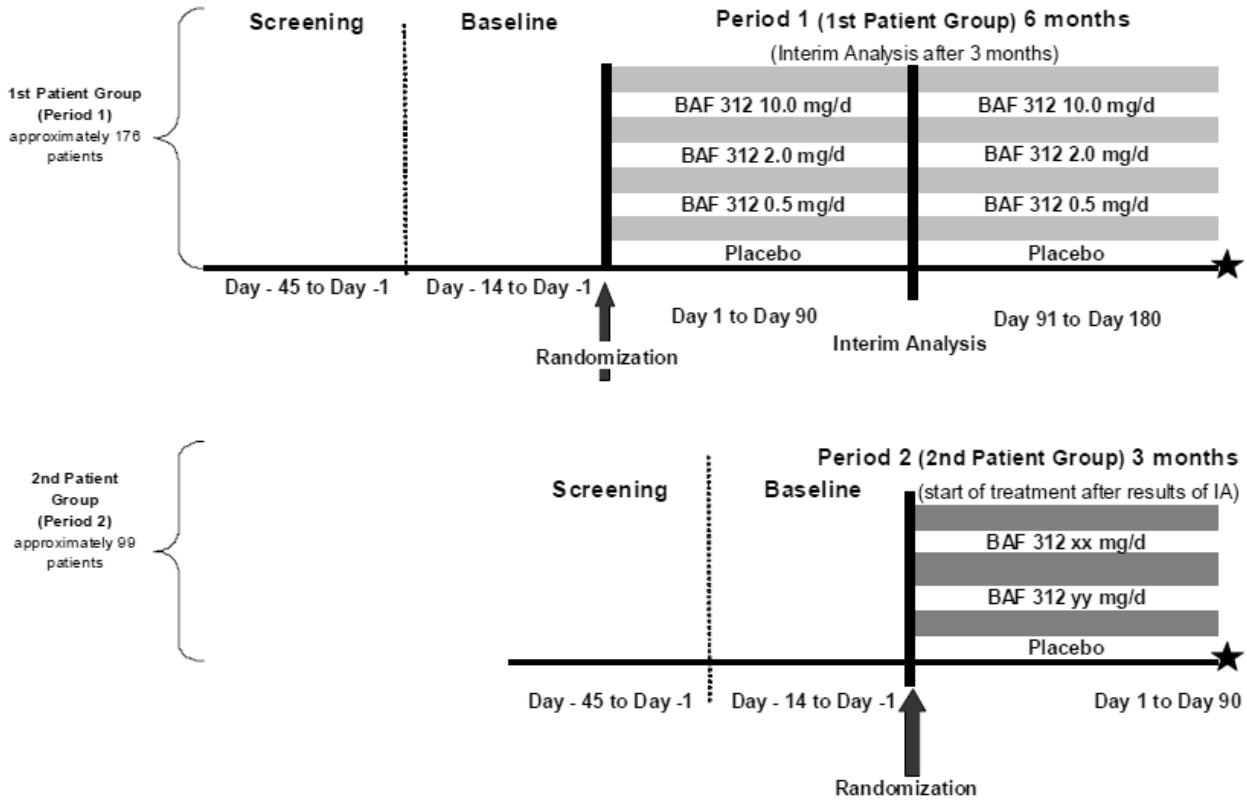
3.2.2 Study A2201

3.2.2.1 Study Design and Endpoints

Study A2201 was initiated on 30 March 2009 and completed on 4 May 2011. This was a double-blind, randomized, multi-center, adaptive dose-ranging, placebo-controlled, parallel-group study in 297 patients with RRMS. The study used an adaptive design in which patients were randomized in two separate cohorts in Period 1 and Period 2, respectively, separated by an interim analysis (IA). In Period 1, patients were randomized in a ratio of 1:1:1:1 to receive siponimod 10mg/d, 2mg/d, 0.5mg/d, or placebo for 6 months. An unblinded IA was performed when 181 patients randomized in Period 1 had completed 3 months. The purpose of the IA was to decide whether to stop the study or to continue the study with sample size re-estimation, and to select two additional doses to be investigated in Period 2. After IA, patients were randomized in a ratio of 4:4:1 to siponimod 1.25mg/day, 0.25mg/day, or placebo for 3 months. MRI

evaluations were performed monthly, neurological evaluations every 3 months and at the time of relapse.

Figure 3. Study A2201: Study design



Source: CSR Figure 9-1.

The primary efficacy objective was to evaluate the dose response relationship among five doses of siponimod and placebo during 3 months of treatment in patients with RRMS. The primary efficacy variable was defined as the monthly number of combined unique active MRI lesions (CUAL) during 3 months of treatment. CUAL were defined as new gadolinium [Gd]-enhanced lesions on T1-weighted MRI scans or new or enlarging lesions on T2-weighted MRI scans, without double-counting of lesions.

Secondary endpoints included MRI variables: number of monthly new Gd-enhanced T1 lesions, number of all monthly Gd-enhanced T1 lesions, number of monthly new or enlarging T2 lesions, number of new T1 hypointense lesions from baseline to end of treatment, proportion of patients without any new MRI disease activity; relapse variables: Annualized Relapse Rate (ARR), i.e. all relapses, confirmed and unconfirmed, ARR (confirmed relapses only), proportion of relapse-free patients (confirmed relapses only); EDSS. All secondary endpoints were considered exploratory as a testing procedure that controls the overall type I error was not pre-specified.

3.2.2.2 Statistical Methodologies

The primary analysis was based on MCP-mod methodology, conducted in 2 steps. In the first step, a test for a dose-response relationship based on pre-specified candidate models was performed (inferential step). If this test was significant, a dose-response model and target doses of interest were estimated (modeling step). Only the first step of testing an overall dose-response signal was evaluated in this review for the purpose of supporting efficacy. The second step of estimating the target dose was not discussed in this review.

In the inferential step, five candidate models to describe the potential dose-response curve were specified. For each candidate model, a t-statistic was derived based on a linear combination of the mean monthly lesion counts for each individual dose, which were estimated by fitting a negative binomial regression model using the CUAL data up to month 3 visit. One-sided p-value was obtained using null multivariate normal distribution. If the resulting p-value was less than 2.5%, the overall null hypothesis of a flat dose-response curve would be rejected and a dose-response in the shape of the candidate models (one or more) was considered established.

3.2.2.3 Results and Conclusions

3.2.2.3.1 Analyses of the Primary Endpoint

A total of 297 patients were randomized to receive 5 siponimod doses (10mg, 2mg, 1.25mg, 0.5mg, and 0.25mg, n ranged between 42 to 51) or placebo (n=62). For the primary endpoint of CUAL, a test for dose response trend was performed based on the five candidate dose response profiles. The test of a flat dose-response was rejected ($p < 0.025$) by the Emax and one of the Hill Emax profiles (Table 15), demonstrating a statistically significant dose-response relationship among the five siponimod doses and placebo.

Table 15: Study A2201: Testing significance of candidate dose response models at 3 months

Candidate Model	T statistic	p-value (one-sided)*
Linear	1.75	0.070
Emax (with ED50=1mg)	3.93	0.0001
Hill Emax 1 (with ED50=2mg and h=2)	2.53	0.012
Hill Emax 2 (with ED50=3mg and h=3)	1.65	0.086
Exponential (with delta=3.633)	1.20	0.182

* Models with a p-value <0.025 are significantly different from a flat dose-response (i.e. no dose-response) model.
Source: CSR Table 11-5, confirmed by this reviewer.

Although the MCP-mod procedure controlled the type I error rate for the multiple testing of 5 candidate dose-response profiles, it did not account for the unblinded interim analysis that was performed to re-estimate the sample size and choose the two additional doses for Stage 2. Therefore, the overall type I error rate for this study was not preserved. Additionally, the statistician who conducted the unblinded interim analysis was also responsible for the programming of the primary efficacy analysis. Therefore, the integrity of the study and the reliability of the study results may be questionable.

3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

The treatment effect on 3-month CDP was generally consistent across the subgroups by age, gender and race, except for the subgroup of Non-White for which there were insufficient subjects to provide a reliable estimate (Table 16).

Table 16: Study A2304: Analyses of time to 3-month CDP by demographic subgroups

Subgroup Category		N		Subjects with 3-month CDP n(%)		BAF312 vs Placebo HR (95% CI)
		BAF312	Placebo	BAF312	Placebo	
Age group Median=49 years	<Median	540	263	152 (28)	90 (34)	0.79 (0.61, 1.03)
	≥ Median	559	283	136 (24)	83 (29)	0.79 (0.60, 1.03)
Sex	Male	435	223	129 (30)	75 (34)	0.81 (0.60, 1.07)
	Female	664	323	159 (24)	98 (30)	0.77 (0.60, 1.00)
Race	White	1046	513	275 (26)	168 (33)	0.75 (0.62, 0.92)
	Non-White	53	33	13 (25)	5 (15)	2.06 (0.72, 5.86)

Source: FDA reviewer.

4.2 Other Special/Subgroup Populations

The treatment effect on 3-month CDP appeared to be larger in the subgroup of patients with superimposed relapses in the 2 years prior to study start (Table 17).

Table 17: Study A2304: Subgroup analyses of time to 3-month CDP

Subgroup	N		Subjects with 3-month CDP n(%)		BAF312 vs Placebo HR (95% CI)
	BAF312	Placebo	BAF312	Placebo	
With superimposed relapses in the 2 years prior to study start	708	343	190 (27)	101 (29)	0.67 (0.49, 0.91)
Without superimposed relapses in the 2 years prior to study start	388	202	98 (25)	72 (36)	0.87 (0.68, 1.11)

Source: FDA reviewer.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study A2304 was intended to enroll patients with SPMS, which was defined by a progressive increase in disability in the absence of relapses or independent of, relapses. However, the clinical distinctions between RRMS and SPMS can be difficult. For this study to be able to claim for

SPMS indication, it is necessary to evaluate whether the population actually enrolled was the intended population. According to medical literature (e.g., Confavreux et al 2000, Vukusic and Confavreux 2003), at this stage of MS, although relapses and focal inflammatory activity may continue to be present, progression develops independent of relapses, i.e., at a similar rate irrespective of individual relapse frequency. However, in Study A2304, the onset of disease progression could be triggered by a relapse, and the proportion of patients with disease progression almost doubled for patients with on-study relapse compared to patients without relapse. This raised the question of whether the study enrollment criteria were sufficient for the intended SPMS population. Additionally, there appeared to be a nominally highly significant effect of siponimod on the annualized relapse rate, suggesting that the effect on disability progression could be partially due to the siponimod's effect on relapses. Given that the study population may be questionable and a strong treatment effect on relapse was observed in this study, evidence of the effect on slowing disability progression independent of an effect on relapses is needed to claim the SPMS indication.

The blinding for Study A2304 may not be adequately maintained throughout the course of the trial. As a measure to minimize the potential unblinding due to heart rate reductions after the first dose, the sponsor utilized a first dose team and a First Dose database that were separate from the treating and evaluating neurologists and the Main study database. However, 34 users of the Main database and 3 EDSS raters had inappropriate access to the First Dose database, which potentially compromised the treatment blinding for over 100 subjects.

Study A2201 was an adaptive dose-ranging study in patients with RRMS. Although the primary analysis based on MCP-mod methodology controlled the type I error rate for the multiple testing of 5 candidate dose-response profiles, it did not account for the unblinded interim analysis that was performed to re-estimate the sample size and choose the two additional doses for Stage 2. Therefore, the overall type I error rate was not preserved. Additionally, the statistician who conducted the unblinded interim analysis was also responsible for the programming of the primary efficacy analysis. Therefore, the integrity of the study and the reliability of the study results may be questionable.

5.2 Collective Evidence

In the pivotal study A2304, the primary efficacy analysis demonstrated a statistically significant reduced risk of 3-month CDP in the siponimod group compared to placebo (HR =0.79, p =0.0134). The treatment effect was robust and consistent across subgroups. Analyses of the treatment effect on 3-month CDP independent of an effect on relapses or in the subgroup of non-relapsing patients suggest a hazard ratio or relative risk in the range of 0.82-0.87, which is smaller and does not reach nominal statistical significance.

The analysis of 3-month CDP after removing the potentially unblinded subjects yielded a relative risk reduction of 17%, which was numerically smaller compared to 21% for FAS. Based on simulation using a bootstrap type process, the p-values approach to the 1-sided significance level of 0.025 for testing if the treatment effect is the same for the population without the affected subjects and for the population after randomly removing the same number of subjects. Therefore,

it is of concern that the smaller treatment effect on CDP after removing the potentially unblinded subjects may be unlikely to occur by chance.

The analysis of the first key secondary endpoint (time to 3-month confirmed worsening in T25W of at least 20% from baseline) showed a risk reduction of 6.2%, which did not reach statistical significance. Benefits in favor of siponimod were observed on T2 lesion volume (the second key secondary; nominal p <0.0001) and annualized relapse rate (exploratory endpoint; nominal p <0.0001). The potential unblinding due to improper dual database access did not affect the results for T2 lesion volume or annualized relapse rate (results not shown in tables).

For the Phase 2 supportive study A2201, the primary efficacy endpoint was met. A dose-response relationship on CUAL was demonstrated among the five doses of siponimod and placebo during 3 months of treatment in patients with RRMS (p =0.0001 for the Emax model).

5.3 Conclusions and Recommendations

The data overall provided statistical evidence to support the efficacy of siponimod in treating patients with relapsing forms of MS. However, the Study A2304 did not appear to provide sufficient evidence that siponimod slows progression independent of relapses to support a claim for SPMS.

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/s/

XIANG LING
03/01/2019 02:54:06 PM

KUN JIN
03/01/2019 03:08:04 PM
I concur with the review.

HSIEN MING J HUNG
03/01/2019 03:25:51 PM

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

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA 209884/SN-0000
Drug Name:	Mayzent™ (siponimod, BAF312) film coated tablets
Indication(s):	Treatment of secondary progressive multiple sclerosis (SPMS)
Applicant:	Novartis Pharmaceuticals Corporation One Health Plaza East Hanover, NJ 07936-1080, USA Laboratory: (b) (4)
Date(s):	Received 3/28/2018
Documents Reviewed:	Studies 0870138 (rats) and 0870139 (mice) were submitted on 3/28/2018 (via SN-0000) and the electronic tumor.xpt files were submitted on 8/13/2018 (via SN-0014).
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Feng Zhou, M.S.
Concurring Reviewers:	Karl Lin, Ph. D., Team Leader
Medical Division:	Division of Neurology Products (DNP)
Nonclinical Team:	Richard Siarey, Ph.D
Project Manager:	Nahleen Lopez
Keywords:	Carcinogenicity, Dose response

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1 Summary

This review evaluates statistically the data of the 2-year oral carcinogenicity studies in rats and mice. The review analyzes the dose-response relationship of tumor incidence and mortality (including tumor-related mortality). The review concludes that BAF312 statistically decreased the survivals in female rats, male mice, and female mice. BAF312 caused statistically significant increases in the incidence of follicular cell adenoma and adenoma and carcinoma combined in gland thyroid in male rats when compared with control. Results of the mouse study showed that BAF312 caused a large increased number of vascular tumors (hemangiosarcoma, hemangioma, or combination of these two tumor types) in multiple organs, these tumor types' incidences rates had statistically significant positive dose responses (marked with *) and statistically significant pairwise comparisons of individual treated groups over the control group (marked with **) in male and female mice as summarized in Table 1.

Table 1: Tumor Types with Statistical Significant Dose Response Relationships and Pairwise Comparisons of Treated Groups and Control

Animals	Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	10 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	90 mg/kg/day High (H) P - C vs. H
Male	Gland, Thyroid	Follicular Cell Adenoma	2/50 (40)	6/50 (41)	7/50 (43)	16/50 (40)
Rats			0.0000*	0.1400	0.0958	0.0001**
		Follicular Cell_A+C	3/50 (40)	8/50 (41)	11/50 (43)	17/50 (40)
			0.0003*	0.1044	0.0266	0.0003**
Animals	**Organ name**	**Tumor name**	**0 mgkg/day Vehicle (C) P - Trend**	**2 mg/kg/day Low (L) P - C vs. L**	**8 mg/kg/day Mid (M) P - C vs. M**	**25 mg/kg/day High (H) P - C vs. H**
Male	Heart	Hemangiosarcoma	0/69 (50)	6/70 (46)	9/70 (37)	7/70 (36)
Mice			0.0185 *	0.0101 **	0.0002 **	0.0016 **
		Hemangi./Hemangiosar.	0/70 (50)	6/70 (46)	10/70 (38)	7/70 (36)
			0.0196 *	0.0101 **	0.0001 **	0.0016 **
	Liver	Hemangiosarcoma	2/70 (50)	23/70 (53)	22/70 (46)	24/70 (44)
			0.0001 *	0.0000 **	0.0000 **	0.0000 **
		Hemangi./Hemangiosar.	2/70 (50)	23/70 (53)	22/70 (46)	25/70 (45)
			0.0001 *	0.0000 **	0.0000 **	0.0000 **
	Lung	Bronchioloalveolar Adenoma	15/70 (55)	12/70 (47)	14/70 (38)	22/70 (43)
			0.0027 **	0.4883	0 2256	0.0135
	Muscle, Skeletal	Hemangiosarcoma	0/69 (49)	9/70 (48)	10/70 (38)	8/70 (36)
			0.0244 *	0.0012 **	0.0001 **	0.0006 **
	Spleen	Hemangiosarcoma	2/70 (51)	11/69 (49)	10/70 (38)	8/70 (36)
			0.0758	0.0059 **	0.0028 **	0.0109
		Hemangi./Hemangiosar.	2/70 (51)	11/70 (49)	10/70 (38)	9/70 (37)
			0.0459	0.0059 **	0.0028 **	0.0055 **
	Subcutis	Hemangi./Hemangiosar.	0/70 (50)	16/70 (50)	21/70 (44)	18/70 (42)
			0.0004 *	0.0000 **	0.0000 **	0.0000 **
	Tail	Hemangi./Hemangiosar.	0/70 (50)	1/70 (45)	1/70 (33)	5/70 (35)
			0.0016 *	0.4737	0 3976	0.0099 **
	Whole Body	Hemangioma	4/70 (51)	10/70 (45)	17/70 (42)	13/70 (38)
			0.0075	0.0438	0.0002 **	0.0021 **
		Hemangiosarcoma	6/70 (51)	44/70 (59)	46/70 (58)	46/70 (55)
			0.0000 *	0.0000 **	0.0000 **	0.0000 **
		Hemangi./Hemangiosar.	10/70 (52)	47/70 (59)	49/70 (59)	48/70 (56)
			0.0000 *	0.0000 **	0.0000 **	0.0000 **

Female Mice	Hemolymphoreticular Tissue	Lymphoma, Malignant	26/70 (55)	42/70 (57)	38/70 (53)	40/70 (53)
			0.0186	0.0037 **	0.0082 **	0.0023 **
	Heart	Hemangiosarcoma	0/70 (49)	10/70 (44)	11/70 (37)	10/70 (37)
			0.0112 *	0.0003 **	0.0000 **	0.0001 **
	Liver	Hemangi./Hemangiosar.	0/70 (49)	11/70 (45)	10/70 (37)	12/70 (38)
			0.0033 *	0.0001 **	0.0001 **	0.0000 **
		Hemangiosarcoma	0/70 (49)	11/70 (45)	10/70 (37)	11/70 (38)
			0.0077 *	0.0001 **	0.0001 **	0.0000 **
	Ovary	Hemangi./Hemangiosar.	0/69 (49)	10/70 (43)	7/70 (37)	9/70 (37)
			0.0202 *	0.0003 **	0.0019 **	0.0003 **
		Hemangiosarcoma	0/69 (48)	7/68 (41)	5/67 (35)	6/69 (35)
			0.0555	0.0033 **	0.0112 **	0.0043 **
	Subcutis	Hemangi./Hemangiosar.	1/70 (49)	8/70 (43)	12/70 (40)	12/70 (39)
			0.0026 *	0.0088 **	0.0002 **	0.0002 **
		Hemangiosarcoma	1/21 (12)	8/26 (16)	11/30 (19)	11/33 (20)
			0.0667	0.0240	0.0068 **	0.0095 **
	Whole Body	Hemangioma	4/70 (50)	11/70 (44)	9/70 (38)	7/70 (36)
			0.2611	0.0242	0.0403	0.1081
		Hemangiosarcoma	6/70 (51)	34/70 (53)	31/70 (48)	39/70 (51)
			0.0000 *	0.0000 **	0.0000 **	0.0000 **
		Hemangi./Hemangiosar.	9/70 (51)	37/70 (54)	34/70 (50)	39/70 (51)
			0.0000 *	0.0000 **	0.0000 **	0.0000 **

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed.
NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0 01 and 0 05 for a common tumor and a rare tumor, respectively.

Rat Study: Rats (50/sex/dose) were dosed by oral gavage with 0 (VC), 10 (LD), 30 (MD), and 90 (HD)-mg/kg/day BAF312 for males and 0 (VC), 3 (LD), 10 (MD), and 30 (HD)-mg/kg/day BAF312 for females twice daily for up to 104 weeks.

The survival analyses didn't show any statistically significant dose response relationship in mortality in males and females. Mortalities in the female LD and HD groups were significantly higher than that of the control group (p=0.0042 and p=0.0148, respectively). The respective survival rates in the VC, LD, MD, or HD groups at the time they were terminated was 60%, 58%, 52%, or 52% in males and 70%, 40%, 54%, or 44% in females.

The tumor analysis (Table 1) showed statistically significant positive dose-response relationships in type tumor of follicular cell adenoma or combined with carcinoma in gland thyroid in male rats were considered as a common tumor and it had a statistically significant positive dose response relationship (Ps<=0.0003<0.005). The pairwise comparisons of this tumor type incidence rates against the controls was statistically significant for high dosed group (Ps<=0.003<0.01).

Mouse Study: CD1 Mice (70/sex/dose) were dosed by oral gavage with 0 (VC), 2 (LD), 8 (MD), or 25 mg/kg/day (HD) for male and female for at least 104 weeks. BAF312 administration at all doses resulted in a decreased survival rate. Treatment was terminated for MD and HD males in Week 91, control and LD female in Week 97, and MD and HD females in Week 92 due to increased mortality.

The survival analysis showed statistically significant dose response relationship in mortality across controls and treated groups in both sexes. Mortalities in all dose groups except the male

LD group were significantly higher than that of the control group (Ps<0.05). The respective survival rates in the VC, LD, MD, or HD groups at the time they were terminated was 37%, 26%, 21%, or 21% in males and 43%, 23%, 23%, or 21% in females.

Results of tumor data analysis of the mouse study (Table 1) showed that BAF312 caused a large increased number of vascular tumors (hemangiosarcoma, hemangioma, or combination of these two tumor types) in multiple organs, these tumor types incidences rates had statistically significant positive dose responses (marked with *) and statistically significant pairwise comparisons of individual treated groups over the control group (marked with **) in male and female mice. Bronchiolalveolar Adenoma in lung was considered as a common tumor and it had a statistically significant positive dose response relationship (p=0.0027 <0.005). The pairwise comparisons of this tumor type incidence rates against the control was not statistically significant for any dosed group. The pairwise comparisons of malignant Lymphoma in Hemolymphoretic ular tissues in female mice was statistically significant for all dose groups compared to vehicle control. This type incidence rates lack of statistically significant positive dose response due to the high background incidence indicated by high tumor counts in vehicle control group.

2 Background

Siponimod is a new member of a class of oral compounds referred to as sphingosine-1-phosphate (S1P) receptor modulators. Sphingosine 1-phosphate (S1P) is a well-described natural ligand with key roles in the immune, cardiovascular, and central nervous systems through its action on five G-protein-coupled receptors (S1P1-5). The sponsor (Novartis) is seeking approval for the use of Mayzent (siponimod) film coated tablets for treatment of patients with secondary progressive multiple sclerosis (SPMS). The sponsor provided the nonclinical study 0870138: "104-week oral (gavage) carcinogenicity study in rats" and study 0870139: "104-week oral (gavage) carcinogenicity study in mice" on 3/28/2018 via submission NDA 209884/SN-0000. The electronic tumor.xpt data files were submitted on 8/13/2018 via submission NDA 209884/SN-0014.

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 incidence rate as dose increases. Results of this review have been discussed with the reviewing pharmacologist Dr. Richard Siarey.

3 Rat Study- 0870138

Study Report: **pcs-r0870138-pre-clincal-study-report.pdf (statistical report on page 1718)**
SAS data: **tumor.xpt**

This study was conducted to evaluate the carcinogenic potential of the test article, BAF312, after twice daily oral gavage administration to male and female Wistar Hannover rats for up to 104 consecutive weeks. The test material was administered at doses of 0, 10, 30, or 90 mg/kg/day (males) and 0, 3, 10, or 30 (females) for at least 104 weeks. The dosing volume was 5 mL/kg for all dose groups. This review refers these dose groups as the vehicle control (VC), low (LD), mid (MD), or high (HD) dose groups, respectively. There were 50 rats/sex/dose in the main study.

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

3.1 Sponsor's Analyses

3.1.1 Survival Analysis

Intercurrent mortality data were analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test[12]. Any animal with accidental injury that caused death or unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. If this overall test was significant ($p < 0.05$) and there were more than two groups, then a follow up analysis was done where each treatment group was compared to the

control group using a log-rank test. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's concluded results: The administration of BAF312 is not considered to have affected the survival rate. At the end of the dosing period, the survival rates varied from 52 to 60% for males and 40 to 70% for females, throughout all groups, including control.

3.1.2 Tumor Data Analysis

Neoplastic findings classified as fatal and incidental were processed using the death rate method and the prevalence method, respectively. The processing of incidental tumors was done by creating a single separate interval for the time following the experimental period (terminal sacrifice period) and by dividing the experimental period into the following fixed intervals [FDA's draft Guidance for industry. 2001]: weeks 1-52, weeks 53-78, weeks 79-92, and over week 92, and over week 92. Using the derived outcomes from the processing of both fatal and incidental tumors, a test statistic was built to perform a global survival-adjusted trend test on tumor data observed in a "mortality dependent" context [Peto et al, 1980].

All p-values are reported using upper-tailed test, unless otherwise indicated. Evaluation criteria (levels of significance) were applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%) The evaluation criteria from the FDA are given in Table F (FDA) [15].

Table F. Evaluation Criteria for Common and Rare Tumors

Test for Positive Trends	Control-High Pair-wise Comparisons
Common and rare tumors will be tested at 0.005 and 0.025 significance levels, respectively	Common and rare tumors will be tested at 0.01 and 0.05 significance levels, respectively

Sponsor's concluded results: The administration of BAF312 was associated with neoplastic changes (follicular cell adenoma at all doses/carcinoma at ≥ 30 mg/kg/day) in the thyroid gland of males only. Based on the survival rate, the Maximum Tolerated Dose (MTD) was the highest doses tested during the study which correspond to 90 mg/kg/day for males and 30 mg/kg/day for females.

3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 8/13/2018 via submission NDA 209884/S0014.

3.2.1 Survival Analysis

The survival distributions of rats in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 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 3A and 3B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 20 (40%), 21 (42%), 24 (48%), or 24 (48%) in male rats and 15 (30%), 30 (60%), 23 (46%), or 28 (56%) in female rats in the VC, LD, MD, and HD groups, respectively. The survival analyses didn't show any statistically significant dose response relationship in mortality in males and females. Mortalities in the female LD and HD groups were significantly higher than that of the control group (p=0.0042 and p=0.0148, respectively).

3.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the papers of Bailer and Portier [2] and Bieler and Williams [3]. In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without developing the tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score s_h < 1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor of the tumor type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. 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.

Multiple testing adjustments currently follow the rule displayed in Table 12.6. [5, 6]

Table 12.6 Recommended decision rules (levels of significance) for controlling the overall false positive rates for various statistical tests performed and submission types

Submission type		Tumor type	Decision rule			
			Trend test alone	Pairwise test alone	Joint test	
					Trend test	Pairwise test
Standard 2 year study with two sexes and two species		Common	0.005	0.01	0.005	0.05
		Rare	0.025	0.05	0.025	0.10
Alternative ICH Studies (One 2-year study in one species and one short- or medium-term alternative study, two sexes)	Two-year study	Common	0.005	0.01	0.005	0.05
		Rare	0.025	0.05	0.025	0.10
	Short- or medium-term alternative study	Common	0.05	0.05	0.05	0.05
		Rare	0.05	0.05	0.05	0.05
Standard 2 year studies with two sexes and one species		Common	0.01	0.025	0.01	0.05
		Rare	0.05	0.10	0.05	0.10

The adjusted levels of significance for testing a positive dose response in the 2-year rat study are 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparison in the 2-year rat study are 0.01 and 0.05 for a common tumor and a rare tumor, respectively. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%.

The tumor rates and the p-values of the tested tumor types are listed in Tables 5A and 5B in the appendix for male and female rats, respectively. Of note, the sponsor considered for statistical analysis only through tumors combinations across whole body for tumor type of hemangioma. The sponsor excluded some tumor types from the statistical analysis due to very few animals were examined. Those tumor types were included in Tables 5A and 5B with grey highlighted.

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

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons of Treated Groups and Controls in Rats

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	10 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	90 mg/kg/day High (H) P - C vs. H
Male	Gland, Thyroid	Follicular Cell Adenoma	2/50 (40)	6/50 (41)	7/50 (43)	16/50 (40)
			0.0000*	0.1400	0.0958	0.0001**
		Follicular Cell Carcinoma	1/50 (40)	2/50 (41)	5/50 (42)	5/50 (39)
			0.0543	0.5094	0.1122	0.0946
		Follicular Cell_A+C	3/50 (40)	8/50 (41)	11/50 (43)	17/50 (40)
			0.0003*	0.1044	0.0266	0.0003**
	Whole Body	Hemangiosarcoma	0/50 (40)	1/50 (41)	2/50 (42)	3/50 (39)
			0.0489	0.5062	0.2593	0.1156

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed.
NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0 01 and 0 05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, follicular cell adenoma or combined with carcinoma in gland thyroid in male rats were considered as a

common tumor and it had a statistically significant positive dose response relationship (Ps<=0.0003<0.005). The pairwise comparisons of this tumor type incidence rates against the controls was statistically significant for high dosed group (Ps<=0.003<0.01).

4 Mouse Study- 0870139

Study Report: pcs-r0870139-pre-clincal-study-report.pdf (statistical report on page 2681)
SAS data: tumor.xpt

This study was conducted to evaluate the carcinogenic potential of the test article, BAF312, after twice daily oral gavage administration to male and female Crl:CD1(ICR)BR mice for up to 104 consecutive weeks. The test material was administered at doses of 0, 2, 8, or 25 mg/kg/day for at least 104 weeks. The dosing volume was 10 mL/kg for all dose groups. This review refers these dose groups as the vehicle control (VC), low (LD), mid (MD), and high (HD) dose groups, respectively. There were 70 mice/sex/dose in the main study. BAF312 administration at all doses resulted in a decreased survival rate. Based on the recommendations of the US Food and Drug Administration (FDA), dosing was suspended until necropsy when animals reached the critical survival limit of 20/70 survivors and when high dose groups of that sex had also reached that survival point. Animals of each gender went to necropsy when they reached the limit of 15/70 survivors. The table below shows the time at which the limits were reached for each group:

	Week (day)			
Group	Males		Females	
	Dosing suspended	Necropsy	Dosing suspended	Necropsy
2	NAP	SCH	97 (678)	101 (706)
3	91 (633)	93 (651)	92 (643)	98 (684)
4	91 (633)	96 (667)	92 (643)	95 (660)

NAP = Not applicable; SCH = As initially scheduled.

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

4.1 Sponsor's Analyses

4.1.1 Survival Analysis

The sponsor used the same survival analysis methods for the rat study in this mouse study.

Sponsor's concluded results: the daily administration of BAF312 by oral gavage to CD1 mice at doses of 2, 8, or 25 mg/kg/day for up to 104 weeks resulted in decreased survival rates.

4.1.2 Tumor Data Analysis

The sponsor used the same tumor data analysis methods for the rat study in this mouse study. Given that animals in several groups were kept without dosing until the scheduled

sacrifice period, the arithmetic dose scores were adjusted accordingly. Therefore, this overall trend test was implemented as a Peto's two-sided test, using the adjusted arithmetic dose level scores multiplied by 100, more precisely (0, 200, 778 and 2372) for the males and (0, 192, 752, and 2436) for the females.

Sponsor's findings: the daily administration of BAF312 by oral gavage to CD1 mice at doses of 2, 8, or 25 mg/kg/day for up to 104 weeks increased incidences of neoplastic changes in the vascular system and lymphoid tissues at all doses. BAF312 -related neoplastic causes of death were hemangiosarcoma in males and females and lymphoma in females at all doses.

4.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 8/13/2018 via submission NDA 209884/S0014.

Based on the recommendations of the US Food and Drug Administration (FDA), dosing was suspended until necropsy when animals reached the critical survival limit of 20/70 survivors and when high dose groups of that sex had also reached that survival point. Animals of each gender went to necropsy when they reached the limit of 15/70 survivors. The table below shows the time at which the limits were reached for each group:

Group	Week (day)			
	Males		Females	
	Dosing suspended	Necropsy	Dosing suspended	Necropsy
2	NAP	SCH	97 (678)	101 (706)
3	91 (633)	93 (651)	92 (643)	98 (684)
4	91 (633)	96 (667)	92 (643)	95 (660)

NAP = Not applicable; SCH = As initially scheduled.

Therefore, the overall trend test was implemented as a Peto's two-sided test, using the adjusted arithmetic dose level scores multiplied by 100, more precisely (0, 200, 778 and 2372) for the males and (0, 192, 752, and 2436) for the females.

4.2.1 Survival Analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 2A and 2B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 44 (63%), 52 (74%), 55 (79%) or 55 (79%) in male mice and 40 (57%), 54 (77%), 54 (77%), or 55 (79%) in female mice in the VC, LD, MD, or HD groups, respectively. The tests show statistically significant dose response relationship in

mortality across controls and treated groups in both sexes. Mortalities in all dose groups except the male LD group were significantly higher than that of the control group (Ps<0.05).

4.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of the water control group and the vehicle control group separately with each of the treated groups using the same method that was used for the rat study. The tumor rates and the p-values of the tested tumor types are listed in Tables 6A, and 6B in the appendix for male and female mice, respectively.

Reviewer's findings: Based on the statistical guideline for transgenic mouse studies, the significance level of 0.05 was used in the tests for dose response and pairwise comparisons in tumor incidences of both rare and common tumors.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons of Treated Groups and Controls in Mice

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - C vs. L	8 mg/kg/day Mid (M) P - C vs. M	25 mg/kg/day High (H) P - C vs. H
Male	Adipose Tissue	Hemangioma	1/14 (12)	7/24 (20)	8/28 (17)	6/25 (15)
			0.1479	0.1004	0.0316	0.0749
		Hemangiosarcoma	0/14 (12)	10/24 (21)	11/28 (19)	9/25 (17)
			0.0563	0.0038 **	0.0009 **	0.0024 **
		Hemangioma/Hemangiosarcoma	1/14 (12)	15/24 (21)	18/28 (19)	13/25 (19)
			0.0111	0.0000#	0.0000#	0.0000#
	Bone Marrow, Femur	Hemangioma	0/69 (49)	2/70 (45)	6/70 (36)	1/70 (33)
			0.3362	0.2265	0.0045 **	0.4024
		Hemangiosarcoma	2/69 (50)	8/70 (48)	9/70 (38)	4/70 (34)
			0.3209	0.0395	0.0070 **	0.1773
		Hemangioma/Hemangiosarcoma	2/69 (50)	10/70 (48)	15/70 (41)	5/70 (35)
			0.2810	0.0103	0.0001 **	0.0937
	Heart	Hemangioma/Hemangiosarcoma	0/70 (50)	6/70 (46)	10/70 (38)	7/70 (36)
			0.0196 *	0.0101 **	0.0001 **	0.0016 **
		Hemangiosarcoma	0/69 (50)	6/70 (46)	9/70 (37)	7/70 (36)
			0.0185 *	0.0101 **	0.0002 **	0.0016 **
	Hemolymphoreticular Tissue	Lymphoma, Malignant	16/70 (55)	25/70 (51)	21/70 (42)	20/70 (44)
			0.1818	0.0282	0.0294	0.0706
	Kidney	Tubular Cell Adenoma	1/70 (50)	1/70 (45)	1/70 (32)	4/70 (35)
			0.0215	0.7256	0.6311	0.0897
		Tubularcell_A+C	1/70 (50)	1/70 (45)	1/70 (32)	5/70 (35)
			0.0065	0.7256	0.6311	0.0408
	Liver	Hemangioma/Hemangiosarcoma	2/70 (50)	23/70 (53)	22/70 (46)	25/70 (45)
			0.0001 *	0.0000 **	0.0000 **	0.0000 **
		Hemangiosarcoma	2/70 (50)	23/70 (53)	22/70 (46)	24/70 (44)
			0.0001 *	0.0000 **	0.0000 **	0.0000 **
	Lung	Bronchioloalveolar Adenoma	15/70 (55)	12/70 (47)	14/70 (38)	22/70 (43)
			0.0027 **	0.4883	0.2256	0.0135

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - C vs. L	8 mg/kg/day Mid (M) P - C vs. M	25 mg/kg/day High (H) P - C vs. H
	Muscle, Skeletal	Hemangiosarcoma	0/69 (49)	9/70 (48)	10/70 (38)	8/70 (36)
			0.0244 *	0.0012 **	0.0001 **	0.0006 **
	Small Intestine, Jejunum	Hemangiosarcoma	0/70 (50)	0/70 (45)	2/69 (33)	2/70 (34)
			0.0401	NC	0.1552	0.1609
	Spleen	Hemangioma/Hemangiosarcoma	2/70 (51)	11/70 (49)	10/70 (38)	9/70 (37)
			0.0459	0.0059 **	0.0028 **	0.0055 **
		Hemangiosarcoma	2/70 (51)	11/69 (49)	10/70 (38)	8/70 (36)
			0.0758	0.0059 **	0.0028 **	0.0109
	Subcutis	Hemangioma/Hemangiosarcoma	0/13 (11)	16/32 (25)	21/38 (27)	18/36 (28)
			0.0004 *	0.0000 **	0.0000 **	0.0000 **
		Hemangiosarcoma	0/13 (11)	15/32 (25)	19/38 (27)	16/36 (28)
			0.1445	0.0006 **	0.0001 **	0.0008 **
	Tail	Hemangioma/Hemangiosarcoma	0/70 (50)	1/70 (45)	1/70 (33)	5/70 (35)
			0.0016 *	0.4737	0.3976	0.0099 **
	Whole Body	Hemangioma	4/70 (51)	10/70 (45)	17/70 (42)	13/70 (38)
			0.0075	0.0438	0.0002 **	0.0021 **
		Hemangioma/Hemangiosarcoma	10/70 (52)	47/70 (59)	49/70 (59)	48/70 (56)
			0.0000 *	0.0000 **	0.0000 **	0.0000 **
		Hemangiosarcoma	6/70 (51)	44/70 (59)	46/70 (58)	46/70 (55)
			0.0000 *	0.0000 **	0.0000 **	0.0000 **
Female	Adipose Tissue	Hemangiosarcoma	0/15 (10)	3/17 (11)	6/26 (15)	8/22 (16)
			0.0144 *	0.1241	0.0283 **	0.0082 **
		Hemangioma/Hemangiosarcoma	1/15 (10)	5/17 (11)	8/26 (15)	8/22 (16)
			0.0131	0.0621	0.0044 **	0.0044 **
	Heart	Hemangiosarcoma	0/70 (49)	10/70 (44)	11/70 (37)	10/70 (37)
			0.0112 *	0.0003 **	0.0000 **	0.0001 **
	Hemolymphoreticular Tiss	Lymphoma, Malignant	26/70 (55)	42/70 (57)	38/70 (53)	40/70 (53)
			0.0186	0.0037 **	0.0082 **	0.0023 **
	Liver	Hemangioma	0/70 (49)	0/70 (40)	0/70 (33)	1/70 (34)
			0.2179	NC	NC	0.4096
		Hemangioma/Hemangiosarcoma	0/70 (49)	11/70 (45)	10/70 (37)	12/70 (38)
			0.0033 *	0.0001 **	0.0001 **	0.0000 **
		Hemangiosarcoma	0/70 (49)	11/70 (45)	10/70 (37)	11/70 (38)
			0.0077 *	0.0001 **	0.0001 **	0.0000 **
	Muscle, Skeletal	Hemangiosarcoma	1/69 (49)	5/70 (41)	5/70 (36)	6/70 (36)
			0.0448	0.0662	0.0467	0.0210
		Hemangioma/Hemangiosarcoma	1/70 (50)	5/70 (41)	5/70 (36)	6/70 (36)
			0.0429	0.0630	0.0442	0.0197
	Ovary	Hemangioma/Hemangiosarcoma	0/70 (49)	10/70 (43)	7/70 (37)	9/70 (37)
			0.0202 *	0.0003 **	0.0019 **	0.0003 **
		Hemangiosarcoma	0/69 (48)	7/68 (41)	5/67 (35)	6/69 (35)

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - C vs. L	8 mg/kg/day Mid (M) P - C vs. M	25 mg/kg/day High (H) P - C vs. H
			0.0555	0.0033 **	0.0112 **	0.0043 **
	Small Intestine, Jejunum	Hemangiosarcoma	0/70 (49)	0/70 (40)	4/69 (35)	2/69 (34)
			0.0813	NC	0.0271 **	0.1649
	Subcutis	Hemangioma/Hemangiosarcoma	1/70 (49)	8/70 (43)	12/70 (40)	12/70 (39)
			0.0026 *	0.0088 **	0.0002 **	0.0002 **
		Hemangiosarcoma	1/21 (12)	8/26 (16)	11/30 (19)	11/33 (20)
			0.0667	0.0240	0.0068 **	0.0095 **
	Uterus	Hemangiosarcoma	2/69 (49)	5/70 (41)	6/69 (36)	7/69 (35)
			0.0307	0.1505	0.0567	0.0248
	Whole Body	Hemangioma	4/70 (50)	11/70 (44)	9/70 (38)	7/70 (36)
			0.2611	0.0242	0.0403	0.1081
		Hemangioma/Hemangiosarcoma	9/70 (51)	37/70 (54)	34/70 (50)	39/70 (51)
			0.0000 *	0.0000 **	0.0000 **	0.0000 **
		Hemangiosarcoma	6/70 (51)	34/70 (53)	31/70 (48)	39/70 (51)
			0.0000 *	0.0000 **	0.0000 **	0.0000 **

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed.
NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0 01 and 0 05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, BAF312 caused a large increased number of vascular tumors (hemangiosarcoma, hemangioma, or combination of these two tumor types) in multiple organs, these tumor types incidences rates had statistically significant positive dose responses (marked with *) and statistically significant pairwise comparisons of individual treated groups over the control group (marked with **) in male and female mice as summarized in above table. Bronchiolalveolar Adenoma in lung was considered as a common tumor and it had a statistically significant positive dose response relationship ($p=0.0027 <0.005$). The pairwise comparisons of this tumor type incidence rates against the control was not statistically significant for any dosed group. The pairwise comparisons of malignant Lymphoma in Hemolymphoretic ular tissues in female mice was statistically significant for all dose groups compared to vehicle control. This type incidence rates lack of statistically significant positive dose response due to the high background incidence indicated by high tumor counts in vehicle control group.

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5 Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Vehicle Control		Low		Mid		High	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 52	1	2.00	2	4.00	1	2.00	5	10.00
53 - 78	7	16.00	6	16.00	1	4.00	3	16.00
79 - 92	8	32.00	3	22.00	15	34.00	6	28.00
93 - 104	4	40.00	10	42.00	7	48.00	9	46.00
Accidental Death							1	2.00
Terminal sacrifice	30	60.00	29	58.00	26	52.00	26	52.00
Total	50		50		50		50	

** All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 1B: Intercurrent Mortality Rate in Female Rats

	Vehicle Control		Low		Mid		High	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 52	1	2.00			1	2.00	1	2.00
53 - 78	3	8.00	5	10.00	4	10.00	2	6.00
79 - 92	6	20.00	15	40.00	10	30.00	13	32.00
93 - 104	5	30.00	10	60.00	8	46.00	12	56.00
Terminal sacrifice	35	70.00	20	40.00	27	54.00	22	44.00
Total	50		50		50		50	

** All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 2A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		Low		Mid		High	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 52	4	5.71	6	8.57	3	4 29	6	8.57
53 - 78	12	22.86	17	32.86	30	47.14	28	48.57
79 - 92	9	35.71	14	52.86	20	75.71	17	72.86
93 - 104	17	60.00	15	74.29	1	77.14	3	77.14
Accidental Death	2	2.86			1	1.43	1	1.43
Terminal sacrifice	26	37.14	18	25.71	15	21.43	15	21.43
Total	70		70		70		70	

** All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 2B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control		Low		Mid		High	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	2	2.86	5	7.14	7	10.00	8	11.43
53 - 78	15	24.29	22	38.57	24	44.29	19	38.57
79 - 92	8	35.71	15	60.00	17	68.57	24	72.86
93 - 104	13	54.29	12	77.14	4	74.29	4	78.57
Accidental Death	2	2.86			2	2.86		
Terminal sacrifice	30	42.86	16	22.86	16	22.86	15	21.43
Total	70		70		70		70	

** All Cum %Cumulative Percentage except for Terminal sacrifice

Table 3A: Intercurrent Mortality Comparison in Male Rats

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.6026	0.9230	0.6663	0.5974
Homogeneity (Log-Rank)	0.9357	0.9226	0.6637	0.5950

**All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 3B: Intercurrent Mortality Comparison in Female Rats

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.1940	0.0042	0.1124	0.0148
Homogeneity (Log-Rank)	0.0274	0.0041	0.1108	0.0145

**All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 4A: Intercurrent Mortality Comparison in Male Mice

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.0001	0.0679	<.0001	<.0001
Homogeneity (Log-Rank)	<.0001	0.0642	<.0001	<.0001

**All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 4B: Intercurrent Mortality Comparison in Female Mice

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.0009	0.0026	0.0002	<.0001
Homogeneity (Log-Rank)	0.0001	0.0022	0.0002	<.0001

**All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 5A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	10 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	90 mg/kg/day High (H) P - C vs. H
Body Cavity, Nasal	Squamous Cell Carcinoma	0/50 (40)	0/50 (41)	1/50 (42)	0/50 (39)
		0.2407	NC	0.5122	NC
Brain	Granular Cell Tumor, Benign	1/50 (40)	2/49 (41)	0/50 (42)	0/50 (39)
		0.8927	0.5094	0.5122	0.4937
Epididymis	Mesothelioma, Benign	0/50 (40)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5000	0.5062	NC	NC
	Mesothelioma, Malignant	0/50 (40)	0/50 (41)	1/50 (42)	0/50 (39)
		0.2407	NC	0.5122	NC
Eye	Meningioma, Benign	0/50 (40)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5000	0.5062	NC	NC
Gland, Adrenal	Cortical Adenoma	1/50 (40)	2/50 (41)	1/50 (42)	3/50 (39)
		0.1609	0.5094	0.2593	0.2980
	Pheochromocytoma, Benign	3/50 (41)	0/50 (41)	1/50 (42)	2/50 (39)
		0.4206	0.8796	0.7012	0.4760
Gland, Mammary	Adenocarcinoma	1/42 (33)	0/39 (30)	0/38 (33)	0/41 (31)
		0.7402	0.4762	0.5000	0.4844
Gland, Parathyroid	Adenoma	2/49 (39)	2/50 (41)	1/50 (42)	0/49 (38)
		0.9162	0.3269	0.5281	0.7468
Gland, Pituitary	Adenoma	19/50 (45)	15/50 (43)	14/49 (44)	8/48 (39)
		0.9810	0.6869	0.7870	0.9715
	Carcinoma	1/50 (40)	0/50 (41)	0/49 (42)	0/48 (38)
		0.7516	0.5062	0.5122	0.4872
	Ganglioneuroma	0/50 (40)	0/50 (41)	0/49 (42)	1/48 (39)
		0.2407	NC	NC	0.4937
Gland, Prostate	Adenoma	0/50 (40)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5000	0.5062	NC	NC
Gland, Salivary, Parotid	Adenoma	0/50 (40)	0/50 (41)	1/50 (42)	0/50 (39)
		0.2407	NC	0.5122	NC
Gland, Thyroid	C-Cell Adenoma	9/50 (41)	11/50 (42)	5/50 (42)	7/50 (40)
		0.7643	0.4232	0.8233	0.5880
	C-Cell Carcinoma	0/50 (40)	0/50 (41)	0/50 (42)	1/50 (39)
		0.2407	NC	NC	0.4937
	Follicular Cell Adenoma	2/50 (40)	6/50 (41)	7/50 (43)	16/50 (40)
		0.0000 **	0.1400	0.0958	0.0001 **
	Follicular Cell Carcinoma	1/50 (40)	2/50 (41)	5/50 (42)	5/50 (39)
		0.0543	0.5094	0.1122	0.0946
	Follicular Cell_A+C	3/50 (40)	8/50 (41)	11/50 (43)	17/50 (40)
		0.0003 **	0.1044	0.0266	0.0003 **
Hemolymphoreticular Tissu	Histiocytic Sarcoma	0/50 (40)	0/50 (41)	1/50 (42)	2/50 (39)
		0.0579	NC	0.5122	0.2405
	Lymphoma, Malignant	3/50 (42)	4/50 (41)	6/50 (43)	3/50 (40)
		0.5351	0.4863	0.2535	0.6385

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	10 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	90 mg/kg/day High (H) P - C vs. H
Kidney	Lipoma	1/50 (40)	0/50 (41)	0/50 (42)	0/50 (39)
		0.7531	0.5062	0.5122	0.4937
Large Intestine, Colon	Lipoma	0/50 (40)	0/50 (41)	1/50 (42)	0/50 (39)
		0.2407	NC	0.5122	NC
Liver	Cholangioma	0/50 (40)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5000	0.5062	NC	NC
	Hepatocellular Adenoma	2/50 (40)	1/50 (41)	3/50 (42)	2/50 (39)
		0.4007	0.5094	0.5234	0.6827
Lung	Bronchioloalveolar Adenoma	0/50 (40)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5000	0.5062	NC	NC
Lymph Node	Hemangioma	0/13 (10)	0/25 (22)	1/20 (18)	0/24 (21)
		0.2958	NC	0.6429	NC
Lymph Node, Mesenteric	Hemangioma	3/50 (40)	4/50 (41)	2/50 (42)	0/50 (39)
		0.9745	0.5140	0.5234	0.8751
	Hemangiosarcoma	0/50 (40)	0/50 (41)	1/50 (42)	1/50 (39)
		0.1824	NC	0.5122	0.4937
Muscle, Skeletal	Fibrosarcoma	0/49 (39)	0/50 (41)	0/50 (42)	1/50 (40)
		0.2469	NC	NC	0.5063
	Hemangiosarcoma	0/49 (39)	0/50 (41)	0/50 (42)	1/50 (39)
		0.2422	NC	NC	0.5000
	Odontoma	0/49 (39)	0/50 (41)	0/50 (42)	1/50 (39)
		0.2422	NC	NC	0.5000
	Osteosarcoma	0/49 (39)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5031	0.5125	NC	NC
	Rhabdomyosarcoma	0/49 (39)	1/50 (42)	0/50 (42)	0/50 (39)
		0.5000	0.5185	NC	NC
	Schwannoma, Malignant	0/49 (39)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5031	0.5125	NC	NC
	Squamous Cell Carcinoma	0/49 (39)	0/50 (41)	1/50 (42)	0/50 (39)
		0.2422	NC	0.5185	NC
Pancreas	Adenoma	0/50 (40)	0/50 (41)	0/50 (42)	1/50 (39)
		0.2407	NC	NC	0.4937
	Islet Cell Adenoma	0/50 (40)	0/50 (41)	1/50 (42)	0/50 (39)
		0.2407	NC	0.5122	NC
	Islet Cell Carcinoma	1/50 (40)	2/50 (42)	0/50 (42)	1/50 (39)
		0.5669	0.5185	0.5122	0.7468
Skin	Adenoma	0/50 (40)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5000	0.5062	NC	NC
	Fibroma	0/50 (40)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5000	0.5062	NC	NC
	Fibrous Histiocytoma, Benign	0/50 (40)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5000	0.5062	NC	NC
	Hair Follicle Tumor, Benign	1/50 (40)	3/50 (41)	0/50 (42)	0/50 (39)
		0.9285	0.3172	0.5122	0.4937
	Keratoacanthoma	5/50 (40)	4/50 (42)	5/50 (42)	1/50 (39)
		0.9405	0.5316	0.4008	0.8939
	Papilloma	0/50 (40)	1/50 (41)	1/50 (42)	1/50 (39)

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	10 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	90 mg/kg/day High (H) P - C vs. H
		0.2890	0.5062	0.5122	0.4937
Small Intestine, Ileum	Mast Cell Tumor, Malignant	0/50 (40)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5000	0.5062	NC	NC
Small Intestine, Jejunum	Hemangiosarcoma	0/50 (40)	0/50 (41)	1/49 (41)	1/50 (39)
		0.1817	NC	0.5062	0.4937
Spinal Cord, Lumbar	Schwannoma, Benign	1/48 (40)	0/49 (40)	0/49 (41)	0/49 (38)
		0.7484	0.5000	0.5062	0.4872
Spleen	Hemangioma	1/50 (40)	0/50 (41)	0/50 (42)	0/50 (39)
		0.7531	0.5062	0.5122	0.4937
	Hemangiosarcoma	0/50 (40)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5000	0.5062	NC	NC
Stomach	Liposarcoma	0/50 (40)	0/50 (41)	1/50 (42)	0/50 (39)
		0.2407	NC	0.5122	NC
	Papilloma	0/50 (40)	1/50 (41)	0/50 (42)	0/50 (39)
		0.5000	0.5062	NC	NC
	Squamous Cell Carcinoma	0/50 (40)	0/50 (41)	1/50 (42)	0/50 (39)
		0.2407	NC	0.5122	NC
Subcutis	Fibroma	1/3 (2)	1/4 (4)	0/3 (3)	0/4 (3)
		0.8636	0.4000	0.6000	0.6000
	Fibrosarcoma	0/3 (2)	1/4 (4)	1/3 (3)	0/4 (3)
		0.5000	0.6667	0.6000	NC
	Hemangiopericytoma	0/3 (2)	1/4 (4)	0/3 (3)	0/4 (3)
		0.5000	0.6667	NC	NC
	Lipoma	1/3 (2)	0/4 (4)	0/3 (3)	0/4 (3)
		0.8333	0.6667	0.6000	0.6000
	Osteosarcoma	0/3 (2)	0/4 (4)	0/3 (3)	1/4 (3)
		0.2500	NC	NC	0.6000
	Schwannoma, Malignant	0/3 (2)	0/4 (4)	1/3 (3)	1/4 (3)
		0.1818	NC	0.6000	0.6000
Testis	Carcinoma	1/50 (40)	0/50 (41)	0/50 (42)	0/50 (39)
		0.7531	0.5062	0.5122	0.4937
	Interstitial (Leydig) Cell Adenoma	1/50 (40)	0/50 (41)	1/50 (42)	1/50 (39)
		0.3832	0.5062	0.2593	0.7468
Thymus	Thymoma, Benign	2/48 (39)	9/50 (43)	5/48 (40)	6/50 (39)
		0.3100	0.0356	0.2263	0.1313
	Thymoma, Malignant	0/48 (39)	1/50 (41)	0/48 (40)	0/50 (39)
		0.4969	0.5125	NC	NC
	Thymoma_M+B	2/48 (39)	10/50 (43)	5/48 (40)	6/50 (39)
		0.3512	0.0180	0.2368	0.1235
Tongue	Osteosarcoma	0/50 (40)	0/50 (41)	0/50 (42)	1/50 (40)
		0.2454	NC	NC	0.5000
Urinary Bladder	Transitional Cell Carcinoma	0/50 (40)	0/48 (40)	1/49 (42)	0/50 (39)
		0.2422	NC	0.5122	NC
Whole Body	Hemangioma	4/50 (40)	4/50 (41)	3/50 (42)	0/50 (39)

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	10 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	90 mg/kg/day High (H) P - C vs. H
		0.9878	0.6579	0.8037	1.0000
	Hemangiosarcoma	0/50 (40)	1/50 (41)	2/50 (42)	3/50 (39)
		0.0489	0.5062	0.2593	0.1156
	Hemangioma/Hemangiosarcoma	4/50 (40)	5/50 (41)	5/50 (42)	3/50 (39)
		0.7107	0.5160	0.5316	0.7737
	Osteosarcoma	0/50 (40)	2/50 (41)	0/50 (42)	3/50 (41)
		0.0725	0.2531	NC	0.1249

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 5B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	3 mg/kg/day Low (L) P - L vs. C	10 mg/kg/day Mid (M) P - M vs. C	30 mg/kg/day High (H) P - H vs. C
Adipose Tissue	Fibrosarcoma	0/6 (5)	0/3 (3)	1/3 (3)	0/1 (1)
		0.3333	NC	0.3750	NC
	Lipoma	1/6 (5)	0/3 (3)	0/3 (3)	0/1 (1)
		0.5833	0.3750	0.3750	0.1667
Body Cavity, Abdominal	Sarcoma	1/2 (2)	0/1 (1)	0/2 (2)	0/1 (1)
		0.6667	0.3333	0.5000	0.3333
Body Cavity, Nasal	Squamous Cell Carcinoma	0/50 (43)	1/50 (39)	0/50 (41)	0/50 (40)
		0.4969	0.4756	NC	NC
Bone, Femur	Osteoma	0/49 (42)	1/50 (39)	0/49 (40)	0/49 (39)
		0.4937	0.4815	NC	NC
Brain	Astrocytoma, Malignant	1/50 (43)	2/50 (39)	0/50 (41)	0/50 (40)
		0.8879	0.4630	0.4881	0.4819
	Medulloblastoma	0/50 (43)	0/50 (39)	0/50 (41)	1/50 (40)
		0.2454	NC	NC	0.4819
	Mixed Glioma, Malignant	0/50 (43)	1/50 (39)	1/50 (41)	0/50 (40)
		0.4938	0.4756	0.4881	NC
	Oligodendroglioma, Malignant	0/50 (43)	1/50 (39)	0/50 (41)	0/50 (40)
		0.4969	0.4756	NC	NC
Cervix	Fibroma	0/50 (43)	0/50 (39)	0/50 (41)	1/50 (40)
		0.2454	NC	NC	0.4819
	Hemangioma	0/50 (43)	1/50 (39)	0/50 (41)	0/50 (40)
		0.4969	0.4756	NC	NC
	Leiomyosarcoma	0/50 (43)	1/50 (39)	0/50 (41)	0/50 (40)
		0.4969	0.4756	NC	NC
	Polyp	0/50 (43)	1/50 (39)	0/50 (41)	0/50 (40)
		0.4969	0.4756	NC	NC
	Schwannoma, Malignant	0/50 (43)	0/50 (39)	0/50 (41)	1/50 (40)
		0.2454	NC	NC	0.4819
	Squamous Cell Carcinoma	0/50 (43)	1/50 (39)	0/50 (41)	0/50 (40)
		0.4969	0.4756	NC	NC
Gland, Adrenal	Cortical Adenoma	2/50 (43)	2/50 (39)	3/50 (41)	2/50 (41)
		0.4654	0.6543	0.4771	0.6738
	Pheochromocytoma, Complex, Be	0/50 (43)	0/50 (39)	1/50 (41)	0/50 (40)

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	3 mg/kg/day Low (L) P - L vs. C	10 mg/kg/day Mid (M) P - M vs. C	30 mg/kg/day High (H) P - H vs. C
		0.2454	NC	0.4881	NC
Gland, Mammary	Adenocarcinoma	5/50 (44)	1/50 (39)	1/49 (40)	0/49 (39)
		0.9894	0.8691	0.8758	0.9626
	Fibroadenoma	15/50 (44)	8/50 (41)	1/49 (40)	3/49 (40)
		0.9989	0.8979	0.9998	0.9972
Gland, Parathyroid	Adenoma	0/48 (42)	1/49 (38)	1/50 (41)	0/49 (39)
		0.4937	0.4750	0.4940	NC
Gland, Pituitary	Adenoma	26/50 (46)	14/50 (41)	12/49 (41)	8/49 (40)
		0.9990	0.9700	0.9907	0.9995
	Carcinoma	2/50 (44)	0/50 (39)	0/49 (40)	0/49 (39)
		0.9275	0.7220	0.7286	0.7220
Gland, Thyroid	C-Cell Adenoma	7/50 (43)	4/50 (39)	3/50 (41)	1/49 (39)
		0.9815	0.6805	0.8235	0.9607
	Follicular Cell Adenoma	2/50 (43)	0/50 (39)	1/50 (41)	1/49 (39)
		0.4945	0.7281	0.4819	0.4630
	Follicular Cell Carcinoma	1/50 (43)	0/50 (39)	0/50 (41)	0/49 (39)
		0.7346	0.4756	0.4881	0.4756
	Follicular Cell_A+C	3/50 (43)	0/50 (39)	1/50 (41)	1/50 (40)
		0.6963	1.0000	0.9360	0.9328
Heart	Rhabdomyosarcoma	0/50 (43)	0/50 (39)	0/50 (41)	1/49 (39)
		0.2407	NC	NC	0.4756
Hemolymphoreticular Tissue	Histiocytic Sarcoma	1/50 (44)	0/50 (39)	2/50 (41)	0/50 (40)
		0.6294	0.4699	0.4732	0.4762
	Leukemia, Granulocytic	0/50 (43)	1/50 (39)	0/50 (41)	0/50 (40)
		0.4969	0.4756	NC	NC
	Lymphoma, Malignant	0/50 (43)	2/50 (39)	2/50 (41)	2/50 (40)
		0.2105	0.2231	0.2352	0.2292
Liver	Cholangioma	0/50 (43)	0/50 (39)	1/50 (41)	1/50 (40)
		0.1833	NC	0.4881	0.4819
	Hepatocellular Adenoma	4/50 (43)	5/50 (39)	3/50 (41)	1/50 (40)
		0.9430	0.4370	0.4730	0.7968
	Sarcoma	0/50 (43)	0/50 (39)	0/50 (41)	1/50 (40)
		0.2454	NC	NC	0.4819
Lymph Node	Hemangioma	0/11 (8)	0/19 (14)	0/17 (15)	1/25 (21)
		0.3621	NC	NC	0.7241
Lymph Node, Mesenteric	Hemangioma	1/50 (43)	1/50 (39)	1/50 (41)	0/50 (40)
		0.7257	0.7281	0.7410	0.4819
Muscle, Skeletal	Hemangiosarcoma	0/50 (43)	0/50 (39)	1/50 (41)	0/50 (40)
		0.2454	NC	0.4881	NC
Ovary	Adenoma	1/50 (43)	1/50 (39)	0/50 (41)	1/50 (40)
		0.5219	0.7281	0.4881	0.7346
	Granulosa Cell Tumor, Benign	0/50 (43)	0/50 (39)	1/50 (41)	0/50 (40)
		0.2454	NC	0.4881	NC
	Thecoma, Benign	0/50 (43)	0/50 (39)	0/50 (41)	1/50 (40)
		0.2454	NC	NC	0.4819

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	3 mg/kg/day Low (L) P - L vs. C	10 mg/kg/day Mid (M) P - M vs. C	30 mg/kg/day High (H) P - H vs. C
	Tubulostromal Adenoma	1/50 (44)	0/50 (39)	0/50 (41)	1/50 (40)
		0.4294	0.4699	0.4824	0.7286
Pancreas	Adenocarcinoma	0/50 (43)	0/50 (39)	1/50 (41)	0/50 (40)
		0.2454	NC	0.4881	NC
	Islet Cell Adenoma	2/50 (43)	0/50 (39)	0/50 (41)	0/50 (40)
		0.9316	0.7281	0.7410	0.7346
Skin	Keratoacanthoma	0/50 (43)	0/50 (39)	2/50 (41)	1/50 (40)
		0.1956	NC	0.2352	0.4819
	Papilloma	0/50 (43)	1/50 (39)	0/50 (41)	0/50 (40)
		0.4969	0.4756	NC	NC
	Squamous Cell Carcinoma	1/50 (43)	0/50 (39)	0/50 (41)	0/50 (40)
		0.7362	0.4756	0.4881	0.4819
Small Intestine, Jejunum	Leiomyoma	0/50 (43)	0/50 (39)	1/50 (41)	1/50 (40)
		0.1833	NC	0.4881	0.4819
	Leiomyosarcoma	0/50 (43)	1/50 (39)	0/50 (41)	0/50 (40)
		0.4969	0.4756	NC	NC
Thymus	Thymoma, Benign	6/49 (42)	5/48 (39)	6/48 (40)	7/48 (40)
		0.2945	0.4466	0.5863	0.4613
	Thymoma, Malignant	0/49 (42)	0/48 (38)	1/48 (40)	0/48 (38)
		0.2405	NC	0.4878	NC
Uterus	Endometrial Adenocarcinoma	5/50 (43)	4/50 (39)	6/50 (41)	6/50 (40)
		0.2804	0.4370	0.4657	0.4479
	Endometrial Adenoma	1/50 (43)	0/50 (39)	0/50 (41)	1/50 (40)
		0.4317	0.4756	0.4881	0.7346
	Endometrial Stromal Sarcoma	2/50 (44)	0/50 (39)	0/50 (41)	1/50 (40)
		0.5179	0.7220	0.7350	0.4639
	Hemangioma	0/50 (43)	0/50 (39)	1/50 (41)	1/50 (40)
		0.1833	NC	0.4881	0.4819
	Hemangiosarcoma	2/50 (43)	2/50 (40)	1/50 (41)	2/50 (40)
		0.4777	0.6642	0.4819	0.6642
	Leiomyosarcoma	0/50 (43)	1/50 (39)	0/50 (41)	0/50 (40)
		0.4969	0.4756	NC	NC
	Polyp	2/50 (44)	8/50 (40)	5/50 (41)	3/50 (41)
		0.7090	0.0310	0.1883	0.4661
	Squamous Cell Carcinoma	0/50 (43)	0/50 (39)	1/50 (41)	0/50 (40)
		0.2454	NC	0.4881	NC
Whole Body	Hemangioma	1/50 (43)	2/50 (39)	2/50 (41)	2/50 (41)
		0.3558	0.4630	0.4819	0.4819
	Hemangioma/Hemangiosarcoma	3/50 (43)	4/50 (40)	4/50 (41)	4/50 (41)
		0.3921	0.4590	0.4730	0.4730
	Hemangiosarcoma	2/50 (43)	2/50 (40)	2/50 (41)	2/50 (40)
		0.4786	0.6642	0.6738	0.6642
	Osteosarcoma	1/50 (43)	0/50 (39)	1/50 (41)	0/50 (40)
		0.7485	1.0000	0.7410	1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Table 6A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Males Mice

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - C vs. L	8 m/kg/day g Mid (M) P - C vs. M	25 mg/kg/day High (H) P - C vs. H
Adipose Tissue	Hemangioma	1/14 (12)	7/24 (20)	8/28 (17)	6/25 (15)
		0 1479	0.1004	0.0316	0.0749
	Hemangiosarcoma	0/14 (12)	10/24 (21)	11/28 (19)	9/25 (17)
		0.0563	0.0038 **	0.0009 **	0.0024 **
	Lipoma	1/14 (12)	0/24 (20)	0/28 (13)	0/25 (13)
		0.7931	0.6250	0.5200	0.5200
Artery, Aorta	Hemangiosarcoma	0/70 (50)	0/68 (43)	1/70 (33)	0/69 (32)
		0.4114	NC	0.3976	NC
Body Cavity, Abdominal	Hemangiosarcoma	0/3 (2)	3/5 (4)	2/2 (2)	2/4 (3)
		0 2485	0.2000	0.1667	0.3000
Body Cavity, Nasal	Hemangiosarcoma	0/70 (50)	1/70 (45)	0/70 (32)	0/70 (33)
		0.4062	0.4737	NC	NC
Body Cavity, Pelvic	Hemangiosarcoma	0/2 (1)	0/3 (1)	0/6 (2)	1/3 (2)
		0 3333	NC	NC	0.6667
Body Cavity, Thoracic	Hemangiosarcoma	0/4 (3)	1/1 (1)	0/1 (1)	0/1 (0)
		NC	0.2500	NC	NC
	Mesothelioma, Malignant	1/4 (3)	0/1 (0)	0/1 (1)	0/1 (0)
		0 2500	NC	0.2500	NC
Bone Marrow, Femur	Hemangioma	0/69 (49)	2/70 (45)	6/70 (36)	1/70 (33)
		0 3362	0.2265	0.0045 **	0.4024
	Hemangiosarcoma	2/69 (50)	8/70 (48)	9/70 (38)	4/70 (34)
		0 3209	0.0395	0.0070 **	0.1773
	Hemangioma/Hemangiosarcoma	2/69 (50)	10/70 (48)	15/70 (41)	5/70 (35)
		0 2810	0.0103	0.0001 **	0.0937
Bone Marrow, Sternum	Hemangiosarcoma	1/70 (51)	1/69 (45)	3/70 (34)	1/70 (33)
		0 3791	0.7204	0.1736	0.6343
Bone, Femur	Hemangiosarcoma	0/69 (49)	1/70 (45)	0/70 (32)	0/70 (33)
		0.4088	0.4787	NC	NC
Brain	Meningioma, Malignant	2/70 (51)	0/70 (45)	0/69 (32)	0/70 (33)
		0 9010	0.7204	0.6253	0.6343
Epididymis	Hemangiosarcoma	1/68 (49)	1/69 (44)	2/70 (33)	1/70 (33)
		0 3679	0.7251	0.3537	0.6459
	Leiomyosarcoma	1/68 (49)	0/69 (44)	0/70 (32)	0/70 (33)
		0.6899	0.4731	0.3951	0.4024
	Sarcoma	1/68 (49)	0/69 (44)	0/70 (32)	0/70 (33)
		0.6899	0.4731	0.3951	0.4024
Esophagus	Hemangiosarcoma	0/69 (49)	0/70 (45)	1/70 (32)	0/69 (33)
		0.4088	NC	0.3951	NC
Gallbladder	Hemangiosarcoma	0/68 (49)	1/69 (44)	0/64 (29)	2/64 (30)
		0.0624	0.4731	NC	0.1412
Gland, Adrenal	Cortical Adenoma	10/70 (53)	7/70 (46)	2/70 (33)	1/69 (33)

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - C vs. L	8 m/kg/day g Mid (M) P - C vs. M	25 mg/kg/day High (H) P - C vs. H
		0 9928	0.5825	0.9145	0.9706
	Hemangioma	0/70 (50)	0/70 (45)	1/70 (33)	0/69 (32)
		0.4063	NC	0.3976	NC
	Pheochromocytoma, Benign	2/70 (51)	0/70 (45)	1/70 (32)	0/69 (32)
		0.7258	0.7204	0.3293	0.6253
Gland, Harderian	Adenoma	6/70 (51)	4/70 (45)	7/70 (35)	2/70 (34)
		0.7419	0.5473	0.2280	0.6950
	Hemangiosarcoma	0/70 (50)	1/70 (45)	0/70 (32)	0/70 (33)
		0.4062	0.4737	NC	NC
Gland, Parathyroid	Adenoma	0/64 (46)	0/60 (39)	1/64 (30)	0/58 (28)
		0.4056	NC	0.3947	NC
Gland, Preputial	Fibrosarcoma	0/70 (50)	1/69 (45)	0/68 (31)	0/69 (32)
		0 3987	0.4737	NC	NC
	Hemangioma	1/70 (50)	0/69 (44)	0/68 (31)	1/69 (33)
		0 3752	0.4681	0.3827	0.6400
	Hemangiosarcoma	0/70 (50)	0/69 (44)	0/68 (31)	1/69 (33)
		0 2089	NC	NC	0.3976
Gland, Prostate	Granular Cell Tumor, Benign	0/68 (49)	1/70 (45)	0/70 (32)	0/70 (33)
		0.4088	0.4787	NC	NC
	Hemangiosarcoma	0/68 (49)	0/70 (45)	1/70 (33)	1/70 (33)
		0 1271	NC	0.4024	0.4024
Gland, Salivary, Mandibular	Hemangiosarcoma	0/70 (50)	1/70 (45)	0/70 (32)	0/70 (33)
		0.4062	0.4737	NC	NC
Gland, Salivary, Sublingual	Hemangiosarcoma	0/64 (47)	1/66 (43)	0/64 (29)	0/65 (31)
		0.4000	0.4778	NC	NC
Gland, Seminal Vesicle	Adenoma	0/69 (49)	0/70 (45)	1/70 (32)	0/70 (33)
		0.4088	NC	0.3951	NC
Gland, Thyroid	Follicular Cell Adenoma	0/70 (50)	1/68 (44)	0/70 (32)	0/69 (33)
		0.4088	0.4681	NC	NC
	Hemangiosarcoma	0/70 (50)	0/68 (44)	1/70 (32)	1/69 (33)
		0 1261	NC	0.3902	0.3976
Gland,preputial	Hemangioma/Hemangiosarcoma	1/70 (50)	0/70 (45)	0/70 (32)	2/70 (34)
		0 1131	1.0000	1.0000	0.3572
Heart	Hemangioma	0/69 (50)	0/70 (45)	1/70 (33)	0/70 (33)
		0.4099	NC	0.3976	NC
	Hemangioma/Hemangiosarcoma	0/69 (50)	6/70 (46)	10/70 (38)	7/70 (36)
		0.0196 **	0.0101 **	0.0001 **	0.0016 **
	Hemangiosarcoma	0/69 (50)	6/70 (46)	9/70 (37)	7/70 (36)
		0.0185 **	0.0101 **	0.0002 **	0.0016 **
Hemolymphoreticular Tissue	Histiocytic Sarcoma	2/70 (51)	0/70 (45)	0/70 (32)	2/70 (33)
		0 1866	0.7204	0.6253	0.5143
	Leukemia, Granulocytic	0/70 (50)	1/70 (45)	0/70 (32)	1/70 (34)
		0 2468	0.4737	NC	0.4048
	Lymphoma, Malignant	16/70 (55)	25/70 (51)	21/70 (42)	20/70 (44)

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - C vs. L	8 m/kg/day g Mid (M) P - C vs. M	25 mg/kg/day High (H) P - C vs. H
		0 1818	0.0282	0.0294	0.0706
Kidney	Hemangioma	0/70 (50)	0/70 (45)	1/70 (33)	0/70 (33)
		0.4099	NC	0.3976	NC
	Tubular Cell Adenoma	1/70 (50)	1/70 (45)	1/70 (32)	4/70 (35)
		0.0215	0.7256	0.6311	0.0897
	Tubular Cell Carcinoma	0/70 (50)	0/70 (45)	0/70 (32)	1/70 (33)
		0 2063	NC	NC	0.3976
	Tubularcell_a+c	1/70 (50)	1/70 (45)	1/70 (32)	5/70 (35)
		0.0065	0.7256	0.6311	0.0408
Large Intestine, Cecum	Hemangioma	0/70 (50)	1/70 (45)	0/70 (32)	0/70 (33)
		0.4062	0.4737	NC	NC
Large Intestine, Colon	Hemangiosarcoma	0/70 (50)	1/70 (46)	0/70 (32)	1/70 (34)
		0 2464	0.4792	NC	0.4048
Large Intestine, Rectum	Adenoma	0/70 (50)	0/70 (45)	1/70 (32)	0/68 (32)
		0.4025	NC	0.3902	NC
Liver	Hemangioma	0/70 (50)	0/70 (45)	1/70 (33)	1/70 (33)
		0 1255	NC	0.3976	0.3976
	Hemangioma/Hemangiosarcoma	2/70 (50)	23/70 (53)	22/70 (46)	25/70 (45)
		0.0001 **	0.0000 **	0.0000 **	0.0000 **
	Hemangiosarcoma	2/70 (50)	23/70 (53)	22/70 (46)	24/70 (44)
		0.0001 **	0.0000 **	0.0000 **	0.0000 **
	Hepatoblastoma	1/70 (50)	0/70 (45)	0/70 (32)	0/70 (33)
		0.6875	0.4737	0.3902	0.3976
	Hepatocellular Adenoma	16/70 (54)	7/70 (46)	1/70 (33)	7/70 (36)
		0.7460	0.9301	0.9985	0.7982
	Hepatocellular Carcinoma	4/70 (51)	2/70 (46)	2/70 (33)	1/70 (33)
		0.7370	0.6107	0.4404	0.6568
	Ito Cell Tumor, Benign	0/70 (50)	0/70 (45)	1/70 (32)	0/70 (33)
		0.4063	NC	0.3902	NC
Lung	Bronchioloalveolar Adenoma	15/70 (55)	12/70 (47)	14/70 (38)	22/70 (43)
		0.0027 **	0.4883	0.2256	0.0135
	Bronchioloalveolar Carcinoma	16/70 (55)	11/70 (49)	10/70 (37)	5/70 (35)
		0 9253	0.7071	0.4891	0.9155
	Bronchioloalveolar_A+C	28/70 (58)	20/70 (50)	22/70 (42)	26/70 (45)
		0.0778	0.8548	0.4198	0.2241
	Hemangioma	0/70 (50)	0/70 (45)	0/70 (32)	1/70 (34)
		0 2112	NC	NC	0.4048
	Hemangioma/Hemangiosarcoma	0/70 (50)	3/70 (46)	0/70 (32)	2/70 (34)
		0 2014	0.1062	NC	0.1609
	Hemangiosarcoma	0/70 (50)	3/70 (46)	0/70 (32)	1/70 (33)
		0.4494	0.1062	NC	0.3976
Lymph Node	Hemangiosarcoma	0/10 (7)	1/22 (15)	2/23 (12)	0/28 (15)
		0.6871	0.6818	0.3860	NC
Lymph Node, Mandibular	Hemangioma	0/66 (48)	0/65 (42)	0/68 (31)	1/68 (32)
		0 2092	NC	NC	0.4000
	Hemangiosarcoma	0/66 (48)	1/65 (42)	0/68 (31)	0/68 (32)
		0.4118	0.4667	NC	NC

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - C vs. L	8 m/kg/day g Mid (M) P - C vs. M	25 mg/kg/day High (H) P - C vs. H
Lymph Node, Mesenteric	Hemangioma	1/69 (50)	0/68 (44)	0/69 (32)	0/69 (33)
		0.6855	0.4681	0.3902	0.3976
	Hemangiosarcoma	2/69 (50)	1/68 (45)	1/69 (32)	2/69 (34)
		0 2757	0.4601	0.3360	0.5353
Lymphnode,mesenteric	Hemangioma/Hemangiosarcoma	3/70 (51)	1/70 (46)	1/70 (33)	2/70 (34)
		0 3775	0.9279	0.8705	NC
Muscle, Skeletal	Hemangiosarcoma	0/69 (49)	9/70 (48)	10/70 (38)	8/70 (36)
		0.0244 **	0.0012 **	0.0001 **	0.0006 **
	Leiomyosarcoma	0/69 (49)	0/70 (45)	1/70 (33)	0/70 (33)
		0.4125	NC	0.4024	NC
Pancreas	Hemangioma	0/70 (50)	1/70 (45)	0/70 (32)	0/70 (33)
		0.4062	0.4737	NC	NC
	Hemangioma/Hemangiosarcoma	0/70 (50)	1/70 (45)	2/70 (33)	1/70 (33)
		0 2223	0.4737	0.1552	0.3976
	Hemangiosarcoma	0/70 (50)	0/70 (45)	2/70 (33)	1/70 (33)
		0 1325	NC	0.1552	0.3976
	Islet Cell Adenoma	1/70 (51)	0/70 (45)	0/70 (32)	0/70 (33)
		0.6832	0.4688	0.3855	0.3929
Skin	Fibrous Histiocytoma, Benign	1/70 (51)	1/69 (45)	0/70 (32)	0/70 (33)
		0.7228	0.7204	0.3855	0.3929
	Hemangiosarcoma	0/70 (50)	0/69 (44)	1/70 (32)	0/70 (33)
		0.4088	NC	0.3902	NC
	Leiomyosarcoma	0/70 (50)	0/69 (44)	0/70 (32)	1/70 (33)
		0 2075	NC	NC	0.3976
	Papilloma	0/70 (50)	0/69 (44)	1/70 (32)	0/70 (33)
		0.4088	NC	0.3902	NC
Small Intestine, Duodenum	Hemangiosarcoma	0/70 (50)	0/70 (45)	1/70 (33)	0/70 (33)
		0.4099	NC	0.3976	NC
Small Intestine, Jejunum	Adenoma	0/70 (50)	0/70 (45)	0/69 (32)	1/70 (33)
		0 2063	NC	NC	0.3976
	Hemangioma	1/70 (50)	0/70 (45)	0/69 (32)	0/70 (33)
		0.6875	0.4737	0.3902	0.3976
	Hemangiosarcoma	0/70 (50)	0/70 (45)	2/69 (33)	2/70 (34)
		0.0401	NC	0.1552	0.1609
Smallintestine,jejunum	Hemangioma/Hemangiosarcoma	1/70 (50)	0/70 (45)	2/70 (33)	2/70 (34)
		0.0985	1.0000	0.3467	0.3572
Spleen	Hemangioma	0/70 (50)	0/69 (45)	0/70 (32)	1/70 (33)
		0 2063	NC	NC	0.3976
	Hemangioma/Hemangiosarcoma	2/70 (51)	11/70 (49)	10/70 (38)	9/70 (37)
		0.0459	0.0059 **	0.0028 **	0.0055 **
	Hemangiosarcoma	2/70 (51)	11/69 (49)	10/70 (38)	8/70 (36)
		0.0758	0.0059 **	0.0028 **	0.0109
Stomach	Adenocarcinoma	1/70 (51)	1/70 (45)	0/69 (31)	1/70 (34)
		0.4481	0.7204	0.3780	0.6429
	Adenoma	0/70 (50)	0/70 (45)	0/69 (31)	2/70 (34)
		0.0441	NC	NC	0.1609

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - C vs. L	8 m/kg/day g Mid (M) P - C vs. M	25 mg/kg/day High (H) P - C vs. H
	Hemangioma	0/70 (50)	0/70 (45)	1/69 (32)	0/70 (33)
		0.4063	NC	0.3902	NC
	Papilloma	0/70 (50)	0/70 (45)	1/69 (32)	0/70 (33)
		0.4063	NC	0.3902	NC
	Squamous Cell Carcinoma	1/70 (50)	0/70 (45)	0/69 (31)	0/70 (33)
		0.6855	0.4737	0.3827	0.3976
Subcutis	Fibroma	2/13 (11)	1/32 (19)	1/38 (16)	0/36 (20)
		0 9351	0.7020	0.6427	0.8817
	Fibrosarcoma	0/13 (11)	2/32 (20)	0/38 (16)	1/36 (20)
		0.4674	0.4086	NC	0.6452
	Hemangioma	0/13 (11)	1/32 (19)	2/38 (17)	3/36 (20)
		0.0975	0.6333	0.3598	0.2536
	Hemangiosarcoma	0/13 (11)	15/32 (25)	19/38 (27)	16/36 (28)
		0 1445	0.0006 **	0.0001 **	0.0008 **
	Lipoma	0/13 (11)	0/32 (19)	1/38 (16)	0/36 (20)
		0 3030	NC	0.5926	NC
	Osteosarcoma	1/13 (12)	0/32 (19)	0/38 (16)	0/36 (20)
		0.8209	0.6129	0.5714	0.6250
	Sarcoma	0/13 (11)	1/32 (20)	0/38 (16)	0/36 (20)
		0 5373	0.6452	NC	NC
Tail	Hemangioma/Hemangiosarcoma	0/70 (50)	1/70 (45)	1/70 (33)	5/70 (35)
		0.0016 **	0.4737	0.3976	0.0099 **
Testis	Hemangioma	0/69 (50)	0/69 (44)	0/70 (32)	1/70 (34)
		0 2125	NC	NC	0.4048
	Hemangioma/Hemangiosarcoma	0/70 (50)	1/70 (45)	0/70 (32)	1/70 (34)
		0 2468	0.4737	NC	0.4048
	Hemangiosarcoma	0/69 (50)	1/69 (44)	0/70 (32)	0/70 (33)
		0.4088	0.4681	NC	NC
	Interstitial (Leydig) Cell Adenoma	1/69 (50)	2/69 (44)	1/70 (32)	0/70 (33)
		0.7303	0.4517	0.6311	0.3976
Thymus	Hemangiosarcoma	1/68 (49)	1/67 (43)	0/63 (29)	0/68 (32)
		0.7177	0.7191	0.3718	0.3951
Whole Body	Hemangioma	4/70 (51)	10/70 (45)	17/70 (42)	13/70 (38)
		0.0075	0.0438	0.0002 **	0.0021 **
	Hemangioma/Hemangiosarcoma	10/70 (52)	47/70 (59)	49/70 (59)	48/70 (56)
		0.0000 **	0.0000 **	0.0000 **	0.0000 **
	Hemangiosarcoma	6/70 (51)	44/70 (59)	46/70 (58)	46/70 (55)
		0.0000 **	0.0000 **	0.0000 **	0.0000 **

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Table 6B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - L vs. C	8 mg/kg/day Mid (M) P - M vs. C	25 mg/kg/day High (H) P - H vs. C
Adipose Tissue	Hemangioma	1/15 (10)	2/17 (11)	3/26 (14)	0/22 (13)
		0.8907	0.5376	0.4368	0.5652

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - L vs. C	8 mg/kg/day Mid (M) P - M vs. C	25 mg/kg/day High (H) P - H vs. C
	Hemangiosarcoma	0/15 (10)	3/17 (11)	6/26 (15)	8/22 (16)
		0.0144 **	0.1241	0.0283 **	0.0082 **
	Lipoma	0/15 (10)	0/17 (11)	1/26 (13)	0/22 (13)
		0.2766	NC	0.5652	NC
	Hemangioma/Hemangiosarcoma	1/70 (49)	5/70 (40)	8/70 (37)	8/70 (37)
		0.0131	0.0621	0.0044 **	0.0044 **
Body Cavity, Abdominal	Hemangiosarcoma	0/6 (3)	1/5 (2)	1/4 (2)	2/7 (4)
		0.1788	0.4000	0.4000	0.2857
Body Cavity, Thoracic	Fibrosarcoma	0/5 (3)	1/3 (2)	0/3 (1)	0/3 (2)
		0.3750	0.4000	NC	NC
	Hemangiosarcoma	0/5 (3)	1/3 (2)	1/3 (1)	0/3 (2)
		0.4643	0.4000	0.2500	NC
Bone Marrow, Femur	Hemangioma	0/70 (49)	1/70 (40)	0/69 (33)	1/70 (34)
		0.2517	0.4494	NC	0.4096
	Hemangiosarcoma	1/70 (50)	5/70 (42)	4/69 (35)	4/70 (36)
		0.1714	0.0670	0.0897	0.0954
	Hemangioma/Hemangiosarcoma	1/70 (50)	6/70 (43)	4/70 (36)	5/70 (36)
		0.1148	0.0356	0.0954	0.0442
Bone Marrow, Sternum	Hemangiosarcoma	0/70 (49)	1/69 (39)	1/70 (34)	1/70 (34)
		0.2233	0.4432	0.4096	0.4096
Brain	Meningioma, Malignant	1/70 (50)	0/70 (40)	0/70 (33)	1/70 (34)
		0.3873	0.4444	0.3976	0.6486
Gallbladder	Hemangioma	0/67 (48)	0/69 (39)	0/68 (32)	1/67 (32)
		0.2119	NC	NC	0.4000
Gland, Adrenal	Cortical Adenoma	0/70 (49)	4/70 (40)	0/70 (33)	1/70 (34)
		0.5717	0.0374 **	NC	0.4096
	Hemangioma	0/70 (49)	0/70 (40)	1/70 (34)	0/70 (33)
		0.4295	NC	0.4096	NC
	Pheochromocytoma, Benign	1/70 (49)	0/70 (40)	0/70 (33)	0/70 (33)
		0.6839	0.4494	0.4024	0.4024
Gland, Harderian	Adenocarcinoma	2/70 (49)	0/70 (40)	1/70 (34)	0/70 (33)
		0.7526	0.6997	0.3643	0.6459
	Adenoma	3/70 (50)	5/70 (41)	3/70 (34)	2/70 (34)
		0.6421	0.2520	0.4658	0.3216
	Hemangiosarcoma	0/70 (49)	1/70 (40)	0/70 (33)	0/70 (33)
		0.4258	0.4494	NC	NC
Gland, Mammary	Adenocarcinoma	1/69 (48)	0/67 (38)	1/69 (33)	0/68 (32)
		0.5374	0.4419	0.6519	0.4000
Gland, Pituitary	Adenoma	5/69 (50)	1/70 (40)	0/69 (33)	0/67 (32)
		0.9942	0.8384	0.9270	0.9223
Gland, Thyroid	Follicular Cell Adenoma	1/70 (49)	0/70 (40)	0/69 (33)	0/70 (33)
		0.6839	0.4494	0.4024	0.4024
Heart	Hemangiosarcoma	0/70 (49)	10/70 (44)	11/70 (37)	10/70 (37)

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - L vs. C	8 mg/kg/day Mid (M) P - M vs. C	25 mg/kg/day High (H) P - H vs. C
		0.0112 **	0.0003 **	0.0000 **	0.0001 **
Hemolymphoreticular Tiss	Histiocytic Sarcoma	1/70 (50)	0/70 (40)	1/70 (34)	0/70 (33)
		0.5341	0.4444	0.6486	0.3976
	Leukemia, Granulocytic	0/70 (49)	0/70 (40)	1/70 (34)	0/70 (33)
		0.4295	NC	0.4096	NC
	Lymphoma, Malignant	26/70 (55)	42/70 (57)	38/70 (53)	40/70 (53)
		0.0186	0.0037 **	0.0082 **	0.0023 **
Kidney	Hemangioma	1/70 (50)	1/70 (40)	0/70 (33)	0/70 (33)
		0.7333	0.6941	0.3976	0.3976
Large Intestine, Colon	Hemangiosarcoma	0/70 (49)	0/70 (40)	1/70 (34)	2/70 (34)
		0.0396	NC	0.4096	0.1649
Large Intestine, Rectum	Adenocarcinoma	0/68 (48)	1/69 (40)	0/68 (33)	0/68 (32)
		0.4248	0.4545	NC	NC
	Adenoma	0/68 (48)	0/69 (39)	0/68 (33)	1/68 (33)
		0.2157	NC	NC	0.4074
	Hemangiosarcoma	0/68 (48)	0/69 (39)	0/68 (33)	1/68 (32)
		0.2105	NC	NC	0.4000
Liver	Hemangioma	0/70 (49)	0/70 (40)	0/70 (33)	1/70 (34)
		0.2179	NC	NC	0.4096
	Hemangioma/Hemangiosarcoma	0/70 (49)	11/70 (45)	10/70 (37)	12/70 (38)
		0.0033 **	0.0001 **	0.0001 **	0.0000 **
	Hemangiosarcoma	0/70 (49)	11/70 (45)	10/70 (37)	11/70 (38)
		0.0077 **	0.0001 **	0.0001 **	0.0000 **
	Hepatocellular Adenoma	3/70 (50)	1/70 (40)	0/70 (33)	1/70 (34)
		0.6748	0.6030	0.7867	0.5353
Lung	Bronchioloalveolar Adenoma	16/70 (52)	13/70 (44)	15/70 (40)	15/70 (40)
		0.2122	0.4621	0.3240	0.3240
	Bronchioloalveolar Carcinoma	7/70 (51)	8/70 (42)	5/70 (36)	0/70 (33)
		0.9948	0.3391	0.6101	0.9744
	Bronchioloalveolar_A+C	20/70 (53)	20/70 (46)	18/70 (42)	15/70 (40)
		0.6062	0.3535	0.3835	0.5936
	Hemangioma	0/70 (49)	1/70 (40)	0/70 (33)	2/70 (34)
		0.0756	0.4494	NC	0.1649
	Hemangioma/Hemangiosarcoma	1/70 (50)	1/70 (40)	1/70 (34)	3/70 (35)
		0.0701	0.6941	0.6486	0.1875
	Hemangiosarcoma	1/70 (50)	0/70 (40)	1/70 (34)	1/70 (34)
		0.3080	0.4444	0.6486	0.6486
	Osteosarcoma	0/70 (49)	0/70 (40)	0/70 (33)	1/70 (34)
		0.2179	NC	NC	0.4096
Lymph Node	Hemangiosarcoma	0/23 (15)	0/44 (25)	1/41 (20)	1/42 (21)
		0.1944	NC	0.5714	0.5833
Lymph Node, Mandibular	Hemangioma	0/67 (48)	0/68 (38)	1/63 (31)	0/68 (32)
		0.4228	NC	0.3924	NC
Lymph Node, Mesenteric	Hemangiosarcoma	1/69 (49)	2/70 (41)	1/66 (33)	1/66 (32)
		0.4732	0.4328	0.6459	0.6370

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - L vs. C	8 mg/kg/day Mid (M) P - M vs. C	25 mg/kg/day High (H) P - H vs. C
Muscle, Skeletal	Hemangioma	0/69 (49)	0/70 (40)	1/70 (34)	0/70 (33)
		0.4295	NC	0.4096	NC
	Hemangiosarcoma	1/69 (49)	5/70 (41)	5/70 (36)	6/70 (36)
		0.0448	0.0662	0.0467	0.0210
	Hemangioma/Hemangiosarcoma	1/70 (50)	5/70 (41)	5/70 (36)	6/70 (36)
		0.0429	0.0630	0.0442	0.0197
Ovary	Cystadenoma	3/69 (49)	0/68 (39)	0/67 (33)	2/69 (33)
		0.3036	0.8321	0.7920	0.3173
	Hemangioma	0/69 (48)	3/68 (40)	2/67 (34)	3/69 (34)
		0.0962	0.0900	0.1689	0.0676
	Hemangioma/Hemangiosarcoma	0/70 (49)	10/70 (43)	7/70 (37)	9/70 (37)
		0.0202 **	0.0003 **	0.0019 **	0.0003 **
	Hemangiosarcoma	0/69 (48)	7/68 (41)	5/67 (35)	6/69 (35)
		0.0555	0.0033 **	0.0112 **	0.0043 **
	Luteoma	1/69 (48)	0/68 (39)	2/67 (34)	0/69 (33)
		0.5642	0.4483	0.3716	0.4074
	Sertoli Cell Tumor, Benign	0/69 (48)	0/68 (39)	1/67 (33)	0/69 (33)
		0.4314	NC	0.4074	NC
	Tubulostromal Adenoma	0/69 (48)	0/68 (39)	0/67 (33)	1/69 (33)
		0.2157	NC	NC	0.4074
Pancreas	Hemangiosarcoma	0/70 (49)	1/69 (40)	0/70 (33)	0/70 (33)
		0.4258	0.4494	NC	NC
	Islet Cell Adenoma	1/70 (49)	0/69 (39)	1/70 (34)	0/70 (33)
		0.5397	0.4432	0.6544	0.4024
Skin	Basal Cell Tumor, Malignant	0/70 (49)	2/70 (40)	0/70 (33)	0/69 (33)
		0.6719	0.1992	NC	NC
	Fibrous Histiocytoma, Benign	0/70 (49)	0/70 (40)	0/70 (33)	1/69 (33)
		0.2129	NC	NC	0.4024
	Hemangiosarcoma	0/70 (49)	0/70 (40)	2/70 (34)	0/69 (33)
		0.4258	NC	0.1649	NC
	Papilloma	1/70 (49)	0/70 (40)	0/70 (33)	0/69 (33)
		0.6839	0.4494	0.4024	0.4024
	Squamous Cell Carcinoma	1/70 (50)	0/70 (40)	0/70 (33)	1/69 (33)
		0.3794	0.4444	0.3976	0.6400
Small Intestine, Duodenum	Hemangiosarcoma	0/70 (49)	1/69 (39)	1/70 (34)	0/70 (33)
		0.4286	0.4432	0.4096	NC
Small Intestine, Jejunum	Hemangiosarcoma	0/70 (49)	0/70 (40)	4/69 (35)	2/69 (34)
		0.0813	NC	0.0271 **	0.1649
Spleen	Hemangioma	1/70 (49)	0/70 (40)	0/70 (33)	0/70 (33)
		0.6839	0.4494	0.4024	0.4024
	Hemangioma/Hemangiosarcoma	3/70 (50)	7/70 (44)	6/70 (36)	4/70 (36)
		0.4108	0.1113	0.1088	0.3205
	Hemangiosarcoma	2/70 (50)	7/70 (44)	6/70 (36)	4/70 (36)
		0.3367	0.0531	0.0534	0.1977
Stomach	Adenoma	0/70 (49)	1/70 (40)	0/70 (33)	0/70 (33)
		0.4258	0.4494	NC	NC
	Hemangiosarcoma	0/70 (49)	0/70 (40)	0/70 (33)	1/70 (34)
		0.2179	NC	NC	0.4096
	Papilloma	1/70 (49)	0/70 (40)	0/70 (33)	0/70 (33)

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	2 mg/kg/day Low (L) P - L vs. C	8 mg/kg/day Mid (M) P - M vs. C	25 mg/kg/day High (H) P - H vs. C
		0.6839	0.4494	0.4024	0.4024
	Squamous Cell Carcinoma	0/70 (49)	1/70 (40)	0/70 (33)	0/70 (33)
		0.4258	0.4494	NC	NC
Subcutis	Fibroma	0/21 (12)	0/26 (13)	1/30 (13)	0/33 (15)
		0.2830	NC	0.5200	NC
	Fibrosarcoma	4/21 (13)	0/26 (13)	2/30 (14)	0/33 (15)
		0.9587	0.9522	0.7135	0.9651
	Hemangioma	0/21 (12)	0/26 (13)	1/30 (13)	2/33 (16)
		0.0855	NC	0.5200	0.3175
	Hemangioma/Hemangiosarcoma	1/70 (49)	8/70 (43)	12/70 (40)	12/70 (39)
		0.0026 **	0.0088 **	0.0002 **	0.0002 **
	Hemangiosarcoma	1/21 (12)	8/26 (16)	11/30 (19)	11/33 (20)
		0.0667	0.0240	0.0068 **	0.0095 **
Thymus	Hemangiosarcoma	0/69 (49)	0/68 (39)	1/68 (33)	0/69 (33)
		0.4286	NC	0.4024	NC
Urinary Bladder	Hemangiosarcoma	0/67 (47)	0/67 (37)	1/66 (33)	0/66 (31)
		0.4324	NC	0.4125	NC
Uterus	Choriocarcinoma	1/69 (48)	0/70 (40)	0/69 (33)	0/69 (33)
		0.6883	0.4545	0.4074	0.4074
	Endometrial Stromal Sarcoma	0/69 (48)	1/70 (40)	0/69 (33)	0/69 (33)
		0.4286	0.4545	NC	NC
	Granular Cell Tumor, Benign	1/69 (49)	0/70 (40)	1/69 (34)	0/69 (33)
		0.5383	0.4494	0.6544	0.4024
	Hemangioma	1/69 (49)	2/70 (40)	0/69 (33)	0/69 (33)
		0.8297	0.4235	0.4024	0.4024
	Hemangioma/Hemangiosarcoma	3/70 (50)	7/70 (42)	6/70 (36)	7/70 (36)
		0.0916	0.0967	0.1088	0.0581
	Hemangiosarcoma	2/69 (49)	5/70 (41)	6/69 (36)	7/69 (35)
		0.0307	0.1505	0.0567	0.0248
	Leiomyoma	6/69 (49)	2/70 (40)	3/69 (34)	2/69 (33)
		0.7070	0.7905	0.5459	0.7007
	Leiomyosarcoma	0/69 (48)	0/70 (40)	1/69 (34)	0/69 (33)
		0.4323	NC	0.4146	NC
	Polyp	5/69 (49)	4/70 (40)	1/69 (34)	1/69 (33)
		0.9187	0.3714	0.7912	0.7804
Vagina	Hemangiosarcoma	0/67 (48)	1/68 (38)	1/65 (33)	1/65 (31)
		0.2087	0.4419	0.4074	0.3924
Whole Body	Hemangioma	4/70 (50)	11/70 (44)	9/70 (38)	7/70 (36)
		0.2611	0.0242	0.0403	0.1081
	Hemangioma/Hemangiosarcoma	9/70 (51)	37/70 (54)	34/70 (50)	39/70 (51)
		0.0000 **	0.0000 **	0.0000 **	0.0000 **
	Hemangiosarcoma	6/70 (51)	34/70 (53)	31/70 (48)	39/70 (51)
		0.0000 **	0.0000 **	0.0000 **	0.0000 **

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

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

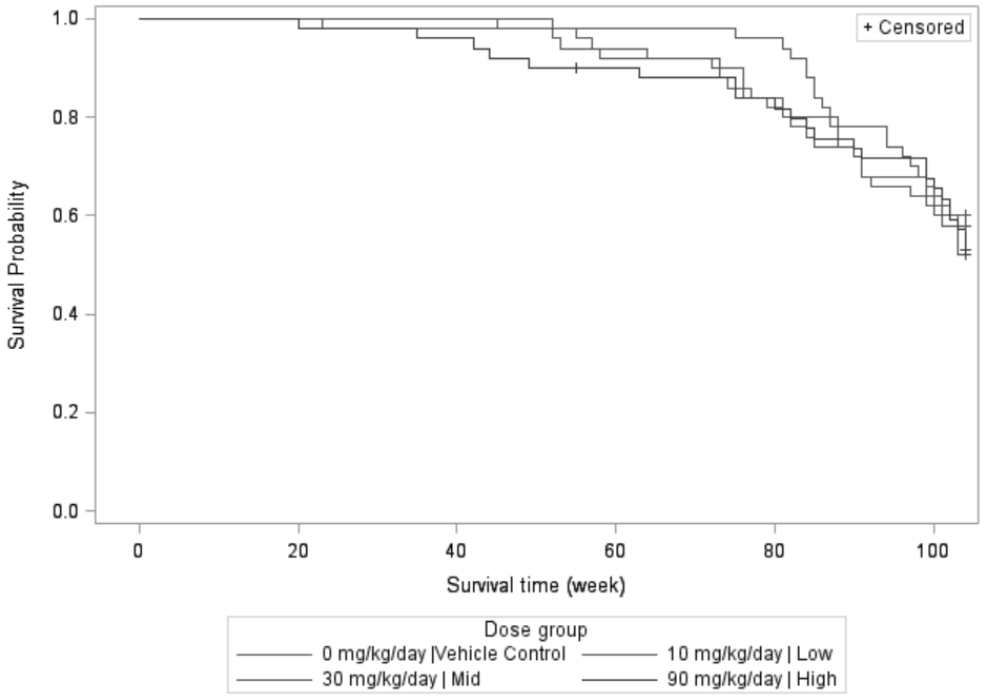


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

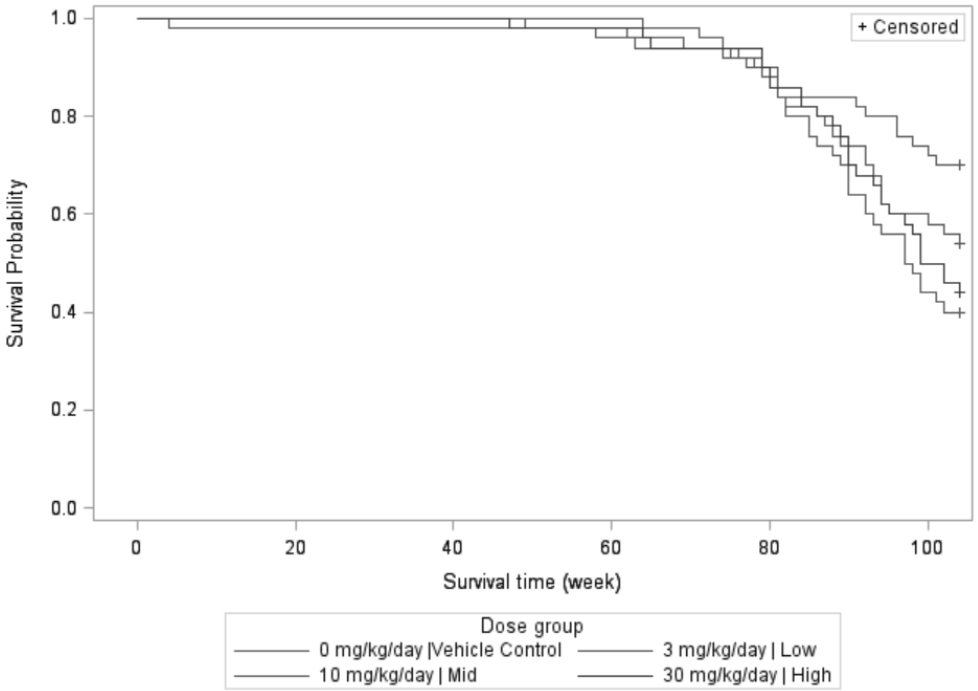


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

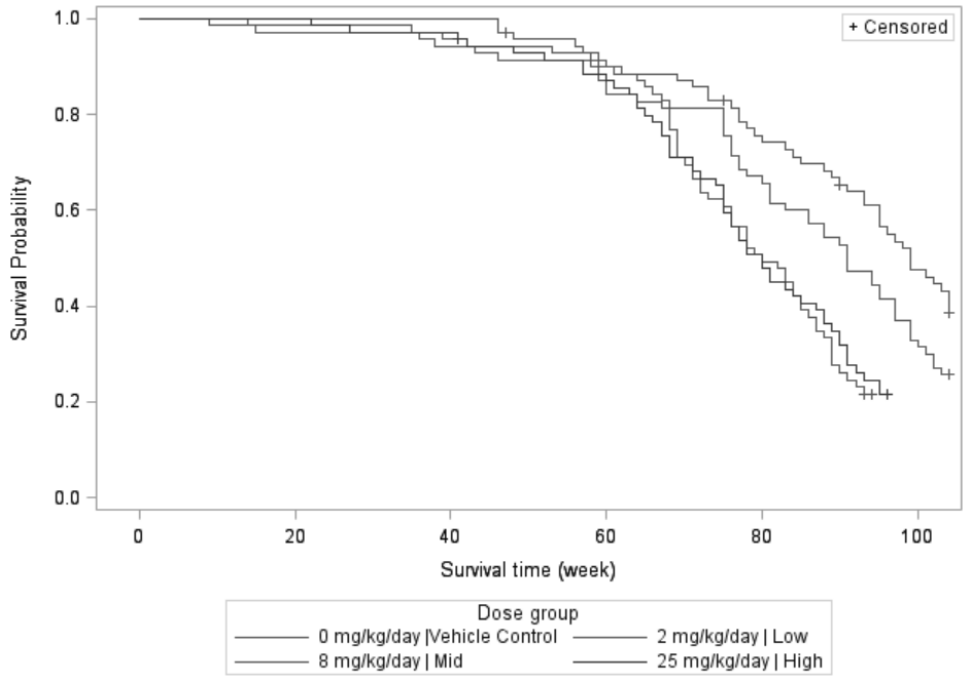
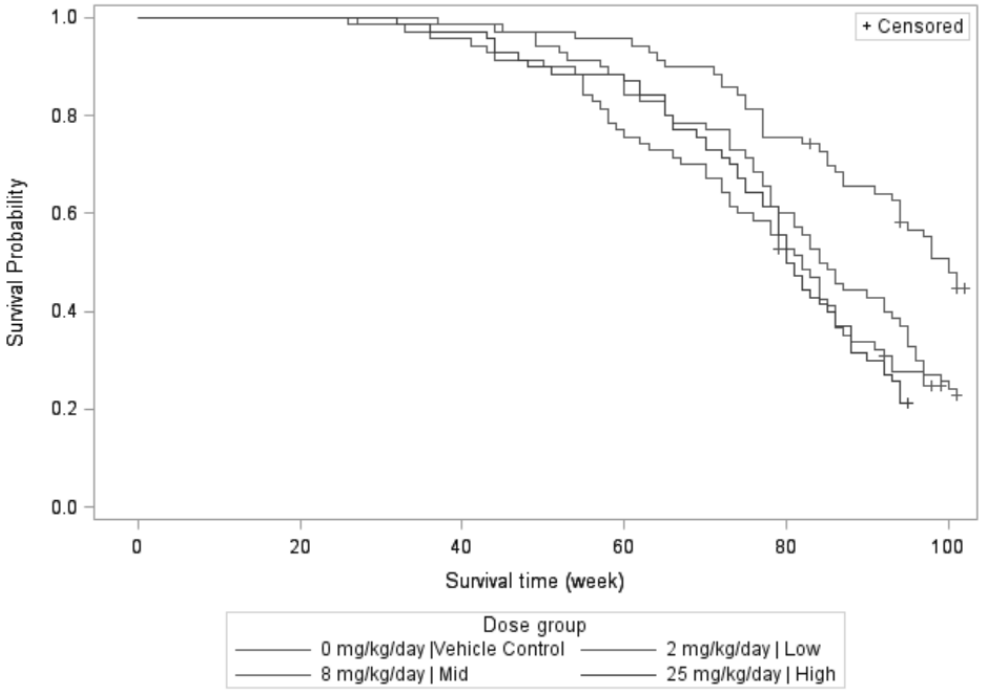


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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12. (b) (4) Historical Control Neoplastic Data, CD-1 Mouse, 2 Year

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