CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 209,899
Drug Name:	ZEPOSIA™ (Ozanimod)
Indication(s):	Multiple Sclerosis
Applicant:	Celgene
Date(s):	Date of Submission: March 25, 2019 PDUFA Date: March 25, 2020
Review Priority:	Standard Review
Biometrics Division:	Division I
Statistical Reviewer:	Sharon Yan, PhD
Concurring Reviewers:	Kun Jin, PhD, Team Leader Jim Hung, PhD, Director
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1 EXECUTIVE SUMMARY

This NDA application for ZEPOSIA™ (ozanimod) is seeking approval for the following indications:

- ZEPOSIA™ (ozanimod) is indicated for the treatment of patients with relapsing forms of multiple sclerosis (RMS).

The Phase 3 program of ozanimod in RMS consisted of two studies, RPC01-201B and RPC01-301. Both studies were randomized, double-blind, double-dummy, active-controlled, parallel-group study, comparing 0.5 mg and 1 mg doses of ozanimod with IFN β-1a.

Study RPC01-201B had a treatment period of 2 years. The treatment duration for Study RPC01-301 varied by patients and the study ended when the last patient completed 12 months of treatment. Other than the difference in duration of the treatment, the two studies were designed similarly with a same set of the primary and key secondary endpoints. The primary efficacy endpoint of the two studies was the annualized relapse rate (ARR) of the protocol defined relapse (PDR). Secondary endpoints included number of new or enlarging T2 lesions, number of Gd-enhancing lesions and time to disability progression confirmed at 3 months. The analysis of disability progression was to be based on the pooled data of the two studies.

In both studies, treatment with ozanimod 1 mg and 0.5 mg resulted in statistically significant reductions in ARR compared with IFN β-1a. A dose-dependent effect was observed favoring the 1 mg dose over the 0.5 mg dose of ozanimod in both studies. In Study RPC01-301, the reduction in ARR at the end of the treatment period was approximately 48% with ozanimod 1 mg and 31% with ozanimod 0.5 mg compared to IFN β-1a. The reduction in ARR at Month 24 in Study RPC01-201B was approximately 38% with ozanimod 1 mg and 21% with ozanimod 0.5 mg.

The pooled analysis of disability progression did not show a statistically significant treatment difference between either of the ozanimod dose groups and IFN β-1a treatment group.

2 INTRODUCTION

2.1 Overview

The clinical development program of ozanimod in RMS consisted of a Phase 2, randomized, double-blind, placebo-controlled study with a blinded extension period (RPC01-201A), a Phase 3, two-year, randomized, double-blind, double-dummy, active-controlled, parallel-group study (RPC01-201B), a Phase 3, one-year, randomized, double-blind, double-dummy, active-controlled, parallel group study (RPC01-301), and an open-label extension (OLE) study (RPC01-3001). The active-controlled Phase 3 studies evaluated the efficacy of ozanimod at dose levels of 0.5 mg and 1 mg administered once daily compared to interferon IFN β -1a 30 µg (Avonex®) intramuscular injection weekly.

The Phase 3 studies in RMS (RPC01-201 Part B and RPC01-301) were conducted under Special Protocol Assessment (SPA) agreements.

In the Phase 3 program, ozanimod demonstrated superior, dose-dependent efficacy compared to IFN β-1a in reducing the annualized relapse rate (ARR). The pre-specified pooled analysis of disability progression did not show a statistically significant treatment difference between ozanimod and IFN β-1a treatment groups. Notably, a low number of confirmed disability progression events was observed across all treatment groups.

The following table presents a summary of the studies included in this review.

Table 1 List of All Studies Included in This Review

	Phase and Design	**Treatment Period**	**Comparator**	**# of Subjects randomized**	**Study Population**
RPC01-301	Phase 3, randomized, double-blind, double-dummy, active-controlled	Varies by patient with minimum treatment of 12 months	IFN β-1a	Ozanimod 0.5 mg: 451 Ozanimod 1 mg: 447 IFNB-1a: 448	Patients with RMS
RPC01-201B	Phase 2B, randomized, double-blind, double-dummy, active-controlled	24 months	IFN β-1a	Ozanimod 0.5 mg: 443 Ozanimod 1 mg: 434 IFNB-1a: 443	Patients with RMS

Source: Reviewer's summary

2.2 Data Sources

Original submission 3/25/2019: \\CDSESUB1\evsprod\NDA209899

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No notable issues were identified in the submission of data and study documents.

3.2 Evaluation of Efficacy

3.2.1 Evaluation of Efficacy for Protocol RPC01-301

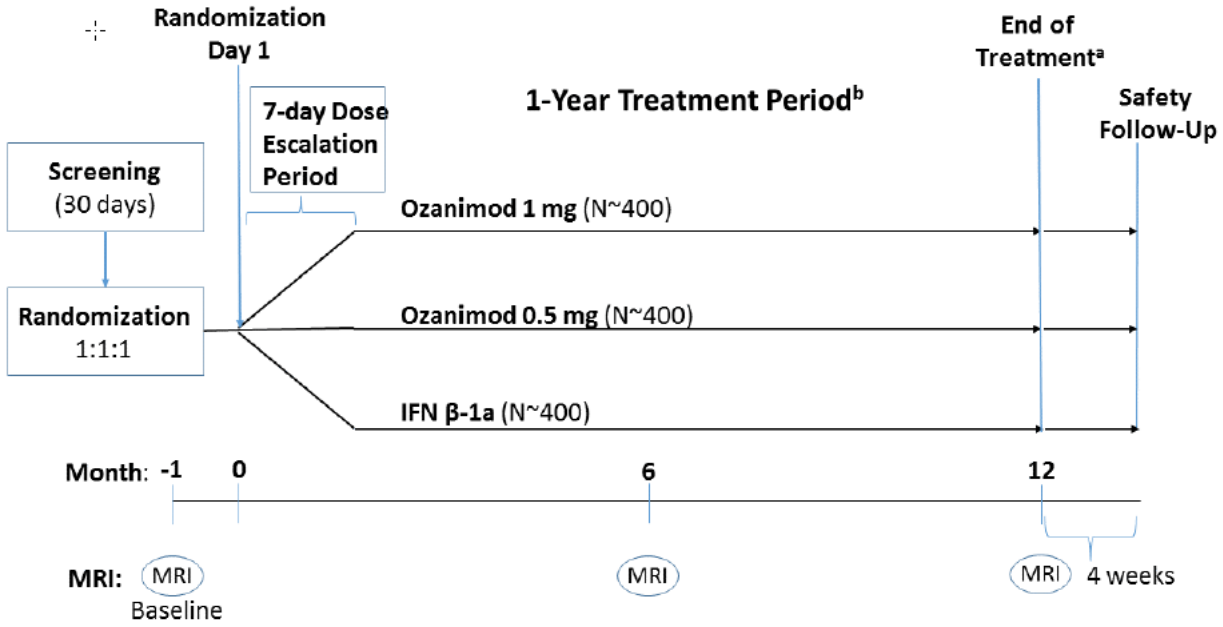
3.2.1.1 Study Design

The primary objective of Study RPC01-301 (referred as 301 thereafter) was to assess whether the clinical efficacy of ozanimod was superior to IFN β-1a (Avonex®) in reducing the rate of clinical relapses in patients with relapsing forms of multiple sclerosis (RMS).

Study 301 was a phase 3, multi-center, randomized, double-blind, double-dummy, active-controlled, parallel group study to evaluate the efficacy and safety of ozanimod administered orally to patients with RMS.

On Day 1, eligible patients were randomized in a 1:1:1 ratio to receive ozanimod 0.5 mg, ozanimod 1 mg, administered daily or IFN β-1a (Avenex) 30 µg intramuscular administered weekly. The randomization was stratified by baseline EDSS (≤ 3.5, > 3.5) and country. Patients continued to receive randomized, blinded treatment until the last active patient had been treated for at least 12 months.

The study planned to enroll 1200 subjects. A total of 1346 subjects were actually randomized at study sites in North America, Europe, and New Zealand. The schematic of the study design is presented in Figure 1.



Abbreviations: EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging.
[a] Treatment continued for at least 12 months and up to approximately 30 months. The end of treatment occurred when the last active subject received 12 months of treatment with study drug.
[b] Subjects received randomized, blinded treatment until the last active subject was treated for at least 12 months or discontinued.

Figure 1 Study Schematic - Protocol 301 (source: CSR)

3.2.1.2 Study Endpoints

The primary efficacy endpoint was the annualized relapse rate (ARR) during the treatment period.

Key Secondary Efficacy Endpoints (rank ordered) were as follows:

- The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 12 months
- The number of GdE brain MRI lesions at Month 12
- Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months

3.2.1.2.1 Definition of Efficacy Endpoints

Protocol Defined Relapse

A relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days. The new or worsening neurological symptoms must be accompanied by objective neurological worsening, based on examination by the blinded evaluator, consistent with an increase of at least half a point on the EDSS, or 2 points on one of the appropriate Functional System (FS) scores, or 1 point on two or more of the appropriate FS scores.

Symptoms must persist for > 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to concomitant medications). EDSS and FS scores documented by the blinded evaluator at the time of the relapse will be verified by the treating investigator who will determine whether the change in EDSS and FS scores meet the protocol defined relapse definitions and determine whether relapse treatment will be administered.

MS Disease Progression

The MS disease progression is defined as a sustained worsening in EDSS of 1.0 points or more, confirmed after a 3-month and 6-month period. Confirmation of MS disease progression must not occur at the time of a relapse. If the patient is scheduled to be evaluated to confirm the disability at the time of a relapse, the disability event must be assessed at a later visit, which may be the next scheduled visit, or an unscheduled visit conducted after the relapse has resolved. In case of MS disease progression, the treating investigator will discuss with the patient the treatment alternatives outside of the study. If the patient decides to continue with the study, the patient will have to re-consent for the study and the Investigator will document that an adequate discussion about treatment alternatives have been taken place.

3.2.1.3 Statistical Methodologies

The Intent-to-Treat (ITT) population was defined as all randomized patients who received at least 1 dose of study medication. This population was to be used as the primary population for all efficacy parameters.

3.2.1.3.1 Analyses of the Primary Endpoints

The relapse rate was to be based on only those relapses that were determined by the treating investigator to meet the protocol-defined definition of relapse.

The primary analysis for the ARR was to be carried out using a Poisson regression model. The model was to compare treatment groups, adjusted for region, age, and the number of Gd-enhancing (GdE) lesions at baseline, with the natural log transformation of time on study as an offset term.

Two sensitivity analyses were to be performed. The first sensitivity analysis was to repeat the primary analysis counting both confirmed and unconfirmed relapses. The second sensitivity analysis was to use a negative binomial regression model, instead of the Poisson regression model, to compare relapse rates. The same covariates and offset term as specified in the primary analysis were to be used. This model was to run twice: once repeating the primary analysis (confirmed relapses only) and once repeating the first sensitivity analysis (confirmed + unconfirmed relapses).

3.2.1.3.2 Analysis of Secondary Endpoints

Analysis of New or Enlarging T2 Lesions and Analysis of T1 Gd-Enhancing Lesions

The key secondary endpoints of cumulative number of new or newly enlarging T2 lesions between baseline and Month 12 and the number of GdE lesions at Month 12 were to be analyzed using a negative binomial regression model with factors for treatment, region, age, and baseline number of GdE lesions, with the natural log transformation of the number of available MRI scans as an offset term.

Analysis of Disability Progression

Disability progression could be confirmed at the early withdrawal visit, as long as the early withdrawal visit was not also a relapse assessment visit.

Death due to MS was to be counted as a confirmed progression. If a patient was in the midst of a tentative progression at the time of death, the progression date would be the date of the start of the progression. Otherwise, the progression date would be the date of death.

A patient was to be censored if follow-up ended before a sustained progression occurred, whether due to the patient completing the study, withdrawing from the study, or due to the cutoff of data collection for the analysis. The censoring date was to be the date of the last EDSS assessment or date of the last dose of the study drug, whichever was later. This was to apply to both 3-month and 6-month confirmations of progression. As such, a patient who was confirmed as having a progression after 3 months but did not have a 6-month confirmation was to be considered as having an event in the 3-month analysis but was to be censored in the 6-month analysis. Patients in the ITT population who withdrew from the study after the Baseline visit but prior to the first scheduled clinical evaluation visit was to be censored at Baseline.

For the key secondary endpoint of time to onset of disability progression, the data from this study were to be pooled with the data from Study 201 Part B, for hypothesis testing.

The primary analysis of time to onset of disability progression was to use a log rank test. In addition, treatment groups were to be compared using Kaplan-Meier estimation and a Cox proportional-hazards model adjusted for region, age, and baseline EDSS score. Disability progressions confirmed at 3 months and at 6 months were to be analyzed separately.

3.2.1.3.3 Handling of Missing Data

Three sensitivity analyses were to be performed for the two key secondary MRI endpoints for imputing the missing data. The primary T2 or GdE analysis was to be repeated

1. using the mean number of T2 or GdE lesions from patients in the same treatment group;
2. using last observation carried forward (LOCF) method. Only data from post-Baseline MRI scans can be carried forward to the Month 6 and Month 12 timepoints for this analysis; and
3. using only patients with complete T2 or GdE data at both Months 6 and 12 (observed cases analysis).

All three sensitivity analyses were to include the natural log transformation of exposure time on study (instead of the number of available MRI scans) as the offset term.

3.2.1.3.4 Multiplicity Consideration

Statistical testing for the primary efficacy endpoint was to be made between each ozanimod dose group and the IFN β-1a group (2 treatment contrasts). To account for multiple comparisons, each of the 2 treatment comparisons with IFN β-1a was to be tested at the $\alpha = 0.025$ level.

The 3 key secondary endpoints were to be tested in a sequential, closed hierarchical testing procedure with ozanimod 1 mg dose to be tested before ozanimod 0.5 mg dose for each key secondary endpoint following the given rank order of the key secondary endpoints.

If both doses were tested significant on the primary endpoint, then the first comparison on the key secondary endpoints was to be the number of new or enlarging T2 lesions between the ozanimod 1 mg group and the IFN β-1a group at the 5% level of significance. If that comparison was successful, then the same endpoint was to be tested for the ozanimod 0.5 mg group vs. the IFN β-1a group comparison at the 5% level of significance. This procedure (Figure 2) was to continue down the rank-ordered key secondary endpoint list until a comparison failed to reach statistical significance, after which all subsequent comparisons were to be considered exploratory.

If only 1 ozanimod dose was significant on the primary endpoint, then the hierarchical testing procedure was to be employed on the rank-ordered key secondary endpoints for the surviving dose only, at the 2.5% level of significance.

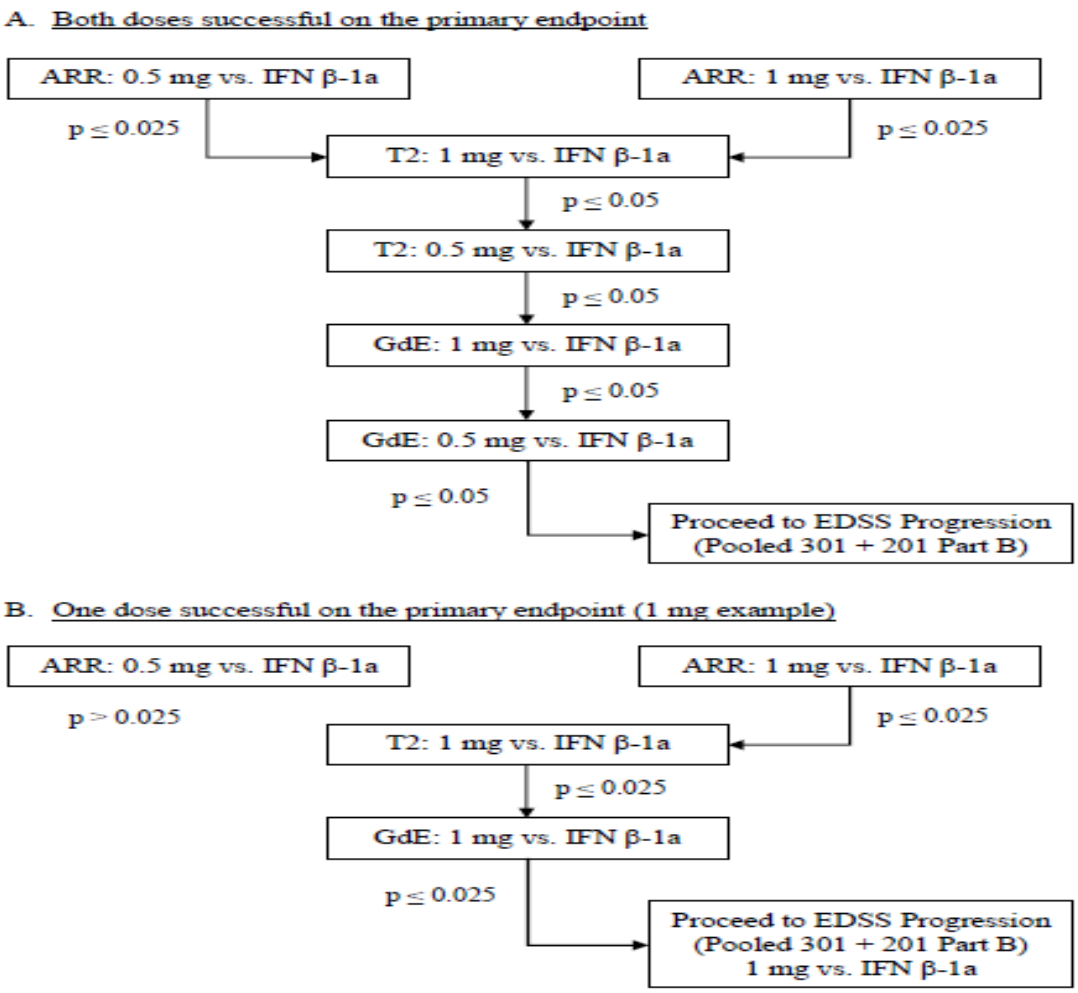


Figure 2 Hierarchical Testing Procedure - Protocol 301 (Source: CSR)

3.2.1.4 Patient Results of Study 301

3.2.1.4.1 Patient Disposition

A total of 1346 subjects were randomized, 448 subjects to IFN β-1a, 451 subjects to ozanimod 0.5 mg, and 447 subjects to ozanimod 1 mg. All 1346 subjects received at least 1 dose of study drug.

Of the 1346 subjects randomized, 1255 (93.2%) subjects completed the study. A total of 1272 (94.5%) subjects completed the Month 12 Visit. The longest period of treatment was 675 days.

Ninety-one (6.8%) subjects withdrew from the study (ozanimod 1 mg: 29 [6.5%] subjects; ozanimod 0.5 mg: 26 [5.8%] subjects; IFN β-1a: 36 [8.0%] subjects).

A summary of patient disposition for Study 301 is presented in Figure 3.

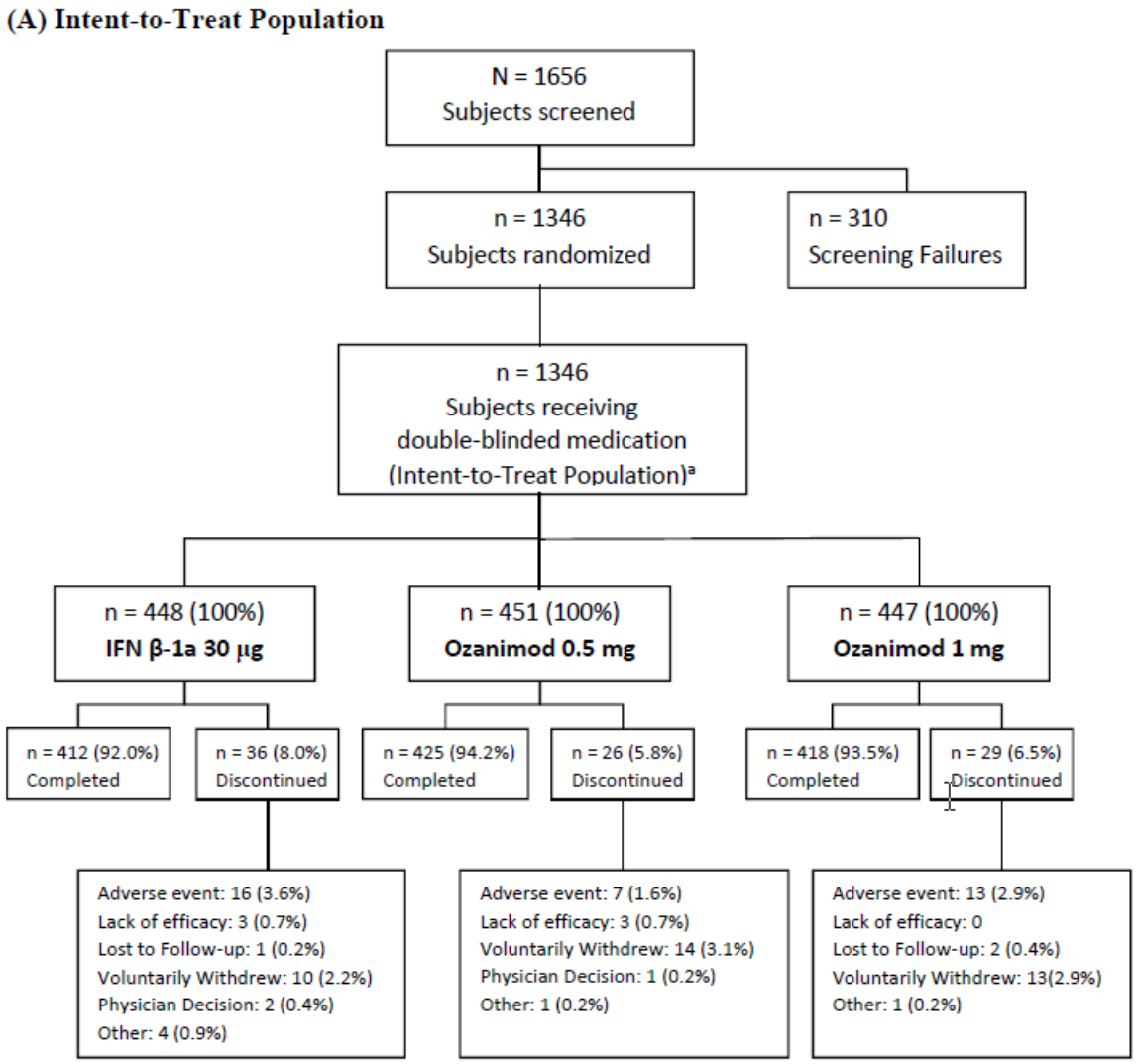


Figure 3 Disposition of Subjects - Protocol 301 (Source: CSR)

3.2.1.4.2 Patient Demographics

Demographic and baseline characteristics are summarized for the ITT population in Table 2.

There were no notable differences among treatment groups in the demographic characteristics at baseline. Almost all subjects in the ITT Population were white (99.6%). Overall, 66.4% of the subjects were female and 33.6% were male. The mean age was 35.6 years.

The majority of the subjects (93.1%) were enrolled in the Eastern European region and the country with the largest number of subjects (28.4%) was Ukraine.

Table 2 Patient Demographics

	IFN β– 1a 30 µg N=448	Ozanimod 0.5 mg N=451	Ozanimod 1 mg N=447
Sex, n (%)			
Female	300 (67.0)	311 (69.0)	283 (63.3)
Male	148 (33.0)	140 (31.0)	164 (36.7)
Age, years			
Mean (SD)	35.9 (9.11)	36.0 (9.43)	34.8 (9.24)
Median	36.0	36.0	33.0
Race, n (%)			
White	447 (99.8)	447 (99.1)	446 (99.8)
Other	1 (0.2)	4 (0.9)	1 (0.2)
Region, n (%)			
Eastern Europe	419 (93.5)	419 (92.9)	415 (92.8)
Rest of the world	29 (6.5)	32 (7.1)	32 (7.2)

Source: CSR

3.2.1.4.3 Patient Baseline Disease Characteristics

Baseline MS disease characteristics were well balanced across treatment groups. The mean age at MS diagnosis was about 32 years. The mean number of years since MS symptom onset was about 7 years. About 98% of patients had relapsing remitting MS while the rest had secondary progressive or progressive relapsing MS.

At baseline, the mean EDSS score was 2.6 for all treatment groups and about 80% of the patients were in the EDSS <=3.5 stratification category. The mean number of relapses in the 12 months prior to screening was 1.3 with median of 1 in all treatment groups. Overall, about 94% of the subjects had prior treatment for MS with about 30% of the subjects treated with a disease modifying therapy.

The MRI scans at the screening showed that the mean number of Gd-enhanced lesions was about 1.7. At least half of the patients did not have Gd-enhanced lesions at baseline. The mean number of T2 lesions was about 54 with median of about 45.

Patients baseline disease characteristics are summarized in Table 3.

Table 3 Patients Baseline Disease Characteristics

	IFN β– 1a 30 µg N=448	Ozanimod 0.5 mg N=451	Ozanimod 1 mg N=447
Age at MS Diagnosis (years)			
Mean (SD)	32.7 (9.01)	32.7 (9.49)	31.6 (8.81)
Median	32.0	32.0	30.0
Years since MS Symptom Onset			
Mean (SD)	6.9 (5.88)	7.2 (6.26)	6.9 (6.45)
Median	5.3	5.6	4.8

Types of MS, n (%)			
Relapsing Remitting MS	441 (98.4)	443 (98.2)	438 (98.0)
Secondary Progressive MS	2 (0.4)	3 (0.7)	0
Progressive Relapsing MS	5 (1.1)	5 (1.1)	9 (2.0)
EDSS Score at Baseline			
Mean (SD)	2.6 (1.14)	2.6 (1.14)	2.6 (1.16)
Median	2.5	2.5	2.5
EDSS Stratification, n (%)			
EDSS <=3.5	362 (80.8)	361 (80.0)	359 (80.3)
EDSS > 3.5	86 (19.2)	90 (20.0)	88 (19.7)
# of Relapses in past 12 months			
Mean (SD)	1.3 (0.55)	1.3 (0.57)	1.3 (0.57)
Median	1.0	1.0	1.0
Number (%) of Subjects with Prior Treatment	427 (95.3)	417 (92.5)	422 (94.4)
With Disease Modifying drug	151 (33.7)	132 (29.3)	128 (28.6)
With Corticosteroids	421 (94.0)	412 (91.4)	416 (93.1)
# of Gd-enhanced Lesions			
Mean (SD)	1.7 (3.22)	1.6 (2.95)	1.8 (3.41)
Median	0.0	0.0	0.0
Baseline T2 Lesion Count			
Mean (SD)	53.7 (37.80)	53.6 (35.56)	54.5 (39.48)
Median	45.0	46.0	45.0

Source: Tables 10, 11, and 12 of Clinical Study Report

3.2.1.5 Efficacy Results of Study 301

3.2.1.5.1 Annualized Relapse Rate (ARR) – Primary Endpoint

The primary efficacy endpoint was the annualized relapse rate (ARR) during the treatment period. The primary analyses were to compare the ARRs in each of the ozanimod dose groups to the IFN β-1a group using a Poisson regression model at the alpha = 0.025 level.

The estimated ARR from the Poisson model was 0.18 for ozanimod 1 mg group, 0.24 for ozanimod 0.5 mg group, compared to 0.35 for IFN β-1a group. The rate ratio versus IFN β-1a group was 0.518 ($p<0.0001$) for ozanimod 1 mg groups and 0.688 ($p=0.0013$) for ozanimod 0.5 mg groups.

The reduction in ARR was more pronounced in ozanimod 1 mg group than in ozanimod 0.5 mg group, indicating a dose response. The ARR rate ratio of ozanimod 1 mg versus ozanimod 0.5 mg was 0.753 ($p=0.0366$), representing a reduction of 25% in ARR.

A total of 8 relapses were not confirmed: 4 in the IFN β-1a group, 1 in ozanimod 0.5 mg group, and 3 in ozanimod 1 mg group. Sensitivity analysis on the confirmed and unconfirmed relapses yielded similar rate ratios.

The results of the analysis of ARR are summarized in Table 4.

Table 4 Summary of Analysis of Annualized Relapse Rate

	IFN β– 1a 30 µg N=448	Ozanimod 0.5 mg N=451	Ozanimod 1 mg N=447
Subjects with Conf. Relapses, n (%)	132 (29.5)	93 (20.6)	84 (18.8)
By Relapse Numbers			
0	316 (70.5)	358 (79.4)	363 (81.2)
1	92 (20.5)	69 (15.3)	71 (15.9)
2	31 (6.9)	19 (4.2)	13 (2.9)
3	6 (1.3)	2 (0.4)	0
>=4	3 (0.7)	3 (0.7)	0
Primary Analysis: Poisson Model			
Adjusted Relapse Rate (95% CI)	0.35 (0.279, 0.440)	0.24 (0.188, 0.308)	0.18 (0.140, 0.236)
Rate Ratio		0.688	0.518
Percent Reduction		31.2%	48.2%
p-value		0.0013	<0.0001
Rate Ratio Oz 1mg/0.5mg (95% CI)			0.75 (0.578, 0.982)
p-value			0.0366
Sensitivity Analysis: Negative Binomial Model			
Adjusted Relapse Rate (95% CI)	0.35 (0.266, 0.449)	0.24 (0.183, 0.318)	0.18 (0.134, 0.240)
Rate Ratio		0.697	0.520
Percent Reduction		30.3%	48.0%
p-value		0.0067	<0.0001
Rate Ratio Oz 1mg/0.5mg (95% CI)			0.75 (0.555, 1.000)
p-value			0.0500
Subjects with Confirmed + Unconfirmed Relapses, n (%)	136 (30.4)	94 (20.8)	87 (19.5)
Adjusted Relapse Rate (Poisson)	0.39 (0.311, 0.477)	0.26 (0.208, 0.331)	0.21 (0.165, 0.270)
Rate Ratio		0.680	0.547
Percent Reduction		32.0%	45.3%
p-value		0.0008	<0.0001
Rate Ratio Oz 1mg/0.5mg (95% CI)			0.81 (0.622, 1.041)
Percent Reduction			19.0%
p-value			0.098

Source: Reviewer's analysis

3.2.1.5.2 Secondary Endpoints

Analysis of New or Enlarging T2 Lesions

The cumulative number of new or enlarging T2 lesions was the sum of the lesions on scans at Month 6 and Month 12. The primary analysis was based on observed cases in which about 87% of the patients had lesion values on both scans. The least square estimated number of lesions per scan (2 scans per patient) was 1.47 for ozanimod 1 mg group and 2.14 for ozanimod 0.5 mg group, compared to 2.84 for IFN β-1a group. The reduction in the number of new or enlarging

T2 lesions per scan was 48% (p<0.0001) for ozanimod 1 mg group and 25% (p=0.0032) for ozanimod 0.5 mg group, versus IFN β-1a group.

In the two sensitivity analyses, missing values were imputed using LOCF or the mean lesion number from the same treatment group and the offset variable was the duration of the exposure instead of the number of scans. Therefore, the estimated number of lesions was interpreted as number of lesions per year instead of per scan.

Table 5 Cumulative Number of New or Enlarging T2 Lesions Over 12 Months

	IFN β– 1a 30 µg N=448	**Ozanimod 0.5 mg N=451**	**Ozanimod 1 mg N=447**
Number of Subjects with M12 Scan	381 (85.0%)	397 (88.0%)	388 (86.8%)
Mean (SD)	7.20 (12.74)	5.23 (8.99)	4.63 (8.93)
Median	3.0	2.0	1.0
Subjects with 0 Lesions, n (%)	105 (27.56)	119 (29.97)	125 (32.22)
Primary Analysis, Observed Cases			
N	381	397	388
LS Mean (95% CI) per scan	2.84 (2.331, 3.451)	2.14 (1.777, 2.575)	1.47 (1.203, 1.784)
Rate Ratio (95% CI)		0.75 (0.625, 0.910)	0.52 (0.427, 0.625)
Percent Reduction		25%	48%
p-value		0.0032	<0.0001
Sensitivity Analysis with LOCF			
N	441	442	439
LS Mean (95% CI) per year	5.42 (4.494, 6.547)	3.93 (3.295, 4.693)	2.80 (2.316, 3.380)
Rate Ratio (95% CI)		0.73 (0.604, 0.870)	0.52 (0.429, 0.620)
Percent Reduction		27%	48%
p-value		0.0005	<0.0001
Sensitivity Analysis with Mean T2			
N	447	450	447
LS Mean (95% CI) per year	6.60 (5.522, 7.894)	4.34 (3.665, 5.135)	3.17 (2.648, 3.792)
Rate Ratio (95% CI)		0.66 (0.553, 0.781)	0.48 (0.403, 0.571)
Percent Reduction		34%	52%
p-value		<0.0001	<0.0001

Source: Reviewer's analysis

Analysis of T1 Gd-Enhancing Lesions

The primary analysis of the number of Gd-enhancing lesions was based on patients who had Month 12 scan. Since Month 6 scan was not used in the primary analysis, the estimate mean lesion number per scan was also interpreted as mean lesion number per year.

At Month 12, the estimated mean lesion number was 0.16 for ozanimod 1 mg group and 0.29 for ozanimod 0.5 mg group, compared to 0.43 for IFN β-1a group. This represented a reduction in lesion numbers of 63% and 34% for ozanimod 1 mg group (p<0.0001) and 0.5 mg group (p=0.0182), respectively, versus IFN β-1a group. The results from the two sensitivity analyses with missing values imputed confirmed results from the primary analysis.

Table 6 Number of Gd-Enhancing Lesions at Month 12

	IFN β– 1a 30 µg N=448	Ozanimod 0.5 mg N=451	Ozanimod 1 mg N=447
Number of Subjects with M12 Scan	381 (85.0%)	397 (88.0%)	388 (86.8%)
Mean (SD)	0.79 (2.99)	0.43 (1.18))	0.31 (1.14)
Median	0.0	0.0	0.0
Subjects with 0 Lesions, n (%)	283 (74.1)	308 (77.6)	331 (85.3)
Primary Analysis, Observed Cases			
N	381	397	388
LS Mean (95% CI) per scan	0.43 (0.295, 0.635)	0.29 (0.197, 0.418)	0.16 (0.106, 0.242)
Rate Ratio (95% CI)		0.66 (0.471, 0.932)	0.37 (0.256, 0.536)
Percent Reduction		34%	63%
p-value		0.0182	<0.0001
Sensitivity Analysis with LOCF			
N	441	442	439
LS Mean (95% CI) per year	0.60 (0.412, 0.863)	0.27 (0.186, 0.389)	0.17 (0.114, 0.250)
Rate Ratio (95% CI)		0.45 (0.319, 0.637)	0.28 (0.196, 0.409)
Percent Reduction		55%	72%
p-value		<0.0001	<0.0001
Sensitivity Analysis with Mean T1			
N	447	450	447
LS Mean (95% CI) per year	0.49 (0.371, 0.653)	0.30 (0.226, 0.403)	0.18 (0.132, 0.248)
Rate Ratio (95% CI)		0.61 (0.471, 0.796)	0.37 (0.276, 0.489)
Percent Reduction		39%	63%
p-value		0.0003	<0.0001

Source: Reviewer's analysis

3-Month and 6-Month Confirmed Disability Progression

The analysis of time to onset of disability progression confirmed at 3 months and 6 months was to be performed on the pooled data of Studies 301 and 201B for the purpose of enhancing the power. First, the analysis on separate study data was performed to examine the appropriateness of the pooling.

For Study 301, the number of patients who had disability progression confirmed at 3 months was 13 for ozanimod 1 mg group and 17 for ozanimod 0.5 mg group, compared with 19 for IFN β-1a group. The hazard ratio estimates from the Cox model yielded 0.69 (p=0.3055) for ozanimod 1 mg group and 0.89 (p=0.7163) for ozanimod 0.5 mg group, versus IFN β-1a group. Neither of the ozanimod dose groups showed statistically significant treatment difference in 3 month disability progression based on this single study.

For Study 201B, the number of patients who had 3-month disability progression was 54 for ozanimod 1 mg group and 41 for ozanimod 0.5 mg group, compared with 50 for IFN β-1a group. The percentage of patients who had 3-month disability progression was much higher in this study compared to the one in Study 301, which could be partly contributed by the longer duration of the study. A higher percentage of patients with 3-month disability progression was observed in ozanimod 1 mg group compared to two other treatment groups. Similarly, more patients treated with ozanimod than patients treated with IFN β-1a had disability progression confirmed at 6 months. Therefore, pooling of the data was not considered appropriate.

Based on the results of 3-month and 6-month disability progression for the two studies, it is concluded that no treatment benefit of ozanimod was observed in the confirmed disability progression.

Table 7 presents a summary of analysis results for 3-month and 6-month disability progression for Studies 301 and 201B. Results from pooled data are also presented although no inferential statement should be made based on the pooled data.

Table 7 Time to Onset of Disability Progression

	IFN β– 1a 30 µg	**Ozanimod 0.5 mg**	**Ozanimod 1 mg**
Study 301	**N=448**	**N=451**	**N=447**
Number of Subjects with **3-month** CDP, n (%)	19 (4.2)	17 (3.8)	13 (2.9)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value		0.89 (0.460, 1.705) 0.7162	0.69 (0.340, 1.402) 0.3055
Number of Subjects with **6-month** CDP, n (%)	7 (1.6)	11 (2.4)	9 (2.0)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value		1.54 (0.595, 3.963) 0.3755	1.24 (0.460, 3.337) 0.6725
Study 201B	**N=441**	**N=439**	**N=433**
Number of Subjects with **3-month** CDP, n (%)	50 (11.3)	41 (9.3)	54 (12.5)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value		0.80 (0.528, 1.206) 0.2849	1.05 (0.711, 1.537) 0.8224
Number of Subjects with 6-**month** CDP, n (%)	29 (6.6)	32 (7.3)	42 (9.7)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value		1.10 (0.664, 1.815) 0.7154	1.44 (0.893, 2.305) 0.1353
Pooled Data	889	890	880
Number of Subjects with **3-month** CDP, n (%)	69 (7.8)	58 (6.5)	67 (7.6)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value		0.86 (0.605, 1.223) 0.4024	1.05 (0.747, 1.463) 0.7959
Number of Subjects with 6-**month** CDP, n (%)	36 (4.1)	43 (4.8)	51 (5.8)
Primary Analysis Hazard Ratio (ozanimod/ IFN β-1a) p-value		1.19 0.764, 1.852) 0.4434	1.42 (0.927, 2.175) 0.1075

Source: Reviewer's analysis

3.2.2 Evaluation of Efficacy for Study RPC01-201B

3.2.2.1 Study Design

The primary objective of Study RPC01-201B (referred as 201B thereafter) was to assess whether the clinical efficacy of ozanimod was superior to IFN β-1a in reducing the rate of clinical relapses at the end of Month 24 in patients with RMS.

On Day 1, 1320 eligible subjects were randomly assigned to receive 1 of the 3 following regimens in a 1:1:1 ratio for 24 months:

- IFN β-1a 30 µg intramuscular (IM) weekly
- ozanimod HCl 0.5 mg oral capsule daily
- ozanimod HCl 1 mg oral capsule daily

The randomization was stratified by baseline EDSS (≤3.5, >3.5) and country. The study was conducted at 150 sites in North America, Europe, and South Africa. The study design is shown in Figure 4.

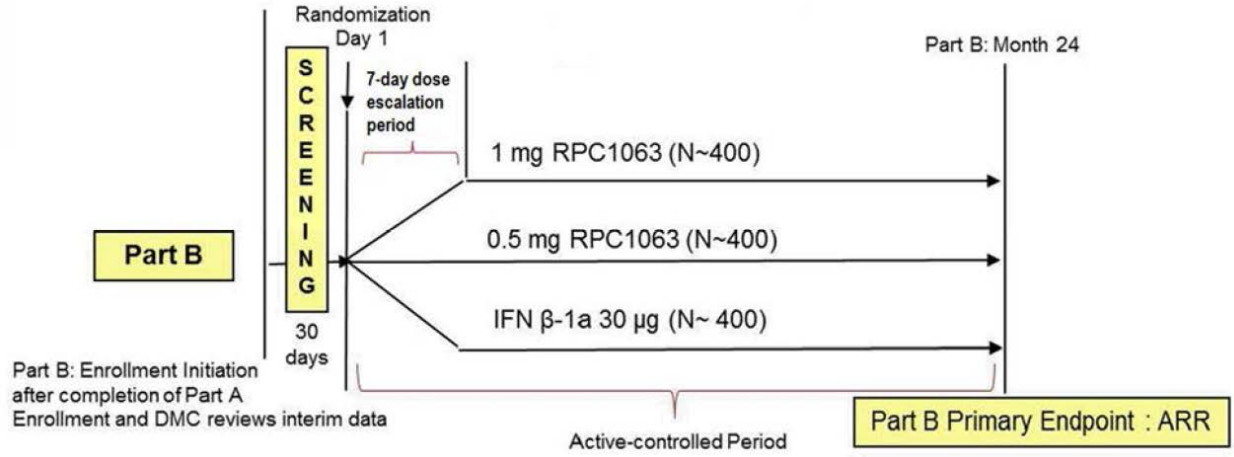


Figure 4 Study Schematic - Protocol 201B (Source: CSR)

3.2.2.2 Study Endpoint

The primary efficacy endpoint was ARR at the end of Month 24.

Key secondary efficacy endpoints (rank ordered) were:

- The number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months
- The number of GdE brain MRI lesions at Month 24
- Time to onset of disability progression as defined by a sustained worsening in EDSS of 1.0 points or more, confirmed after 3 months and after 6 months

3.2.2.3 Statistical Analysis Methods

The same statistical analysis methods for Study 301 were specified for this study except that this was a 24-month trial while duration for Study 301 varied by subjects. All efficacy variables were assessed over the period of 24 month or at the end of 24 month for this study.

3.2.2.4 Patient Results of Study 201B

3.2.2.4.1 Patient Disposition

A total of 1200 subjects were planned, and 1320 subjects were actually randomized. Of those subjects, 1313 subjects received at least 1 dose of IFN β-1a (n = 441), ozanimod 0.5 mg (n = 439), or ozanimod 1 mg (n = 433).

Of the 1313 subjects in the ITT Population, 1139 (86.7%) subjects (ozanimod 1 mg: 389 [89.8%] subjects; ozanimod 0.5 mg: 374 [85.2%] subjects; IFN β-1a: 376 [85.3%] subjects) completed the study.

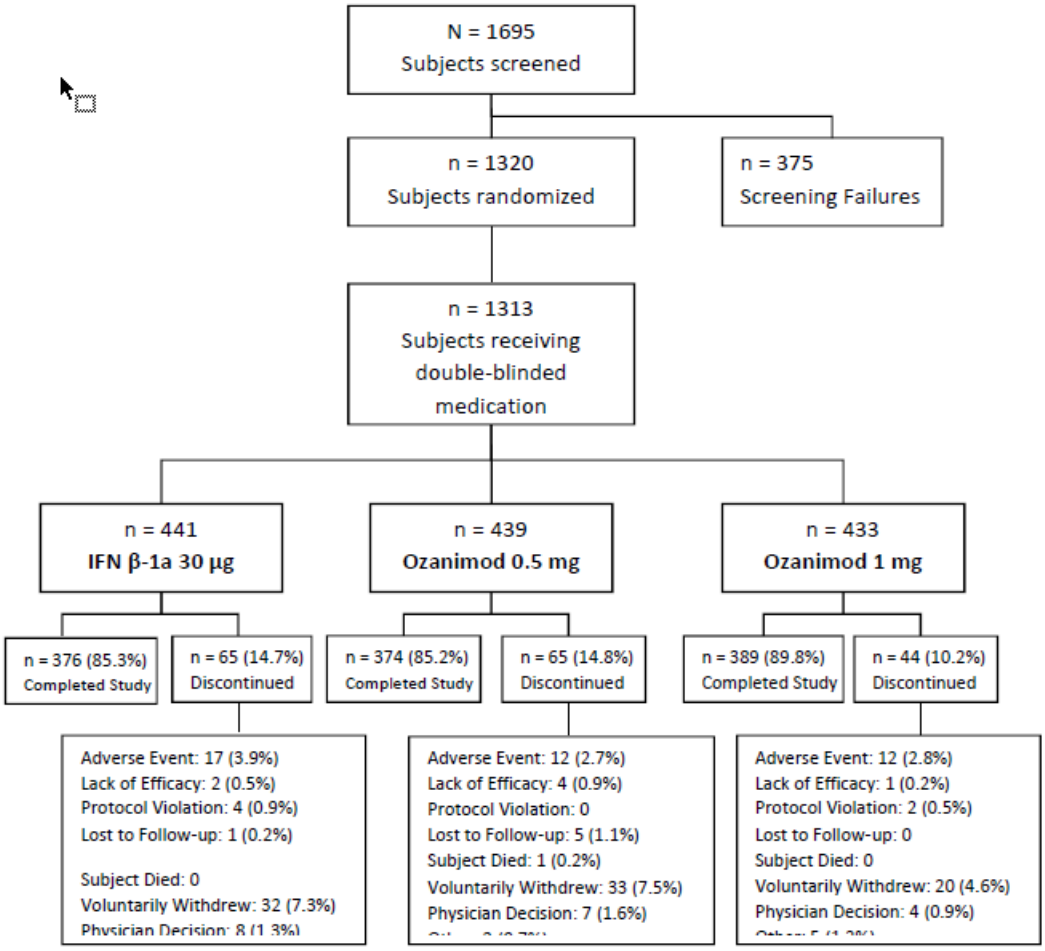


Figure 5 Overview of Patient Disposition
Source: CSR

3.2.2.4.2 Patient Demographics

There were no notable differences among treatment groups in demographic characteristics. The majority of subjects in the ITT Population were female (67.2% of subjects overall). Over 98% of the subjects were White. The mean age overall was 35.5 years. About 86% of the subjects were enrolled in the Eastern European region and the country with the largest number of subjects was Poland (28.4% of subjects).

Table 8 Summary of Demographic Data (ITT Population)

	IFN β– 1a 30 µg N=441	Ozanimod 0.5 mg N=439	Ozanimod 1 mg N=433
Sex, n (%)			
Female	304 (68.9)	287 (65.4)	291 (67.2)
Male	137 (31.1)	152 (34.6)	142 (32.8)

Age, years			
Mean (SD)	35.1 (9.07)	35.4 (8.82)	36.0 (8.89)
Median	35.0	35.0	36.0
Race, n (%)			
White	432 (98.0)	431 (98.2)	428 (98.8)
Other	9 (2.0)	8 (1.8)	5 (1.2)
Region, n (%)			
Eastern Europe	379 (85.9)	378 (86.1)	374 (86.4)
Rest of the world	62 (14.1)	61 (13.9)	59 (13.6)
North America	16 (3.6)	16 (3.6)	16 (3.7)
Western Europe	40 (9.1)	40 (9.1)	36 (8.3)
Southern Africa	6 (1.4)	5 (1.1)	7 (1.6)

Source: CSR

3.2.2.4.3 Patient Baseline Disease Characteristics

There were no notable differences among treatment groups in baseline disease characteristics. The overall mean age at MS diagnosis was 31.9 years. The mean EDSS score at baseline was about 2.5 with about 85% of patients in the category of EDSS $\leq$ 3.5. The mean number of relapses within the last 12 months prior to screening was 1.3 overall with median of 1, and the mean number of relapses within the last 24 months prior to screening was 1.8 overall.

The percentage of subjects who reported prior MS medication use was similar across treatment groups, with 1213 (92.4%) subjects reported taking prior MS medication. About 29% of the patients were previously treated with MS disease modifying drugs.

The mean number of GdE lesions and T2 lesions at baseline were similar across treatment groups with an overall mean of 1.7 for the GdE lesion count and an overall mean of 48.4 for the T2 lesion count. About 57% of the patients were free of GdE lesions at baseline.

Table 9 Summary of baseline disease characteristics (ITT Population)

	IFN β– 1a 30 µg N=441	**Ozanimod 0.5 mg N=439**	**Ozanimod 1 mg N=433**
Age at MS symptom onset (years) Mean (SD)	28.9 (8.60)	29.3 (8.41)	29.2 (8.67)
Age at MS diagnosis (years) Mean (SD)	31.6 (8.82)	32.0 (8.59)	32.1 (8.95)
EDSS Score at Baseline			
Mean (SD)	2.5 (1.16)	2.5 (1.17)	2.6 (1.15)
Median	2.5	2.0	2.5

EDSS Stratification n (%) EDSS ≤ 3.5 EDSS > 3.5	 375 (85.0) 66 (15.0)	 374 (85.2) 65 (14.8)	 371 (85.7) 62 (14.3)
Number of Relapses in the Last 12 Months Mean (SD) Median	 1.3 (0.58) 1.0	 1.4 (0.64) 1.0	 1.3 (0.56) 1.0
Number of Relapses in the Last 24 Months Mean (SD) Median	 1.8 (0.86) 2.0	 1.8 (0.90) 2.0	 1.7 (0.82) 1.0
Baseline GdEh Lesion Count Mean (SD)	 1.8 (3.54)	 1.8 (3.62)	 1.6 (3.78)
Number (%) of Patients with 0 GdE Lesions	244 (55.3)	249 (56.7)	255 (58.9)
Baseline T2 Lesion Count Mean (SD)	 48.7 (32.62)	 48.7 (36.27)	 47.9 (32.37)
Number (%) of Subjects with Prior MS Treatment	407 (92.3)	404 (92.0)	402 (92.8)
Number (%) of Subjects Treated with Disease-Modifying Treatment	126 (28.6)	131 (29.8)	123 (28.4)

Source: CSR

3.2.2.5 Efficacy Results of Study 201B

3.2.2.5.1 Annualized Relapse Rate (ARR) – Primary Endpoint

The primary efficacy endpoint was the annualized relapse rate (ARR) at the end of Month 24. The primary analysis was to compare the ARRs in each of the ozanimod dose groups to the IFN β-1a group using a Poisson regression model at the alpha = 0.025 level.

The ARR and percent reduction during the treatment period is summarized for the ITT Population in Table 10. Treatment with ozanimod resulted in statistically significantly lower ARR compared to IFN β-1a with adjusted ARR of 0.172 for the ozanimod 1 mg group and 0.218 for the ozanimod 0.5 mg group, compared to 0.276 for the IFN β-1a group. The corresponding reduction in ARR versus IFN β-1a was 37.66% ($p<0.0001$) for ozanimod 1 mg group and 20.95% ($p=0.0167$) for ozanimod 0.5 mg group.

The reduction in ARR was more pronounced in the ozanimod 1 mg group than in the ozanimod 0.5 mg group, indicating a dose response. The reduction of ARR for ozanimod 0.5 mg to placebo was about the same as the reduction of ARR for ozanimod 1 mg to ozanimod 0.5 mg at about 21%.

Table 10 Summary of Analysis of ARR

	IFN β– 1a 30 µg N=441	Ozanimod 0.5 mg N=439	Ozanimod 1 mg N=433
Subjects with Relapses n (%)	149 (33.8)	121 (27.6)	102 (23.6)
0	292 (66.2)	318 (72.4)	331 (76.4)
1	92 (20.9)	76 (17.3)	75 (17.3)
2	39 (8.8)	32 (7.3)	17 (3.9)
3	12 (2.7)	8 (1.8)	6 (1.4)
≥ 4	6 (1.4)	5 (1.1)	4 (0.9)
Primary Analysis: Poisson Model			
Adjusted ARR (95% CI)	0.276 (0.234, 0.324)	0.218 (0.183, 0.259)	0.172 (0.142, 0.208)
Rate Ratio Oz/IFN β (95% CI)		0.791 (0.652, 0.958)	0.623 (0.506, 0.768)
Percent Reduction		78.9%	37.7%
p-value		0.0167	<0.0001
Rate Ratio Oz 1mg/0.5mg (95% CI)			0.789 (0.634, 0.981)
Percent Reduction			21.1%
p-value			0.0331
Sensitivity Analysis: Negative Binomial Model			
Adjusted ARR (95% CI)	0.288 (0.226, 0.366)	0.226 (0.176, 0.291)	0.178 (0.137, 0.233)
Rate Ratio Oz/IFN β (95% CI)		0.786 (0.611, 1.010)	0.620 (0.477, 0.806)
Percent Reduction		21.4%	38.0%
p-value		0.0593	0.0004
Rate Ratio Oz 1mg/0.5mg (95% CI)			0.789 (0.602, 1.034)
Percent Reduction			21.1%
p-value			0.086
Subjects with Confirmed + Unconfirmed Relapses, n (%)	155 (35.1)	129 (29.4)	108 (24.9)
Adjusted ARR (95% CI) (Poisson)	0.308 (0.264, 0.358)	0.252 (0.215, 297)	0.191 (0.159, 0.228)
Rate Ratio Oz/IFN β (95% CI)		0.820 (0.682, 0.987)	0.620 (0.506, 0.759)
Percent Reduction		18.0%	38.0%
p-value		0.0354	<0.0001

Source: Reviewer's Analysis

3.2.2.5.2 Analysis of Secondary Endpoints

Analysis of New or Enlarging T2 Lesions

MRI scans were performed at Month 12 and Month 24. The cumulative number of new or enlarging T2 lesions for the analysis was the sum of the new or enlarging T2 lesions on the two scans. A large number of subjects (105 in the IFN β-1a group, 110 in the ozanimod 0.5 mg group and 106 in the ozanimod 1mg group) did not have MRI scan at Month 24. The primary analysis was based on subjects who had MRI scan at Month 24.

At Month 24, the adjusted mean for the cumulative number of new or enlarging T2 lesions per scan was 1.84 for ozanimod 1 mg group and 2.09 for ozanimod 0.5 mg group, compared to 3.18 for IFN β-1a group. A statistically significant treatment difference was achieved in both ozanimod dose groups as compared to IFN β-1a group with a p-value of < 0.0001.

Two prespecified sensitivity analyses were also performed. One was using the mean number of T2 lesions from patients of the same treatment group to impute missing T2 values and the other was using the method of last observation carry forward to impute the missing T2 values.

A summary of the results from the primary and sensitivity analyses are presented in Table 11.

Table 11 Cumulative Number of New or Enlarging T2 Lesions Over 24 Months

	IFN β– 1a 30 µg N=441	**Ozanimod 0.5 mg N=439**	**Ozanimod 1 mg N=433**
Analysis at Month 24			
Number of Subjects with M24 Scan	336	329	327
Mean (SD)	11.0 (18.84)	6.5 (11.42)	5.8 (11.77)
Median	4.0	2.0	2.0
Subjects with 0 Lesions, n (%)	81 (24.1)	103 (31.3)	103 (31.5)
Primary Analysis, Observed Cases			
N	336	329	327
LS Mean (95% CI) per scan	3.18 (2.640, 3.838)	2.09 (1.741, 2.514)	1.84 (1.523, 2.211)
Rate Ratio (95% CI)		0.66 (0.531, 0.813)	0.58 (0.465, 0.714)
Percent Reduction		34%	42%
p-value		< 0.0001	<0.0001
Sensitivity Analysis with LOCF			
N	425	427	420
LS Mean (95% CI) per year	3.84 (3.25, 4.54)	2.63 (2.23, 3.10)	1.93 (1.63, 2.29)
Rate Ratio (95% CI)		0.68 (0.562, 0.834)	0.50 (0.412, 0.614)
Percent Reduction		32%	50%
p-value		< 0.0001	< 0.0001
Sensitivity Analysis with Mean T2			
N	440	439	433
LS Mean (95% CI) per year	6.27 (5.361, 7.326)	3.81 (3.257, 4.446)	2.76 (2.343, 3.245)
Rate Ratio (95% CI)		0.61 (0.504, 0.731)	0.44 (0.364, 0.531)
Percent Reduction		39%	56%
p-value		<0.0001	<0.0001

Source: Reviewer's Analysis

It should be noted that a selection bias could be imbedded in the estimates due to missing values and the schemes of imputation for missing values. On one hand, estimates from the primary analysis only represented the patients who had Month 24 scan. On the other hand, lesion number could be overestimated in the sensitivity analysis when the missing values were imputed by the mean value from the same treatment group. This was because the estimated mean value of new or enlarging T2 lesions were adjusted by duration of exposure instead of by the number of scans. For instance, a patient who dropped out of the study early would have the value imputed as the average lesion number of the patients who had completed the study and who had accumulated lesions over 2 years.

In summary, although both dose groups of ozanimod achieved statistical significance in the reduction of lesion numbers over IFN β-1a group, neither the estimates of the lesion numbers nor the p-values could be certain in their accuracy.

Analysis of T1 Gd-Enhancing Lesions

The primary analysis of the number of Gd-enhancing lesions was based on patients who had Month 24 scan. At Month 24, the estimated mean lesion number was 0.18 for ozanimod 1 mg group and 0.20 for ozanimod 0.5 mg group, compared to 0.37 for IFN β-1a group. This represented a reduction in lesion numbers of 53% and 47% for ozanimod 1 mg group (p=0.0006) and 0.5 mg group (p=0.0030), respectively, versus IFN β-1a group.

For the same reason as in the analysis of new or enlarging T2 lesions, estimates from the primary or sensitivity analyses could be biased due to large number of missing scans.

Table 12 Number of Gd-Enhancing Lesions at Month 24

	IFN β– 1a 30 µg N=441	**Ozanimod 0.5 mg N=439**	**Ozanimod 1 mg N=433**
Analysis at Month 24			
Number of Subjects with M24 Scan	336	329	327
Mean (SD)	0.91 (2.50)	0.39 (1.29)	0.30 (1.24)
Median	0.0	0.0	0.0
Subjects with 0 Lesions, n (%)	248 (73.8)	278 (84.5)	284 (86.9)
Primary Analysis, Observed Cases			
N	336	329	327
LS Mean (95% CI) per scan	0.37 (0.256, 0.544)	0.20 (0.131, 0.296)	0.18 (0.116, 0.266)
Rate Ratio (95% CI)		0.53 (0.346, 0.805)	0.47 (0.306, 0.725)
Percent Reduction		47%	53%
p-value		0.0030	0.0006
Sensitivity Analysis with LOCF			
N	425	427	420
LS Mean (95% CI) per year	0.44 (0.326, 0.603)	0.23 (0.167, 0.320)	0.18 (0.127, 0.257)
Rate Ratio (95% CI)		0.52 (0.366, 0.741)	0.41 (0.282, 0.591)
Percent Reduction		48%	59%
p-value		0.0003	<0.0001
Sensitivity Analysis with Mean T1			
N	440	439	433
LS Mean (95% CI) per year	0.62 (0.503, 0.756)	0.28 (0.223, 0.357)	0.25 (0.192, 0.316)
Rate Ratio (95% CI)		0.46 (0.356, 0.587)	0.40 (0.307, 0.518)
Percent Reduction		54%	60%
p-value		<0.0001	<0.0001

Source: Reviewer's Analysis

3 Month and 6 Month Confirmed Disability Progression

Please see Section 3.2.1.5.2 and Table 7 for analysis results of disability progression.

3.3 Evaluation of Safety

Please refer to Evaluation of Safety by Dr. Lawrence Rodichok.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Analyses of the primary endpoint of ARR on subpopulations of age group and sex were performed. Almost all patients were white and thus analysis by race was not performed.

Countries were pooled into two regions (Eastern Europe and Rest of World). Most patients (n=1253 [93%] for Study 301 and n=1131 [86%] for Study 201B) were in Eastern Europe region. The Rest of World consisted of 93 (7%) patients for Study 301 and 182 (14%) for Study 201B, including 36 patients in Study 301 and 46 patients in Study 201B from the United State. The 4 countries that enrolled the largest number of patients were Belarus, Poland, Russia and Ukraine, together they consisted of 77% of the patients in Study 301 and 64% of the patients in Study 201B. Therefore, instead of analysis by region, analysis by country was performed and only for these 4 countries and United States only. Analysis results of ARR by subgroups are presented in the following table.

Table 13 Subgroup Analysis of ARR by Gender and Age, and Country – Studies 301 and 201B

	Study 301			Study 201B		
	IFN β– 1a 30 µg N=448	**Ozanimod 0.5 mg N=451**	**Ozanimod 1 mg N=447**	**IFN β– 1a 30 µg N=441**	**Ozanimod 0.5 mg N=439**	**Ozanimod 1 mg N=433**
Age Group						
≤ 40						
N	307	293	324	311	320	295
ARR	0.46	0.29	0.22	0.31	0.25	0.19
Rate Ratio		0.62	0.47		0.78	0.61
> 40						
N	141	158	123	130	119	138
ARR	0.21	0.17	0.13	0.20	0.16	0.14
Rate Ratio		0.81	0.62		0.79	0.68
Sex						
Female						
N	300	311	283	304	287	291
ARR	0.34	0.22	0.18	0.30	0.20	0.20
Rate Ratio		0.63	0.53		0.68	0.68
Male						
N	148	140	164	137	152	142
ARR	0.35	0.27	0.17	0.24	0.24	0.12
Rate Ratio		0.77	0.49		1.04	0.51
Country						
Belarus						
N	41	41	41	40	38	37
ARR	0.31	0.23	0.14	0.42	0.37	0.27
Rate Ratio		0.76	0.46		0.89	0.64
Poland						
N	87	85	87	125	124	124
ARR	0.27	0.20	0.12	0.27	0.21	0.19
Rate Ratio		0.72	0.44		0.79	0.71

Russia						
N	90	91	91	41	40	40
ARR	0.36	0.12	0.08	0.13	0.05	0.19
Rate Ratio		0.33	0.23		0.40	0.52
Ukraine						
N	126	128	128	77	78	78
ARR	0.38	0.33	0.29	0.36	0.21	0.14
Rate Ratio		0.87	0.77		0.59	0.37
United States						
N	11	13	12	15	15	16
ARR	0.09	0.08	0.12	0.25	0.29	0.07
Rate Ratio		0.87	1.28		1.16	0.29

Source: Reviewer's analysis

ARRs were lower in the older age group than in the younger age group in all treatment groups and in both studies. The ARRs in the two gender groups appeared to be similar. However, male patients in Study 201B did not show treatment benefit in the ozanimod 0.5 mg group.

Among the 4 countries being analyzed, patients from Russia sites appeared to have extremely low estimated ARRs in both studies.

The estimated ARRs from patients in US sites appeared to be in the wrong direction in Study 301 with ozanimod 1 mg group showing the highest ARR. In Study 201B, the estimated ARR in ozanimod 0.5 mg group was higher than estimated ARR for the IFN β– 1a group. It is difficult to interpret or explain the results from US sites as the number of patients in were small for both studies.

4.2 Other Special/Subgroup Populations

No other subgroup analyses were performed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The two pivotal studies 301 and 201B conducted in relapsing forms of MS patients produced similar and consistent efficacy results in the annualized relapsing rate as well as in MRI imaging on new or enlarging T2 lesions and Gd-enhancing T1 lesions. The two studies did not provide evidence that ozanimod is effective in reducing or delaying disability progression. No major issues were identified in the efficacy results of the two studies.

5.2 Collective Evidence

Studies 301 and 201B met the study objectives by demonstrating statistically significant treatment effects in the primary endpoint of annualized relapse rate and key secondary endpoints of new or enlarging T2 lesions and Gd-enhancing lesions on MRI scans. The results appeared to be consistent under sensitivity analyses and across demographic and baseline characteristics in both studies.

It was in an agreement between the sponsor and the Division that the analysis of disability progression was to be based on the pooled data of the two studies due to the difficulty of achieving the required power to detect the treatment difference in individual studies. The two studies did not show a treatment benefit in disability progression numerically or statistically with or without pooling.

5.3 Conclusions and Recommendations

Studies 301 and 201B provided consistent evidence that the treatment of ozanimod was effective as compared to interferon beta-1a in reducing the relapse rate in patients with relapsing forms of MS. There is no evidence that ozanimod has benefit in delaying disability progression.

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/s/

XIAORONG YAN
02/03/2020 03:30:42 PM

KUN JIN
02/04/2020 05:09:00 PM
I concur with the review.

HSIEN MING J HUNG
02/05/2020 08:18:26 AM

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

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 209899
Drug Name:	RPC1063
Indication:	Treatment of patients with relapsing forms of multiple sclerosis
Applicant:	(b) (4) Celgene Corporation 86 Morris Avenue, Summit, New Jersey 07901 Test Facility for Rats Study: (b) (4) (b) (4) Test Facility for Mice Study: (b) (4) (b) (4)
Documents Reviewed:	Study reports (Study (b) (4)-72515 and AE18BZ.7G8R.(b) (4)) submitted on December 22, 2017 via NDA209899/0001; Electronic data submitted on December 22, 2017 via NDA209899/0001;
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Zhuang Miao, Ph.D.
Concurring Reviewer:	Feng Zhou, MS Karl Lin, Ph.D.
Medical Division:	Division of Neurology Products
Reviewing Pharmacologist:	Christopher Toscano, Ph.D.
Project Manager:	Lopez, Nahleen
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Crl:CD(SD) rats and one in hemizygous Tg.rasH2 mice. These studies were intended to assess the carcinogenic potential of RPC1063 when administered orally by gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice.

Rat Study: . Two hundred and sixty Crl:CD(SD) rats of each sex were randomly assigned to the treated and vehicle control group in equal size of 65 rats per group. The dose levels for treated groups were 0.2, 0.7, and 2 mg/kg/day. The rats in the vehicle control group received the vehicle(0.5% carboxymethylcellulose in deionized water [pH 2.2 ± 0.1]).

The survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle control group and the treated groups in either male or female rats. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and each of the treated groups in either male or female rats.

Tumor analysis: No tumor types had a statistically significant positive dose response in either males or females. The pairwise comparisons did not show any statistically significant increases in incidence for any observed tumor types in any treated groups in either males or females when compared with the vehicle control group.

Mouse Study: One hundred hemizygous Tg.rasH2 mice of each sex were randomly assigned to the treated and vehicle control group in equal size of 25 mice per group. There were 10 mice of each sex in the positive control group. The dose levels for treated groups were 8, 25, and 80 mg/kg/day for male mice and female mice.

The survival analyses showed a statistically significant dose response relationship in mortality across vehicle control and treated groups for both and females. The pairwise comparisons showed statistically significant differences in mortality between the vehicle control and the 25 mg/kg/day group for both males and females. The pairwise comparisons also showed statistically significant differences in mortality between the vehicle control and the 80 mg/kg/day group for both males and females.

Tumor analysis:

1. For male mice, trend test showed a statistically significant positive dose-responses in incidence of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (P-value=<0.001) and hemangiosarcoma in Skin (P-value=<0.001). The pairwise comparisons between the vehicle control and each of the treated groups showed statistically significant increases in incidence of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (P-value=0.0251) in 8 mg/kg/day group, of the combined tumor of Hemangiomar and of Hemangiosarcoma in Whole body (P-value<0.001), of Hemangiosarcoma, Multicentric (P-value=0.0027) and of Hemangiosarcoma in skin (p-value=0.0367) in 25 mg/kg/day group and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) and of Hemangiosarcoma in skin (p-value=0.0410) in 80 mg/kg/day group
2. For female mice, the trend test showed statistically significant positive dose-responses in incidence of the Hemangiosarcoma, Multicentric (P-value=0.0093), of Hemangiosarcoma in Skin (P-value<0.001) and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (P-value<0.001). The pairwise comparisons between the vehicle control and each of the treated groups showed statistically significant increases in incidence of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value=0.0016) in 25 mg/kg/day group, of Hemangiosarcoma,

Multicentric (P-value=0.041) of Hemangiosarcoma in Skin (P-value=0.0172) and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) in 80 mg/kg/day group.

3. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of Hemangiosarcoma in Spleen (P-value<0.001), and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) in male mice.
4. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value=0.0232), of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of Hemangiosarcoma in Spleen (P-value<0.001), and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) in female mice.

2. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Crl:CD(SD) rats and one in hemizygous Tg.rasH2 mice. These studies were intended to assess the carcinogenic potential of RPC1063 when administered orally by gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Christopher Toscano. This review analyzed the SAS data sets of these studies received from the sponsor on December 22, 2017 via NDA209899/0001.

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

3. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and sixty Crl:CD(SD) rats of each sex were randomly assigned to the treated and vehicle control group in equal size of 65 rats per group. The dose levels for treated groups were 0.2, 0.7, and 2 mg/kg/day. The rats in the vehicle control group received the vehicle(0.5% carboxymethylcellulose in deionized water [pH 2.2 ± 0.1]). The study for the rats was designed to continue for up to 104 weeks. In accordance with study termination criteria, all surviving male rats were sacrificed during Week 105.

Table 1: Study Design in Rat Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Vehicle	65	65
2	0.2	Low	65	65
3	0.7	Med	65	65
4	2	High	65	65

3.1. Sponsor's analyses

3.1.1. Survival analysis

Kaplan-Meier estimates of group survival rates were calculated, by sex, and shown graphically. The generalized Wilcoxon test for survival was used to compare the homogeneity of survival rates across the groups at the 0.05 significance level. If the survival rates were significantly different, the generalized Wilcoxon test was used to make pairwise comparisons of each treated group with the control group. A log-rank dose response trend test of survival rates was performed including the control group and active treatment groups. Survival times in which the status of the animal's death was classified as an accidental death, planned interim sacrifice or terminal sacrifice, were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings: Sponsor's analysis showed the numbers (percents) of death were 47 (72%), 44 (68%), 36 (55%), and 48 (74%) in vehicle control, 0.2 mg/kg/day, 0.7 mg/kg/day and 2 mg/kg/day dose groups, respectively in males and 48 (74%), 43 (66%), 41 (63%), and 40 (62%) in vehicle controls, 0.2 mg/kg/day, 0.7 mg/kg/day and 2 mg/kg/day dose groups, respectively in females. The sponsor concluded that, there were no test article-related findings associated with group survival rates in either sex.

3.1.2. Tumor data analysis

The incidences of tumors were analyzed by Peto's mortality-prevalence methods, without continuity correction, incorporating the-context (incidental or fatal) in which tumors were observed. Because of the sparse numbers of deaths in the protocol specified fixed intervals, the intervals were adjusted for the tumor analysis performed.

For each sex, tumors that were detected, either by palpation or necropsy, after the first animal of that sex was terminally sacrificed were considered incidental and included in the scheduled terminal sacrifice interval for analyses.

Tumors classified as mortality-independent, such as, but not limited to, those of the mammary gland and skin, were analyzed with Peto's mortality-independent (onset-rate) method incorporating the day of detection. Each diagnosed tumor type was analyzed separately. Tumor types reported as both singular and "multiple" were combined for statistical analysis and the results were reported under the singular listing. In addition, tumors were combined for analysis purposes at the discretion of the Study Director

For organs in which an exhaustive examination of animals was planned (all animals in all dose groups), the incidence of each tumor type was analyzed with a 1-sided trend test using ordinal coefficients. In addition, pairwise comparisons with the control group were conducted for each active treatment group.

An exact permutation test was conducted for analyses of tumor types with small numbers of tumor bearing animals across the control and treated groups. The statistical significance was 0.01 for common tumors and 0.05 for rare tumors for both trend and pairwise tests. A rare tumor was defined as one in which the historical spontaneous tumor rate was less than 1%.

Sponsor's findings: The sponsor's analyses showed a statistically significant increase in the incidence of adrenal medulla pheochromocytoma, malignant when comparing the 0.7 mg/kg/day treatment group with the control group in males and a statistically significant increase in the incidence of pancreas islet cell carcinoma/adenoma when comparing the 0.2 mg/kg/day treatment group with the control group in females.

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on December 22, 2017 via NDA209899/0001.

3.2.1. Survival analysis

The survival distributions of animals in all four groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested for the vehicle controls, low, medium and high dose groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 7 and 8 in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1 and 2 in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 9 and 10 in the appendix for males and females, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percents) of death were 47 (72%), 44 (68%), 36 (55%), and 48 (74%) in vehicle control, 0.2 mg/kg/day, 0.7 mg/kg/day, and 2 mg/kg/day dose groups, respectively in males and 48 (74%), 43 (66%), 41 (63%), and 40 (62%) in vehicle controls, 0.2 mg/kg/day, 0.7 mg/kg/day, and 2 mg/kg/day dose groups, respectively in females.

The survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle control group and treated groups in either male or female rats. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and each of the treated groups in either male or female rats.

3.2.2. Tumor data analysis

The tumor data were analyzed for the positive dose response relationships and the positive pairwise comparison increases between each of the treated groups with control group. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). 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 a 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, otherwise the adjusted group size is less than N. These adjusted group sizes were 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. The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons are listed in Tables 11 and 12 in the appendix for male and female rats, respectively.

Adjustment for multiple testing: For the chronic study in rats, the adjustment of multiple testing of the dose response relationship for a submission with one chronic rat study and one transgenic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels α =0.005 for common tumors and α=0.025 for rare tumors for the chronic rat study. For pairwise comparisonsfor the chronic rat study in the above type of submission with one chronic rat study and one transgenic mouse study, the same guidance document suggests the use of test levels α =0.01 for common tumors and α =0.05 for rare tumors for the chronic rat study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: Based on the above criterion for multiple testing adjustment, we make the folloing statistical conclusions: No tumor types had a statistically significant positive dose response in either males or females. The pairwise comparisons did not show any statistically significant increases in incidence for any observed tumor types in any treated groups in either males or females when compared with the vehicle control group.

4. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred hemizygous Tg.rasH2 mice of each sex were randomly assigned to the treated and vehicle control group in equal size of 25 mice per group. There were 10 mice of each sex in the positive control group. The dose levels for treated groups were 8, 25, and 80 mg/kg/day for males and females. The mice in the vehicle control group received the vehicle (0.5% carboxymethylcellulose (CMC) in deionized (DI) water, pH adjusted to approximately 2.2 with 1N hydrochloric acid). The study was designed to continue for up to 26 weeks for both sexes, however in accordance with study termination criteria, all surviving mice were sacrificed during Week 27. The mice in the positive control group received 3 intra-peritoneal (i.p.) injections of urethane formulated in saline (1000 mg/kg/dose, one each on Days 1, 3 and 5) administered at a dose volume of 10 mL/kg body weight.

Table 2: Study Design in Mouse Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Vehicle	25	25
2	8	Low	25	25
3	25	Middle	25	25
4	80	High	25	25
5	1000	Positive	10	10

4.1. Sponsor's analyses

4.1.1. Survival analysis

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

Sponsor's findings: The sponsor's analysis showed that the numbers (percents) of death were 0 (0%), 1 (4%), 10 (40%), 9 (36%), and 0 (0%) in male mice, and 0 (0%), 1 (4%), 3 (12%), 9 (36%), and 0 (0%) in female mice in vehicol control, low, medium, high dose groups and positive control group, respectively. Note that, Due to the high mortality (10/25 early deaths), the surviving 25 mg/kg/day males were terminated on Day 177.

The sponsor concluded that, there was a statistically significant increase in mortality rates when comparing the 25 and 80 mg/kg/day groups with vehicle control in males and a statistically significant increase in mortality rates when comparing the 80 mg/kg/day group with vehicle control in females.

4.1.2. Tumor data analysis

The sponsor used the same tumor data analysis methods used for the rat study in this mouse study

Sponsor's findings: For males, there was a statistically significant increase in multicentric hemangiosarcoma when comparing the 25 mg/kg/day dose group to vehicle control. In addition there were statistically significant increases in the hemangiosarcoma/hemangioma combination in multiple organs when comparing the 8, 25 and 80 mg/kg/day dose groups to vehicle control.

For females, there was a statistically significant increase in multicentric hemangiosarcoma when comparing the 80 mg/kg/day dose group to vehicle control. In addition there were statistically significant increase in the

hemangiosarcoma/hemangioma combination in multiple organs when comparing the 25 and 80 mg/kg/day dose groups to vehicle control.

4.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on December 22, 2017 via NDA209899/0001.

4.2.1. Survival analysis

The survival distributions of three treated groups, one vehical control group, and one positive control group were estimated using the Kaplan-Meier product limit method. The dose response relationship in survival 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 3 and 4 in the appendix for male and female mice, respectively. The intercurrent mortality data are given in Tables 13 and 14 in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals among the vehicle control and three treated groups are given in Tables 15 and 16 in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percents) of death 0 (0%), 1 (4%), 10 (40%), 9 (36%), and 0 (0%) in male mice, and and 0 (0%), 1 (4%), 3 (12%), 9 (36%), and 0 (0%) in female mice in vehicol control, low, medium, high dose groups and positive control group, respectively.

The survival analyses showed a statistically significant dose response relationship in mortality across vehicle control and treated groups for both males (P-value for Likelihood Ratio test is 0.0045 and P-value for Log-Rank test is <0.0001) and females (P-value for Likelihood Ratio test is <0.0001 and P-value for Log-Rank test is 0.0004).

The pairwise comparisons showed statistically significant differences in mortality between the vehicle control and the 25 mg/kg/day group for both males (P-value for Likelihood Ratio test is <0.0001and P-value for Log-Rank test is 0.0004) and females (P-value for Likelihood Ratio test is 0.0384).

The pairwise comparisons also showed statistically significant differences in mortality between the vehicle control and the 80 mg/kg/day group for both males (P-value for Likelihood Ratio test is 0.0002 and P-value for Log-Rank test is 0.001) and females (P-value for Likelihood Ratio test is 0.0002 and P-value for Log-Rank test is 0.001) . The pairwise comparisons did not show any statistically significant increase in mortality in the positive control group when compared with the vehicle control for males or females.

4.2.2. Tumor data analysis

The reviewer used the same tumor data analysis methods for the rat study in this mouse study.

The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons between vehicle control and three treated groups, and between vehicle control and positive control are listed in Tables 17, 18, 19, 20 in the appendix for male and female mice, respectively.

Adjustment for multiple testing: For the adjustment of multiple testing of dose response relationship for the transgenic mouse study in a submission with one chronic rat study and one transgenic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of

test levels α =0.05 for both common tumors and rare tumors for the mouse study. For pairwise, the same guidance document suggests the use of test levels α =0.05 for both common tumors and rare tumors for the mouse study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: The tumor types in Tables 3 and 4 (both trend tests and pairwise comparison using data of venicle control and treated groups for male and female mice); and 5 and 6 (pairwise comparisons between vehicle and positive control groups for male mice and female mice, respectively) below showed p-values less than or equal to 0.05 in the tests for trend and for pairwise comparisons between the vehicle control goup and each of the treated groups; and in comparison tests between the vehicle control group and the positive control group.

Table 3: Tumor Types with P-Values ⩽ 0.05 for Dose Response Relationship or Pairwise Comparisons between the Vehicle Controls and the Treated Groups-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	8 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	80 mg/kg/day High (N=25) P-value - Vehicle vs. High
Whole Body	C_Hemangioma+Hemangiosarcoma	0/25 (25) 0.0049	5/25 (25) 0.0251	17/25 (24) <0.001	10/25 (23) <0.001
multicentric	hemangiosarcoma	0/25 (25) 0.2412	1/25 (25) 0.5000	7/25 (22) 0.0027	2/25 (22) 0.2137
skin	hemangiosarcoma	0/25 (25) 0.0146	0/25 (25) NC	4/25 (21) 0.0367	4/25 (22) 0.0410

& 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 4: Tumor Types with P-Values ⩽ 0.05 for Dose Response Relationship or Pairwise Comparisons between the Vehicle Controls and the Treated Groups-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	8 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	80 mg/kg/day High (N=25) P-value - Vehicle vs. High
Whole Body	C_Hemangioma+Hemangiosarcoma	0/25 (25) <0.001	3/25 (25) 0.1173	8/25 (24) 0.0016	11/25 (23) <0.001
multicentric	hemangiosarcoma	0/25 (25) 0.0093	1/25 (25) 0.5000	1/25 (23) 0.4792	4/25 (22) 0.0410

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	8 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	80 mg/kg/day High (N=25) P-value - Vehicle vs. High
skin	hemangiosarcoma	0/25 (25) <0.001	0/25 (25) NC	1/25 (23) 0.4792	5/25 (22) 0.0172
& 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 5: Tumor Types with P-Values ⩽ 0.05 for Comparisons between Vehicle Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
LUNGS WITH BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	0/25 (25)	10/10 (10) <0.001
	C_alveolar bronchiolar Adeno+Carcin	1/25 (25)	10/10 (10) <0.001
SPLEEN	HEMANGIOSARCOMA	0/25 (25)	7/10 (7) <0.001
Whole Body	C_Hemangioma+Hemangiosarcoma	0/25 (25)	7/10 (7) <0.001

Table 6: Tumor Types with P-Values ⩽ 0.05 for Comparisons between Vehicle Control and Positive Control-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
LUNGS WITH BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	3/25 (25)	10/10 (10) <0.001
	ALVEOLAR BRONCHIOLAR CARCINOMA	1/25 (25)	2/10 (3) 0.0232
	C_alveolar bronchiolar Adeno+Carcin	4/25 (25)	10/10 (10) <0.001
SPLEEN	HEMANGIOSARCOMA	0/25 (25)	4/10 (4) <0.001
Whole Body	C_Hemangioma+Hemangiosarcoma	0/25 (25)	4/10 (4) <0.001

Reviewer's findings: Based on the criteria of adjustment for multiple testing discussed in the mouse data analysis section, we make the following statistical conclusions:

1. For male mice, trend test showed a statistically significant positive dose-responses in incidence of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (P-value=<0.001) and hemangiosarcoma in Skin (P-value=<0.001). The pairwise comparisons between the vehicle control and each of the treated groups showed statistically significant increases in incidence of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (P-value=0.0251) in 8 mg/kg/day group, of the combined tumor of Hemangiomar and of Hemangiosarcoma in Whole body (P-value<0.001), of Hemangiosarcoma, Multicentric (P-value=0.0027) and of Hemangiosarcoma in skin (p-value=0.0367) in 25 mg/kg/day group and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) and of Hemangiosarcoma in skin (p-value=0.0410) in 80 mg/kg/day group
2. For female mice, the trend test showed statistically significant positive dose-responses in incidence of the Hemangiosarcoma, Multicentric (P-value=0.0093), of Hemangiosarcoma in Skin (P-value<0.001) and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (P-value<0.001). The pairwise comparisons between the vehicle control and each of the treated groups showed statistically significant increases in incidence of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value=0.0016) in 25 mg/kg/day group, of Hemangiosarcoma, Multicentric (P-value=0.041) of Hemangiosarcoma in Skin (P-value=0.0172) and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) in 80 mg/kg/day group.
3. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of Hemangiosarcoma in Spleen (P-value<0.001), and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) in male mice.
4. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value=0.0232), of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of Hemangiosarcoma in Spleen (P-value<0.001), and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) in female mice.

5. Conclusion

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Crl:CD(SD) rats and one in hemizygous Tg.rasH2 mice. These studies were intended to assess the carcinogenic potential of RPC1063 when administered orally by gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice.

Rat Study: . Two hundred and sixty Crl:CD(SD) rats of each sex were randomly assigned to the treated and vehicle control group in equal size of 65 rats per group. The dose levels for treated groups were 0.2, 0.7, and 2 mg/kg/day. The rats in the vehicle control group received the vehicle(0.5% carboxymethylcellulose in deionized water [pH 2.2 ± 0.1]).

The survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle control group and the treated groups in either male or female rats. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and each of the treated groups in either male or female rats.

Tumor analysis: No tumor types had a statistically significant positive dose response in either males or females. The pairwise comparisons did not show any statistically significant increases in incidence for any observed tumor types in any treated groups in either males or females when compared with the vehicle control group.

Mouse Study: One hundred hemizygous Tg.rasH2 mice of each sex were randomly assigned to the treated and vehicle control group in equal size of 25 mice per group. There were 10 mice of each sex in the positive control group. The dose levels for treated groups were 8, 25, and 80 mg/kg/day for male mice and female mice.

The survival analyses showed a statistically significant dose response relationship in mortality across vehicle control and treated groups for both and females. The pairwise comparisons showed statistically significant differences in mortality between the vehicle control and the 25 mg/kg/day group for both males and females. The pairwise comparisons also showed statistically significant differences in mortality between the vehicle control and the 80 mg/kg/day group for both males and females.

Tumor analysis:

1. For male mice, trend test showed a statistically significant positive dose-responses in incidence of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (P-value=<0.001) and hemangiosarcoma in Skin (P-value=<0.001). The pairwise comparisons between the vehicle control and each of the treated groups showed statistically significant increases in incidence of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (P-value=0.0251) in 8 mg/kg/day group, of the combined tumor of Hemangiomar and of Hemangiosarcoma in Whole body (P-value<0.001), of Hemangiosarcoma, Multicentric (P-value=0.0027) and of Hemangiosarcoma in skin (p-value=0.0367) in 25 mg/kg/day group and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) and of Hemangiosarcoma in skin (p-value=0.0410) in 80 mg/kg/day group
2. For female mice, the trend test showed statistically significant positive dose-responses in incidence of the Hemangiosarcoma, Multicentric (P-value=0.0093), of Hemangiosarcoma in Skin (P-value<0.001) and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (P-value<0.001). The pairwise comparisons between the vehicle control and each of the treated groups showed statistically significant increases in incidence of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value=0.0016) in 25 mg/kg/day group, of Hemangiosarcoma,

Multicentric (P-value=0.041) of Hemangiosarcoma in Skin (P-value=0.0172) and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) in 80 mg/kg/day group.

3. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of Hemangiosarcoma in Spleen (P-value<0.001), and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) in male mice.
4. The pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value=0.0232), of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001), of Hemangiosarcoma in Spleen (P-value<0.001), and of the combined tumor of Hemangiomar and Hemangiosarcoma in Whole body (p-value<0.001) in female mice.

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6. Appendix

Table 7: Intercurrent Mortality Rate -Male Rats

	Vehicle Control 0 mg|kg|day (N=65)		0.2 mg|kg|day (N=65)		0.7 mg|kg|day (N=65)		2 mg|kg|day (N=65)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	4	6.15	3	4.62	3	4.62	3	4.62
53 - 78	12	24.62	8	16.92	10	20.00	16	29.23
79 - 91	14	46.15	16	41.54	11	36.92	17	55.38
92 - 104	17	72.31	17	67.69	12	55.38	12	73.85
Ter. Sac.	18	27.69	21	32.31	29	44.62	17	26.15

Cum. %: Cumulative percentage except for Ter. Sac.

Table 8: Intercurrent Mortality Rate -Female Rats

	Vehicle Control 0 mg|kg|day (N=65)		0.2 mg|kg|day (N=65)		0.7 mg|kg|day (N=65)		2 mg|kg|day (N=65)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	3	4.62	.	.	1	1.54	2	3.08
53 - 78	18	32.31	17	26.15	13	21.54	8	15.38
79 - 91	12	50.77	16	50.77	18	49.23	23	50.77
92 - 103	15	73.85	10	66.15	9	63.08	7	61.54
Ter. Sac.	17	26.15	22	33.85	24	36.92	25	38.46

Cum. %: Cumulative percentage except for Ter. Sac.

Table 9: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Male Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.4111	0.5357	0.0654	0.6367
Homogeneity	Log-Rank	0.1188	0.5283	0.0620	0.6315

Table 10: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Female Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicles vs. Low	P_Value Vehicles vs. Medium	P_Value Vehicles vs. High
Dose-Response	Likelihood Ratio	0.1578	0.4306	0.1981	0.1376
Homogeneity	Log-Rank	0.4143	0.4220	0.1914	0.1288

Table 11: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Vehicle Controls and the Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	0.2 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	0.7 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	2 mg/kg/day High (N=65) P-value - Vehicle vs. High
ADIPOSE TISSUE	#B FIBROMA; MULTIPLE	0/65 (44) 0.7556	1/65 (46) 0.5111	0/65 (48) NC	0/65 (42) NC
	#M SCHWANNOMA, MALIGNANT	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884
ADRENAL CORTEX	#B ADENOMA	0/65 (44) 0.1786	0/65 (46) NC	1/65 (48) 0.5217	1/65 (42) 0.4884
ADRENAL MEDULLA	#B PHEOCHROMOCYTOMA, BENIGN	6/65 (46) 0.9152	9/65 (47) 0.3029	6/65 (48) 0.6508	3/64 (42) 0.8982
	#M PHEOCHROMOCYTOMA, MALIGNANT	2/65 (44) 0.6056	4/65 (47) 0.3705	7/65 (49) 0.1073	2/64 (42) 0.6741
Adrenals Medulla	C_PHEOCHROMOCYTOMA B+M	8/65 (46) 0.8982	13/65 (48) 0.1897	13/65 (49) 0.2049	5/65 (42) 0.8473
BONE	#B OSTEOMA	0/65 (44) 0.7294	2/65 (46) 0.2584	1/65 (49) 0.5269	0/65 (42) NC
	#M OSTEOSARCOMA	0/65 (44) 0.7569	1/65 (47) 0.5165	0/65 (48) NC	0/65 (42) NC
All Bone	C_Osteoma+Osteosarcoma	0/65 (44) 0.5275	3/65 (47) 0.1335	1/65 (49) 0.5269	1/65 (42) 0.4884
BRAIN	#B MENINGIOMA	0/65 (44) 0.5028	0/65 (46) NC	1/65 (49) 0.5269	0/65 (42) NC
	#M ASTROCYTOMA, MALIGNANT, HIGH GRADE	2/65 (45) 0.6130	1/65 (46) 0.8832	3/65 (50) 0.5503	1/65 (42) 0.8661
	#M MENINGIOMA, MALIGNANT	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884
	#M OLIGODENDROGLIOMA, MALIGNANT, LOW GRADE	0/65 (44) 0.7556	1/65 (46) 0.5111	0/65 (48) NC	0/65 (42) NC
	C_MENINGIOMA B+M	0/65 (44) 0.1792	0/65 (46) NC	1/65 (49) 0.5269	1/65 (42) 0.4884
CAVITY, THORACIC	#B HIBERNOMA, BENIGN	1/65 (45) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/65 (42) 1.0000
EARS	#M FIBROSARCOMA	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884
FEMUR	#M OSTEOSARCOMA	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884
HARDERIAN GLANDS	#M SCHWANNOMA, MALIGNANT	0/65 (44) 0.5028	0/65 (46) NC	1/65 (49) 0.5269	0/65 (42) NC
KIDNEYS	#B ADENOMA, AMPHOPHILIC VACUOLAR	2/65 (44) 0.2763	0/65 (46) 1.0000	1/65 (49) 0.8979	2/65 (43) 0.6832
	#M CARCINOMA	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	0.2 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	0.7 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	2 mg/kg/day High (N=65) P-value - Vehicle vs. High
	#M LIPOSARCOMA	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884
	#M MESENCHYMAL TUMOR	0/65 (44) 0.7556	1/65 (46) 0.5111	0/65 (48) NC	0/65 (42) NC
LIVER	#B ADENOMA, HEPATOCELLULAR	3/65 (45) 0.6812	0/65 (46) 1.0000	1/65 (48) 0.9490	1/65 (42) 0.9331
	#B CHOLANGIOMA	1/65 (44) 0.9413	1/65 (46) 0.7638	0/65 (48) 1.0000	0/65 (42) 1.0000
	#M CARCINOMA, HEPATOCELLULAR	1/65 (44) 0.6863	0/65 (46) 1.0000	3/65 (48) 0.3420	0/65 (42) 1.0000
	C_ADENOMA+CARCINOMA HEPATOCELLULAR	4/65 (45) 0.7378	0/65 (46) 1.0000	4/65 (48) 0.6788	1/65 (42) 0.9669
LN, INGUINAL	#M FIBROSARCOMA	1/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/65 (42) 1.0000
LUNGS	#M HIBERNOMA, MALIGNANT	0/65 (44) 0.5028	0/65 (46) NC	1/65 (49) 0.5269	0/65 (42) NC
	#M SARCOMA, NOS; UNKNOWN	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884
MAMMARY GLAND	#B FIBROADENOMA	2/65 (44) 0.6612	1/65 (47) 0.8910	1/65 (48) 0.8945	1/65 (43) 0.8751
	#M ADENOCARCINOMA	3/65 (44) 0.9434	0/65 (46) 1.0000	1/65 (48) 0.9514	0/65 (42) 1.0000
PANCREAS	#B ADENOMA, ACINAR CELL	2/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/65 (42) 1.0000
	#B ADENOMA, ISLET CELL	4/65 (44) 0.8814	2/65 (46) 0.9084	2/65 (49) 0.9209	1/65 (42) 0.9688
	#B ADENOMA, MIXED ACINAR-ISLET CELL	0/65 (44) 0.7556	1/65 (46) 0.5111	0/65 (48) NC	0/65 (42) NC
	#M ADENOCARCINOMA	1/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/65 (42) 1.0000
	#M CARCINOMA, ISLET CELL	0/65 (44) 0.5275	0/65 (46) NC	3/65 (49) 0.1420	0/65 (42) NC
	#M MAST CELL TUMOR, MALIGNANT	0/65 (44) 0.7556	1/65 (46) 0.5111	0/65 (48) NC	0/65 (42) NC
	C_Adenoma	6/65 (45) 0.9560	2/65 (46) 0.9729	2/65 (49) 0.9781	1/65 (42) 0.9922
PARATHYROIDS	#B ADENOMA	1/60 (41) 0.4224	0/56 (39) 1.0000	0/58 (44) 1.0000	1/60 (39) 0.7405
PAWS	#M FIBROSARCOMA	1/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/65 (42) 1.0000
PITUITARY	#B ADENOMA	38/65 (57) 0.1087	40/65 (58) 0.4743	45/65 (56) 0.0753	43/65 (56) 0.1624

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	0.2 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	0.7 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	2 mg/kg/day High (N=65) P-value - Vehicle vs. High
	#M CARCINOMA	1/65 (44) 0.4132	0/65 (46) 1.0000	0/65 (48) 1.0000	1/65 (42) 0.7412
Pituitary	C_Adenoma+Carcinoma	39/65 (57) 0.0868	40/65 (58) 0.5548	45/65 (56) 0.1078	44/65 (56) 0.1566
PREPUTIAL GLANDS	#B PAPILLOMA	0/65 (44) 0.2360	0/65 (46) NC	0/62 (46) NC	1/65 (42) 0.4884
SKIN	#B ADENOMA, BASAL CELL	0/65 (44) 0.7556	1/65 (46) 0.5111	0/65 (48) NC	0/65 (42) NC
	#B ADENOMA, SEBACEOUS CELL	1/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/65 (42) 1.0000
	#B FIBROMA	3/65 (45) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/65 (42) 1.0000
	#B KERATOACANTHOMA, BENIGN	0/65 (44) 0.5275	0/65 (46) NC	3/65 (49) 0.1420	0/65 (42) NC
	#B MAST CELL TUMOR, BENIGN	0/65 (44) 0.2376	0/65 (46) NC	0/65 (48) NC	1/65 (43) 0.4943
	#B PAPILLOMA	1/65 (44) 0.8752	2/65 (46) 0.5169	1/65 (48) 0.7740	0/65 (42) 1.0000
	#M CARCINOMA, BASAL CELL	1/65 (44) 0.7514	0/65 (46) 1.0000	1/65 (48) 0.7740	0/65 (42) 1.0000
	#M CARCINOMA, SEBACEOUS CELL	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884
	#M CARCINOMA, SQUAMOUS CELL	1/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/65 (42) 1.0000
	#M FIBROSARCOMA	0/65 (44) 0.2978	1/65 (47) 0.5165	0/65 (48) NC	1/65 (42) 0.4884
	#M SCHWANNOMA, MALIGNANT	0/65 (44) 0.6218	1/65 (46) 0.5111	1/65 (49) 0.5269	0/65 (42) NC
Skin	C_ADENOMA+CARCINOMA BASAL CELL	1/65 (44) 0.8296	1/65 (46) 0.7638	1/65 (48) 0.7740	0/65 (42) 1.0000
	C_Keratoa+Papilloma+SQUAMOUS CELL Carcinoma	2/65 (44) 0.8835	2/65 (46) 0.7084	4/65 (49) 0.3914	0/65 (42) 1.0000
SOFT TISSUE- ABD	#M LIPOSARCOMA	0/65 (44) 0.7556	1/65 (46) 0.5111	0/65 (48) NC	0/65 (42) NC
	#M SARCOMA, NOS; UNKNOWN	1/65 (45) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/65 (42) 1.0000
	#M SCHWANNOMA, MALIGNANT	0/65 (44) 0.7556	1/65 (46) 0.5111	0/65 (48) NC	0/65 (42) NC
SOFT TISSUE- THO	#M HIBERNOMA, MALIGNANT	0/65 (44) 0.6205	1/65 (47) 0.5165	1/65 (49) 0.5269	0/65 (42) NC
SPINAL CORD	#M ASTROCYTOMA, MALIGNANT, LOW GRADE	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	0.2 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	0.7 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	2 mg/kg/day High (N=65) P-value - Vehicle vs. High
SPLEEN	#M SARCOMA, NOS	0/65 (44) 0.5000	0/65 (46) NC	1/65 (48) 0.5217	0/65 (42) NC
STOMACH	#B LIPOMA	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884
STOMACH, GLAN	#B LIPOMA	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884
SUBCUTIS	#B FIBROMA	5/65 (45) 0.2508	1/65 (46) 0.9878	9/65 (49) 0.2440	5/65 (44) 0.6160
	#B KERATOACANTHOMA, BENIGN	0/65 (44) 0.7556	1/65 (46) 0.5111	0/65 (48) NC	0/65 (42) NC
	#B LIPOMA	4/65 (45) 0.6234	1/65 (46) 0.9737	1/65 (48) 0.9765	2/65 (42) 0.8823
	#M ADENOCARCINOMA, PREPUTIAL GLAND	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884
	#M CARCINOMA, SQUAMOUS CELL	0/65 (44) 0.7556	1/65 (46) 0.5111	0/65 (48) NC	0/65 (42) NC
	#M FIBROSARCOMA	2/65 (44) 0.8771	0/65 (46) 1.0000	1/65 (48) 0.8945	0/65 (42) 1.0000
	#M MYXOSARCOMA	0/65 (44) 0.2333	0/65 (46) NC	0/65 (48) NC	1/65 (42) 0.4884
SYSTEMIC TUMORS	#B HEMANGIOMA	1/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/65 (42) 1.0000
	#B LYMPHANGIOMA	0/65 (44) 0.7569	1/65 (47) 0.5165	0/65 (48) NC	0/65 (42) NC
	#M HEMANGIOSARCOMA	1/65 (44) 0.6861	0/65 (46) 1.0000	3/65 (49) 0.3502	0/65 (42) 1.0000
	#M LEUKEMIA	1/65 (44) 0.7514	0/65 (46) 1.0000	1/65 (48) 0.7740	0/65 (42) 1.0000
	#M LYMPHOMA, MALIGNANT	2/65 (45) 0.1952	1/65 (46) 0.8832	2/65 (50) 0.7303	3/65 (43) 0.4782
	#M MESOTHELIOMA, MALIGNANT	1/65 (44) 0.2198	1/65 (46) 0.7638	0/65 (48) 1.0000	2/65 (43) 0.4913
	#M SARCOMA, HISTIOCYTIC	3/65 (44) 0.5042	1/65 (46) 0.9469	0/65 (48) 1.0000	2/65 (43) 0.8126
TAIL	#B PAPILLOMA	0/65 (44) 0.6203	1/65 (46) 0.5111	1/65 (48) 0.5217	0/64 (42) NC
	#M FIBROSARCOMA	1/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/64 (42) 1.0000
TEETH	#M CARCINOMA, SQUAMOUS CELL; ORAL MUCOSA	1/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (48) 1.0000	0/65 (42) 1.0000
TESTES	#B ADENOMA, LEYDIG CELL	0/65 (44) 0.0552	0/65 (46) NC	1/65 (49) 0.5269	2/65 (42) 0.2356

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	0.2 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	0.7 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	2 mg/kg/day High (N=65) P-value - Vehicle vs. High
THYMUS	#M HIBERNOMA, MALIGNANT	0/60 (40) 0.2428	0/62 (44) NC	0/62 (47) NC	1/64 (42) 0.5122
THYROID GLANDS	#B ADENOMA, C-CELL	5/65 (45) 0.5518	4/65 (46) 0.7685	5/64 (48) 0.6709	4/65 (43) 0.7346
	#B ADENOMA, FOLLICULAR CELL	1/65 (44) 0.0919	2/65 (46) 0.5169	3/64 (49) 0.3502	4/65 (44) 0.1802
	#M CARCINOMA, C-CELL	0/65 (44) 0.1953	2/65 (47) 0.2640	2/64 (49) 0.2749	2/65 (42) 0.2356
Thyroid GLANDS	C_C-cell Adenoma+Carcinoma	5/65 (45) 0.3589	6/65 (48) 0.5462	7/65 (49) 0.4415	6/65 (43) 0.4673
URINARY BLADDER	#B PAPILLOMA, TRANSITIONAL CELL	0/65 (44) 0.7556	1/65 (46) 0.5111	0/65 (48) NC	0/65 (42) NC
ZYMBAL'S GLANDS	#B ADENOMA	0/63 (42) 0.7455	1/62 (43) 0.5059	0/59 (44) NC	0/59 (36) NC
	#M CARCINOMA	0/63 (42) 0.2773	1/62 (44) 0.5116	0/59 (44) NC	1/59 (36) 0.4615
Whold Body	C_hemangiomas+hemangiosarcoma	2/65 (44) 0.7956	0/65 (46) 1.0000	3/65 (49) 0.5514	0/65 (42) 1.0000

Table 12: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Vehicle Controls and the Treated Groups-Female Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	0.2 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	0.7 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	2 mg/kg/day High (N=65) P-value - Vehicle vs. High
ADRENAL CORTEX	#B ADENOMA	1/65 (43) 0.4923	3/65 (44) 0.3168	2/65 (46) 0.5256	2/65 (47) 0.5337
	#M CARCINOMA	0/65 (42) 0.7654	1/65 (44) 0.5116	0/65 (46) NC	0/65 (47) NC
Adrenals Cortex	C_Adenoma+carcinoma	1/65 (43) 0.5863	4/65 (44) 0.1874	2/65 (46) 0.5256	2/65 (47) 0.5337
ADRENAL MEDULLA	#B PHEOCHROMOCYTOMA, BENIGN	1/65 (42) 0.9460	1/65 (44) 0.7644	0/65 (46) 1.0000	0/65 (47) 1.0000
BRAIN	#M ASTROCYTOMA, MALIGNANT, HIGH GRADE	0/65 (42) 0.7654	1/65 (44) 0.5116	0/65 (46) NC	0/65 (47) NC
	#M ASTROCYTOMA, MALIGNANT, LOW GRADE	1/65 (42) 1.0000	0/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (47) 1.0000
	#M MENINGIOMA, MALIGNANT	1/65 (42) 0.7706	0/65 (44) 1.0000	1/65 (46) 0.7751	0/65 (47) 1.0000
	#M OLIGODENDROGLIOMA, MALIGNANT, LOW GRADE	0/65 (42) 0.7654	1/65 (44) 0.5116	0/65 (46) NC	0/65 (47) NC
CECUM	#B LEIOMYOMA	0/65 (42) 0.2626	0/65 (44) NC	0/65 (46) NC	1/65 (47) 0.5281
CERVIX	#M CARCINOMA, SQUAMOUS CELL	0/65 (42) 0.3382	1/65 (44) 0.5116	0/65 (46) NC	1/65 (48) 0.5333
	#M SARCOMA, NOS	0/65 (42) 0.2667	0/65 (44) NC	0/65 (46) NC	1/65 (48) 0.5333
CLITORAL GLANDS	#B PAPILLOMA	0/61 (39) 0.5260	0/64 (43) NC	1/62 (44) 0.5301	0/65 (47) NC
DUODENUM	#B LEIOMYOMA	0/65 (42) 0.2626	0/65 (44) NC	0/65 (46) NC	1/65 (47) 0.5281
EARS	#M FIBROSARCOMA	0/65 (42) 0.5196	0/65 (44) NC	1/65 (46) 0.5227	0/65 (47) NC
	#M NEURAL CREST TUMOR, MALIGNANT	0/65 (42) 0.0700	0/65 (44) NC	0/65 (46) NC	2/65 (48) 0.2816
KIDNEYS	#B ADENOMA, AMPHOPHILIC VACUOLAR	2/65 (43) 0.8891	0/65 (44) 1.0000	1/65 (46) 0.8913	0/65 (47) 1.0000
	#M CARCINOMA, AMPHOPHILIC VACUOLAR	1/65 (43) 0.9439	1/65 (44) 0.7586	0/65 (46) 1.0000	0/65 (47) 1.0000
LIVER	#B ADENOMA, HEPATOCELLULAR	1/65 (43) 0.3965	0/65 (44) 1.0000	2/65 (46) 0.5256	1/65 (47) 0.7745
	#B CHOLANGIOMA	0/65 (42) 0.2626	0/65 (44) NC	0/65 (46) NC	1/65 (47) 0.5281
	#M CARCINOMA, HEPATOCELLULAR	0/65 (42) 0.2667	0/65 (44) NC	0/65 (46) NC	1/65 (48) 0.5333

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	0.2 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	0.7 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	2 mg/kg/day High (N=65) P-value - Vehicle vs. High
LN, INGUINAL	#M ADENOCARCINOMA; MAMMARY GLAND	0/65 (42) 0.7654	1/65 (44) 0.5116	0/65 (46) NC	0/65 (47) NC
MAMMARY GLAND	#B ADENOMA	5/64 (43) 0.9549	3/65 (46) 0.8876	3/64 (46) 0.8876	1/64 (47) 0.9902
	#B FIBROADENOMA	22/64 (47) 0.1033	18/65 (49) 0.8865	28/64 (52) 0.3093	29/64 (54) 0.3115
	#B FIBROADENOMA; MULTIPLE	9/64 (43) 0.6973	9/65 (47) 0.6828	13/64 (47) 0.3106	8/64 (48) 0.7853
	#M ADENOCARCINOMA	18/64 (49) 0.9560	11/65 (46) 0.9434	15/64 (49) 0.8036	9/64 (49) 0.9886
	#M ADENOCARCINOMA ARISING IN FIBROADENOMA	6/64 (42) 0.8422	1/65 (44) 0.9950	6/64 (47) 0.6989	2/64 (47) 0.9804
	#M ADENOCARCINOMA ARISING IN FIBROADENOMA; MULTIPLE	0/64 (41) 0.6523	1/65 (44) 0.5176	1/64 (45) 0.5233	0/64 (47) NC
	#M ADENOCARCINOMA; MULTIPLE	6/64 (43) 0.9465	8/65 (47) 0.4576	4/64 (46) 0.8688	3/64 (48) 0.9440
Mammary Gland	C_ADENOCARCINOMA	24/65 (52) 0.9918	19/65 (49) 0.8291	19/65 (51) 0.8677	12/65 (51) 0.9958
	C_ADENOCARCINOMA ARISING IN FIBROADENOMA	6/65 (42) 0.8735	2/65 (45) 0.9772	7/65 (48) 0.6040	2/65 (47) 0.9804
	C_FIBROADENOMA	30/65 (49) 0.1209	27/65 (52) 0.8735	41/65 (56) 0.1355	37/65 (55) 0.3305
OVARIES	#M GRANULOSA CELL TUMOR, MALIGNANT	1/65 (42) 1.0000	0/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (47) 1.0000
PANCREAS	#B ADENOMA	0/65 (42) 0.2626	0/65 (44) NC	0/65 (46) NC	1/65 (47) 0.5281
	#B ADENOMA, ISLET CELL	0/65 (42) 0.2903	4/65 (44) 0.0639	3/65 (46) 0.1383	3/65 (47) 0.1428
	#M CARCINOMA, ISLET CELL	0/65 (42) 0.6171	3/65 (44) 0.1294	0/65 (46) NC	1/65 (48) 0.5333
PARATHYROIDS	#B ADENOMA	0/61 (39) 0.7622	1/61 (41) 0.5125	0/56 (40) NC	0/60 (44) NC
PITUITARY	#B ADENOMA	58/65 (62) 0.9784	54/65 (59) 0.7788	57/65 (62) 0.7544	48/65 (58) 0.9843
	#M CARCINOMA	1/65 (42) 0.1865	0/65 (44) 1.0000	1/65 (46) 0.7751	2/65 (47) 0.5426
Pituitary	C_Adenoma+Carcinoma	59/65 (63) 0.9582	54/65 (59) 0.7862	58/65 (62) 0.6502	50/65 (59) 0.9716
RECTUM	#B ADENOMA	0/65 (42) 0.2667	0/65 (44) NC	0/65 (46) NC	1/65 (48) 0.5333
SKIN	#M FIBROSARCOMA	0/65 (42) 0.2036	0/65 (44) NC	1/65 (46) 0.5227	1/65 (47) 0.5281

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	0.2 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	0.7 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	2 mg/kg/day High (N=65) P-value - Vehicle vs. High
	#M SCHWANNOMA, MALIGNANT	1/65 (42) 1.0000	0/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (47) 1.0000
SOFT TISSUE- THO	#M HIBERNOMA, MALIGNANT	0/65 (42) 0.5222	0/65 (44) NC	1/65 (47) 0.5281	0/65 (47) NC
SPINAL CORD	#M ASTROCYTOMA, MALIGNANT, LOW GRADE	0/65 (42) 0.7654	1/65 (44) 0.5116	0/65 (46) NC	0/65 (47) NC
SUBCUTIS	#B FIBROMA	0/65 (42) 0.7585	2/65 (44) 0.2588	1/65 (46) 0.5227	0/65 (47) NC
	#B LIPOMA	1/65 (43) 0.4551	0/65 (44) 1.0000	0/65 (46) 1.0000	1/65 (47) 0.7745
	#M FIBROSARCOMA	0/65 (42) 0.2626	0/65 (44) NC	0/65 (46) NC	1/65 (47) 0.5281
SYSTEMIC TUMORS	#M HEMANGIOSARCOMA	0/65 (42) 0.6633	1/65 (45) 0.5172	2/65 (47) 0.2760	0/65 (47) NC
	#M LYMPHOMA, MALIGNANT	0/65 (42) 0.1243	1/65 (44) 0.5116	0/65 (46) NC	2/65 (48) 0.2816
	#M MESOTHELIOMA, MALIGNANT	0/65 (42) 0.7654	1/65 (44) 0.5116	0/65 (46) NC	0/65 (47) NC
	#M SARCOMA, HISTIOCYTIC	2/65 (44) 0.4040	1/65 (44) 0.8793	0/65 (46) 1.0000	2/65 (47) 0.7163
TAIL	#B PAPILLOMA	0/65 (42) 0.2626	0/65 (44) NC	0/65 (46) NC	1/65 (47) 0.5281
THYMUS	#B THYMOMA, BENIGN	1/65 (42) 0.7096	0/64 (43) 1.0000	2/62 (45) 0.5262	0/64 (46) 1.0000
	#M FIBROSARCOMA	0/65 (42) 0.5170	0/64 (43) NC	1/62 (45) 0.5172	0/64 (46) NC
	#M THYMOMA, MALIGNANT	0/65 (42) 0.2009	0/64 (43) NC	1/62 (44) 0.5116	1/64 (46) 0.5227
THYROID GLANDS	#B ADENOMA, C-CELL	6/65 (42) 0.2807	3/65 (45) 0.9367	7/64 (46) 0.5714	7/64 (48) 0.6040
	#B ADENOMA, FOLLICULAR CELL	1/65 (42) 0.5465	1/65 (44) 0.7644	1/64 (46) 0.7751	1/64 (47) 0.7801
	#M CARCINOMA, C-CELL	2/65 (42) 0.5911	5/65 (45) 0.2463	3/64 (46) 0.5436	3/64 (47) 0.5538
	#M CARCINOMA, FOLLICULAR CELL	0/65 (42) 0.5196	0/65 (44) NC	1/64 (46) 0.5227	0/64 (47) NC
Thyroid GLANDS	C_C cell Adenoma+Carcinoma	8/65 (43) 0.3549	8/65 (46) 0.6647	10/65 (47) 0.4800	10/65 (48) 0.5000
	C_Follicular cell Adenoma+Carcinoma	1/65 (42) 0.5436	1/65 (44) 0.7644	2/65 (47) 0.5426	1/65 (48) 0.7850
UTERUS	#B ADENOMA	0/65 (42) 0.3382	1/65 (44) 0.5116	0/65 (46) NC	1/65 (48) 0.5333

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	0.2 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	0.7 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	2 mg/kg/day High (N=65) P-value - Vehicle vs. High
	#B DECIDUOMA	0/65 (42) 0.2667	0/65 (44) NC	0/65 (46) NC	1/65 (48) 0.5333
	#B POLYP, ENDOMETRIAL STROMAL	4/65 (43) 0.1983	8/65 (47) 0.2231	8/65 (49) 0.2474	9/65 (49) 0.1727
	#B POLYP, GLANDULAR	1/65 (42) 1.0000	0/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (47) 1.0000
	#M ADENOCARCINOMA	0/65 (42) 0.5196	0/65 (44) NC	1/65 (46) 0.5227	0/65 (47) NC
	#M SARCOMA, ENDOMETRIAL STROMAL	1/65 (42) 1.0000	0/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (47) 1.0000
Uterus	C_ADENOMA+ADENOCARCINOMA	0/65 (42) 0.3275	1/65 (44) 0.5116	1/65 (46) 0.5227	1/65 (48) 0.5333
	C_ENDOMETRIAL STROMAL Polyp+Sarcoma	5/65 (43) 0.2578	8/65 (47) 0.3364	8/65 (49) 0.3671	9/65 (49) 0.2736
VAGINA	#B POLYP, VAGINAL	0/65 (42) 0.2667	0/65 (44) NC	0/65 (46) NC	1/65 (48) 0.5333
	#B TUMOR, GRANULAR CELL, BENIGN	0/65 (42) 0.5196	0/65 (44) NC	1/65 (46) 0.5227	0/65 (47) NC
	#M ADENOCARCINOMA; MAMMARY GLAND	2/65 (43) 1.0000	0/65 (44) 1.0000	0/65 (46) 1.0000	0/65 (47) 1.0000
	#M CARCINOMA, SQUAMOUS CELL	0/65 (42) 0.6493	1/65 (44) 0.5116	1/65 (46) 0.5227	0/65 (47) NC
ZYMBAL'S GLANDS	#M ADENOCARCINOMA	0/65 (42) 0.2619	0/62 (41) NC	0/59 (41) NC	1/61 (44) 0.5116

Table 13: Intercurrent Mortality Rate -Male Mice

	Vehicle 0 mg|kg|day (N=25)		Low 8 mg|kg|day (N=25)		Middle 25 mg|kg|day (N=25)		High 80 mg|kg|day (N=25)		Positive (N=10)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 13	.	.	.	.	.	.	.	.	.	.
14 - 26	.	.	1	4.00	10	40.00	9	36.00	.	.
Ter. Sac.	25	100.00	24	96.00	15	60.00	16	64.00	10	100.00

Cum. %: Cumulative percentage except for Ter. Sac.

Table 14: Intercurrent Mortality Rate -Female Mice

	Vehicle 0 mg|kg|day (N=25)		Low 8 mg|kg|day (N=25)		Middle 25 mg|kg|day (N=25)		High 80 mg|kg|day (N=25)		Positive (N=10)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 13	.	.	.	.	1	4.00	1	4.00	10	100.00
14 - 26	.	.	1	4.00	2	12.00	8	36.00	.	.
Ter. Sac.	25	100.00	24	96.00	22	88.00	16	64.00	.	.

Cum. %: Cumulative percentage except for Ter. Sac.

Table 15: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control, Positive Control and Vehicle Control -Male Mice

Test	**Statistic**	**P_Value Vehicle vs Treated Groups Dose Response**	**P_Value Vehicle vs. Low**	**P_Value Vehicle vs. Med**	**P_Value Vehicle vs. High**	**P_Value Vehicle vs. Positive**
Dose-Response	Likelihood Ratio	0.0045	0.2390	<0.0001	0.0002	.
Homogeneity	Log-Rank	<0.0001	0.3173	0.0004	0.0010	.

Table 16: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control, Positive Control and Vehicle Control --Female Mice

Test	**Statistic**	**P_Value Vehicle vs Treated Groups Dose Response**	**P_Value Vehicle vs. Low**	**P_Value Vehicle vs. Med**	**P_Value Vehicle vs. High**	**P_Value Vehicle vs. Positive**
Dose-Response	Likelihood Ratio	<0.0001	0.2390	0.0384	0.0002	.
Homogeneity	Log-Rank	0.0004	0.3173	0.0770	0.0010	.

Table 17: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	8 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	80 mg/kg/day High (N=25) P-value - Vehicle vs. High
Whole Body	C_Hemangioma+Hemangiosarcoma	0/25 (25) 0.0049	5/25 (25) 0.0251	17/25 (24) <0.001	10/25 (23) <0.001
bone marrow, femur	hemangiosarcoma	0/25 (25) 0.7283	1/25 (25) 0.5000	0/25 (20) NC	0/25 (22) NC
intestine, ileum	hemangiosarcoma	0/25 (25) 0.4685	0/25 (25) NC	2/25 (20) 0.1919	0/25 (22) NC
intestine, jejunum	hemangiosarcoma	0/25 (25) 0.4565	0/25 (25) NC	1/25 (20) 0.4444	0/25 (22) NC
intestine, rectum	hemangiosarcoma	0/25 (25) 0.4565	0/25 (25) NC	1/25 (20) 0.4444	0/25 (22) NC
lungs with bronchi	C_alveolar bronchiolar Adeno+Carcin	1/25 (25) 0.5691	3/25 (25) 0.3046	0/25 (20) 1.0000	1/25 (22) 0.7225
	alveolar bronchiolar adenoma	0/25 (25) 0.3145	2/25 (25) 0.2449	0/25 (20) NC	1/25 (22) 0.4681
	alveolar bronchiolar carcinoma	1/25 (25) 0.9283	1/25 (25) 0.7551	0/25 (20) 1.0000	0/25 (22) 1.0000
	hemangiosarcoma	0/25 (25) 0.7283	1/25 (25) 0.5000	0/25 (20) NC	0/25 (22) NC
multicentric	hemangioma	0/25 (25) 0.2391	0/25 (25) NC	0/25 (20) NC	1/25 (22) 0.4681
	hemangiosarcoma	0/25 (25) 0.2412	1/25 (25) 0.5000	7/25 (22) 0.0027	2/25 (22) 0.2137
	mesothelioma	0/25 (25) 0.7283	1/25 (25) 0.5000	0/25 (20) NC	0/25 (22) NC
skeletal muscle	hemangiosarcoma	0/25 (25) 0.0569	0/25 (25) NC	2/25 (20) 0.1919	2/25 (22) 0.2137
skin	hemangioma	0/25 (25) 0.2391	0/25 (25) NC	0/25 (20) NC	1/25 (22) 0.4681
	hemangiosarcoma	0/25 (25) 0.0146	0/25 (25) NC	4/25 (21) 0.0367	4/25 (22) 0.0410
spinal cord, lumba	hemangiosarcoma	0/25 (25) 0.7283	1/25 (25) 0.5000	0/25 (20) NC	0/25 (22) NC
spleen	hemangiosarcoma	0/25 (25) 0.7283	1/25 (25) 0.5000	0/25 (20) NC	0/25 (22) NC
thyroid glands	cystadenoma	0/25 (25) 0.2391	0/25 (25) NC	0/25 (20) NC	1/25 (22) 0.4681

Table 18: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
Whole Body	C_Hemangioma+Hemangiosarcoma	0/25 (25)	7/10 (7) <0.001
lungs with bronchi	C_alveolar bronchiolar Adeno+Carcin	1/25 (25)	10/10 (10) <0.001
	alveolar bronchiolar adenoma	0/25 (25)	10/10 (10) <0.001
	alveolar bronchiolar carcinoma	1/25 (25)	1/10 (2) 0.1453
multicentric	hemangiosarcoma	0/25 (25)	0/10 (1) NC
spleen	hemangiosarcoma	0/25 (25)	7/10 (7) <0.001

Table 19: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	8 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	80 mg/kg/day High (N=25) P-value - Vehicle vs. High
Whole Body	C_Hemangioma+Hemangiosarcoma	0/25 (25) <0.001	3/25 (25) 0.1173	8/25 (24) 0.0016	11/25 (23) <0.001
bone marrow, femur	hemangiosarcoma	0/25 (25) 0.4681	0/25 (25) NC	1/25 (23) 0.4792	0/25 (21) NC
cavity, nasal	adenocarcinoma	0/25 (25) 0.6568	2/25 (25) 0.2449	0/25 (23) NC	0/25 (21) NC
harderian glands	carcinoma	0/25 (25) 0.4681	0/25 (25) NC	1/25 (23) 0.4792	0/25 (21) NC
intestine, cecum	leiomyoma	0/25 (25) 0.4681	0/25 (25) NC	1/25 (23) 0.4792	0/25 (21) NC
intestine, ileum	hemangiosarcoma	0/25 (25) 0.4681	0/25 (25) NC	1/25 (23) 0.4792	0/25 (21) NC
kidneys	mesothelioma	0/25 (25) 0.7340	1/25 (25) 0.5000	0/25 (23) NC	0/25 (21) NC
lungs with bronchi	C_alveolar bronchiolar Adeno+Carcin	4/25 (25) 0.9733	3/25 (25) 0.7913	4/25 (23) 0.5997	0/25 (21) 1.0000
	alveolar bronchiolar adenoma	3/25 (25) 0.9479	3/25 (25) 0.6664	4/25 (23) 0.4513	0/25 (21) 1.0000
	alveolar bronchiolar carcinoma	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000	0/25 (21) 1.0000
mammary gland	hemangioma	0/25 (25) 0.7340	1/25 (25) 0.5000	0/25 (23) NC	0/25 (21) NC
	lymphangioma	0/25 (25) 0.7340	1/25 (25) 0.5000	0/25 (23) NC	0/25 (21) NC
multicentric	hemangiosarcoma	0/25 (25) 0.0093	1/25 (25) 0.5000	1/25 (23) 0.4792	4/25 (22) 0.0410
ovaries	hemangioma	0/25 (25) 0.4681	0/25 (25) NC	1/25 (23) 0.4792	0/25 (21) NC
	hemangiosarcoma	0/25 (25) 0.7340	1/25 (25) 0.5000	0/25 (23) NC	0/25 (21) NC
pancreas	hemangiosarcoma	0/25 (25) 0.5882	1/25 (25) 0.5000	1/25 (23) 0.4792	0/25 (21) NC
skeletal muscle	hemangiosarcoma	0/25 (25) 0.2234	0/25 (25) NC	0/25 (23) NC	1/25 (21) 0.4565
skin	hemangiosarcoma	0/25 (25) <0.001	0/25 (25) NC	1/25 (23) 0.4792	5/25 (22) 0.0172
spleen	hemangiosarcoma	0/25 (25) 0.1599	0/25 (25) NC	1/25 (24) 0.4898	1/25 (21) 0.4565
stomach	hemangiosarcoma	0/25 (25) 0.4681	0/25 (25) NC	1/25 (23) 0.4792	0/25 (21) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	8 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	25 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	80 mg/kg/day High (N=25) P-value - Vehicle vs. High
	squamous cell carcinoma	0/25 (25) 0.7340	1/25 (25) 0.5000	0/25 (23) NC	0/25 (21) NC
thymus	mesothelioma	0/25 (25) 0.2234	0/25 (25) NC	0/25 (23) NC	1/25 (21) 0.4565
	thymoma	1/25 (25) 0.1243	0/25 (25) 1.0000	0/25 (23) 1.0000	2/25 (21) 0.4335

Table 20: Tumor Rates and P-Values for Comparisons between Vehicle Control and Positive Control -Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25)	Positive (N=10) P-value - Vehicle vs. Positive
Whole Body	C_Hemangioma+Hemangiosarcoma	0/25 (25) <0.001	4/10 (4) <0.001
lungs with bronchi	C_alveolar bronchiolar Adeno+Carcin	4/25 (25) <0.001	10/10 (10) <0.001
	alveolar bronchiolar adenoma	3/25 (25) <0.001	10/10 (10) <0.001
	alveolar bronchiolar carcinoma	1/25 (25) 0.0031	2/10 (3) 0.0232
spleen	hemangiosarcoma	0/25 (25) <0.001	4/10 (4) <0.001

Figure 1: Kaplan-Meier Survival Functions for Male Rats

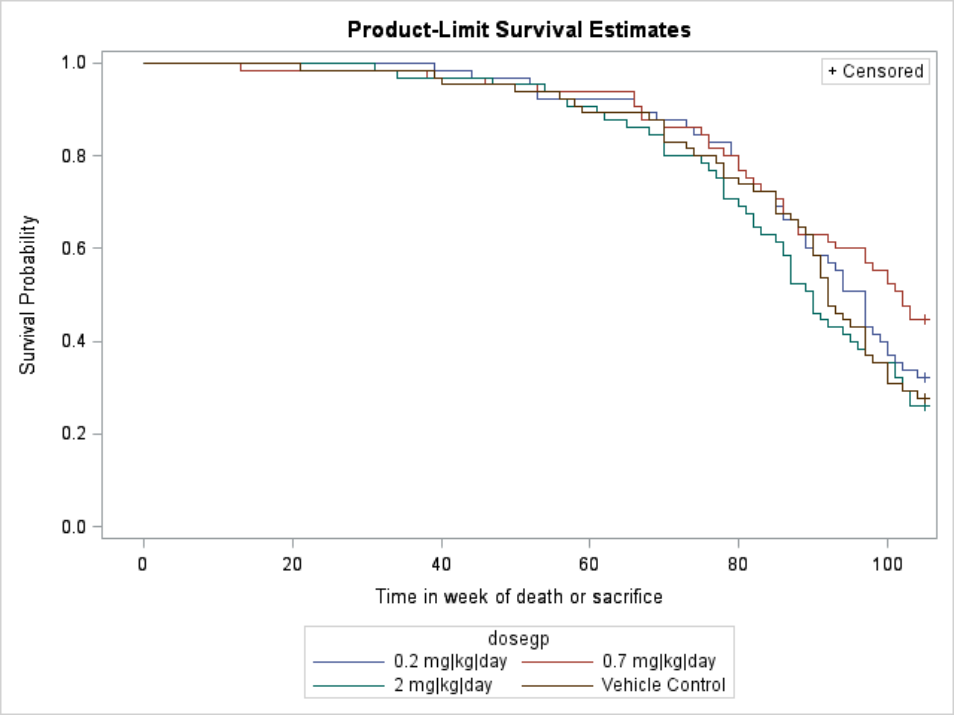


Figure 2: Kaplan-Meier Survival Functions for Female Rats

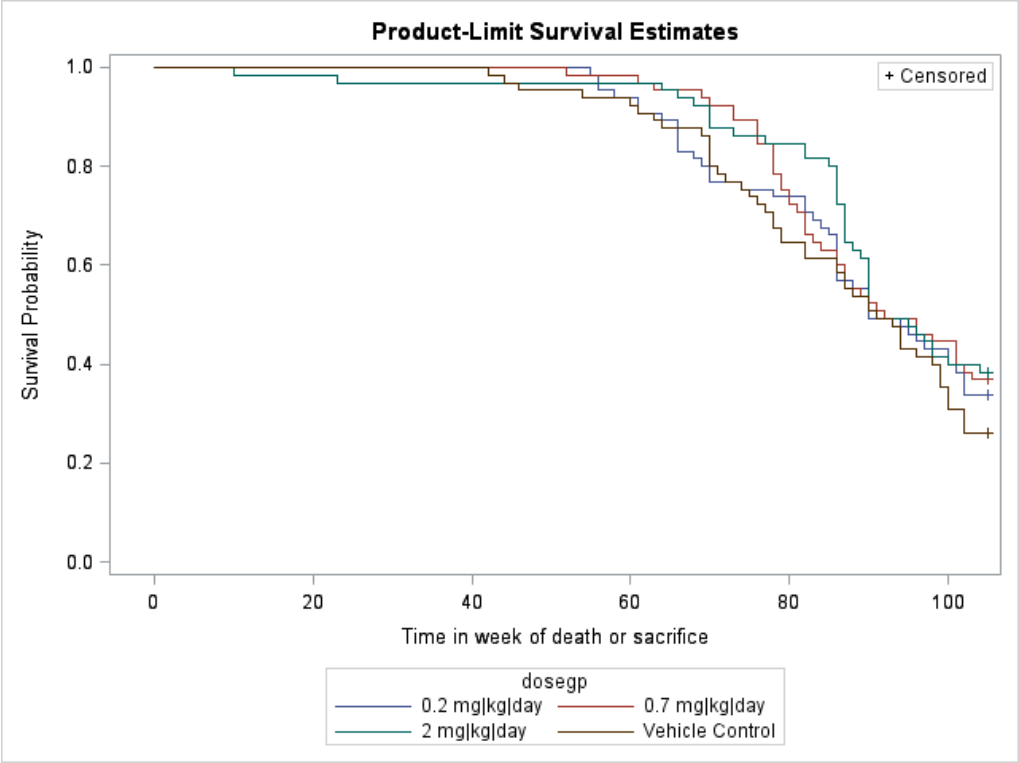


Figure 3: Kaplan-Meier Survival Functions for Male Mice

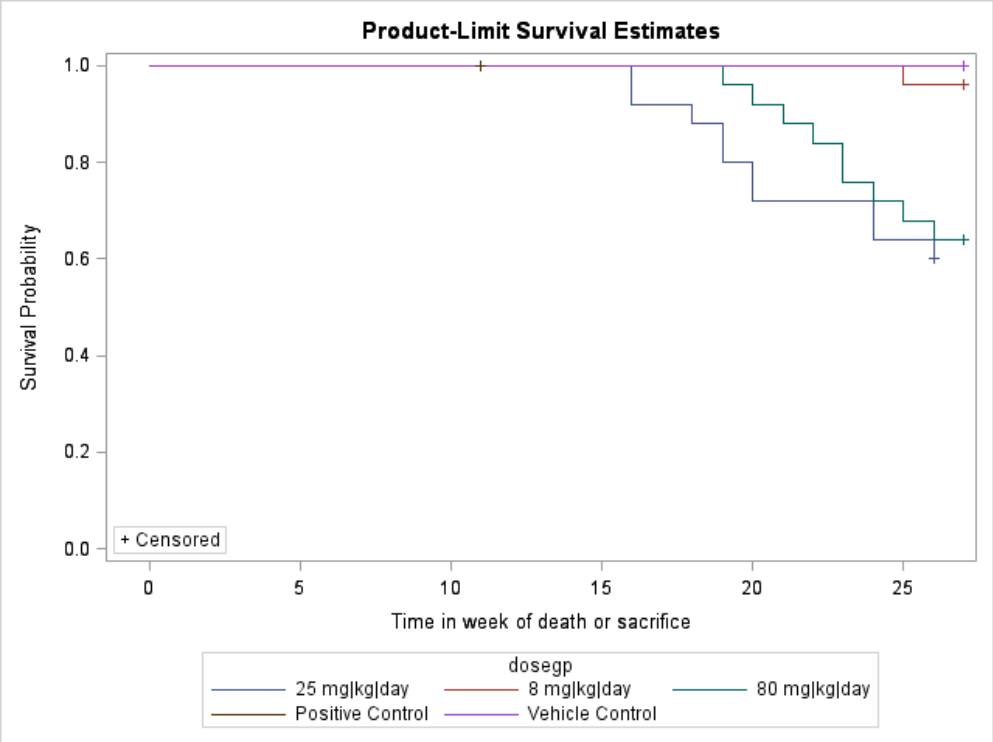
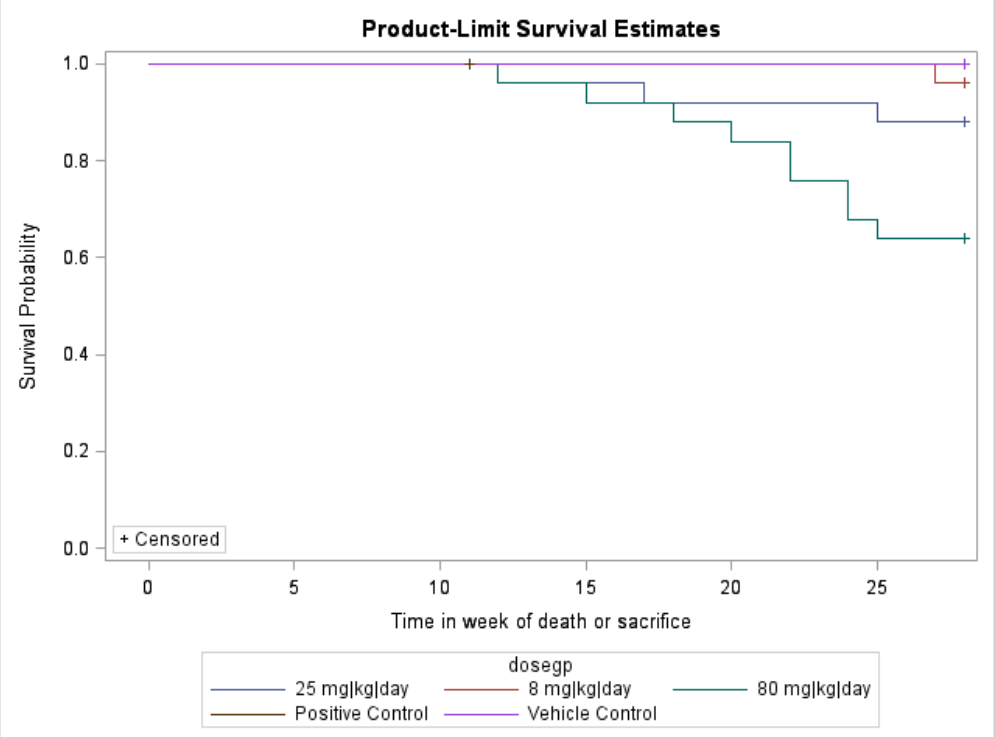


Figure 4: Kaplan-Meier Survival Functions for Female Mice



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Concur with review.