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

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA 213498/SN-0001
Drug Name:	Ponvory tablet
Indication(s):	Treatment of adult patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease
Applicant:	Janssen Pharmaceuticals Inc.
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Date(s):	Received 4/29/2020
Documents Reviewed:	Study t-13-023 (mouse), study t-13-024 (rat), and the electronic tumor.xpt files were submitted on 3/18/2020 (via NDA 213498/SN0001).
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics VI
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Keywords:	Carcinogenicity, Dose response, Mortality

Table of Contents

1 Summary

This review evaluates statistically the data of the 2-year oral (gavage) carcinogenicity study in Wistar rats and 2-year oral (gavage) carcinogenicity study in CD-1 mice. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality). From the statistical point of view, the review concludes that ACT-128800 significantly increased mortality in mid and high dosed groups in female rats and male mice; ACT-128800 caused statistically significant increases in the incidence of vascular tumors (hemangioma, hemangiosarcoma, and the combination of hemangiosarcoma and hemangioma) in male and female mice. See Table 1 for tumor incidences and p-values of the tumor types mentioned above.

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

Animal Sex	Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	3 mg/kg/day Low (L) P - C vs. L	10 mg/kg/day Mid (M) P - C vs. M	30 mg/kg/day High (H) P - C vs. H
Rats	Testes	Adenoma, Leydig	0/102 (89)	4/51 (49)	1/51 (47)	0/51 (45)
Male		Cell	0.7701	0.0146 **	0.3456	NS

Animal Sex	Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	50 mg/kg/day Low (L) P - C vs. L	150 mg/kg/day Mid (M) P - C vs. M	400 mg/kg/day High (H) P - C vs. H
Mice	Liver	Hemangiosarcoma	0/120 (96)	4/60 (46)	5/60 (41)	4/60 (41)
Male			0.0245*	0.0101**	0.0020**	0.0072**
	Whole body	Hemangiosarcoma	3/120 (96)	8/60 (47)	8/60 (43)	13/60 (44)
			0.0001*	0.0060**	0.0038**	0.0000**
		Hemangioma/	9/120 (96)	14/60 (47)	14/60 (44)	15/60 (44)
		Hemangiosarcoma	0.0021**	0.0025**	0.0014**	0.0006**

Animal Sex	Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	30 mg/kg/day Low (L) P - C vs. L	100 mg/kg/day Mid (M) P - C vs. M	300 mg/kg/day High (H) P - C vs. H
Mice	Liver	Hemangiosarcoma	0/120 (67)	0/60 (40)	0/60 (37)	3/60 (38)
Female			0.0085*	NS	NS	0.0450**
	Uterus	Hemangioma	0/120 (67)	3/60 (42)	3/60 (38)	0/60 (36)
			0.6868	0.0547	0.0450**	NS
		Hemangiosarcoma	1/120 (67)	1/60 (40)	0/60 (37)	7/60 (40)
			0.0003*	0.6101	NS	0.0041**
	Whole body	Hemangioma	1/120 (67)	5/60 (42)	7/60 (39)	2/60 (37)
			0.3734	0.0307	0.0036**	0.2877
		Hemangiosarcoma	4/120 (68)	1/60 (40)	0/60 (37)	13/60 (43)
			0.0000*	0.9065	1.0000	0.0007**
		Hemangioma/	4/120 (68)	6/60 (42)	7/60 (39)	14/60 (43)
		Hemangiosarcoma	0.0003*	0.1263	0.0521	0.0003**

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

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Rat Study: Rats (51/sex/group) were dosed by oral gavage with ACT-128800 once daily for up to 104 weeks. The respective ACT-128800 doses in the control 1 (C1), control 2 (C2), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 3, 10, and 30 mg/kg/day for males and 0, 0, 10, 30, and 100 mg/kg/day in females. The high dose females were terminated in Week 96 due to the number of surviving animals in the group reaching 15. All other groups were terminated in Week 104. There were two identical control groups, the control animals were treated with the vehicle, 0.25%(w/w) methylcellulose and Tween 80 (0.05% (v/v), only.

The survival analyses showed statistically significant dose response relationship in mortality in female rats. The overall intercurrent mortality was significantly increased at 30 and 100 mg/kg/day. The respective survival rates in the C1, C2, LD, MD, or HD of ACT-128800 at the time they were terminated were 69%, 67%, 82%, 76%, and 67% in males and 51%, 63%, 61%, 35%, and 33% in females.

The tumor analysis showed that there were no statistically significant positive dose response relationships between the ACT-128800 treated groups and combined control group for male and female rats. However, the incidence rates of tumor types of adenoma Leydig in testes were statistically significantly higher for low dose group compared to combined control group.

Mouse Study: Mice (60/sex/group) were dosed by oral gavage with ACT-128800 once daily for up to 104 weeks. The respective ACT-128800 doses in the control 1 (C1), control 2 (C2), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 50, 150, and 400 mg/kg/day for males and 0, 0, 30, 100, and 300 mg/kg/day in females. All male groups were terminated in Week 104 and female groups were terminated in Week 103. There were two identical control groups, the control animals were treated with the vehicle, 0.25%(w/w) methylcellulose and Tween 80 (0.05% (v/v), only.

The survival analyses showed statistically significant dose response relationship in mortality in male mice only. The overall intercurrent mortality was significantly increased in males at 150 and 400 mg/kg/day dosed groups. The respective survival rates in the C1, C2, LD, MD, or HD of ACT-128800 at the time they were terminated were 43%, 53%, 50%, 28%, and 28% in males and 18%, 28%, 45%, 35%, and 25% in females.

Tumor analysis results (Table 1) showed that there were a statistically significant increases for liver hemangiosarcomas and the combination of liver hemangiosarcomas and hemangiomas, and of whole body hemangiosarcomas and the combination of whole body hemangiosarcomas and hemangiomas in both male and female mice; and of Uterus hemangiosarcomas in female mice. The liver was the mainly affected organ in both male and female mice. The uterus was also affected in female mice.

2 Background

Janssen Pharmaceuticals, Inc. (JPI) submitted a New Drug Application (NDA) 213498 for Ponvory for the treatment of adult patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. The sponsor hereby submitted the final nonclinical reports: Study t-13-023: "A 104-week oral (gavage) carcinogenicity study in mouse" and Study t-13-024: "A 104-week oral (gavage) carcinogenicity Study in rat" The study reports were submitted on 3/18/2020 (via NDA213498/SN0001) and the electronic tumor.xpt files were submitted on the same time.

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases. Results of this review have been discussed with the nonclinical team.

3 Rat Study- t-13-024

Study Report: t-13-024.pdf (statistical report on page 3494)
SAS data: tumor.xpt

The objective of this study was to evaluate the carcinogenic potential of the test item, ACT-128800, following once daily oral administration (gavage) to (b) (4) Wistar rats for 104 weeks. The dose levels were 0, 0, 3, 10 and 30 mg/kg/day for males and 0, 0, 10, 30, and 100 mg/kg/day for females. There were 51 animals per sex per group. The female rats dosed with 100 mg/kg/day were terminated in Week 96 due to the number of surviving animals in the group reaching 15. All other groups were terminated in Week 104. There were two identical control groups, the control animals were treated with the vehicle, 0.25%(w/w) methylcellulose and Tween 80 (0.05% (v/v), only.

The comparisons of interest for the sponsor's analyses were defined as: control 1 and control 2 combined vs. treated groups.

Assessment of carcinogenicity was based on anatomic pathology to include incidences of masses or tumors and possible effects on survival. Mortality, clinical observations, body weight, and food consumption were also monitored and evaluated.

3.1 Sponsor's Analyses

3.1.1 Survival Analysis

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

0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests. The treated group were compared against the combined control groups

Sponsor's concluded results: The overall intercurrent mortality was about evenly distributed among the male groups. In females, the intercurrent mortality was increased at 30 and 100 mg/kg/day: it was associated with an increased proportion of animals with kidney disease, especially chronic progressive nephropathy.

3.1.2 Tumor Data Analysis

Neoplastic findings classified as fatal and incidental were processed using the death rate method and the prevalence method, respectively. The processing of incidental tumors was done by creating a single separate interval for the time following the experimental period (terminal sacrifice period) and by dividing the experimental period into the following fixed intervals [FDA's draft Guidance for industry. 2001]: weeks 1-52, weeks 53-78, weeks 79-92, and weeks 93-104. Using the derived outcomes from the processing of both fatal and incidental tumors, a test statistic was built to perform a global survival-adjusted trend test on tumor data observed in a "mortality dependent" context [Peto et al, 1980]. The treated group were compared against the combined control groups

All p-values are reported using upper-tailed test, unless otherwise indicated. Evaluation criteria (levels of significance) were applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%).

Since the PETO test is a trend test, it is unclear which of the dose groups made the test positive. Therefore, in cases of statistical significance, a step-down procedure was applied by omitting the high dose and re-testing the remaining data. If the test is still significant, the mid dose group was omitted, and the test was repeated with the control groups and the low dose group. By that procedure the dose group(s) that were responsible for the positive trend test should be identified.

Sponsor's concluded results: Statistical trend test indicated significant results for selected neoplasms, when the criteria for rare tumors were applied. In males they were cholangioma in the liver, pheochromocytoma in the adrenal glands, rhabdomyoma and hair follicle tumor in the skin; in females atriocaval mesothelioma in the heart and glandular polyp in the uterus.

All these neoplasms occurred with a low incidence, amounting to one or two cases per group, and represented findings which can occur spontaneously in rats. Therefore, their distribution among the groups is considered to be fortuitous and not to provide an evidence of carcinogenic effect. Moreover, selected neoplasms, such as those in the pituitary gland or the mammary gland, occurred with dose-related decreased incidence. The results of present study indicate that the test item is devoid of carcinogenic effect. Analysis of the neoplastic lesions revealed no carcinogenic potential of the ACT-128800.

3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 3/18/2020 via NDA213498/SN001. Since the animals in the two the control groups were treated with the identical vehicle, 0.25%(w/w) methylcellulose and Tween 80 (0.05% (v/v), all analyses in this review were based on the combined two controls group and treated group.

3.2.1 Data Quality

The sponsor submitted only tumor.xpt file on 3/18/2020 (via NDA 213498/SN0001. The data quality of tumor.xpt was acceptable.

3.2.2 Survival Analysis

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

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 16 (31%), 17 (33%), 9 (18%), 12 (24%), or 17 (33%) in male rats and 25 (49%), 19 (37%), 20 (39%), 33 (65%), or 34 (67%) in female rats in the C1, C2, LD, MD, or HD groups, respectively. The survival analyses showed statistically significant dose response relationship in mortality in female rats only. The overall intercurrent mortality was significantly increased at 30 and 100 mg/kg/day in female rats.

3.2.3 Tumor Data Analysis

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

being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

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

The tumor rates and the p-values of the tested tumor types are listed in Tables 5A and 5B in the appendix for male and female rats, respectively.

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

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships and Pairwise Comparisons of Treated Groups and Controls in Rats

Sex	Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	3 mg/kg/day Low (L) P - C vs. L	10 mg/kg/day Mid (M) P - C vs. M	30 mg/kg/day High (H) P - C vs. H
Male	Adrenal Gland	Pheochromocytoma,	0/102 (89)	0/51 (49)	2/51 (47)	2/51 (45)
		Benign	0.0338	NS	0.1178	0.1111
	Skin/Subcutis	Tumor, Hair Follicle	0/102 (89)	0/51 (49)	1/51 (47)	2/51 (45)
		Benign	0.0303	NS	0.3456	0.1111
	Testes	Adenoma, Leydig	0/102 (89)	4/51 (49)	1/51 (47)	0/51 (45)
		Cell	0.7701	0.0146 **	0.3456	NS
Sex	**Organ name**	**Tumor name**	**0 mg/kg/day Comb. Control (C) P - Trend**	**10 mg/kg/day Low (L) P - L vs. C**	**30 mg/kg/day Mid (M) P - M vs. C**	**100 mg/kg/day High (H) P - H vs. C**
Female	Uterus	Polyp, Glandular	0/101 (82)	1/51 (45)	0/51 (39)	2/51 (33)
			0.0385	0.3543	NS	0.0805

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

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Reviewer's findings: Based on the criteria of adjustment for multiple testing discussed above, there were no statistically significant positive dose response relationships between the ACT-128800 treated groups and combined control group for male and female rats. However, the incidence rates of tumor types of adenoma Leydig in testes were statistically significantly higher for low dose group compared to combined control group ($p=0.0146 < 0.05$).

4 Mouse Study- t-13-023

Study Report: t-13-023.pdf (statistical report on page 3927)
SAS data: tumor.xpt

The objective of this study was to evaluate the carcinogenic potential of the test item, ACT-128800, following once daily oral administration (gavage) to Crl:CD1(ICR) mice for 104 weeks. The dose levels were 0, 0, 50, 150 and 400 mg/kg/day in males and 0, 0, 30, 100, and 300 mg/kg/day in females. There were 60 animals per sex per group. All male groups were terminated in Week 104 and all female groups were terminated in Week 103. There were two identical control groups, the control animals were treated with the vehicle, 0.25%(w/w) methylcellulose and Tween 80 (0.05% (v/v), only.

The comparisons of interest for the sponsor's analyses were defined as: control 1 and control 2 combined vs. treated groups.

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

4.1 Sponsor's Analyses

4.1.1 Survival Analysis

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

Survival probability functions were estimated by the Kaplan-Meier technique. Survival curves were compared by the log-rank procedure, according to Peto's method (Peto et al., 1980). Animals killed at the terminal sacrifice were considered as censored observations in the statistical analysis. Other causes of death (i.e. natural death, moribund sacrifice or accidental death) were not considered as censored observations.

Sponsor's concluded results: All groups of males completed the full 104-week treatment period, but mortality was slightly increased in males at 150 and 400 mg/kg/day when compared to the two vehicle control groups.

4.1.2 Tumor Data Analysis

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

Statistical analysis of the incidence of tumors based on the principles outlined by Peto et al (1980) are not applied in short-term studies due to the low mortality compared to a 2-year carcinogenicity study. The incidence of hemangiosarcoma was tested for each tissue as well as pooled tissues. Analysis of tumor incidences was performed, sex separately, for each tumor type.

Sponsor's findings: The incidence of vascular tumors (hemangioma and hemangiosarcoma) was increased in test item-treated groups when compared to concurrent controls. There was a statistically significant increase for hemangiosarcomas and the combination of hemangiosarcomas and hemangiomas in males and in females. In males, the incidence of combined vascular tumors increased in all test item-treated groups. The liver and spleen were the mainly affected organs. In females, the incidence of combined vascular neoplasms and hemangiosarcoma alone increased in the high dose group. The uterus, ovaries, liver, and spleen were the mainly affected organs.

4.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 3/18/2020 via NDA213498/SN001. Since the animals in the two the control groups were treated with the identical vehicle, 0.25%(w/w) methylcellulose and Tween 80 (0.05% (v/v), all analyses in this review were based on the combined two controls group and treated group

4.2.1 Data Quality

The sponsor submitted only tumor.xpt file on 3/18/2020 (via NDA 213498/SN0001. The data quality of tumor.xpt was acceptable.

4.2.2 Survival Analysis

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

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 34 (57%), 28 (47%), 30 (50%), 43 (72%) and 43 (72%) in male mice and 49 (82%), 43 (72%), 33 (55%), 39 (65%), and 45 (75%) in female mice in the C1, C2, LD, MD, and HD groups, respectively. The survival analyses showed statistically significant dose response relationship in mortality in male mice. The overall intercurrent mortality was significantly increased in males at 150 and 400 mg/kg/day dosed groups. No impact on survival was observed in females.

4.2.3 Tumor Data Analysis

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

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

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships and Pairwise Comparisons of Treated Groups and Controls in Mice

Sex	Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	50 mg/kg/day Low (L) P - C vs. L	150 mg/kg/day Mid (M) P - C vs. M	400 mg/kg/day High (H) P - C vs. H
Male	Epididymides	Hemangiosarcoma	0/120 (96)	0/60 (45)	0/60 (40)	2/60 (41)
			0.0334	NS	NS	0.0880
	Liver	Hemangioma	1/120 (96)	2/60 (45)	4/60 (41)	2/60 (41)
			0.1410	0.2389	0.0280	0.2132
		Hemangiosarcoma	0/120 (96)	4/60 (46)	5/60 (41)	4/60 (41)
			0.0245*	0.0101**	0.0020**	0.0072**
	Skin/Subcutis	Malignant	0/120 (96)	0/60 (45)	0/60 (40)	2/60 (42)
		Schwannoma	0.0348	NS	NS	0.0911
	Whole body	Hemangioma	6/120 (96)	6/60 (45)	6/60 (41)	3/60 (41)
			0.4611	0.1404	0.1064	0.5392
		Hemangiosarcoma	3/120 (96)	8/60 (47)	8/60 (43)	13/60 (44)
			0.0001*	0.0060**	0.0038**	0.0000**
		Hemangioma/	9/120 (96)	14/60 (47)	14/60 (44)	15/60 (44)
		Hemangiosarcoma	0.0021**	0.0025**	0.0014**	0.0006**

Sex	Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	30 mg/kg/day Low (L) P - C vs. L	100 mg/kg/day Mid (M) P - C vs. M	300 mg/kg/day High (H) P - C vs. H
Female	Liver	Hemangiosarcoma	0/120 (67)	0/60 (40)	0/60 (37)	3/60 (38)
			0.0085*	NS	NS	0.0450**
		Hepatocellular	0/120 (67)	0/60 (40)	0/60 (37)	2/60 (37)
		Adenoma	0.0409	NS	NS	0.1243
	Ovaries	Cystadenoma	1/120 (67)	0/59 (39)	0/60 (37)	3/59 (37)
			0.0278	NS	NS	0.1276
	Pituitary Gland	Adenoma: Pars	2/119 (67)	1/60 (40)	6/58 (38)	0/60 (36)
		Anterior	0.6687	0.7586	0.0251	NS
	Spleen	Hemangiosarcoma	0/120 (67)	0/60 (40)	0/60 (37)	2/60 (37)
			0.0409	NS	NS	0.1243
	Uterus	Hemangioma	0/120 (67)	3/60 (42)	3/60 (38)	0/60 (36)
			0.6868	0.0547	0.0450**	NS
		Hemangiosarcoma	1/120 (67)	1/60 (40)	0/60 (37)	7/60 (40)
			0.0003*	0.6101	NS	0.0041**
	Whole body	Hemangioma	1/120 (67)	5/60 (42)	7/60 (39)	2/60 (37)
			0.3734	0.0307	0.0036**	0.2877
		Hemangiosarcoma	4/120 (68)	1/60 (40)	0/60 (37)	13/60 (43)
			0.0000*	0.9065	1.0000	0.0007**
		Hemangioma/	4/120 (68)	6/60 (42)	7/60 (39)	14/60 (43)
		Hemangiosarcoma	0.0003*	0.1263	0.0521	0.0003**

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

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, there were a statistically significant increases for liver hemangiosarcomas and the combination of liver hemangiosarcomas and hemangiomas, and of whole body hemangiosarcomas and the

combination of whole body hemangiosarcomas and hemangiomas in both male and female mice; and of Uterus hemangiosarcomas in female mice. The liver was the mainly affected organ in both male and female mice. The uterus was also affected in female mice.

5 Conclusion

This review evaluates statistically the data of the 2-year oral (gavage) carcinogenicity study in Wistar rats and 2-year oral (gavage) carcinogenicity study in CD-1 mice. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality). From the statistical point of view, the review concludes that ACT-128800 significantly increased mortality in mid and high dosed groups in female rats and male mice; ACT-128800 caused statistically significant increases in the incidence of vascular tumors (hemangioma, hemangiosarcoma, and the combination of hemangiosarcoma and hemangioma) in male and female mice. See Table 1 for tumor incidences and p-values of the tumor types mentioned above.

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

Animal Sex	Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	3 mg/kg/day Low (L) P - C vs. L	10 mg/kg/day Mid (M) P - C vs. M	30 mg/kg/day High (H) P - C vs. H
Rats	Testes	Adenoma, Leydig	0/102 (89)	4/51 (49)	1/51 (47)	0/51 (45)
Male		Cell	0.7701	0.0146 **	0.3456	NS

Animal Sex	Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	50 mg/kg/day Low (L) P - C vs. L	150 mg/kg/day Mid (M) P - C vs. M	400 mg/kg/day High (H) P - C vs. H
Mice	Liver	Hemangiosarcoma	0/120 (96)	4/60 (46)	5/60 (41)	4/60 (41)
Male			0.0245*	0.0101**	0.0020**	0.0072**
	Whole body	Hemangiosarcoma	3/120 (96)	8/60 (47)	8/60 (43)	13/60 (44)
			0.0001*	0.0060**	0.0038**	0.0000**
		Hemangioma/	9/120 (96)	14/60 (47)	14/60 (44)	15/60 (44)
		Hemangiosarcoma	0.0021**	0.0025**	0.0014**	0.0006**

Animal Sex	Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	30 mg/kg/day Low (L) P - C vs. L	100 mg/kg/day Mid (M) P - C vs. M	300 mg/kg/day High (H) P - C vs. H
Mice	Liver	Hemangiosarcoma	0/120 (67)	0/60 (40)	0/60 (37)	3/60 (38)
Female			0.0085*	NS	NS	0.0450**
	Uterus	Hemangioma	0/120 (67)	3/60 (42)	3/60 (38)	0/60 (36)
			0.6868	0.0547	0.0450**	NS
		Hemangiosarcoma	1/120 (67)	1/60 (40)	0/60 (37)	7/60 (40)
			0.0003*	0.6101	NS	0.0041**
	Whole body	Hemangioma	1/120 (67)	5/60 (42)	7/60 (39)	2/60 (37)
			0.3734	0.0307	0.0036**	0.2877
		Hemangiosarcoma	4/120 (68)	1/60 (40)	0/60 (37)	13/60 (43)
			0.0000*	0.9065	1.0000	0.0007**
		Hemangioma/	4/120 (68)	6/60 (42)	7/60 (39)	14/60 (43)
		Hemangiosarcoma	0.0003*	0.1263	0.0521	0.0003**

Animal Sex	Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	3 mg/kg/day Low (L) P - C vs. L	10 mg/kg/day Mid (M) P - C vs. M	30 mg/kg/day High (H) P - C vs. H
Rats Male	Testes	Adenoma, Leydig Cell	0/102 (89) 0.7701	4/51 (49) 0.0146 **	1/51 (47) 0.3456	0/51 (45) NS

Animal Sex	Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	50 mg/kg/day Low (L) P - C vs. L	150 mg/kg/day Mid (M) P - C vs. M	400 mg/kg/day High (H) P - C vs. H

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

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Rat Study: Rats (51/sex/group) were dosed by oral gavage with ACT-128800 once daily for up to 104 weeks. The respective ACT-128800 doses in the control 1 (C1), control 2 (C2), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 3, 10, and 30 mg/kg/day for males and 0, 0, 10, 30, and 100 mg/kg/day in females. The high dose females were terminated in Week 96 due to the number of surviving animals in the group reaching 15. All other groups were terminated in Week 104. There were two identical control groups, the control animals were treated with the vehicle, 0.25%(w/w) methylcellulose and Tween 80 (0.05% (v/v), only.

The survival analyses showed statistically significant dose response relationship in mortality in female rats. The overall intercurrent mortality was significantly increased at 30 and 100 mg/kg/day. The respective survival rates in the C1, C2, LD, MD, or HD of ACT-128800 at the time they were terminated were 69%, 67%, 82%, 76%, and 67% in males and 51%, 63%, 61%, 35%, and 33% in females.

The tumor analysis showed that there were no statistically significant positive dose response relationships between the ACT-128800 treated groups and combined control group for male and female rats. However, the incidence rates of tumor types of adenoma Leydig in testes were statistically significantly higher for low dose group compared to combined control group.

Mouse Study: Mice (60/sex/group) were dosed by oral gavage with ACT-128800 once daily for up to 104 weeks. The respective ACT-128800 doses in the control 1 (C1), control 2 (C2), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 50, 150, and 400 mg/kg/day for males and 0, 0, 30, 100, and 300 mg/kg/day in females. All male groups were terminated in Week 104 and female groups were terminated in Week 103. There were two identical control groups, the control animals were treated with the vehicle, 0.25%(w/w) methylcellulose and Tween 80 (0.05% (v/v), only.

The survival analyses showed statistically significant dose response relationship in mortality in male mice only. The overall intercurrent mortality was significantly increased in males at 150 and 400 mg/kg/day dosed groups. The respective survival rates in the C1, C2, LD, MD, or HD of ACT-128800 at the time they were terminated were 43%, 53%, 50%, 28%, and 28% in males and 18%, 28%, 45%, 35%, and 25% in females.

Tumor analysis results (Table 1) showed that there were a statistically significant increases for liver hemangiosarcomas and the combination of liver hemangiosarcomas and hemangiomas, and of whole body hemangiosarcomas and the combination of whole body hemangiosarcomas and hemangiomas in both male and female mice; and of Uterus hemangiosarcomas in female mice. The liver was the mainly affected organ in both male and female mice. The uterus was also affected in female mice.

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6 Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Control 1		Control 2		Low Dose		Mid Dose		High Dose	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 52			2	3.92						
53 - 78	3	5.88	4	11.76	1	1.96	3	5.88	3	5.88
79 - 92	5	15.69	6	23.53	2	5.88	4	13.73	5	15.69
93 - 104	8	31.37	5	33.33	6	17.65	5	23.53	9	33.33
Terminal sacrifice	35	68.63	34	66.67	42	82.35	39	76.47	34	66.67
Total	51		51		51		51		51	

Table 1B: Intercurrent Mortality Rate in Female Rats

	Control 1		Control 2		Low Dose		Mid Dose		High Dose	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 52	1	1.96			2	3.92	1	1.96	3	5.88
53 - 78	4	9.80	7	13.73	2	7.84	9	19.61	13	31.37
79 - 92	14	37.25	7	27.45	7	21.57	4	27.45	8	47.06
93 - 104	6	49.02	5	37.25	9	39.22	19	64.71	10	66.67
Terminal sacrifice	26	50.98	32	62.75	31	60.78	18	35.29	17	33.33
Total	51		51		51		51		51	

Table 2A: Intercurrent Mortality Rate in Male Mice

	Control 1		Control 2		Low Dose		Mid Dose		High Dose	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 52	3	5.00	2	3.33	1	1.67	4	6.67	2	3.33
53 - 78	5	13.33	4	10.00	13	23.33	11	25.00	17	31.67
79 - 92	11	31.67	8	23.33	6	33.33	19	56.67	7	43.33
93 - 104	15	56.67	14	46.67	10	50.00	9	71.67	17	71.67
Terminal sacrifice	26	43.33	32	53.33	30	50.00	17	28.33	17	28.33
Total	60		60		60		60		60	

Table 2B: Intercurrent Mortality Rate in Female Mice

	Control 1		Control 2		Low Dose		Mid Dose		High Dose	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 52	9	15.00	9	15.00	8	13.33	4	6.67	2	3.33
53 - 78	14	38.33	15	40.00	10	30.00	18	36.67	15	28.33
79 - 92	15	63.33	12	60.00	9	45.00	12	56.67	20	61.67
93 - 104	11	81.67	7	71.67	6	55.00	5	65.00	8	75.00
Terminal sacrifice	11	18.33	17	28.33	27	45.00	21	35.00	15	25.00
Total	60		60		60		60		60	

Table 3A: Intercurrent Mortality Comparison with Combined Control in Male Rats

Test	All Dose Groups	Combined Control vs. Low	Combined Control vs. Mid	Combined Control vs. High
Dose-Response (Likelihood Ratio)	0.5987	0.0373	0.2435	0.9700
Homogeneity (Log-Rank)	0.1581	0.0448	0.2513	0.9698

Table 3B: Intercurrent Mortality Comparison with Combined Control in Female Rats

Test	All Dose Groups	Combined Control vs. Low	Combined Control vs. Mid	Combined Control vs. High
Dose-Response (Likelihood Ratio)	0.0006	0.4907	0.0345	0.0030
Homogeneity (Log-Rank)	0.0008	0.4913	0.0285	0.0018

Table 4A: Intercurrent Mortality Comparison with Combined Controls in Male Mice

Test	All Dose Groups	Combined Control vs. Low	Combined Control vs. Mid	Combined Control vs. High
Dose-Response (Likelihood Ratio)	0.0025	0 9185	0.0033	0.0059
Homogeneity (Log-Rank)	0.0023	0 9177	0.0020	0.0040

Table 4B: Intercurrent Mortality Comparison with Combined Controls in Female Mice

Test	All Dose Groups	Combined Control vs. Low	Combined Control vs. Mid	Combined Control vs. High
Dose-Response (Likelihood Ratio)	0.9660	0.0097	0.1912	0.5806
Homogeneity (Log-Rank)	0.0715	0.0110	0.1931	0.5780

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

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	3 mg/kg/day Low (L) P - C vs. L	10 mg/kg/day Mid (M) P - C vs. M	30 mg/kg/day High (H) P - C vs. H
Adrenal Gland	Pheochromocytoma, Benign	0/102 (89)	0/51 (49)	2/51 (47)	2/51 (45)
		0.0338	NS	0.1178	0.1111
Comb_Bone/Skin	Osteosarcoma	0/102 (89)	1/51 (49)	1/51 (47)	0/51 (45)
		0.4822	0 3551	0.3456	NS
Brain	Oligodendroglioma	1/102 (89)	0/51 (49)	0/51 (47)	2/51 (46)
		0.1019	NS	NS	0.2676
	Tumor, Granular Cell Benign	3/102 (89)	0/51 (49)	0/51 (47)	1/51 (45)
		0.6054	NS	NS	0.8099
Cecum	Fibroma	1/102 (89)	0/51 (49)	0/51 (47)	0/51 (45)
		NS	NS	NS	NS
Epididymides	Hemangioma	0/102 (89)	0/51 (49)	0/51 (47)	1/51 (45)
		0.1957	NS	NS	0.3358
Eyes	Melanoma, Malignant	1/102 (89)	0/51 (49)	0/51 (47)	0/51 (45)
		NS	NS	NS	NS
Liver	Cholangioma	0/102 (89)	0/51 (49)	0/51 (47)	1/51 (45)
		0.1957	NS	NS	0.3358
Lung	Adenoma, Bronchiolo-Alveolar	0/102 (89)	1/51 (49)	0/51 (47)	0/51 (45)
		0.6130	0 3551	NS	NS
Mesenteric Ln	Hemangioma	3/102 (89)	0/51 (49)	0/51 (47)	1/50 (45)
		0.6054	NS	NS	0.8099
	Hemangiosarcoma	0/102 (89)	1/51 (49)	1/51 (47)	0/50 (45)
		0.4822	0 3551	0.3456	NS
Nasal Cavity	Carcinoma, Squamous Cell	0/101 (88)	0/51 (49)	0/51 (47)	1/51 (45)
		0.1965	NS	NS	0.3383
Pancreas	Adenoma, Acinar Cell	1/101 (88)	0/51 (49)	0/51 (47)	0/51 (45)
		NS	NS	NS	NS
	Adenoma, Islet Cell	8/101 (89)	1/51 (49)	5/51 (47)	2/51 (45)
		0.6945	0 9834	0.4876	0.9076
	Carcinoma, Islet Cell	0/101 (88)	1/51 (49)	0/51 (47)	0/51 (45)
		0.6157	0 3577	NS	NS
Pituitary Gland	Adenoma, Pars Distalis	29/102 (97)	13/51 (50)	15/51 (48)	8/51 (47)
		0.9409	0.7526	0.5066	0.9713
Preputial Gland	Carcinoma, Squamous Cell	0/99 (86)	0/51 (49)	1/51 (47)	0/51 (45)
		0.4053	NS	0.3534	NS
Prostate Gland	Adenocarcinoma	0/102 (89)	1/51 (49)	0/51 (47)	0/51 (45)
		0.6130	0 3551	NS	NS
Skin/Subcutis	Adenoma, Sebaceous Cell	0/102 (89)	1/51 (49)	0/51 (47)	0/51 (45)
		0.6130	0 3551	NS	NS

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	3 mg/kg/day Low (L) P - C vs. L	10 mg/kg/day Mid (M) P - C vs. M	30 mg/kg/day High (H) P - C vs. H
	Carcinoma, Basal Cell	0/102 (89)	0/51 (49)	1/51 (47)	0/51 (45)
		0.4000	NS	0.3456	NS
	Fibroma	1/102 (89)	0/51 (49)	1/51 (47)	2/51 (46)
		0.0935	NS	0.5734	0.2676
	Keratoacanthoma	3/102 (89)	1/51 (49)	3/51 (48)	4/51 (46)
		0.0694	0.8312	0.3517	0.1791
	Lipoma	2/102 (89)	1/51 (49)	2/51 (47)	0/51 (45)
		0.7682	0.7350	0.4294	NS
	Osteosarcoma	0/102 (89)	1/51 (49)	0/51 (47)	0/51 (45)
		0.6130	0 3551	NS	NS
	Papilloma, Squamous Cell	1/102 (89)	0/51 (49)	2/51 (47)	0/51 (45)
		0.5639	NS	0.2742	NS
	Rhabdomyoma	0/102 (89)	0/51 (49)	0/51 (47)	1/51 (45)
		0.1957	NS	NS	0.3358
	Schwannoma, Benign, Plexiform	0/102 (89)	0/51 (49)	1/51 (47)	0/51 (45)
		0.4000	NS	0.3456	NS
	Schwannoma, Malignant,	1/102 (89)	0/51 (49)	0/51 (47)	0/51 (45)
	Plexiform Variant	NS	NS	NS	NS
	Tumor, Hair Follicle Benign	0/102 (89)	0/51 (49)	1/51 (47)	2/51 (45)
		0.0303	NS	0.3456	0.1111
Spleen	Hemangiosarcoma	0/102 (89)	1/51 (49)	0/51 (47)	0/51 (45)
		0.6130	0 3551	NS	NS
Systemic	Lymphoblastic Malignant	0/102 (89)	0/51 (49)	0/51 (47)	1/51 (46)
	Lymphoma	0.1991	NS	NS	0.3407
	Lymphocytic Malignant	1/102 (89)	0/51 (49)	1/51 (47)	0/51 (45)
	Lymphoma	0.6410	NS	0.5734	NS
	Pleomorphic Malignant Lymphoma	3/102 (90)	0/51 (49)	0/51 (47)	1/51 (46)
		0.6102	NS	NS	0.8126
Testes	Adenoma, Leydig Cell	0/102 (89)	4/51 (49)	1/51 (47)	0/51 (45)
		0.7701	0.0146 **	0.3456	NS
Thymus	Carcinoma, Squamous Cell	0/96 (83)	0/49 (47)	1/46 (42)	0/48 (43)
		0.3953	NS	0.3360	NS
Thyroid Gland	Adenoma, C-Cell	11/102 (89)	6/51 (49)	2/51 (47)	2/51 (45)
		0.9617	0.6065	0.9740	0.9694
	Adenoma, Follicular Cell	3/102 (89)	3/51 (49)	3/51 (47)	3/51 (46)
		0.2567	0 3615	0.3419	0.3320
	Carcinoma, C-Cell	1/102 (89)	0/51 (49)	0/51 (47)	0/51 (45)
		NS	NS	NS	NS
	Carcinoma, Follicular Cell	0/102 (89)	1/51 (49)	1/51 (47)	1/51 (45)
		0.1747	0 3551	0.3456	0.3358
Zymbals Gland	Carcinoma, Sebaceous Cell	0/86 (75)	1/37 (35)	0/39 (36)	0/43 (39)
		0.5946	0 3182	NS	NS
	Carcinoma, Squamous Cell	0/86 (75)	1/37 (35)	1/39 (37)	0/43 (39)
		0.4903	0 3182	0.3304	NS

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

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

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	10 mg/kg/day Low (L) P - L vs. C	30 mg/kg/day Mid (M) P - M vs. C	100 mg/kg/day High (H) P - H vs. C
Adrenal Gland	Adenoma, C-Cell	0/102 (83)	1/51 (44)	0/51 (39)	0/51 (33)
		0.5829	0.3465	NS	NS
	Pheochromocytoma, Benign	0/102 (83)	0/51 (44)	1/51 (39)	1/51 (33)
		0.0921	NS	0.3197	0.2845
Bone	Osteosarcoma	0/102 (83)	0/51 (44)	0/51 (39)	1/51 (34)
		0.1700	NS	NS	0.2906
Brain	Tumor, Granular Cell Benign	1/102 (83)	0/51 (44)	1/51 (39)	2/51 (33)
		0.0624	NS	0.5390	0.1944
Heart	Mesothelioma, Atriocaval	0/102 (83)	0/51 (44)	0/51 (39)	1/51 (33)
		0.1658	NS	NS	0.2845
Kidneys	Tumor, Mesenchymal Malignant	1/102 (83)	0/51 (44)	0/51 (39)	0/51 (33)
		NS	NS	NS	NS
Liver	Adenoma, Hepatocellular	0/102 (83)	0/51 (44)	1/51 (39)	0/51 (33)
		0.3618	NS	0.3197	NS
Mammary Gland	Adenocarcinoma	15/100 (85)	4/50 (44)	4/46 (37)	1/47 (32)
		0.9846	0.9456	0.8935	0.9961
	Carcinoma, Adenosquamous	1/100 (82)	0/50 (43)	0/46 (37)	0/47 (32)
		NS	NS	NS	NS
	Fibroadenoma	21/100 (87)	14/50 (45)	6/46 (38)	4/47 (32)
		0.9605	0.2553	0.9022	0.9544
Mesenteric Ln	Sarcoma, Site of Primary Tumor Unknown	1/102 (83)	0/51 (44)	0/51 (39)	0/51 (33)
		NS	NS	NS	NS
Ovaries	Tumor, Granulosa Cell, Benign	3/102 (83)	0/51 (44)	1/50 (38)	0/51 (33)
		0.8535	NS	0.7837	NS
	Tumor, Sertoli Cell, Benign	1/102 (83)	0/51 (44)	0/50 (38)	0/51 (33)
		NS	NS	NS	NS
Pancreas	Adenoma, Islet Cell	1/102 (83)	1/51 (44)	0/51 (39)	0/51 (33)
		0.8273	0.5747	NS	NS
Pituitary Gland	Adenoma, Pars Distalis	58/102 (95)	13/51 (46)	15/51 (42)	9/50 (34)
		0.9990	0.9999	0.9983	0.9999
	Adenoma, Pars Intermedia	1/102 (83)	0/51 (44)	0/51 (39)	0/50 (32)
		NS	NS	NS	NS
	Carcinoma	2/102 (83)	0/51 (44)	0/51 (39)	0/50 (32)
		NS	NS	NS	NS
	Carcinoma, Invasion to Pars Intermedia	2/102 (83)	0/51 (44)	0/51 (39)	0/50 (32)
		NS	NS	NS	NS
Skin/Subcutis	Carcinoma, Basal Cell	1/102 (83)	0/51 (44)	1/51 (39)	0/51 (33)
		0.5939	NS	0.5390	NS
	Carcinoma, Squamous Cell	1/102 (83)	0/51 (44)	0/51 (39)	0/51 (33)

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	10 mg/kg/day Low (L) P - L vs. C	30 mg/kg/day Mid (M) P - M vs. C	100 mg/kg/day High (H) P - H vs. C
		NS	NS	NS	NS
	Fibroma	1/102 (83)	0/51 (44)	1/51 (39)	0/51 (33)
		0.5939	NS	0.5390	NS
	Keratoacanthoma	1/102 (83)	0/51 (44)	0/51 (39)	0/51 (33)
		NS	NS	NS	NS
	Lipoma	2/102 (83)	0/51 (44)	0/51 (39)	0/51 (33)
		NS	NS	NS	NS
	Papilloma, Squamous Cell	1/102 (83)	0/51 (44)	0/51 (39)	0/51 (33)
		NS	NS	NS	NS
Systemic	Histiocytic Sarcoma	1/102 (83)	0/51 (44)	0/51 (39)	0/51 (33)
		NS	NS	NS	NS
	Lymphocytic Malignant Lymphoma	0/102 (83)	0/51 (44)	1/51 (39)	0/51 (33)
		0.3618	NS	0.3197	NS
Thymus	Thymoma, Benign	0/101 (82)	0/49 (42)	0/49 (37)	1/50 (33)
		0.1701	NS	NS	0.2870
Thyroid Gland	Adenoma, C-Cell	6/102 (83)	4/51 (44)	5/51 (39)	4/51 (34)
		0.2268	0.4778	0.2471	0.3208
	Adenoma, Follicular Cell	3/102 (83)	0/51 (44)	1/51 (39)	1/51 (33)
		0.4804	NS	0.7908	0.7434
	Carcinoma, Follicular Cell	4/102 (83)	1/51 (44)	1/51 (39)	0/51 (33)
		0.9282	0.8858	0.8599	NS
Uterus	Adenocarcinoma, Endometrial	2/101 (82)	5/51 (45)	4/51 (39)	4/51 (33)
		0.0793	0.0534	0.0842	0.0556
	Carcinoma, Squamous Cell	0/101 (82)	1/51 (44)	0/51 (39)	0/51 (33)
		0.5859	0.3492	NS	NS
	Hemangioma	1/101 (83)	0/51 (44)	0/51 (39)	0/51 (33)
		NS	NS	NS	NS
	Leiomyosarcoma	1/101 (82)	1/51 (44)	0/51 (39)	0/51 (33)
		0.8297	0.5783	NS	NS
	Polyp, Endometrial Stromal	7/101 (82)	8/51 (44)	5/51 (40)	6/51 (35)
		0.1750	0.0977	0.3479	0.1504
	Polyp, Glandular	0/101 (82)	1/51 (45)	0/51 (39)	2/51 (33)
		0.0385	0.3543	NS	0.0805
	Comb_Polyp	7/102 (83)	9/51 (45)	5/51 (40)	7/51 (35)
		0.1054	0.0561	0.3401	0.0752
	Schwannoma, Benign	0/101 (82)	2/51 (44)	1/51 (39)	1/51 (33)
		0.2042	0.1201	0.3223	0.2870
	Schwannoma, Malignant	2/101 (82)	0/51 (44)	1/51 (39)	0/51 (33)
		0.7549	NS	0.6925	NS

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 6A: Tumor Rates and P-Values for Trend and Pairwise Comparisons with Combined Control in Male Mice

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	50 mg/kg/day Low (L) P - C vs. L	150 mg/kg/day Mid (M) P - C vs. M	400 mg/kg/day High (H) P - C vs. H

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	50 mg/kg/day Low (L) P - C vs. L	150 mg/kg/day Mid (M) P - C vs. M	400 mg/kg/day High (H) P - C vs. H
Adrenal Cortex	Adenoma: Cortical	13/119 (97)	6/60 (47)	6/60 (41)	3/59 (40)
		0.8218	0.6356	0 5203	0.9027
	Adenoma: Subcapsular Cells	3/119 (95)	0/60 (45)	0/60 (40)	2/59 (39)
		0.2391	NS	NS	0.4546
	Carcinoma	1/119 (95)	0/60 (45)	0/60 (40)	0/59 (39)
		NS	NS	NS	NS
Body Cavities	Hemangioma	0/9 (6)	0/5 (3)	1/4 (3)	0/3 (1)
		0.3077	NS	0 3333	NS
	Hemangiosarcoma	0/9 (6)	1/5 (3)	0/4 (3)	0/3 (1)
		0.5385	0.3333	NS	NS
	Osteosarcoma	1/9 (6)	0/5 (3)	0/4 (3)	0/3 (1)
		NS	NS	NS	NS
Bulboureth. Gland	Leiomyosarcoma	1/9 (6)	0/4 (2)	0/8 (4)	0/5 (3)
		NS	NS	NS	NS
Cerebrum	Malignant Schwannoma	0/120 (96)	0/60 (45)	1/60 (41)	0/60 (40)
		0.3649	NS	0 2993	NS
Epididymides	Adenoma, Leydig Cell	1/120 (96)	0/60 (45)	0/60 (40)	0/60 (40)
		NS	NS	NS	NS
	Hemangiosarcoma	0/120 (96)	0/60 (45)	0/60 (40)	2/60 (41)
		0.0334	NS	NS	0.0880
Femur Marrow	Hemangioma	0/119 (95)	1/60 (45)	0/60 (40)	0/60 (40)
		0.5682	0.3214	NS	NS
Gallbladder	Carcinoma	0/120 (96)	1/59 (45)	0/60 (40)	0/60 (40)
		0.5656	0.3191	NS	NS
Harderian Gland	Adenocarcinoma, Tubular,	0/118 (94)	2/60 (45)	0/60 (40)	1/59 (40)
	Squamous Differentiation	0.2564	0.1032	NS	0.2985
	Adenoma	16/118 (98)	5/60 (46)	4/60 (40)	3/59 (40)
		0.9232	0.8697	0.8929	0.9561
Heart	Hemangiosarcoma	0/120 (96)	0/60 (45)	0/60 (40)	1/59 (40)
		0.1810	NS	NS	0.2941
Ileum	Hemangiosarcoma	0/120 (96)	0/60 (45)	1/60 (40)	0/60 (40)
		0.3620	NS	0 2941	NS
Jejunum	Adenoma	0/120 (96)	0/60 (45)	1/60 (40)	0/60 (40)
		0.3620	NS	0 2941	NS
Kidneys	Tubular Adenoma	2/120 (96)	1/60 (45)	0/60 (40)	0/60 (40)
		0.9195	0.6876	NS	NS
	Tubular Carcinoma	0/120 (96)	0/60 (45)	1/60 (40)	1/60 (40)
		0.0979	NS	0 2941	0.2941
Liver	Hemangioma	1/120 (96)	2/60 (45)	4/60 (41)	2/60 (41)
		0.1410	0.2389	0.0280	0.2132
	Hemangiosarcoma	0/120 (96)	4/60 (46)	5/60 (41)	4/60 (41)
		0.0245*	0.0101**	0.0020**	0.0072**
	Hepatocellular Adenoma	13/120 (96)	6/60 (45)	7/60 (41)	1/60 (40)

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	50 mg/kg/day Low (L) P - C vs. L	150 mg/kg/day Mid (M) P - C vs. M	400 mg/kg/day High (H) P - C vs. H
		0.9654	0.6084	0 3841	0.9944
	Hepatocellular Carcinoma	12/120 (98)	3/60 (46)	5/60 (41)	5/60 (41)
		0.4160	0.9151	0.6036	0.6036
Lung	Alveolar/Bronchial Adenoma	7/120 (97)	5/60 (46)	4/60 (41)	6/60 (41)
		0.1166	0.3306	0.4215	0.1483
	Alveolar/Bronchiolar	23/120 (98)	8/60 (47)	8/60 (43)	12/60 (44)
	Adenocarcinoma	0.2687	0.8658	0.8046	0.3867
Mammary Gland	Adenocarcinoma	0/119 (96)	1/57 (45)	0/57 (39)	0/58 (40)
		0.5636	0.3191	NS	NS
Mandibular Gland	Adenocarcinoma	0/120 (96)	0/60 (45)	1/60 (40)	0/60 (40)
		0.3620	NS	0 2941	NS
Mesenteric Ln	Hemangioma	1/115 (94)	1/59 (45)	1/60 (40)	0/58 (39)
		0.6402	0.5443	0 5095	NS
	Hemangiosarcoma	1/115 (94)	0/59 (45)	0/60 (40)	0/58 (39)
		NS	NS	NS	NS
Pancreas	Hemangiosarcoma	0/119 (95)	0/59 (44)	0/60 (40)	1/59 (40)
		0.1826	NS	NS	0.2963
	Islet Cell Adenoma	1/119 (95)	0/59 (44)	0/60 (40)	0/59 (40)
		NS	NS	NS	NS
Parathyroid Gland	Adenocarcinoma	0/88 (71)	0/42 (33)	0/41 (29)	1/36 (24)
		0.1529	NS	NS	0.2526
Pituitary Gland	Ganglioneuroma	0/117 (93)	0/59 (44)	0/59 (39)	1/59 (41)
		0.1889	NS	NS	0.3060
Prostate Gland	Adenocarcinoma	0/118 (94)	0/59 (44)	1/60 (40)	0/60 (40)
		0.3670	NS	0 2985	NS
Rectum	Polyp	0/119 (95)	1/60 (45)	0/60 (40)	0/59 (39)
		0.5662	0.3214	NS	NS
Seminal Ves	Adenoma	1/120 (96)	0/60 (45)	0/60 (40)	0/60 (40)
		NS	NS	NS	NS
Skeletal Muscle	Hemangiosarcoma	0/120 (96)	0/60 (45)	0/60 (40)	1/60 (40)
		0.1810	NS	NS	0.2941
Skin/Subcutis	Fibrosarcoma	0/120 (96)	0/60 (45)	0/60 (40)	1/60 (41)
		0.1847	NS	NS	0.2993
	Hemangioma	1/120 (96)	0/60 (45)	0/60 (40)	0/60 (40)
		NS	NS	NS	NS
	Hibernoma	1/120 (97)	0/60 (45)	0/60 (40)	0/60 (40)
		NS	NS	NS	NS
	Malignant Schwannoma	0/120 (96)	0/60 (45)	0/60 (40)	2/60 (42)
		0.0348	NS	NS	0.0911
	Osteosarcoma	0/120 (96)	1/60 (46)	0/60 (40)	0/60 (40)
		0.5676	0.3239	NS	NS
	Papilloma	0/120 (96)	0/60 (45)	0/60 (40)	1/60 (41)
		0.1847	NS	NS	0.2993

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	50 mg/kg/day Low (L) P - C vs. L	150 mg/kg/day Mid (M) P - C vs. M	400 mg/kg/day High (H) P - C vs. H
Spleen	Hemangioma	1/120 (96)	0/60 (45)	0/60 (40)	0/60 (40)
		NS	NS	NS	NS
	Hemangiosarcoma	2/120 (96)	3/60 (46)	0/60 (40)	2/60 (41)
		0.3369	0.1925	NS	0.3463
Sternum Marrow	Hemangioma	0/120 (96)	0/60 (45)	0/60 (40)	1/60 (40)
		0.1810	NS	NS	0.2941
Stomach	Adenocarcinoma	1/120 (96)	0/60 (45)	0/60 (40)	0/60 (40)
		NS	NS	NS	NS
	Hemangiosarcoma	0/120 (96)	0/60 (45)	1/60 (40)	0/60 (40)
		0.3620	NS	0 2941	NS
	Leiomyosarcoma	1/120 (96)	0/60 (45)	0/60 (40)	0/60 (40)
		NS	NS	NS	NS
Systemic	Histiocytic Sarcoma	1/120 (96)	0/60 (45)	0/60 (40)	0/60 (40)
		NS	NS	NS	NS
	Malignant Lymphoma	21/120 (103)	15/60 (50)	10/60 (43)	11/60 (45)
		0.3936	0.1337	0.4281	0.3638
Testes	Hemangioma	2/120 (96)	0/60 (45)	0/60 (40)	0/60 (40)
		NS	NS	NS	NS
	Hemangiosarcoma	0/120 (96)	0/60 (45)	0/60 (40)	1/60 (40)
		0.1810	NS	NS	0.2941
	Leydig Cell Adenoma	6/120 (96)	6/60 (45)	1/60 (40)	1/60 (40)
		0.9150	0.1404	0 9183	0.9183
	Leydig Cell Carcinoma	1/120 (96)	0/60 (45)	0/60 (40)	0/60 (40)
		NS	NS	NS	NS
Thymus	Hemangioma	0/111 (90)	1/58 (43)	0/57 (38)	0/54 (35)
		0.5631	0.3233	NS	NS
Thyroid Gland	Follicular Adenoma	1/120 (96)	0/60 (45)	0/60 (40)	0/59 (40)
		NS	NS	NS	NS
	Follicular Carcinoma	0/120 (96)	0/60 (45)	1/60 (40)	0/59 (40)
		0.3620	NS	0 2941	NS
Tongue	Hemangioma	0/120 (96)	1/60 (45)	0/60 (40)	0/60 (40)
		0.5656	0.3191	NS	NS
Urinary Bladder	Mesenchymal Tumor, Benign	0/119 (96)	0/60 (45)	1/60 (40)	0/60 (40)
		0.3620	NS	0 2941	NS
Whole body	Hemangioma	6/120 (96)	6/60 (45)	6/60 (41)	3/60 (41)
		0.4611	0.1404	0 1064	0.5392
	Hemangiosarcoma	3/120 (96)	8/60 (47)	8/60 (43)	13/60 (44)
		0.0001*	0.0060**	0.0038**	0.0000**
	Hemangioma/	9/120 (96)	14/60 (47)	14/60 (44)	15/60 (44)
	Hemangiosarcoma	0.0021**	0.0025**	0.0014**	0.0006**

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	50 mg/kg/day Low (L) P - C vs. L	150 mg/kg/day Mid (M) P - C vs. M	400 mg/kg/day High (H) P - C vs. H

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

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

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

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	30 mg/kg/day Low (L) P - C vs. L	100 mg/kg/day Mid (M) P - C vs. M	300 mg/kg/day High (H) P - C vs. H
Adrenal Cortex	Adenoma: Subcapsular Cells	1/119 (67)	0/60 (40)	1/59 (37)	0/60 (36)
		0.6480	NS	0.5872	NS
Adrenal Medulla	Pheochromocytoma Malignant	1/115 (67)	0/57 (39)	0/58 (36)	0/58 (36)
		NS	NS	NS	NS
Bone	Chondro-Osteosarcoma	0/4 (3)	0/2 (1)	1/2 (2)	0/2 (1)
		0.4286	NS	0.4000	NS
	Chondroma	2/4 (4)	0/2 (1)	1/2 (1)	0/2 (1)
		0.7143	NS	0.6000	NS
Cervix	Leiomyosarcoma	0/120 (67)	0/60 (40)	1/60 (37)	0/60 (36)
		0.4056	NS	0.3558	NS
Harderian Gl	Adenocarcinoma, Tubular, Squamous Differentiation	1/120 (67)	0/60 (40)	0/60 (37)	1/60 (36)
		0 3609	NS	NS	0.5791
	Adenoma	1/120 (67)	4/60 (41)	1/60 (37)	2/60 (37)
		0 3490	0.0676	0.5872	0.2877
Kidneys	Urothelial Carcinoma	1/120 (67)	0/60 (40)	0/60 (37)	0/60 (36)
		NS	NS	NS	NS
Liver	Hemangioma	0/120 (67)	0/60 (40)	2/60 (37)	1/60 (36)
		0 1275	NS	0.1243	0.3495
	Hemangiosarcoma	0/120 (67)	0/60 (40)	0/60 (37)	3/60 (38)
		0.0085*	NS	NS	0.0450**
	Hepatocellular Adenoma	0/120 (67)	0/60 (40)	0/60 (37)	2/60 (37)
		0.0409	NS	NS	0.1243
	Hepatocellular Carcinoma	0/120 (67)	0/60 (40)	0/60 (37)	1/60 (37)
		0 2044	NS	NS	0.3558
Lung	Alveolar/Bronchial Adenoma	4/120 (68)	4/60 (40)	4/60 (38)	3/60 (37)
		0.4029	0.3338	0.3066	0.4745
	Alveolar/Bronchiolar Adenocarcinoma	8/120 (68)	6/60 (42)	6/60 (39)	8/60 (40)
		0 1337	0.4569	0.3994	0.1878
Lymph Nodes	Fibrosarcoma	1/41 (20)	0/13 (6)	0/13 (6)	0/9 (6)
		NS	NS	NS	NS
Mammary Gland	Adenoacanthoma	2/118 (67)	0/58 (39)	0/56 (36)	0/59 (36)
		NS	NS	NS	NS

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	30 mg/kg/day Low (L) P - C vs. L	100 mg/kg/day Mid (M) P - C vs. M	300 mg/kg/day High (H) P - C vs. H
	Adenocarcinoma	8/118 (70)	4/58 (41)	1/56 (36)	1/59 (37)
		0 9684	0.7165	0.9802	0.9819
	Adenoma	2/118 (67)	1/58 (40)	0/56 (36)	0/59 (36)
		0 9490	0.7586	NS	NS
Mesenteric Ln	Hemangioma	0/118 (66)	0/58 (38)	1/58 (36)	0/58 (36)
		0.4091	NS	0.3529	NS
	Hemangiosarcoma	1/118 (66)	0/58 (38)	0/58 (36)	0/58 (36)
		NS	NS	NS	NS
Ovaries	Cystadenoma	1/120 (67)	0/59 (39)	0/60 (37)	3/59 (37)
		0.0278	NS	NS	0.1276
	Granulosa Cell Tumor, Benign	2/120 (67)	1/59 (39)	0/60 (37)	1/59 (36)
		0 5634	0.7517	NS	0.7291
	Granulosa Cell Tumor, Malignant	0/120 (67)	0/59 (39)	0/60 (37)	1/59 (37)
		0 2056	NS	NS	0.3558
	Hemangioma	0/120 (67)	2/59 (39)	2/60 (38)	0/59 (36)
		0.6291	0.1332	0.1288	NS
	Hemangiosarcoma	1/120 (67)	0/59 (39)	0/60 (37)	0/59 (36)
		NS	NS	NS	NS
	Luteoma	1/120 (67)	0/59 (39)	2/60 (37)	1/59 (36)
		0 2490	NS	0.2877	0.5791
	Sertoli Cell Tumor Benign	1/120 (67)	0/59 (39)	0/60 (37)	0/59 (36)
		NS	NS	NS	NS
Pancreas	Exocrine Carcinoma	1/120 (67)	0/60 (40)	0/60 (37)	0/60 (36)
		NS	NS	NS	NS
	Islet Cell Adenoma	1/120 (67)	0/60 (40)	0/60 (37)	0/60 (36)
		NS	NS	NS	NS
	Malignant Schwannoma	0/120 (67)	0/60 (40)	0/60 (37)	1/60 (37)
		0 2044	NS	NS	0.3558
Parathyroid Gland	Adenocarcinoma	0/99 (55)	1/47 (29)	0/41 (24)	0/49 (30)
		0.6014	0.3452	NS	NS
Pituitary Gland	Adenoma: Pars Anterior	2/119 (67)	1/60 (40)	6/58 (38)	0/60 (36)
		0.6687	0.7586	0.0251	NS
Skeletal Muscle	Malignant Schwannoma	1/120 (67)	0/60 (40)	0/60 (37)	0/60 (36)
		NS	NS	NS	NS
Skin/Subcutis	Fibrosarcoma	1/120 (67)	1/59 (39)	1/60 (37)	2/60 (38)
		0 1561	0.6027	0.5872	0.2963
	Hemangiosarcoma	0/120 (67)	0/59 (39)	0/60 (37)	1/60 (37)
		0 2056	NS	NS	0.3558
	Histiocytic Sarcoma	1/120 (67)	0/59 (39)	0/60 (37)	0/60 (36)
		NS	NS	NS	NS
	Lipoma	0/120 (67)	0/59 (39)	0/60 (37)	1/60 (37)
		0 2056	NS	NS	0.3558
	Sarcoma Nos	0/120 (67)	0/59 (39)	1/60 (37)	1/60 (37)
		0 1263	NS	0.3558	0.3558
	Squamous Carcinoma	1/120 (67)	1/59 (39)	0/60 (37)	0/60 (36)
		0.8612	0.6027	NS	NS
Spleen	Hemangioma	1/120 (67)	0/60 (40)	0/60 (37)	1/60 (37)
		0 3680	NS	NS	0.5872

Organ name	Tumor name	0 mg/kg/day Comb. Control (C) P - Trend	30 mg/kg/day Low (L) P - C vs. L	100 mg/kg/day Mid (M) P - C vs. M	300 mg/kg/day High (H) P - C vs. H
	Hemangiosarcoma	0/120 (67)	0/60 (40)	0/60 (37)	2/60 (37)
		0.0409	NS	NS	0.1243
Stomach	Adenocarcinoma	0/120 (67)	0/60 (40)	0/60 (37)	1/60 (36)
		0 2000	NS	NS	0.3495
	Papilloma	0/120 (67)	1/60 (40)	0/60 (37)	0/60 (36)
		0.6278	0.3738	NS	NS
Systemic	Histiocytic Sarcoma	7/120 (70)	3/60 (41)	3/60 (39)	0/60 (36)
		0 9811	0.7904	0.7671	NS
	Malignant Lymphoma	73/120 (97)	32/60 (53)	33/60 (49)	32/60 (48)
		0.7397	0.9808	0.8859	0.9000
Thyroid Gland	Follicular Adenoma	0/120 (67)	0/59 (39)	0/60 (37)	1/60 (36)
		0 2011	NS	NS	0.3495
	Follicular Carcinoma	2/120 (67)	0/59 (39)	0/60 (37)	0/60 (36)
		NS	NS	NS	NS
Uterus	Adenocarcinoma	1/120 (67)	0/60 (40)	0/60 (37)	0/60 (36)
		NS	NS	NS	NS
	Hemangioma	0/120 (67)	3/60 (42)	3/60 (38)	0/60 (36)
		0.6868	0.0547	0.0450**	NS
	Hemangiosarcoma	1/120 (67)	1/60 (40)	0/60 (37)	7/60 (40)
		0.0003*	0.6101	NS	0.0041**
	Leiomyoma	2/120 (67)	0/60 (40)	0/60 (37)	0/60 (36)
		NS	NS	NS	NS
	Leiomyosarcoma	5/120 (68)	0/60 (40)	2/60 (37)	4/60 (38)
		0 1326	NS	0.7795	0.4107
	Malignant Schwannoma	0/120 (67)	0/60 (40)	0/60 (37)	1/60 (37)
		0 2044	NS	NS	0.3558
	Polyp	7/120 (70)	4/60 (41)	3/60 (37)	4/60 (39)
		0.4790	0.6357	0.7413	0.6036
	Stromal Sarcoma	4/120 (67)	0/60 (40)	0/60 (37)	1/60 (36)
		0.7116	NS	NS	0.8897
Vagina	Leiomyoma	1/120 (67)	0/60 (40)	0/60 (37)	0/60 (36)
		NS	NS	NS	NS
	Polyp	0/120 (67)	0/60 (40)	0/60 (37)	1/60 (37)
		0 2044	NS	NS	0.3558
Whole body	Hemangioma	1/120 (67)	5/60 (42)	7/60 (39)	2/60 (37)
		0 3734	0.0307	0.0036**	0.2877
	Hemangiosarcoma	4/120 (68)	1/60 (40)	0/60 (37)	13/60 (43)
		0.0000*	0.9065	1.0000	0.0007**
	Hemangioma/	4/120 (68)	6/60 (42)	7/60 (39)	14/60 (43)
	Hemangiosarcoma	0.0003*	0.1263	0.0521	0.0003**

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

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

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

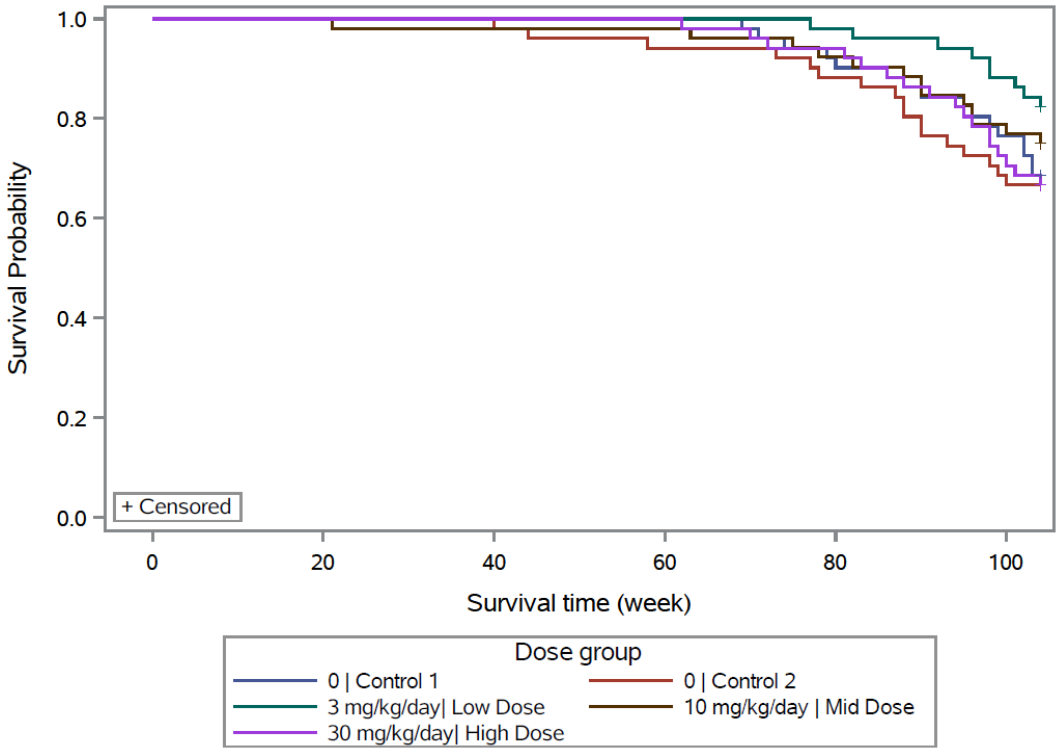


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

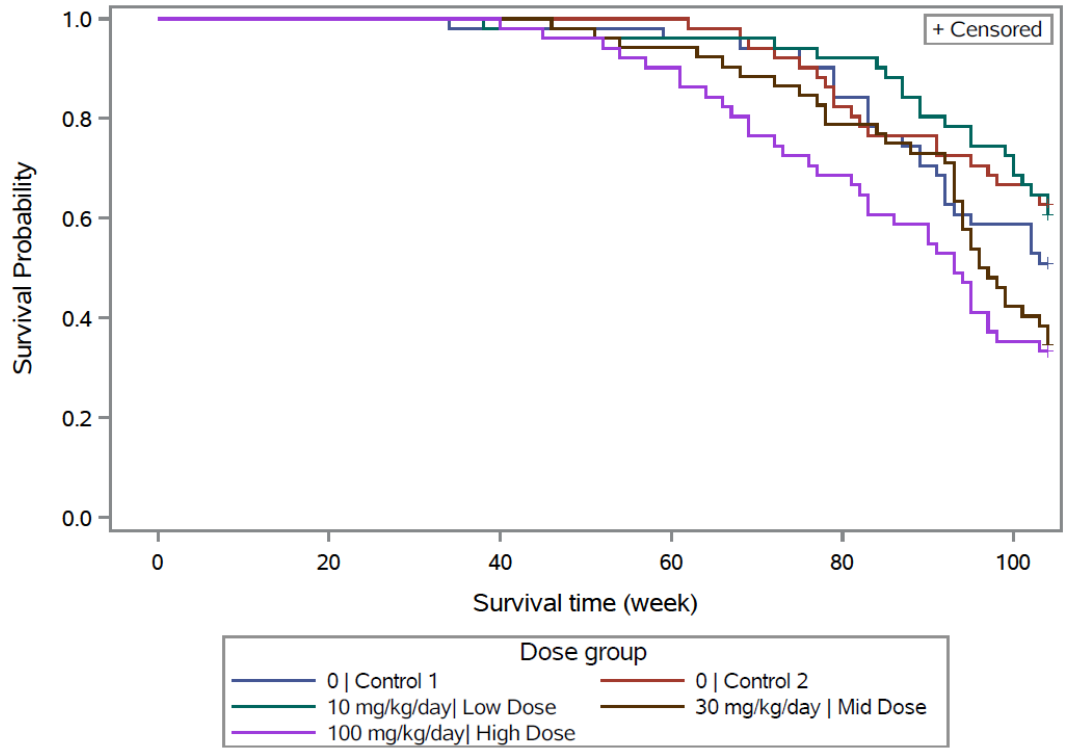


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

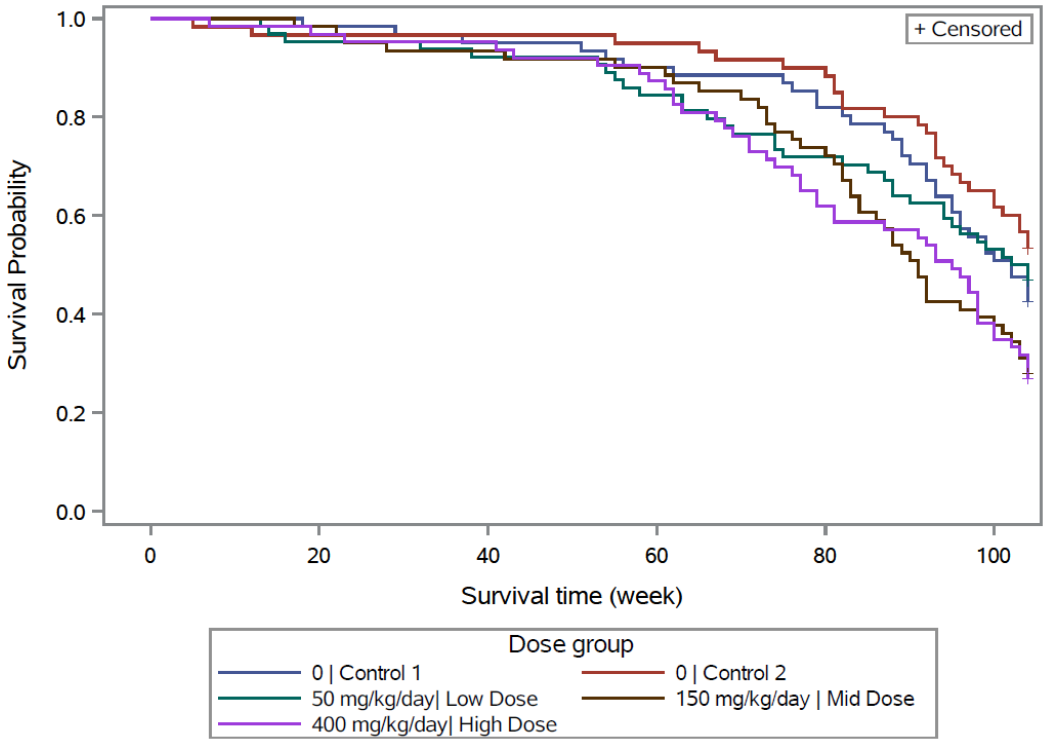
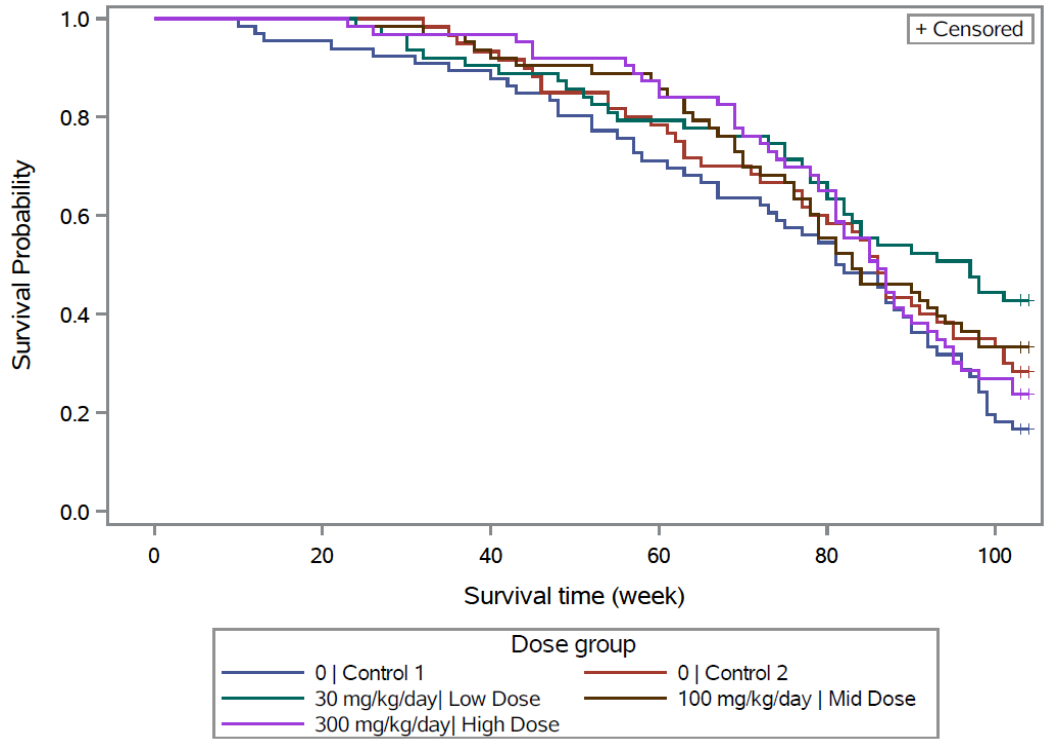


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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/s/

FENG ZHOU
02/12/2021 10:27:10 AM
This is the updated version for the Carci Stats review which checked in on 11/18/2020. Just updated the product name.

KARL K LIN
02/12/2021 02:31:11 PM
The final report was checked into DARRTS on 11/18/2020. The same report is checked into DARRTS second time on 2/12/2021 due to the drug name update.

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 213498
Drug Name:	Ponesimod
Indication(s):	Relapsing Forms of Multiple Sclerosis
Applicant:	Janssen Pharmaceuticals Inc.
Date(s):	Submission date: 3/18/2020
	PDUFA Date: 3/18/2021
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiang Ling, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader
	James Hung, Ph.D., Director
Medical Division:	Division of Neurology 2
Clinical Team:	David Jones, M.D., Clinical reviewer
	Paul Lee, M.D., Clinical Team Leader
Project Manager:	Kristen Haslam

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

The data overall provided adequate evidence to support for the efficacy of ponesimod as treatment of subjects with relapsing multiple sclerosis.

In the pivotal study B301, treatment with ponesimod 20 mg resulted in statistically significantly effect on relapses, fatigue symptom and MRI lesion accumulation, compared to teriflunomide 14 mg. Statistical significance was not achieved for Confirmed Disability Accumulation (CDA) endpoints although ponesimod group had numerically fewer subjects with disability accumulation.

2 INTRODUCTION

2.1 Overview

Ponesimod is an orally active, selective modulator of the Sphingosphine-1 phosphate (S1P) receptor for the intended treatment of subjects with relapsing multiple sclerosis (MS). Ponesimod was developed under IND 101722. Studies contributing to the evaluation of the efficacy of ponesimod (Table 1) include a pivotal Phase 3 active-controlled superiority study B301, with supportive results from a Phase 2b placebo-controlled dose-finding study B201. In study B201, 3 doses of ponesimod (10 mg, 20 mg, and 40 mg) were compared to placebo on the primary outcome of cumulative number of new Gd+ T1 lesions over Weeks 12, 16, 20, and 24 after study drug initiation. The B301 study evaluated the efficacy and safety of ponesimod 20 mg versus teriflunomide 14 mg, with Annualized Relapse Rate (ARR) as primary endpoint over a 108-week treatment period.

Table 1. Phase 2 and Phase 3 Studies Supporting the Efficacy of Subjects with Relapsing Multiple Sclerosis

Study ID (Status)	Study Description	Study Treatments	Number of Subjects
Phase 3 Studies			
AC-058B301 (completed)	Multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study designed to compare the efficacy and safety and tolerability of ponesimod versus teriflunomide in subjects with RMS	Ponesimod 20 mg qd Teriflunomide 14 mg qd Treatment duration: 108 weeks	Randomized: 1133 subjects (1131 treated): 567 to ponesimod 20 mg 566 to teriflunomide 14 mg
Phase 2 Studies			
AC-058B201 (completed)	Multicenter, double-blind, randomized, 4-arm, parallel-group, dose-finding, placebo-controlled superiority study to evaluate efficacy, safety, and tolerability of ponesimod in subjects with RRMS	Ponesimod 10 mg qd Ponesimod 20 mg qd Ponesimod 40 mg qd Placebo qd Treatment duration: 24 weeks	Randomized: 464 subjects (462 treated): 108 to 10 mg ponesimod; 116 to 20 mg ponesimod; 119 to 40 mg ponesimod; 121 to placebo

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directories: \\CDSESUB1\evsprod\NDA213498\0001.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 301 was initiated on April 27, 2015 and completed on May 16, 2019. The original SAP was dated December 11, 2018 and updated on June 20, 2019. The original protocol was issued on January 6, 2015 and the final protocol was dated December 5, 2018.

Study Design
The study was a multicenter, randomized, double-blind, active-controlled, parallel-group, Phase 3 study in adult subjects with relapsing forms of MS. A total of 1133 subjects were randomized in a 1:1 ratio to two groups: ponesimod 20 mg or teriflunomide 14 mg, stratified by use of multiple sclerosis (MS) disease-modifying treatment (DMT) in the last two years prior to randomization (yes, no) and by baseline Expanded Disability Status Scale (EDSS) score (≤ 3.5, > 3.5). Neurological evaluations were performed at baseline and every 12 weeks as well as at the time of a suspected relapse. Brain Magnetic Resonance Imagings (MRIs) were performed at baseline and at Weeks 60 and 108.

Efficacy Endpoint
The primary endpoint was Annualized Relapse Rate (ARR) up to end of study (EOS), defined as the number of confirmed relapses per subject-year. A relapse was confirmed by the treating neurologist only when the subjects' symptoms were accompanied by an increase in EDSS and Functional System (FS) scores, obtained by the efficacy assessor.

The secondary efficacy variables were as follows:

- Change from baseline to Week 108 in fatigue-related symptoms as measured by the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS) symptoms score, normalized to a 0 to 100 scale (higher score implies greater fatigue).
- Cumulative number of combined unique active lesions (CUAL).
- Time to 12-week Confirmed Disability Accumulation (CDA) up to EOS.
- Time to 24-week CDA

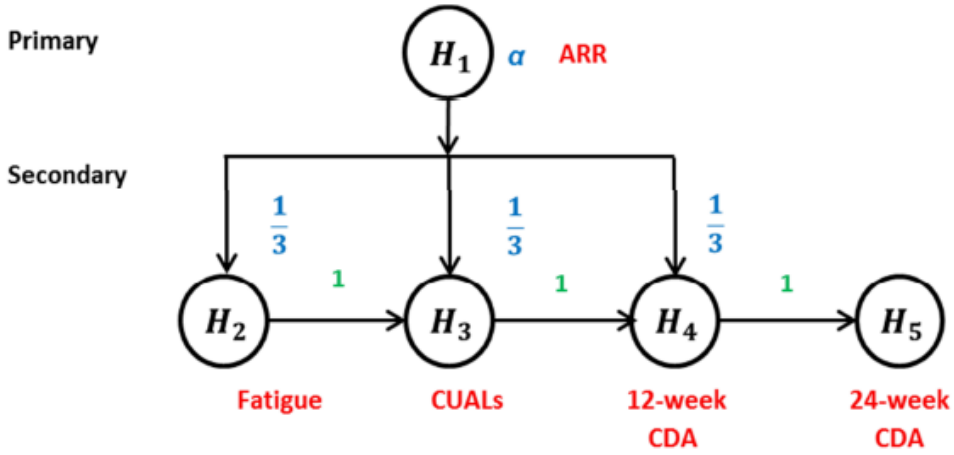
3.2.2 Statistical Methodologies

Analysis Population
The main efficacy analyses were based on the Full Analysis Set (FAS) which included all randomized subjects.

Statistical Testing Procedures

The testing strategy started with testing the primary endpoint at full alpha, followed hierarchically by a fallback type procedure for the secondary endpoints. If the primary endpoint null hypothesis was rejected, the alpha would be split evenly (1/3 of alpha) among the following 3 secondary endpoints: Fatigue, CUALs and 12-week CDA. If a secondary endpoint listed as part of the fallback procedure above was successful, the preserved alpha in the sequence was passed along to the next secondary endpoint in the sequence and the summed alpha was used for testing that endpoint. In a last step, the secondary endpoint of 24-week CDA was tested with the remaining alpha if the endpoint of 12-week CDA was successful.

Figure 1. Multiple testing procedure



Analysis Method

Annualized Relapse Rate (ARR)

The primary statistical analysis was performed based on the FAS using a negative binomial (NB) regression model for confirmed relapses up to EOS, with treatment as a factor and the binary stratification variables (EDSS ≤3.5 versus EDSS >3.5; DMT within last 2 years prior to randomization [Yes/No]) and the number of relapses in the year prior to study entry (categories ≤1 [or missing, in order to avoid excluding subjects from the analysis] and ≥2) included in the model. The model also included an offset variable defined as the log of time on study (in years) from randomization up to EOS.

Various sensitivity analyses were planned as follows:

1. Covariate adjustment
   - ARR based on confirmed relapses up to EOS on the FAS - unadjusted analysis.
   - ARR based on confirmed relapses up to EOS including stratification variables derived from eCRF.
2. Missing data
   - Missing at random (MAR) MI approach: Under this approach, the rate after withdrawal for each treatment arm was assumed to be the rate in the respective arm before withdrawal.

- Reference-based MI approaches: The rate in the reference (teriflunomide 14 mg) arm was used for imputation in both the ponesimod and teriflunomide arms.
- Delta adjustment MI approach: the rate after withdrawal was multiplied by δ_P, ranging from 1 (MAR, i.e. same rate as prior to withdrawal) to 3.1 (~tripling of relapse rate) in steps of 0.3 for the ponesimod arm, and by δ_T, ranging from 0.1 (relapse rate reduced by 90%) over 1 to 3.1 in steps of 0.3 for the teriflunomide arm.

Additional supplementary analyses were conducted, including

- ARR up to end-of-treatment (EOT)+7 days for confirmed relapses on the FAS.
- ARR based on confirmed relapses up to EOS - Per- protocol analysis.
- ARR based on all relapses up to EOS on the FAS.
- ARR based on confirmed relapses up to the start of new MS DMTs on the FAS.
- ARR up to EOS for imputed confirmed relapses.
- ARR post EOT+7 days following premature treatment discontinuation.
- ARR by time period.

Change from Baseline in FSIQ-RMS Weekly Symptoms Score (Fatigue) to Week 108

FSIQ-RMS score was analyzed using a mixed effect model repeated measures (MMRM) which includes baseline and the two stratification factors as covariates, treatment, visit, treatment by visit interaction, and baseline by visit interaction. An unstructured co-variance structure was used to model within patient errors. The Kenwood Roger approximation was used to estimate denominator degree of freedom and adjusted standard errors.

Cumulative Number of Combined Unique Active Lesions (CUAL)

CUALs were new Gd+ T1 lesions plus new or enlarging T2 lesions, based on all available MRI scans up to the Week 108 visit (or EOS if missing). CUAL was analyzed using a negative binomial regression model with treatment, the binary stratification variables and Gd+ T1 lesions at baseline (absent or present) included in the model. The log-transformed time up to the last post-baseline MRI was used as an offset in the model.

Confirmed Disability Accumulation

The EDSS is a disability scale that ranges from 0 (normal) to 10.0 (death) in 0.5-point steps (1-point step from 0 to 1). The following criteria for an increase in EDSS in derivation of disability accumulation apply:

- Increase of at least 1.5 in EDSS for subjects with a baseline EDSS score of 0;
- Increase of at least 1.0 in EDSS for subjects with a baseline EDSS score of 1.0 to 5.0;
- Increase of at least 0.5 in EDSS for subjects with a baseline EDSS score ≥ 5.5;

A 12-week CDA was an increase in EDSS as compared to baseline according to the criteria above which was confirmed at a scheduled visit after 12 weeks. The increase needed to be persistent at all EDSS assessments (scheduled or unscheduled) between onset and confirmation. Disability progression could only be confirmed at a scheduled visit, outside of an ongoing relapse. In this context, relapse duration was defined as period between start date (inclusive) and end date (exclusive) if available and limited to 90 days from onset if end date was not available

or duration was longer than 90 days. Death due to MS was counted as CDA. Analogously, a 24-week CDA was defined as an increase from baseline in EDSS sustained for at least 24 weeks.

The main analysis of Time to 12-Week CDA up to EOS were performed using a stratified log-rank test with stratification factors (EDSS ≤ 3.5 versus EDSS > 3.5; DMT within last 2 years prior to randomization [Yes/No]) as stratification variables.

Subjects who did not have CDA were censored. Censoring time was the date of last EDSS assessment without an EDSS increase. Subjects without post-baseline assessment were censored on randomization date. Similarly, subjects without CDA who had only EDSS assessments with an EDSS increase that could not be confirmed, were censored on randomization date. Alternatively, in a sensitivity analysis, subjects without CDA were censored at their last scheduled EDSS assessment minus 12 weeks as the onset of CDA could only occur 12 weeks prior to the last scheduled assessment. Additional analysis was conducted in which all subjects with an EDSS increase at the last EDSS assessment in the study were considered as having a potential 12-week CDA, although the confirmation was missing.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 1133 subjects were randomized to either ponesimod (N=567) or teriflunomide (N=566) at 162 centers in 28 countries in North America, Eastern and Western Europe, and Pacific region. Of those randomized, 2 subjects in the ponesimod group did not receive any dose of study treatment. Overall treatment and study discontinuations were balanced across the two treatment groups, with 83.3% of subjects completing treatment and 86.9% completing study (Table 2).

Table 2. Subject Disposition

	Ponesimod n (%)	Teriflunomide n (%)	Total n (%)
Subjects randomized	567 (100)	566 (100)	1133 (100)
Subjects treated	565 (99.6)	566 (100)	1131 (99.8)
Subjects completed treatment	471 (83.1)	473 (83.6)	944 (83.3)
Subjects completed study	490 (86.4)	495 (87.5)	985 (86.9)
Subjects completed treatment and study	465 (82.0)	465 (82.2)	930 (82.1)
Subjects who discontinued from the study	77 (13.6)	71 (12.5)	148 (13.1)
Subject decision	54 (9.5)	60 (10.6)	114 (10.1)
Withdrawal of consent	41 (7.2)	36 (6.4)	77 (6.8)
Efficacy related	3 (0.5)	10 (1.8)	13 (1.1)
Other	10 (1.8)	14 (2.5)	24 (2.1)
Physician decision	21 (3.7)	6 (1.1)	27 (2.4)
Adverse event	13 (2.3)	3 (0.5)	16 (1.4)
Other	8 (1.4)	3 (0.5)	11 (1.0)
Lost to follow-up	2 (0.4)	3 (0.5)	5 (0.4)
Death	0	2 (0.4)	2 (0.2)

Source: CSR Table T_DS_02_SC & T_DS_04_F.

The demographic characteristics were comparable between the two treatment groups. Overall, majority of the study population was White (97%) and female (65%). The mean age at baseline was 37 years (Table 3).

Table 3. Demography

	Ponesimod N=567	Teriflunomide N=566	Total N=1133
Sex [n (%)]			
n	567	566	1133
Male	204 (36.0)	194 (34.3)	398 (35.1)
Female	363 (64.0)	372 (65.7)	735 (64.9)
Age (years)			
n	567	566	1133
Mean	36.7	36.8	36.7
SD	8.74	8.74	8.74
Race [n (%)]			
n	567	566	1133
American Indian or Alaska Native	0	1 (0.2)	1 (0.1)
Asian	0	0	0
Black or African American	3 (0.5)	2 (0.4)	5 (0.4)
Native Hawaiian or Other Pacific Islander	0	0	0
White	551 (97.2)	553 (97.7)	1104 (97.4)
Other	5 (0.9)	2 (0.4)	7 (0.6)
Not applicable	8 (1.4)	8 (1.4)	16 (1.4)
Geographical region of enrolling site [n(%)]			
European Union (EU) + UK	289 (51.0)	284 (50.2)	573 (50.6)
Europe Non-EU + Russia	233 (41.1)	239 (42.2)	472 (41.7)
North America	32 (5.6)	24 (4.2)	56 (4.9)
Rest of World	13 (2.3)	19 (3.4)	32 (2.8)

Source: CSR Table 5.

The baseline disease characteristics were generally balanced between the two treatment groups. The study population mostly included RRMS subjects (97%). Mean time since first MS symptoms was 7.6 years and the mean baseline EDSS score was 2.6. The mean number of relapses in the previous year was 1.3 (Table 4).

Table 4. Baseline Disease Characteristics

	Ponesimod N=567	Teriflunomide N=566	Total N=1133
Baseline EDSS			
n	567	566	1133
Mean	2.57	2.56	2.56
SD	1.174	1.229	1.201
Median	2.50	2.50	2.50
Q1, Q3	1.50, 3.50	1.50, 3.50	1.50, 3.50
Min, Max	0.0, 5.5	0.0, 5.5	0.0, 5.5
Time since first symptoms (years)			
n	567	566	1133
Mean	7.63	7.65	7.64
SD	6.781	6.782	6.779
Median	5.84	5.70	5.77
Q1, Q3	2.40, 10.97	2.24, 11.03	2.32, 11.01
Min, Max	0.2, 40.8	0.2, 30.8	0.2, 40.8
Time since most recent relapse (months)			
n	562	557	1119
Mean	5.41	5.04	5.23
SD	4.005	3.719	3.868
Median	4.47	4.07	4.27
Q1, Q3	2.56, 7.33	2.10, 7.13	2.37, 7.26
Min, Max	0.2, 44.9	0.3, 26.2	0.2, 44.9
Number of relapses in last year prior to study entry			
n	567	565	1132
Mean	1.2	1.3	1.3
SD	0.61	0.65	0.63
Median	1.0	1.0	1.0
Q1, Q3	1.0, 1.0	1.0, 2.0	1.0, 1.0
Min, Max	0, 4	0, 5	0, 5
Multiple sclerosis subtype [n (%)]			
n	567	566	1133
RRMS	552 (97.4)	552 (97.5)	1104 (97.4)
SPMS	15 (2.6)	14 (2.5)	29 (2.6)
Any MS disease-modifying treatment received within 2 years prior to randomization [n (%)]			
n	567	566	1133
Yes	213 (37.6)	211 (37.3)	424 (37.4)
No	354 (62.4)	355 (62.7)	709 (62.6)
Highly active disease [n (%)]			
n	567	566	1133
Yes	202 (35.6)	200 (35.3)	402 (35.5)
No	365 (64.4)	366 (64.7)	731 (64.5)

Source: CSR Table 6.

3.2.4 Results and Conclusions

Annualized Relapse Rate (ARR)

Patients treated with ponesimod had a 30.5% relative reduction in ARR, compared to patients on teriflunomide (p =0.0003). The adjusted ARR was 0.202 and 0.290 in the ponesimod and teriflunomide groups, respectively (Table 5).

Table 5. Summary of Annualized Relapse Rate

	Ponesimod N=567	Teriflunomide N=566
Number of subjects in the analysis	567	566
Mean estimate (ARR)	0.202	0.290
95% CL	(0.173 , 0.235)	(0.254 , 0.331)
Treatment effect (rate ratio)	0.695	
95% CL	(0.570 , 0.848)	
p-value	0.0003	

Source: CSR Table 11, confirmed by the reviewer.

Results of sensitivity analyses and supplement analyses with respect to missing data, treatment interruption (treatment discontinuation or use of new disease modifying therapy for MS, all relapses (including unconfirmed relapses), analysis timepoint and populations were all consistent with the primary results. The delta adjustment (tipping point) analysis showed that assuming an increase in ARR of 2.2 times as compared to the missing at random assumption for subjects with missing data in ponesimod group still resulted in significant results at α=1% (p=0.0093), and an increase of 3.1 times still resulted in significant results at α=5% (p=0.0494; results not shown in table).

The reviewer conducted an analysis of the proportion of subjects relapsed at Week 108. The Kaplan-Meier estimate of the proportion of subjects relapsed at Week 108 was 30% in the ponesimod group compared with 40% in the teriflunomide group. The hazard ratio (95% CI) was 0.76 (0.62, 0.93), corresponding to a reduction of 24% (nominal p =0.0029) in the risk of relapse following treatment with ponesimod compared with teriflunomide (Table 6). The result supported the primary analysis.

Table 6. Summary of Proportion of Subjects Relapsed at Week 108

	Ponesimod N=567	Teriflunomide N=566
Number of subjects with relapses n(%)	166 (29.3)	223 (39.4)
Kaplan-Meier estimate at Week 108 (%)	30.3	39.9
95% CL	(26.6,34.3)	(35.9,44.1)
Treatment effect (Hazard ratio)	0.76	
95% CL	(0.62, 0.93)	
Log-rank p-value	0.0029	

Source: FDA reviewer.

Change from Baseline in FSIQ-RMS Weekly Symptoms Score (Fatigue) to Week 108

The mean difference between the 2 groups in the change from baseline in FSIQ-RMS symptoms score was -3.57 favoring the ponesimod group and was statistically significant (p =0.0019). An increase from baseline indicates worsening in fatigue symptoms. The least square [LS] mean change from baseline to Week 108 was -0.01 for the ponesimod arm and 3.56 for the teriflunomide arm (Table 7).

Table 7. Summary of Change from Baseline in FSIQ-RMS Symptoms Score (Fatigue) to Week 108

	Ponesimod N=567	Teriflunomide N=566
	449	458
Mean Change	-0.01	3.56
95% CL	(-1.60, 1.58)	(1.96, 5.16)
Treatment effect (difference)	-3.57	
95% CL	(-5.83, -1.32)	
p-value	0.0019	

Source: CSR T_FSIQ_SS_01_F, confirmed by the reviewer.

The FSIQ symptoms score at Week 108 was available for 70.0% and 66.6% of subjects in the ponesimod and teriflunomide groups, respectively, and change from baseline to Week 108 was available for 60.7% and 58.0%, respectively. Results of all sensitivity analyses were consistent with the primary results. The tipping point analysis showed that assuming a worsening of 1.5 for subjects with missing data in the ponesimod group resulted in a p-value of 0.0227 (results not shown in table), representing the lowest worsening not achieving statistical significance with an α=0.05/3 as per testing strategy.

Cumulative Number of Combined Unique Active Lesions (CUAL)

Ponesimod reduced the number of CUALs on brain MRIs from baseline to Week 108 by 56%, compared with teriflunomide (p <0.0001). The mean CUALs per year estimated using the NB regression model were 1.4 for ponesimod group compared to 3.2 for teriflunomide.

Table 8. Summary of Cumulative Number of Combined Unique Active Lesions (CUAL)

	Ponesimod N=567	Teriflunomide N=566
Number of subjects in the analysis	539	536
Mean estimate (Lesions per year)	1.405	3.164
95% CL	(1.215 , 1.624)	(2.757 , 3.631)
Treatment effect (rate ratio)	0.444	
95% CL	(0.364 , 0.542)	
p-value	<0.0001	

Source: CSR Table 12, confirmed by the reviewer.

CUALs included new Gd+ T1 lesions plus new or enlarging T2 lesions. The number of T2 lesions was expected to increase with observation time, while the number of new T1 Gd+ lesions was expected to increase with the number of MRI scans conducted. As MRI scans were scheduled less frequently in this study (Baseline, at the Week 60 Visit, and the Week 108 Visit), the CUAL count was expected to be mainly driven by new T2 lesions. Consequently, the primary analysis used the log-transformed time up to the last post-baseline MRI as an offset in the model. However, this may not be appropriate for analyzing the number of Gd+ T1 lesions.

Table 9 shows the results for each component of this endpoint. Log-transformed number of MRI scans was used an offset in the analysis of Gd+ T1 lesions component and log-transformed time was used for the analysis of T2 lesions. Ponesimod reduced the cumulative number of both new Gd+ T1 and new or enlarging T2 lesions by 58% and 56%, respectively, compared with teriflunomide.

Table 9. Summary of the Components of CUAL

	Ponesimod N=567	Teriflunomide N=566
new or enlarging T2 lesions		
Number of subjects in the analysis	539	536
Mean estimate (Lesions per year)	1.397	3.156
95% CL	(1.209 , 1.615)	(2.750 , 3.622)
Treatment effect (rate ratio)	0.443	
95% CL	(0.362 , 0.541)	
p-value	<0.0001	
new Gd+ T1 lesions		
Number of subjects in the analysis	540	538
Mean estimate (Lesions per scan)	0.178	0.429
95% CL	(0.141 , 0.224)	(0.351 , 0.525)
Treatment effect (rate ratio)	0.415	
95% CL	(0.307 , 0.561)	
p-value	<0.0001	

Source: FDA reviewer.

Confirmed Disability Accumulation

The primary analysis of 12-week CDA did not achieve statistical significance. Ponesimod numerically reduced the risk of 12-week CDA by 17% compared to teriflunomide (p =0.2939). Consequently, 24-week CDA was not formally tested. The reduction of the risk of 24-week CDA was 16% compared to teriflunomide (nominal p =0.3720). Results of the sensitivity and supplementary analyses were consistent with the primary analysis.

Table 10. Summary of Confirmed Disability Accumulation (CDA)

	Ponesimod N=567	Teriflunomide N=566
12-week CDA		
Number of subjects with 12-week CDA n(%)	57 (10.1)	70 (12.4)
Kaplan-Meier estimate at Week 108 (%)	10.8	13.2
95% CL	(8.4,13.7)	(10.6,16.3)
Treatment effect (Hazard ratio)	0.83	
95% CL	(0.58, 1.18)	
p-value	0.2939	
24-week CDA		
Number of subjects with 24-week CDA n(%)	46 (8.1)	56 (9.9)
Kaplan-Meier estimate at Week 108 (%)	8.7	10.5
95% CL	(6.6,11.4)	(8.2,13.4)
Treatment effect (Hazard ratio)	0.84	
95% CL	(0.57, 1.24)	
p-value	0.3720	

p-values were from stratified log-rank tests.
Source: FDA reviewer.

3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The results of subgroup analyses for the primary endpoint of ARR were in Table 11. Subgroups of race were not included as majority of the subjects were White and the number of subjects of other races was limited. The treatment effect appeared consistent across the subgroups except for North America and Rest of World due to the limited sample size.

Table 11. Summary of ARR by Demographics Subgroups

	Ponesimod		Teriflunomide		Ponesimod vs. Teriflunomide	
	N	ARR	N	ARR	Rate Ratio	95% CI
Age						
<40 years	349	0.238	342	0.343	0.694	(0.545, 0.886)
>=40 years	218	0.188	224	0.261	0.720	(0.500, 1.036)
Gender						
Male	204	0.229	194	0.306	0.747	(0.541, 1.033)
Female	363	0.214	372	0.312	0.684	(0.528, 0.888)
Geographical Region						
European Union (EU) + UK	289	0.157	284	0.281	0.559	(0.413, 0.757)
Europe Non-EU + Russia	233	0.284	239	0.366	0.778	(0.584, 1.035)
North America	32	0.378	24	0.205	1.847	(0.693, 4.924)
Rest of World	13	0.043	19	0.155	0.274	(0.033, 2.277)

Source: FDA reviewer.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The pivotal study B301 evaluated the efficacy and safety of oral ponesimod 20 mg versus teriflunomide 14 mg, with ARR over a 108-week treatment period as primary endpoint and 4 key secondary endpoints. The testing strategy started with testing the primary endpoint at full alpha, followed hierarchically by a fallback type procedure for the secondary endpoints. The alpha allocated for each endpoint was shown in Table 12. Treatment with ponesimod 20 mg resulted in statistically significantly effect on relapses, fatigue symptom and MRI lesion accumulation, compared to teriflunomide 14 mg. Statistical significance was not achieved for CDA endpoints although ponesimod group had numerically fewer subjects with disability accumulation.

Table 12. Summary of Results

Endpoint	Effect Measure	Estimate	95% CL	alpha	p-value	Significant
ARR	Rate ratio	0.695	0.570, 0.848	0.0500	0.0003	Yes
FSIQ-RMS	Mean difference	-3.57	-5.83, -1.32	0.0167	0.0019	Yes
CUAL	Rate ratio	0.44	0.36, 0.54	0.0333	<.0001	Yes
12-week CDA	Hazard ratio	0.83	0.58, 1.18	0.0500	0.2939	No
24-week CDA	Hazard ratio	0.84	0.57, 1.24	0.0000	0.3720	NA

5.2 Collective Evidence

As there was a single pivotal study, a summary of the collective evidence of effectiveness was not applicable.

5.3 Conclusions and Recommendations

The data overall provided adequate evidence to support for the efficacy of ponesimod as treatment of subjects with relapsing forms of multiple sclerosis.

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/s/

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I concur with the review.

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