CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212728Orig1s000

STATISTICAL REVIEW(S)

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 [redacted]
Drug Name:	BHV-3000
Indication:	Treatment of Migraine
Applicant:	Biohaven Pharmaceuticals, Inc. 234 Church Street New Haven, CT 06510 Test Facility for Rats Study: [redacted] Test Facility for Mice Study: [redacted]
Documents Reviewed:	Study reports [redacted] Project No. 2664-001; [redacted] Study Number; AE92RE.7G8R.BTL) submitted on June 28, 2019 via NDA [redacted]/0001; Electronic data submitted on June 28, 2019 via NDA [redacted]/0001
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Keywords:	Carcinogenicity, Dose response

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Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Crl:CD(SD) rats and one in Tg.rasH2 mice. These studies were intended to assess the carcinogenic potential of BHV-3000 when administered orally by gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice.

Rat Study: . Three hundred and twenty five Sprague Dawley [CD® IGS;Crl:CD(SD)] rats of each sex were randomly assigned to the treated, water and vehicle control groups in equal size of 65 rats per group. The dose levels for the treated groups were 5, 20, 45 mg/kg/day.

The survival analyses showed a statistically significant dose response relationship in mortality across the vehicle control group and treated groups (p-value for log-rank test is 0.0402) in male rats. The pairwise comparisons showed a statistically significant difference in mortality between the water control group and the 20 mg/kg/day group (p-value for likelihood ratio test is 0.0372, p-value for log-rank test is 0.0341) for male 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/water control group.

Mouse Study: One hundred and twenty five hemizygous Tg.rasH2 mice of each sex were randomly assigned to the treated, water 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 30, 100, and 300 mg/kg/day for males and females.

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

Tumor analysis:

1. For male mice, the pairwise comparisons between the vehicle control and the positive control showed a statistically significant increase in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).
2. For male mice, the pairwise comparisons between the water control and the positive control showed a statistically significant increase in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).
3. For female mice, 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), and of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).
4. For female mice, the pairwise comparisons between the water 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), and of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Sprague Dawley rats and one in Tg.rasH2 mice. These studies were intended to assess the carcinogenic potential of BHV-3000 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. David Carbone. This review analyzed the SAS data sets of these studies received from the sponsor on June 28, 2019 via NDA (b) (4) /0001 and on November 18, 2019 via NDA (b) (4) /0020.

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.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one water control group and one vehicle control group. Three hundred and twenty five Sprague Dawley [CD® IGS;Crl:CD(SD)] rats of each sex were randomly assigned to the treated, water and vehicle control groups in equal size of 65 rats per group. The dose levels for treated groups were 5, 20, 45 mg/kg/day. The rats in the water control group received the water. The rats in the vehicle control group received the vehicle(a solution of 20:5:75% (w/w) PEG 400: Povidone K-30:water). 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	Water	65	65
2	0	Vehicle	65	65
3	5	Low	65	65
4	20	Med	65	65
5	45	High	65	65

2.1. Sponsor's analyses

2.1.1. 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 vehicle 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 41 (63%), 38 (58%), 43 (66%), 50 (77%) and 34 (52%) in water control, vehicle control, 5 mg/kg/day, 20 mg/kg/day and 45 mg/kg/day dose groups, respectively in males and 36 (55%), 47 (72%), 38 (58%), 45 (69%) and 43 (66%) in water control, vehicle control, 5 mg/kg/day, 20 mg/kg/day and 45 mg/kg/day dose groups, respectively in females.

The sponsor concluded that among males the pairwise test of the BHV-3000 20 mg/kg/day group versus

vehicle control was statistically significant. There were no other statistically significant findings among males for survival rates. There were no statistically significant findings among females for survival rates.

2.1.2. Tumor data analysis

The FDA draft Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (May 2001) was used as a guidance for the statistical analysis of tumor incidence data.

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 method incorporating the day of detection.

For all organs, the incidence of each tumor type was analyzed with a 1-sided pairwise comparison of the high dose group with each control group separately. In addition, a 1-sided comparison of the vehicle control group with the water control group was conducted. There were no target organs in which an exhaustive microscopic examination of low and mid dose animals was conducted and therefore no trend tests were performed. An exact permutation test was conducted for analyses with low tumor incidences.

In addition to the Peto analysis, tumors were statistically analyzed using the poly-3 statistical analysis as first described by Bailer and Portier (1988) and modified by Bieler and Williams (1993).

For each tumor type, tumor bearing animals were assigned a weighted at risk score = 1. Likewise, non-tumor bearing animals that lived the full study period were assigned a weighted at risk score = 1. Non-tumor bearing animals that died prior to the end of the full study period were assigned a weighted at-risk score, based on the time of death, according to the following formula: (day of death/full study period)**3. The weighted number of animals at-risk (Nw) in each group was calculated for each tumor individually and defined as the sum of these weighted at-risk scores across a treatment group.

Conceptually, Nw estimates the weighted number of animals at risk based on the cumulative time on study of all animals in a group. If all non-tumor bearing animals in a group survived until the scheduled terminal sacrifice then Nw = N (the weighted number of animals at risk = the original number of animals in the group). If at least one nontumor bearing animal died prior to the scheduled terminal sacrifice then Nw < N. Thus, Nw is a reflection of group mortality in that early deaths of non-tumor bearing animals yield a smaller Nw relative to N.

Pairwise comparisons for the poly-3 analysis were conducted as described previously for the Peto analysis. Conditional exact p-values were calculated using SAS® PROC MULTTEST with dose level coefficients, the weighted number of animals at risk (rounded to the nearest integer) and assuming the row and column totals are fixed.

Sponsor's findings: The sponsor concluded that there were no statistically significant tumor findings among males or females.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on November 18, 2019 via NDA (b) (4) /0020.

2.2.1. Survival analysis

The survival distributions of animals in all five 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 5 and 6 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 7, 8, 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 41 (63%), 38 (58%), 43 (66%), 50 (77%) and 34 (52%) in water control, vehicle control, 5 mg/kg/day, 20 mg/kg/day and 45 mg/kg/day dose groups, respectively in males and 36 (55%), 47 (72%), 38 (58%), 45 (69%) and 43 (66%) in water control, vehicle control, 5 mg/kg/day, 20 mg/kg/day and 45 mg/kg/day dose groups, respectively in females.

The survival analyses showed a statistically significant dose response relationship in mortality across the vehicle control group and treated groups (p-value for log-rank test is 0.0402) in male rats. The pairwise comparisons showed a statistically significant difference in mortality between the water control group and the 20 mg/kg/day group (p-value for likelihood ratio test is 0.0372, p-value for log-rank test is 0.0341) for male rats.

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

2.2.2. 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, 12, 13 and 14 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/water control group.

3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one water control group, one vehicle control group, and one positive control group. One hundred and twenty five hemizygous Tg.rasH2 mice of each sex were randomly assigned to the treated, water 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 30, 100, and 300 mg/kg/day for males and females. The mice in the vehicle control group received the vehicle (75% (w/w) deionized (DI) water, 20% (w/w) PEG 400, 5% (w/w) Povidone K-30). 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 Urethane in 0.9% Sodium Chloride (Sterile Saline) (1000 mg/kg/dose, a total of 3 i.p. injections, one each on Days 1, 3 and 5).

Table 2: Study Design in Mouse Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Water	25	25
2	0	Vehicle	25	25
3	30	Low	25	25
4	100	Middle	25	25
5	300	High	25	25
6	1000	Positive	10	10

3.1. Sponsor's analyses

3.1.1. 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 1 (4%), 1 (4%), 1 (4%), 0 (4%), 1 (4%) and 0 (0%) in male mice, and 0 (0%), 0 (0%), 0 (0%), 1 (4%), 0 (0%) 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 were no statistically significant findings among males or females for survival rates.

3.1.2. Tumor data analysis

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

Sponsor's findings: The sponsor concluded that There were no statistically significant tumor findings in the test article groups when compared to the vehicle control group or the water control.

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 June 28, 2019 via NDA (b) (4) /0001.

3.2.1. 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 15 and 16 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 (or the water control group) and three treated groups are given in Tables 17, 18, 19 and 20 in the appendix for male and female mice, respectively.

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

The survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle/water control group and treated groups in either male or female mice.

The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle/water control group and each of the treated groups in either male or female mice.

3.2.2. 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 (or the water control group) and three treated groups, and between vehicle control and positive control are listed in Tables 21, 22, 23, 24, 25, 26, 27, and 28 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 below showed p-values less than or equal to 0.05 in the tests for pairwise comparisons between vehicle/water and positive control groups for male mice and female mice, respectively.

Table 3: 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) P-value - Vehicle vs. Positive	0 mg/kg/day Water (N=25) P-value - Water vs. Positive	Positive (N=10)
LUNGS WITH BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	3/25 (25) <0.001	2/25 (25) <0.001	10/10 (10)

Table 4: 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) P-value - Vehicle vs. Positive	0 mg/kg/day Water (N=25) P-value - Water vs. Positive	Positive (N=10)
LUNGS WITH BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	3/25 (25) <0.001	0/25 (25) <0.001	10/10 (10)
	ALVEOLAR BRONCHIOLAR CARCINOMA	1/25 (25) 0.0232	0/25 (25) 0.0079	2/10 (3)
	ALVEOLAR BRONCHIOLAR ADENOMA+CARCINOMA	4/25 (25) <0.001	0/25 (25) <0.001	10/10 (10)

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, the pairwise comparisons between the vehicle control and the positive control showed a statistically significant increase in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).
2. For male mice, the pairwise comparisons between the water control and the positive control showed a statistically significant increase in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).
3. For female mice, 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), and of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).
4. For female mice, the pairwise comparisons between the water 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), and of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).

4. Conclusion

In this submission the sponsor included reports of two animal carcinogenicity studies, one in Crl:CD(SD) rats and one in Tg.rasH2 mice. These studies were intended to assess the carcinogenic potential of BHV-3000 when administered orally by gavage at appropriate drug levels for 104 weeks in rats and 26 weeks in mice.

Rat Study: . Three hundred and twenty five Sprague Dawley [CD® IGS;Crl:CD(SD)] rats of each sex were randomly assigned to the treated, water and vehicle control groups in equal size of 65 rats per group. The dose levels for the treated groups were 5, 20, 45 mg/kg/day.

The survival analyses showed a statistically significant dose response relationship in mortality across the vehicle control group and treated groups (p-value for log-rank test is 0.0402) in male rats. The pairwise comparisons showed a statistically difference in mortality between the water control group and the 20 mg/kg/day group (p-value for likelihood ratio test is 0.0372, p-value for log-rank test is 0.0341) for male 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/water control group.

Mouse Study: One hundred and twenty five hemizygous Tg.rasH2 mice of each sex were randomly assigned to the treated, water 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 30, 100, and 300 mg/kg/day for males and females.

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

Tumor analysis:

1. For male mice, the pairwise comparisons between the vehicle control and the positive control showed a statistically significant increase in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).
2. For male mice, the pairwise comparisons between the water control and the positive control showed a statistically significant increase in incidence of Adenoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).
3. For female mice, 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), and of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).
4. For female mice, the pairwise comparisons between the water 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), and of the combined tumors of Adenoma and Carcinoma, Alveolar Bronchiolar in Lung with Bronchi (P-value<0.001).

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Archival NDA (b) (4)
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5. Appendix

Table 5: Intercurrent Mortality Rate -Male Rats

	Water Control 0 mg|kg|day (N=65)		Vehicle Control 0 mg|kg|day (N=65)		5 mg|kg|day (N=65)		20 mg|kg|day (N=65)		45 mg|kg|day (N=65)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	4	6.15	3	4.62	5	7.69	3	4.62	3	4.62
53 - 78	13	26.15	12	23.08	8	20.00	12	23.08	10	20.00
79 - 91	9	40.00	15	46.15	18	47.69	22	56.92	13	40.00
92 - 100	15	63.08	8	58.46	12	66.15	13	76.92	8	52.31
Ter. Sac.	24	36.92	27	41.54	22	33.85	15	23.08	31	47.69

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

Table 6: Intercurrent Mortality Rate -Female Rats

	Water Control 0 mg|kg|day (N=65)		Vehicle Control 0 mg|kg|day (N=65)		5 mg|kg|day (N=65)		20 mg|kg|day (N=65)		45 mg|kg|day (N=65)	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	3	4.62	9	13.85	5	7.69	7	10.77	6	9.23
53 - 78	24	41.54	19	43.08	22	41.54	21	43.08	20	40.00
79 - 91	9	55.38	19	72.31	11	58.46	16	67.69	17	66.15
92 - 100	.	.	.	.	.	.	1	69.23	.	.
Ter. Sac.	29	44.62	18	27.69	27	41.54	20	30.77	22	33.85

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

Table 7: 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	0.8846	0.4415	0.0372	0.5557
Homogeneity	Log-Rank	0.0402	0.4360	0.0341	0.5517

Table 8: Intercurrent Mortality Comparison between Treated Groups and Water 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	0.7981	0.7093	0.0846	0.3281
Homogeneity	Log-Rank	0.0553	0.7053	0.0791	0.3239

Table 9: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Female 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	0.7255	0.1577	0.7137	0.4817
Homogeneity	Log-Rank	0.5349	0.1519	0.7093	0.4754

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

Test	Statistic	P_Value Dose Response	P_Value Water vs. Low	P_Value Water vs. Medium	P_Value Water vs. High
Dose-Response	Likelihood Ratio	0.2420	0.7746	0.2454	0.3578
Homogeneity	Log-Rank	0.5788	0.7727	0.2396	0.3537

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	5 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	20 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	45 mg/kg/day High (N=65) P-value - Vehicle vs. High
ARTERY, AORTA	PARAGANGLIOMA, BENIGN	1/65 (43) 1.0000	0/43 (22) 1.0000	0/50 (26) 1.0000	0/65 (44) 1.0000
BRAIN	ASTROCYTOMA, MALIGNANT	1/65 (44) 0.2240	0/48 (28) 1.0000	0/51 (27) 1.0000	2/65 (44) 0.5000
EYE	LEIOMYOMA	0/65 (43) 0.3259	0/43 (22) NC	0/50 (26) NC	1/65 (44) 0.5057
GLAND, ADRENAL, CO	CORTICAL ADENOMA	0/65 (43) 0.7733	2/44 (24) 0.1248	2/50 (26) 0.1385	0/65 (44) NC
GLAND, ADRENAL, ME	PHEOCHROMOCYTOMA, BENIGN	9/63 (44) 0.9121	5/44 (25) 0.6328	1/50 (26) 0.9937	5/63 (43) 0.9219

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	5 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	20 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	45 mg/kg/day High (N=65) P-value - Vehicle vs. High
	PHEOCHROMOCYTOMA, MALIGNANT	1/63 (42) 0.5639	1/44 (23) 0.5861	1/50 (26) 0.6220	1/63 (42) 0.7530
GLAND, MAMMARY	ADENOCARCINOMA	0/3 (3) 0.6912	1/7 (6) 0.6667	1/3 (2) 0.4000	0/8 (6) NC
	CARCINOSARCOMA	0/3 (3) 0.3529	0/7 (6) NC	0/3 (2) NC	1/8 (6) 0.6667
	FIBROADENOMA	1/3 (3) 0.1109	1/7 (6) 0.9167	0/3 (2) 1.0000	4/8 (7) 0.5000
GLAND, PARATHYROID	ADENOMA	0/49 (32) 0.7289	1/33 (18) 0.3600	2/38 (18) 0.1249	0/51 (34) NC
GLAND, PITUITARY	ADENOMA, PARS DISTALIS	36/64 (51) 0.1907	37/57 (46) 0.1879	35/56 (44) 0.2227	46/65 (57) 0.1582
	ADENOMA, PARS INTERMEDIA	0/64 (42) 0.2895	0/57 (35) NC	0/56 (31) NC	1/65 (44) 0.5116
	CARCINOMA, PARS DISTALIS	2/64 (43) 0.7752	3/57 (36) 0.4152	4/56 (33) 0.2208	1/65 (44) 0.8836
GLAND, PROSTATE	ADENOMA	0/65 (43) 0.6446	1/43 (23) 0.3485	1/50 (26) 0.3768	0/65 (44) NC
	SARCOMA	0/65 (43) 0.5185	0/43 (22) NC	1/50 (26) 0.3768	0/65 (44) NC
GLAND, THYROID	C-CELL ADENOMA	3/65 (43) 0.3727	0/43 (22) 1.0000	0/51 (27) 1.0000	3/65 (44) 0.6729
	FOLLICULAR CELL ADENOMA	4/65 (45) 0.1649	4/43 (24) 0.2794	3/51 (28) 0.5487	8/65 (45) 0.1765
	FOLLICULAR CELL CARCINOMA	1/65 (43) 0.5732	1/43 (23) 0.5790	3/51 (27) 0.1563	1/65 (44) 0.7586
GLAND, ZYMBALS	SEBACEOUS CELL ADENOMA	0/64 (42) 0.6493	1/43 (23) 0.3538	1/50 (26) 0.3824	0/65 (44) NC
	SQUAMOUS CELL CARCINOMA	0/64 (42) 0.6889	1/43 (23) 0.3538	0/50 (26) NC	0/65 (44) NC
Gland Adrenals Med	C_Pheochromocytoma B+M	10/65 (45) 0.9209	6/63 (42) 0.8915	2/62 (37) 0.9951	5/65 (45) 0.9563
HEMOLYMPHORETICULA	HISTIOCYTIC SARCOMA	3/5 (4) 0.8571	0/1 (0) NC	0/2 (1) 1.0000	1/2 (2) 0.9333
	LEUKEMIA	2/5 (4) 0.2857	0/1 (0) NC	2/2 (2) 0.4000	1/2 (1) 0.6000
	LYMPHOMA, MALIGNANT	0/5 (2) 0.6000	1/1 (1) 0.3333	0/2 (1) NC	0/2 (1) NC
KIDNEY	ADENOMA	0/65 (43) 0.3372	1/44 (24) 0.3582	0/53 (28) NC	1/65 (44) 0.5057
	AMPHOPHILIC VACUOLAR TUBULAR ADENOMA	0/65 (43) 0.1467	1/44 (24) 0.3582	0/53 (28) NC	2/65 (45) 0.2586

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	5 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	20 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	45 mg/kg/day High (N=65) P-value - Vehicle vs. High
	SARCOMA	1/65 (43) 1.0000	0/44 (23) 1.0000	0/53 (28) 1.0000	0/65 (44) 1.0000
LIVER	HEPATOCELLULAR ADENOMA	2/65 (43) 0.4713	1/58 (36) 0.8439	0/55 (30) 1.0000	2/65 (44) 0.7006
	HEPATOCELLULAR CARCINOMA	0/65 (43) 0.1975	0/58 (35) NC	1/55 (30) 0.4110	1/65 (44) 0.5057
LUNG	BRONCHIOLOALVEOLAR ADENOMA	0/65 (43) 0.3259	0/43 (22) NC	0/50 (26) NC	1/65 (44) 0.5057
LYMPH NODE, MESENT	HEMANGIOMA	0/64 (42) 0.6912	1/44 (24) 0.3636	0/50 (26) NC	0/65 (44) NC
Liver	C_Hepatocellular Adenoma+Carcinoma	2/65 (43) 0.2460	1/63 (40) 0.8657	1/62 (36) 0.8439	3/65 (44) 0.5110
MESENTERY	HEMANGIOSARCOMA	1/2 (1) 1.0000	0/0 (1) NC	0/1 (2) 1.0000	0/2 (.) 1.0000
PANCREAS	ACINAR ADENOMA	1/65 (43) 0.8311	1/43 (23) 0.5790	1/50 (26) 0.6151	0/65 (44) 1.0000
	ISLET CELL ADENOMA	4/65 (43) 0.4251	1/43 (23) 0.8923	0/50 (26) 1.0000	4/65 (44) 0.6564
	ISLET CELL CARCINOMA	1/65 (43) 1.0000	0/43 (22) 1.0000	0/50 (26) 1.0000	0/65 (44) 1.0000
Pancreas	C_Adenoma+Carcinoma	6/65 (44) 0.6327	2/63 (40) 0.9608	1/62 (37) 0.9890	4/65 (44) 0.8430
SKIN	ADENOCARCINOMA	0/65 (43) 0.7075	1/53 (31) 0.4189	0/53 (29) NC	0/65 (44) NC
	CHORDOMA, MALIGNANT	0/65 (43) 0.2993	0/53 (31) NC	0/53 (29) NC	1/65 (44) 0.5057
	FIBROMA	3/65 (43) 0.9971	7/53 (32) 0.0631	1/53 (29) 0.8800	0/65 (44) 1.0000
	FIBROSARCOMA	1/65 (43) 0.5105	0/53 (31) 1.0000	0/53 (29) 1.0000	1/65 (44) 0.7586
	HAIR FOLLICLE TUMOR, BENIGN	1/65 (43) 1.0000	0/53 (31) 1.0000	0/53 (29) 1.0000	0/65 (44) 1.0000
	LIPOMA	1/65 (43) 0.4299	0/53 (31) 1.0000	1/53 (29) 0.6467	1/65 (44) 0.7586
	PAPILLOMA	0/65 (43) 0.5881	3/53 (32) 0.0735	2/53 (29) 0.1588	1/65 (44) 0.5057
	SARCOMA	1/65 (43) 0.4299	0/53 (31) 1.0000	1/53 (29) 0.6467	1/65 (44) 0.7586
	SEBACEOUS CELL ADENOMA	0/65 (43) 0.4966	0/53 (31) NC	1/53 (29) 0.4028	0/65 (44) NC
	SEBACEOUS CELL CARCINOMA	0/65 (43) 0.7095	1/53 (32) 0.4267	0/53 (29) NC	0/65 (44) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	5 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	20 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	45 mg/kg/day High (N=65) P-value - Vehicle vs. High
SPINAL CORD	ASTROCYTOMA, MALIGNANT	0/65 (43) 0.6838	1/43 (23) 0.3485	0/50 (26) NC	0/65 (44) NC
SPLEEN	HEMANGIOSARCOMA	0/65 (43) 0.3235	0/44 (23) NC	0/50 (26) NC	1/65 (44) 0.5057
	UNCLASSIFIABLE TUMOR, BENIGN	0/65 (43) 0.5147	0/44 (23) NC	1/50 (26) 0.3768	0/65 (44) NC
Skin	C_Sarcoma+Fibrosarcomas	2/65 (43) 0.3380	0/63 (40) 1.0000	1/62 (36) 0.8439	2/65 (45) 0.7089
TESTIS	INTERSTITIAL (LEYDIG) CELL ADENOMA	3/65 (43) 0.9657	1/45 (24) 0.8390	1/50 (26) 0.8572	0/65 (44) 1.0000
Whold Body	C_hemangiosar+heman	1/65 (43) 0.5676	1/63 (40) 0.7346	0/62 (36) 1.0000	1/65 (44) 0.7586

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

Organ Name	Tumor Name	0 mg/kg/day Water (N=65) P-value - Trend	5 mg/kg/day Low (N=65) P-value - Water vs. Low	20 mg/kg/day Med (N=65) P-value - Water vs. Med	45 mg/kg/day High (N=65) P-value - Water vs. High
BONE, STERNUM	OSTEOBLASTOMA, BENIGN	1/65 (43) 1.0000	0/43 (22) 1.0000	0/50 (26) 1.0000	0/65 (44) 1.0000
BRAIN	ASTROCYTOMA, MALIGNANT	4/65 (43) 0.7109	0/48 (28) 1.0000	0/51 (27) 1.0000	2/65 (44) 0.9041
EYE	LEIOMYOMA	0/65 (42) 0.3284	0/43 (22) NC	0/50 (26) NC	1/65 (44) 0.5116
	SARCOMA	1/65 (42) 1.0000	0/43 (22) 1.0000	0/50 (26) 1.0000	0/65 (44) 1.0000
GLAND, ADRENAL, CO	CORTICAL ADENOMA	5/65 (43) 0.9924	2/44 (24) 0.7947	2/50 (26) 0.8232	0/65 (44) 1.0000
GLAND, ADRENAL, ME	PHEOCHROMOCYTOMA, BENIGN	9/63 (42) 0.9233	5/44 (25) 0.6682	1/50 (26) 0.9949	5/63 (43) 0.9354
	PHEOCHROMOCYTOMA, MALIGNANT	2/63 (41) 0.7394	1/44 (23) 0.7441	1/50 (26) 0.7775	1/63 (42) 0.8840
GLAND, MAMMARY	ADENOCARCINOMA	0/6 (5) 0.6199	1/7 (6) 0.5455	1/3 (2) 0.2857	0/8 (6) NC
	CARCINOSARCOMA	0/6 (5) 0.3158	0/7 (6) NC	0/3 (2) NC	1/8 (6) 0.5455
	FIBROADENOMA	4/6 (6) 0.3610	1/7 (6) 0.9924	0/3 (2) 1.0000	4/8 (7) 0.8205
GLAND, PARATHYROID	ADENOMA	1/51 (32) 0.8449	1/33 (18) 0.5951	2/38 (18) 0.2914	0/51 (34) 1.0000
GLAND, PITUITARY	ADENOMA, PARS DISTALIS	42/64 (52) 0.5125	37/57 (46) 0.6179	35/56 (44) 0.6590	46/65 (57) 0.5984
	ADENOMA, PARS INTERMEDIA	0/64 (41) 0.2914	0/57 (35) NC	0/56 (31) NC	1/65 (44) 0.5176
	CARCINOMA, PARS DISTALIS	2/64 (42) 0.7816	3/57 (36) 0.4262	4/56 (33) 0.2300	1/65 (44) 0.8878
GLAND, PROSTATE	ADENOCARCINOMA	1/64 (42) 1.0000	0/43 (22) 1.0000	0/50 (26) 1.0000	0/65 (44) 1.0000
	ADENOMA	0/64 (41) 0.6541	1/43 (23) 0.3594	1/50 (26) 0.3881	0/65 (44) NC
	SARCOMA	0/64 (41) 0.5263	0/43 (22) NC	1/50 (26) 0.3881	0/65 (44) NC
GLAND, THYROID	C-CELL ADENOMA	9/65 (43) 0.9451	0/43 (22) 1.0000	0/51 (27) 1.0000	3/65 (44) 0.9883
	C-CELL CARCINOMA	1/65 (42) 1.0000	0/43 (22) 1.0000	0/51 (27) 1.0000	0/65 (44) 1.0000
	FOLLICULAR CELL ADENOMA	6/65 (43) 0.3437	4/43 (24) 0.5133	3/51 (28) 0.7744	8/65 (45) 0.4222

Organ Name	Tumor Name	0 mg/kg/day Water (N=65) P-value - Trend	5 mg/kg/day Low (N=65) P-value - Water vs. Low	20 mg/kg/day Med (N=65) P-value - Water vs. Med	45 mg/kg/day High (N=65) P-value - Water vs. High
	FOLLICULAR CELL CARCINOMA	0/65 (42) 0.4174	1/43 (23) 0.3538	3/51 (27) 0.0558	1/65 (44) 0.5116
GLAND, ZYMBALS	SEBACEOUS CELL ADENOMA	0/65 (42) 0.6493	1/43 (23) 0.3538	1/50 (26) 0.3824	0/65 (44) NC
	SQUAMOUS CELL CARCINOMA	0/65 (42) 0.6889	1/43 (23) 0.3538	0/50 (26) NC	0/65 (44) NC
Gland Adrenals Med	C_Pheochromocytoma B+M	11/65 (45) 0.9467	6/63 (42) 0.9295	2/62 (37) 0.9975	5/65 (45) 0.9744
HEMOLYMPHORETICULA	HISTIOCYTIC SARCOMA	1/3 (2) 0.7000	0/1 (0) NC	0/2 (1) 1.0000	1/2 (2) 0.8333
	LEUKEMIA	2/3 (3) 0.5000	0/1 (0) NC	2/2 (2) 0.6000	1/2 (1) 0.7500
	LYMPHOMA, MALIGNANT	0/3 (2) 0.6000	1/1 (1) 0.3333	0/2 (1) NC	0/2 (1) NC
KIDNEY	ADENOMA	0/65 (42) 0.3421	1/44 (24) 0.3636	0/53 (28) NC	1/65 (44) 0.5116
	AMPHOPHILIC VACUOLAR TUBULAR ADENOMA	2/65 (43) 0.5256	1/44 (24) 0.7424	0/53 (28) 1.0000	2/65 (45) 0.7089
	SARCOMA	1/65 (42) 1.0000	0/44 (23) 1.0000	0/53 (28) 1.0000	0/65 (44) 1.0000
LIVER	HEPATOCELLULAR ADENOMA	0/65 (42) 0.1319	1/58 (36) 0.4615	0/55 (30) NC	2/65 (44) 0.2588
	HEPATOCELLULAR CARCINOMA	2/65 (42) 0.6055	0/58 (35) 1.0000	1/55 (30) 0.8075	1/65 (44) 0.8878
LUNG	BRONCHIOLOALVEOLAR ADENOMA	0/65 (42) 0.3284	0/43 (22) NC	0/50 (26) NC	1/65 (44) 0.5116
LYMPH NODE, MESENT	HEMANGIOMA	0/65 (42) 0.6912	1/44 (24) 0.3636	0/50 (26) NC	0/65 (44) NC
Liver	C_Hepatocellular Adenoma+Carcinoma	2/65 (42) 0.2510	1/63 (40) 0.8704	1/62 (36) 0.8491	3/65 (44) 0.5223
MUSCLE, SKELETAL	HEMANGIOSARCOMA	1/65 (43) 1.0000	0/43 (22) 1.0000	0/50 (26) 1.0000	0/65 (44) 1.0000
PANCREAS	ACINAR ADENOMA	0/65 (42) 0.6493	1/43 (23) 0.3538	1/50 (26) 0.3824	0/65 (44) NC
	ISLET CELL ADENOMA	4/65 (42) 0.4343	1/43 (23) 0.8970	0/50 (26) 1.0000	4/65 (44) 0.6695
	ISLET CELL CARCINOMA	1/65 (42) 1.0000	0/43 (22) 1.0000	0/50 (26) 1.0000	0/65 (44) 1.0000
Pancreas	C_Adenoma+Carcinoma	5/65 (43) 0.5317	2/63 (40) 0.9335	1/62 (37) 0.9797	4/65 (44) 0.7696
SKIN	ADENOCARCINOMA	0/65 (42) 0.7123	1/53 (31) 0.4247	0/53 (29) NC	0/65 (44) NC

Organ Name	Tumor Name	0 mg/kg/day Water (N=65) P-value - Trend	5 mg/kg/day Low (N=65) P-value - Water vs. Low	20 mg/kg/day Med (N=65) P-value - Water vs. Med	45 mg/kg/day High (N=65) P-value - Water vs. High
	BASAL CELL TUMOR, MALIGNANT	2/65 (42) 1.0000	0/53 (31) 1.0000	0/53 (29) 1.0000	0/65 (44) 1.0000
	CHORDOMA, MALIGNANT	0/65 (42) 0.3014	0/53 (31) NC	0/53 (29) NC	1/65 (44) 0.5116
	FIBROMA	4/65 (42) 0.9988	7/53 (32) 0.1255	1/53 (29) 0.9347	0/65 (44) 1.0000
	FIBROSARCOMA	2/65 (42) 0.6940	0/53 (31) 1.0000	0/53 (29) 1.0000	1/65 (44) 0.8878
	LIPOMA	2/65 (42) 0.6229	0/53 (31) 1.0000	1/53 (29) 0.7991	1/65 (44) 0.8878
	PAPILLOMA	1/65 (42) 0.7307	3/53 (32) 0.2123	2/53 (29) 0.3623	1/65 (44) 0.7644
	SARCOMA	0/65 (42) 0.2099	0/53 (31) NC	1/53 (29) 0.4085	1/65 (44) 0.5116
	SCHWANNOMA, BENIGN	1/65 (42) 1.0000	0/53 (31) 1.0000	0/53 (29) 1.0000	0/65 (44) 1.0000
	SCHWANNOMA, MALIGNANT	1/65 (42) 1.0000	0/53 (31) 1.0000	0/53 (29) 1.0000	0/65 (44) 1.0000
	SEBACEOUS CELL ADENOMA	0/65 (42) 0.5000	0/53 (31) NC	1/53 (29) 0.4085	0/65 (44) NC
	SEBACEOUS CELL CARCINOMA	0/65 (42) 0.7143	1/53 (32) 0.4324	0/53 (29) NC	0/65 (44) NC
	SQUAMOUS CELL CARCINOMA	2/65 (42) 1.0000	0/53 (31) 1.0000	0/53 (29) 1.0000	0/65 (44) 1.0000
SPINAL CORD	ASTROCYTOMA, MALIGNANT	0/65 (42) 0.6889	1/43 (23) 0.3538	0/50 (26) NC	0/65 (44) NC
	OLIGODENDROGLIOMA, MALIGNANT	1/65 (42) 1.0000	0/43 (22) 1.0000	0/50 (26) 1.0000	0/65 (44) 1.0000
SPLEEN	HEMANGIOMA	1/65 (42) 1.0000	0/44 (23) 1.0000	0/50 (26) 1.0000	0/65 (44) 1.0000
	HEMANGIOSARCOMA	0/65 (42) 0.3259	0/44 (23) NC	0/50 (26) NC	1/65 (44) 0.5116
	UNCLASSIFIABLE TUMOR, BENIGN	0/65 (42) 0.5185	0/44 (23) NC	1/50 (26) 0.3824	0/65 (44) NC
Skin	C_Sarcoma+Fibrosarcomas	2/65 (42) 0.3427	0/63 (40) 1.0000	1/62 (36) 0.8491	2/65 (45) 0.7176
TESTIS	INTERSTITIAL (LEYDIG) CELL ADENOMA	0/65 (42) 0.6474	1/45 (24) 0.3636	1/50 (26) 0.3824	0/65 (44) NC
Whold Body	C_hemangiosar+heman	2/65 (43) 0.7410	1/63 (40) 0.8657	0/62 (36) 1.0000	1/65 (44) 0.8836

Table 13: 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	5 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	20 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	45 mg/kg/day High (N=65) P-value - Vehicle vs. High
ADIPOSE TISSUE	LIPOMA	1/3 (2) 1.0000	0/3 (2) 1.0000	0/1 (1) 1.0000	0/3 (2) 1.0000
BRAIN	ASTROCYTOMA, MALIGNANT	0/65 (29) 0.3010	0/50 (21) NC	0/54 (22) NC	1/65 (31) 0.5167
	MENINGIOMA, BENIGN	0/65 (29) 0.3010	0/50 (21) NC	0/54 (22) NC	1/65 (31) 0.5167
GLAND, ADRENAL, CO	CORTICAL ADENOMA	0/65 (29) 0.3481	1/41 (15) 0.3409	0/47 (17) NC	1/65 (31) 0.5167
	CORTICAL CARCINOMA	0/65 (29) 0.0991	0/41 (15) NC	1/47 (18) 0.3830	2/65 (31) 0.2627
GLAND, ADRENAL, ME	PHEOCHROMOCYTOMA, BENIGN	1/64 (28) 0.2012	1/38 (14) 0.5610	1/43 (16) 0.6004	3/62 (30) 0.3325
	PHEOCHROMOCYTOMA, MALIGNANT	0/64 (28) 0.3372	0/38 (14) NC	0/43 (15) NC	1/62 (29) 0.5088
GLAND, MAMMARY	ADENOCARCINOMA	10/61 (33) 0.8047	15/58 (34) 0.1799	16/61 (35) 0.1452	9/63 (34) 0.7318
	ADENOCARCINOMA ARISING IN FIBROADENOMA	2/61 (29) 0.9370	4/58 (29) 0.3351	4/61 (29) 0.3351	0/63 (30) 1.0000
	ADENOMA	0/61 (28) 0.0687	0/58 (27) NC	0/61 (28) NC	2/63 (30) 0.2632
	FIBROADENOMA	22/61 (37) 0.8597	26/58 (39) 0.3398	20/61 (38) 0.7961	20/63 (38) 0.7961
GLAND, PARATHYROID	ADENOMA	0/56 (26) 0.3289	0/34 (11) NC	0/39 (14) NC	1/55 (25) 0.4902
GLAND, PITUITARY	ADENOMA, PARS DISTALIS	49/64 (55) 0.8323	51/62 (55) 0.3710	49/62 (54) 0.5130	48/65 (56) 0.7938
	CARCINOMA, PARS DISTALIS	6/64 (31) 0.8049	4/62 (32) 0.8619	6/62 (30) 0.6012	3/65 (32) 0.9334
GLAND, THYROID	C-CELL ADENOMA	1/65 (29) 1.0000	0/38 (13) 1.0000	0/45 (16) 1.0000	0/65 (30) 1.0000
	FOLLICULAR CELL ADENOMA	0/65 (29) 0.7769	2/38 (14) 0.1008	1/45 (16) 0.3556	0/65 (30) NC
	FOLLICULAR CELL CARCINOMA	0/65 (29) 0.3483	0/38 (13) NC	0/45 (16) NC	1/65 (31) 0.5167
Gland Adrenals Cor	C_Cortical Adenoma+Carcinoma	0/65 (29) 0.0492	1/65 (31) 0.5167	1/65 (30) 0.5085	3/65 (32) 0.1378
Gland Adrenals Med	C_Pheochromocytoma B+M	1/65 (29) 0.0535	1/65 (31) 0.7706	1/65 (30) 0.7627	4/65 (32) 0.2091
Gland Pituitary	C_pars distalis Adenoma+Carcinoma	55/65 (59) 0.8077	55/65 (59) 0.6416	55/65 (59) 0.6416	51/65 (57) 0.8529

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	5 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	20 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	45 mg/kg/day High (N=65) P-value - Vehicle vs. High
Gland Thyroid	C_C cell Adenoma+Carcinoma	1/65 (29) 1.0000	0/65 (31) 1.0000	0/65 (29) 1.0000	0/65 (30) 1.0000
	C_Follicular cell Adenoma+Carcinoma	0/65 (29) 0.4306	2/65 (32) 0.2710	1/65 (30) 0.5085	1/65 (31) 0.5167
KIDNEY	AMPHOPHILIC VACUOLAR TUBULAR ADENOMA	4/65 (32) 0.9499	2/40 (16) 0.6636	0/47 (17) 1.0000	1/65 (31) 0.9714
	AMPHOPHILIC VACUOLAR TUBULAR CARCINOMA	0/65 (29) 0.3407	0/40 (14) NC	0/47 (17) NC	1/65 (31) 0.5167
LIVER	HEPATOCELLULAR ADENOMA	1/65 (29) 0.5406	3/49 (22) 0.2080	1/49 (20) 0.6548	2/65 (31) 0.5254
OVARY	CYSTADENOCARCINOMA	0/65 (29) 0.3298	0/43 (16) NC	0/48 (18) NC	1/65 (31) 0.5167
	GRANULOSA CELL TUMOR, MALIGNANT	0/65 (29) 0.3298	0/43 (16) NC	0/48 (18) NC	1/65 (31) 0.5167
	HEMANGIOMA	0/65 (29) 0.6915	1/43 (17) 0.3696	0/48 (18) NC	0/65 (30) NC
	MIXED SEX CORD STROMAL TUMOR, BENIGN	1/65 (29) 1.0000	0/43 (16) 1.0000	0/48 (18) 1.0000	0/65 (30) 1.0000
PANCREAS	ISLET CELL ADENOMA	1/65 (29) 0.3604	1/38 (14) 0.5504	0/45 (16) 1.0000	2/65 (31) 0.5254
SKIN	LIPOMA	1/65 (29) 1.0000	0/42 (16) 1.0000	0/47 (17) 1.0000	0/65 (30) 1.0000
	SCHWANNOMA, MALIGNANT	0/65 (29) 0.5161	0/42 (16) NC	1/47 (18) 0.3830	0/65 (30) NC
	UNCLASSIFIABLE TUMOR, MALIGNANT	0/65 (29) 0.5161	0/42 (16) NC	1/47 (18) 0.3830	0/65 (30) NC
SPLEEN	HEMANGIOSARCOMA	0/64 (29) 0.3409	0/39 (14) NC	0/44 (15) NC	1/64 (30) 0.5085
THYMUS	THYMOMA, BENIGN	0/64 (28) 0.6818	1/35 (13) 0.3171	0/46 (17) NC	0/63 (30) NC
UTERUS	ENDOMETRIAL ADENOCARCINOMA	0/65 (29) 0.6848	1/38 (14) 0.3256	0/49 (19) NC	0/65 (30) NC
	ENDOMETRIAL STROMAL POLYP	4/65 (31) 0.3766	0/38 (13) 1.0000	2/49 (19) 0.7505	4/65 (32) 0.6643
	LEIOMYOMA	0/65 (29) 0.3370	0/38 (13) NC	0/49 (19) NC	1/65 (31) 0.5167
	LEIOMYOSARCOMA	1/65 (29) 0.9030	1/38 (14) 0.5504	0/49 (19) 1.0000	0/65 (30) 1.0000
	SCHWANNOMA, MALIGNANT	0/65 (29) 0.6848	1/38 (14) 0.3256	0/49 (19) NC	0/65 (30) NC
	SQUAMOUS CELL CARCINOMA	1/65 (29) 0.7897	0/38 (13) 1.0000	1/49 (19) 0.6401	0/65 (30) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=65) P-value - Trend	5 mg/kg/day Low (N=65) P-value - Vehicle vs. Low	20 mg/kg/day Med (N=65) P-value - Vehicle vs. Med	45 mg/kg/day High (N=65) P-value - Vehicle vs. High
VAGINA	GRANULAR CELL TUMOR, BENIGN	1/65 (29) 0.4933	0/38 (13) 1.0000	1/45 (16) 0.5899	1/65 (31) 0.7706
Whold Body	C_hemangiosar+heman	0/65 (29) 0.3245	1/65 (32) 0.5246	0/65 (29) NC	1/65 (31) 0.5167

Table 14: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Water Controls and the Treated Groups-Female Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=65) P-value - Trend	5 mg/kg/day Low (N=65) P-value - Water vs. Low	20 mg/kg/day Med (N=65) P-value - Water vs. Med	45 mg/kg/day High (N=65) P-value - Water vs. High
BRAIN	ASTROCYTOMA, MALIGNANT	0/65 (31) 0.2952	0/50 (21) NC	0/54 (22) NC	1/65 (31) 0.5000
	MENINGIOMA, BENIGN	0/65 (31) 0.2952	0/50 (21) NC	0/54 (22) NC	1/65 (31) 0.5000
GLAND, ADRENAL, CO	CORTICAL ADENOMA	4/65 (33) 0.9294	1/41 (15) 0.8614	0/47 (17) 1.0000	1/65 (31) 0.9689
	CORTICAL CARCINOMA	2/65 (32) 0.4059	0/41 (15) 1.0000	1/47 (18) 0.7469	2/65 (31) 0.6815
GLAND, ADRENAL, ME	PHEOCHROMOCYTOMA, BENIGN	2/65 (32) 0.3066	1/38 (14) 0.6733	1/43 (16) 0.7132	3/62 (30) 0.4687
	PHEOCHROMOCYTOMA, MALIGNANT	0/65 (31) 0.3258	0/38 (14) NC	0/43 (15) NC	1/62 (29) 0.4833
GLAND, MAMMARY	ADENOCARCINOMA	20/65 (41) 0.9756	15/58 (34) 0.7372	16/61 (35) 0.6903	9/63 (34) 0.9872
	ADENOCARCINOMA ARISING IN FIBROADENOMA	3/65 (33) 0.9544	4/58 (29) 0.4260	4/61 (29) 0.4260	0/63 (30) 1.0000
	ADENOMA	1/65 (32) 0.1611	0/58 (27) 1.0000	0/61 (28) 1.0000	2/63 (30) 0.4754
	FIBROADENOMA	26/65 (42) 0.8920	26/58 (39) 0.4154	20/61 (38) 0.8564	20/63 (38) 0.8564
GLAND, PARATHYROID	ADENOMA	0/55 (26) 0.3289	0/34 (11) NC	0/39 (14) NC	1/55 (25) 0.4902
GLAND, PITUITARY	ADENOMA, PARS DISTALIS	57/65 (60) 0.9634	51/62 (55) 0.8151	49/62 (54) 0.8957	48/65 (56) 0.9800
	CARCINOMA, PARS DISTALIS	5/65 (34) 0.6950	4/62 (32) 0.7306	6/62 (30) 0.4085	3/65 (32) 0.8507
GLAND, SALIVARY	ADENOCARCINOMA	1/65 (32) 1.0000	0/38 (13) 1.0000	0/45 (16) 1.0000	0/65 (30) 1.0000
GLAND, THYROID	C-CELL ADENOMA	4/65 (33) 1.0000	0/38 (13) 1.0000	0/45 (16) 1.0000	0/65 (30) 1.0000
	C-CELL CARCINOMA	4/65 (33) 1.0000	0/38 (13) 1.0000	0/45 (16) 1.0000	0/65 (30) 1.0000
	FOLLICULAR CELL ADENOMA	0/65 (31) 0.7648	2/38 (14) 0.0919	1/45 (16) 0.3404	0/65 (30) NC
	FOLLICULAR CELL CARCINOMA	0/65 (31) 0.3407	0/38 (13) NC	0/45 (16) NC	1/65 (31) 0.5000
Gland Adrenals Cor	C_Cortical Adenoma+Carcinoma	6/65 (34) 0.7117	1/65 (31) 0.9923	1/65 (30) 0.9913	3/65 (32) 0.9108
Gland Adrenals Med	C_Pheochromocytoma B+M	2/65 (32) 0.1084	1/65 (31) 0.8751	1/65 (30) 0.8689	4/65 (32) 0.3359

Organ Name	Tumor Name	0 mg/kg/day Water (N=65) P-value - Trend	5 mg/kg/day Low (N=65) P-value - Water vs. Low	20 mg/kg/day Med (N=65) P-value - Water vs. Med	45 mg/kg/day High (N=65) P-value - Water vs. High
Gland Pituitary	C_pars distalis Adenoma+Carcinoma	62/65 (63) 0.9602	55/65 (59) 0.9758	55/65 (59) 0.9758	51/65 (57) 0.9956
Gland Thyroid	C_C cell Adenoma+Carcinoma	8/65 (35) 1.0000	0/65 (31) 1.0000	0/65 (29) 1.0000	0/65 (30) 1.0000
	C_Follicular cell Adenoma+Carcinoma	0/65 (31) 0.4160	2/65 (32) 0.2540	1/65 (30) 0.4918	1/65 (31) 0.5000
KIDNEY	ADENOMA	1/65 (32) 1.0000	0/40 (14) 1.0000	0/47 (17) 1.0000	0/65 (30) 1.0000
	AMPHOPHILIC VACUOLAR TUBULAR ADENOMA	4/65 (34) 0.9432	2/40 (16) 0.6352	0/47 (17) 1.0000	1/65 (31) 0.9663
	AMPHOPHILIC VACUOLAR TUBULAR CARCINOMA	0/65 (31) 0.3333	0/40 (14) NC	0/47 (17) NC	1/65 (31) 0.5000
	CARCINOMA	1/65 (32) 1.0000	0/40 (14) 1.0000	0/47 (17) 1.0000	0/65 (30) 1.0000
LIVER	HEPATOCELLULAR ADENOMA	0/65 (31) 0.3626	3/49 (22) 0.0657	1/49 (20) 0.3922	2/65 (31) 0.2459
	SARCOMA	1/65 (32) 1.0000	0/49 (20) 1.0000	0/49 (19) 1.0000	0/65 (30) 1.0000
OVARY	CYSTADENOCARCINOMA	0/65 (31) 0.3229	0/43 (16) NC	0/48 (18) NC	1/65 (31) 0.5000
	GRANULOSA CELL TUMOR, BENIGN	1/65 (32) 1.0000	0/43 (16) 1.0000	0/48 (18) 1.0000	0/65 (30) 1.0000
	GRANULOSA CELL TUMOR, MALIGNANT	1/65 (32) 0.5393	0/43 (16) 1.0000	0/48 (18) 1.0000	1/65 (31) 0.7460
	HEMANGIOMA	1/65 (32) 0.8935	1/43 (17) 0.5782	0/48 (18) 1.0000	0/65 (30) 1.0000
	MIXED SEX CORD STROMAL TUMOR, BENIGN	1/65 (32) 1.0000	0/43 (16) 1.0000	0/48 (18) 1.0000	0/65 (30) 1.0000
	THECOMA, BENIGN	1/65 (32) 1.0000	0/43 (16) 1.0000	0/48 (18) 1.0000	0/65 (30) 1.0000
	YOLK SAC CARCINOMA	1/65 (32) 1.0000	0/43 (16) 1.0000	0/48 (18) 1.0000	0/65 (30) 1.0000
PANCREAS	ISLET CELL ADENOMA	1/65 (32) 0.3343	1/38 (14) 0.5208	0/45 (16) 1.0000	2/65 (31) 0.4879
SKIN	LIPOMA	1/65 (32) 1.0000	0/42 (16) 1.0000	0/47 (17) 1.0000	0/65 (30) 1.0000
	OSTEOSARCOMA	1/65 (32) 1.0000	0/42 (16) 1.0000	0/47 (17) 1.0000	0/65 (30) 1.0000
	SCHWANNOMA, MALIGNANT	0/65 (31) 0.5053	0/42 (16) NC	1/47 (18) 0.3673	0/65 (30) NC
	UNCLASSIFIABLE TUMOR, MALIGNANT	0/65 (31) 0.5053	0/42 (16) NC	1/47 (18) 0.3673	0/65 (30) NC

Organ Name	Tumor Name	0 mg/kg/day Water (N=65) P-value - Trend	5 mg/kg/day Low (N=65) P-value - Water vs. Low	20 mg/kg/day Med (N=65) P-value - Water vs. Med	45 mg/kg/day High (N=65) P-value - Water vs. High
SPLEEN	HEMANGIOSARCOMA	0/65 (31) 0.3333	0/39 (14) NC	0/44 (15) NC	1/64 (30) 0.4918
THYMUS	THYMOMA, BENIGN	0/64 (31) 0.6593	1/35 (13) 0.2955	0/46 (17) NC	0/63 (30) NC
UTERUS	ENDOMETRIAL ADENOCARCINOMA	3/65 (33) 0.9877	1/38 (14) 0.7706	0/49 (19) 1.0000	0/65 (30) 1.0000
	ENDOMETRIAL STROMAL POLYP	3/65 (33) 0.2330	0/38 (13) 1.0000	2/49 (19) 0.6095	4/65 (32) 0.4823
	HEMANGIOSARCOMA	1/65 (32) 1.0000	0/38 (13) 1.0000	0/49 (19) 1.0000	0/65 (30) 1.0000
	LEIOMYOMA	0/65 (31) 0.3298	0/38 (13) NC	0/49 (19) NC	1/65 (31) 0.5000
	LEIOMYOSARCOMA	0/65 (31) 0.6702	1/38 (14) 0.3111	0/49 (19) NC	0/65 (30) NC
	SCHWANNOMA, MALIGNANT	0/65 (31) 0.6702	1/38 (14) 0.3111	0/49 (19) NC	0/65 (30) NC
	SQUAMOUS CELL CARCINOMA	0/65 (31) 0.5269	0/38 (13) NC	1/49 (19) 0.3800	0/65 (30) NC
VAGINA	GRANULAR CELL TUMOR, BENIGN	0/64 (31) 0.2347	0/38 (13) NC	1/45 (16) 0.3404	1/65 (31) 0.5000
Whold Body	C_hemangiosar+heman	2/65 (32) 0.7213	1/65 (32) 0.8810	0/65 (29) 1.0000	1/65 (31) 0.8751

Table 15: Intercurrent Mortality Rate -Male Mice

	Water 0 mg|kg|day (N=25)		Vehicle 0 mg|kg|day (N=25)		30 mg|kg|day (N=25)		100 mg|kg|day (N=25)		300 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. %**	**No. of Death**	**Cum. %**
0 - 13	.	.	.	.	.	.	.	.	1	4.00	10	100.00
14 - 26	1	4.00	1	4.00	1	4.00	.	.	.	.	.	.
Ter. Sac.	24	96.00	24	96.00	24	96.00	25	100.00	24	96.00	.	.

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

Table 16: Intercurrent Mortality Rate -Female Mice

	Water 0 mg|kg|day (N=25)		Vehicle 0 mg|kg|day (N=25)		30 mg|kg|day (N=25)		100 mg|kg|day (N=25)		300 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. %**	**No. of Death**	**Cum. %**
0 - 13	.	.	.	.	.	.	.	.	.	.	10	100.00
14 - 26	.	.	.	.	.	.	1	4.00	.	.	.	.
Ter. Sac.	25	100.00	25	100.00	25	100.00	24	96.00	25	100.00	.	.

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

Table 17: 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	0.8012	0.9885	0.2390	0.9885	.
Homogeneity	Log-Rank	0.7978	0.9885	0.3173	0.9885	.

Table 18: Intercurrent Mortality Comparison between Treated Groups and Water Control, Positive Control and Water Control -Male Mice

Test	Statistic	P_Value Water vs Treated Groups Dose Response	P_Value Water vs. Low	P_Value Water vs. Med	P_Value Water vs. High	P_Value Water vs. Positive
Dose-Response	Likelihood Ratio	0.7749	0.9885	0.2390	0.9885	.
Homogeneity	Log-Rank	0.7978	0.9885	0.3173	0.9885	.

Table 19: 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	0.6509	.	0.2390	.	.
Homogeneity	Log-Rank	0.3916	.	0.3173	.	.

Table 20: Intercurrent Mortality Comparison between Treated Groups and Water Control, Positive Control and Water Control -Female Mice

Test	Statistic	P_Value Water vs Treated Groups Dose Response	P_Value Water vs. Low	P_Value Water vs. Med	P_Value Water vs. High	P_Value Water vs. Positive
Dose-Response	Likelihood Ratio	0.5912	.	0.2390	.	.
Homogeneity	Log-Rank	0.3916	.	0.3173	.	.

Table 21: 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	30 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	100 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	300 mg/kg/day High (N=25) P-value - Vehicle vs. High
HARDERIAN GLAND	ADENOMA	1/25 (25) 0.8093	0/25 (25) 1.0000	1/25 (25) 0.7551	0/25 (24) 1.0000
	CARCINOMA	1/25 (25) 0.6817	1/25 (25) 0.7551	0/25 (25) 1.0000	1/25 (24) 0.7449
harderian gland	C_adenoma+carcinoma	2/25 (25) 0.7802	1/25 (25) 0.8827	1/25 (25) 0.8827	1/25 (24) 0.8752
LIVER	HEMANGIOSARCOMA	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000
	HEPATOCELLULAR ADENOMA	0/25 (25) 0.6186	1/25 (25) 0.5000	1/25 (25) 0.5000	0/25 (24) NC
	HEPATOCELLULAR CARCINOMA	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000
Liver	C_hepatocellular adenoma+carcinoma	1/25 (25) 0.8419	1/25 (25) 0.7551	1/25 (25) 0.7551	0/25 (24) 1.0000
LUNGS WITH BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	3/25 (25) 0.8653	3/25 (25) 0.6664	0/25 (25) 1.0000	2/25 (24) 0.8129
	ALVEOLAR BRONCHIOLAR CARCINOMA	0/25 (25) 0.3661	1/25 (25) 0.5000	0/25 (25) NC	1/25 (24) 0.4898
	SARCOMA	0/25 (25) 0.7475	1/25 (25) 0.5000	0/25 (25) NC	0/25 (24) NC
lungs with bronchi	alveolar bronchiolar adenoma+carcinoma	3/25 (25) 0.7556	4/25 (25) 0.5000	0/25 (25) 1.0000	3/25 (24) 0.6465
MULTICENTRIC	HEMANGIOSARCOMA	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000
SPLEEN	HEMANGIOSARCOMA	0/25 (25) 0.4014	2/25 (25) 0.2449	1/25 (25) 0.5000	1/25 (24) 0.4898
Whole Body	C_Hemangiosarcoma	1/25 (25) 0.6981	3/25 (25) 0.3046	1/25 (25) 0.7551	1/25 (24) 0.7449

Table 22: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25) P-value - Trend	30 mg/kg/day Low (N=25) P-value - Water vs. Low	100 mg/kg/day Med (N=25) P-value - Water vs. Med	300 mg/kg/day High (N=25) P-value - Water vs. High
HARDERIAN GLAND	ADENOMA	1/25 (25) 0.8093	0/25 (25) 1.0000	1/25 (25) 0.7551	0/25 (24) 1.0000
	CARCINOMA	0/25 (25) 0.3661	1/25 (25) 0.5000	0/25 (25) NC	1/25 (24) 0.4898
harderian gland	C_adenoma+carcinoma	1/25 (25) 0.5768	1/25 (25) 0.7551	1/25 (25) 0.7551	1/25 (24) 0.7449
LIVER	HEPATOCELLULAR ADENOMA	0/25 (25) 0.6186	1/25 (25) 0.5000	1/25 (25) 0.5000	0/25 (24) NC
LUNGS WITH BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	2/25 (25) 0.7430	3/25 (25) 0.5000	0/25 (25) 1.0000	2/25 (24) 0.6798
	ALVEOLAR BRONCHIOLAR CARCINOMA	0/25 (25) 0.3661	1/25 (25) 0.5000	0/25 (25) NC	1/25 (24) 0.4898
	SARCOMA	0/25 (25) 0.7475	1/25 (25) 0.5000	0/25 (25) NC	0/25 (24) NC
lungs with bronchi	alveolar bronchiolar adenoma+carcinoma	2/25 (25) 0.6046	4/25 (25) 0.3336	0/25 (25) 1.0000	3/25 (24) 0.4800
SPLEEN	HEMANGIOSARCOMA	3/25 (25) 0.9129	2/25 (25) 0.8257	1/25 (25) 0.9451	1/25 (24) 0.9403
Whole Body	C_Hemangiosarcoma	3/25 (25) 0.9252	3/25 (25) 0.6664	1/25 (25) 0.9451	1/25 (24) 0.9403

Table 23: 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
LUNGS WITH BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	3/25 (25)	10/10 (10) <0.001
Liver	C_hepatocellular adenoma+carcinoma	1/25 (25)	0/10 (1) 1.0000
MULTICENTRIC	HEMANGIOSARCOMA	1/25 (25)	0/10 (1) 1.0000
Whole Body	C_Hemangiosarcoma	1/25 (25)	0/10 (1) 1.0000
harderian gland	C_adenoma+carcinoma	2/25 (25)	0/10 (1) 1.0000

Table 24: Tumor Rates and P-Values for Comparisons between Water Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	Positive (N=10) P-value - Water vs. Positive
LUNGS WITH BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	2/25 (25)	10/10 (10) <0.001
Whole Body	C_Hemangiosarcoma	3/25 (25)	0/10 (1) 1.0000
harderian gland	C_adenoma+carcinoma	1/25 (25)	0/10 (1) 1.0000
lungs with bronchi	alveolar bronchiolar adenoma+carcinoma	2/25 (25)	10/10 (10) <0.001

Table 25: 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	30 mg/kg/day Low (N=25) P-value - Vehicle vs. Low	100 mg/kg/day Med (N=25) P-value - Vehicle vs. Med	300 mg/kg/day High (N=25) P-value - Vehicle vs. High
HARDERIAN GLAND	ADENOMA	1/25 (25) 0.1780	1/25 (25) 0.7551	1/25 (25) 0.7551	3/25 (25) 0.3046
	CARCINOMA	0/25 (25) 0.1534	1/25 (25) 0.5000	0/25 (25) NC	2/25 (25) 0.2449
harderian gland	C_adenoma+carcinoma	1/25 (25) 0.0599	2/25 (25) 0.5000	1/25 (25) 0.7551	5/25 (25) 0.0947
LUNGS WITH BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	3/25 (25) 0.7911	2/25 (25) 0.8257	1/25 (25) 0.9451	2/25 (25) 0.8257
	ALVEOLAR BRONCHIOLAR CARCINOMA	1/25 (25) 0.8131	0/25 (25) 1.0000	1/25 (25) 0.7551	0/25 (25) 1.0000
lungs with bronchi	alveolar bronchiolar adenoma+carcinoma	4/25 (25) 0.8487	2/25 (25) 0.9053	2/25 (25) 0.9053	2/25 (25) 0.9053
SPLEEN	HEMANGIOSARCOMA	1/25 (25) 0.9394	1/25 (25) 0.7551	0/25 (25) 1.0000	0/25 (25) 1.0000
THYMUS	THYMOMA	0/25 (25) 0.2500	0/25 (25) NC	0/25 (25) NC	1/25 (25) 0.5000

Table 26: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25) P-value - Trend	30 mg/kg/day Low (N=25) P-value - Water vs. Low	100 mg/kg/day Med (N=25) P-value - Water vs. Med	300 mg/kg/day High (N=25) P-value - Water vs. High
HARDERIAN GLAND	ADENOMA	2/25 (25) 0.3660	1/25 (25) 0.8827	1/25 (25) 0.8827	3/25 (25) 0.5000
	CARCINOMA	0/25 (25) 0.1534	1/25 (25) 0.5000	0/25 (25) NC	2/25 (25) 0.2449
harderian gland	C_adenoma+carcinoma	2/25 (25) 0.1513	2/25 (25) 0.6954	1/25 (25) 0.8827	5/25 (25) 0.2087
LUNGS WITH BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	0/25 (25) 0.2117	2/25 (25) 0.2449	1/25 (25) 0.5000	2/25 (25) 0.2449
	ALVEOLAR BRONCHIOLAR CARCINOMA	0/25 (25) 0.5000	0/25 (25) NC	1/25 (25) 0.5000	0/25 (25) NC
lungs with bronchi	alveolar bronchiolar adenoma+carcinoma	0/25 (25) 0.1780	2/25 (25) 0.2449	2/25 (25) 0.2449	2/25 (25) 0.2449
SPLEEN	HEMANGIOSARCOMA	1/25 (25) 0.9394	1/25 (25) 0.7551	0/25 (25) 1.0000	0/25 (25) 1.0000
THYMUS	THYMOMA	0/25 (25) 0.2500	0/25 (25) NC	0/25 (25) NC	1/25 (25) 0.5000

Table 27: 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
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
lungs with bronchi	alveolar bronchiolar adenoma+carcinoma	4/25 (25)	10/10 (10) <0.001
harderian gland	C_adenoma+carcinoma	1/25 (25)	0/10 (1) 1.0000

Table 28: Tumor Rates and P-Values for Comparisons between Water Control and Positive Control -Female Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	Positive (N=10) P-value - Water vs. Positive
LUNGS WITH BRONCHI	ALVEOLAR BRONCHIOLAR ADENOMA	0/25 (25)	10/10 (10) <0.001
	ALVEOLAR BRONCHIOLAR CARCINOMA	0/25 (25)	2/10 (3) 0.0079
lungs with bronchi	alveolar bronchiolar adenoma+carcinoma	0/25 (25)	10/10 (10) <0.001
harderian gland	C_adenoma+carcinoma	2/25 (25)	0/10 (1) 1.0000

Figure 1: Kaplan-Meier Survival Functions for Male Rats

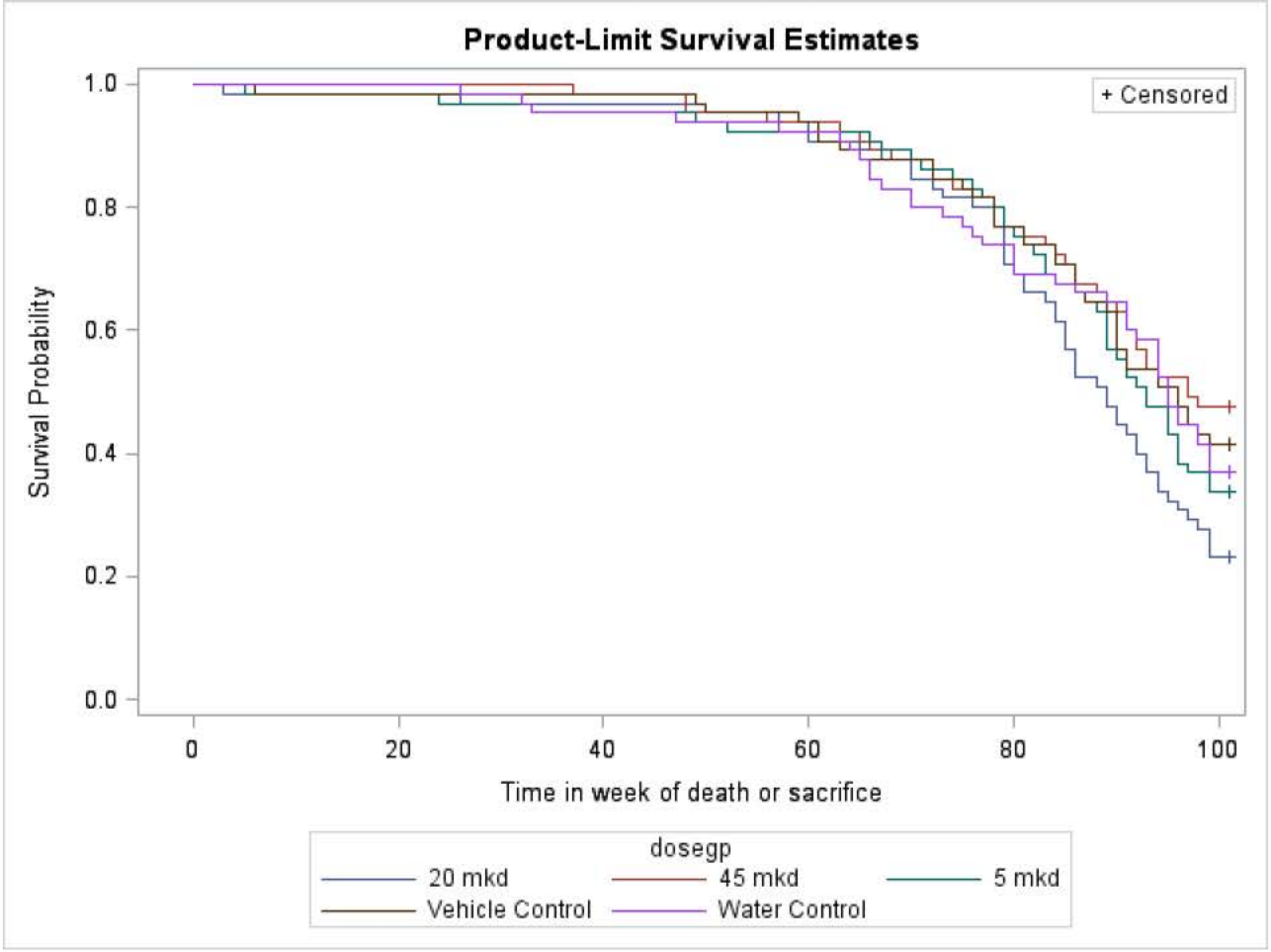


Figure 2: Kaplan-Meier Survival Functions for Female Rats

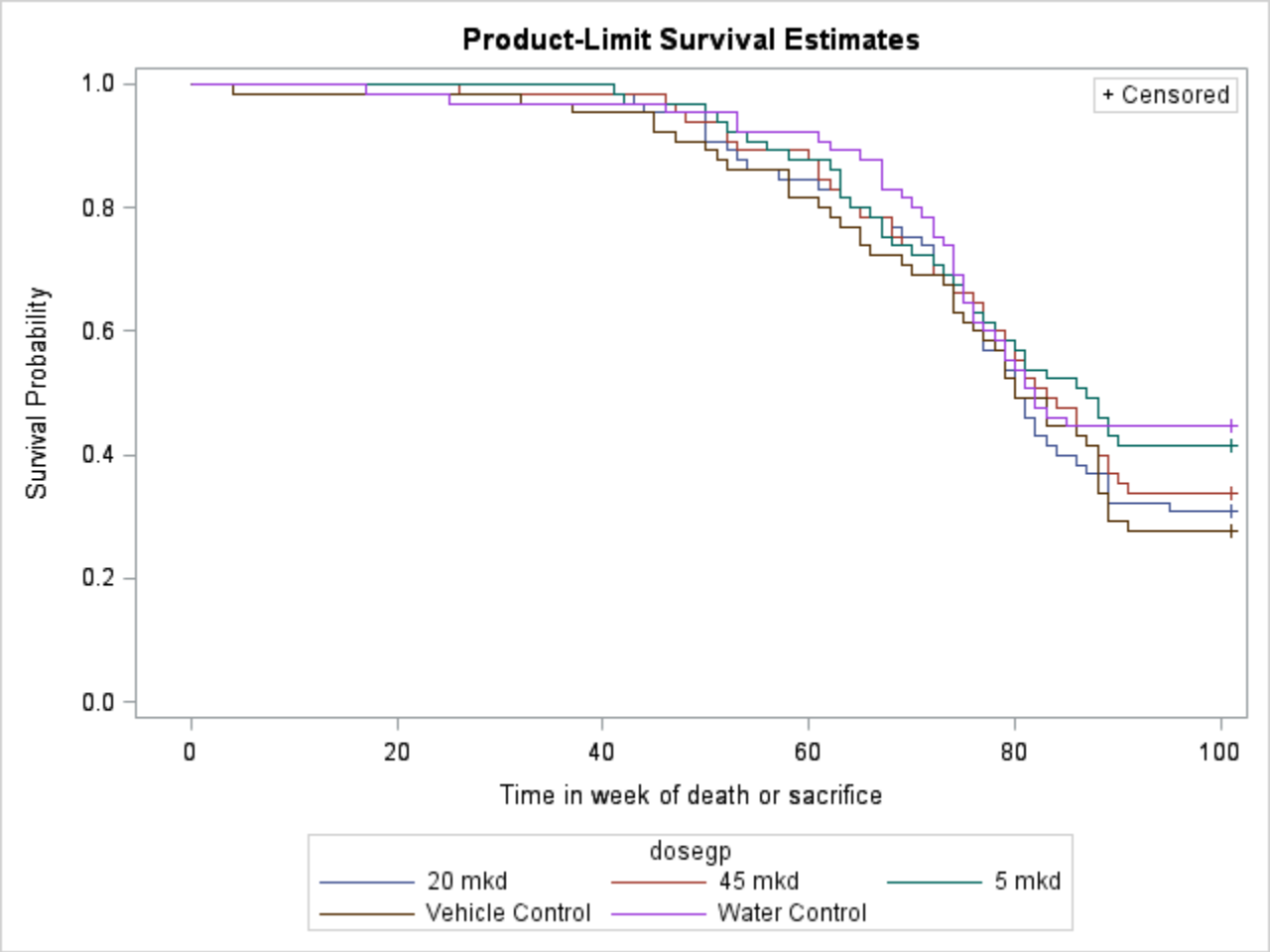


Figure 3: Kaplan-Meier Survival Functions for Male Mice

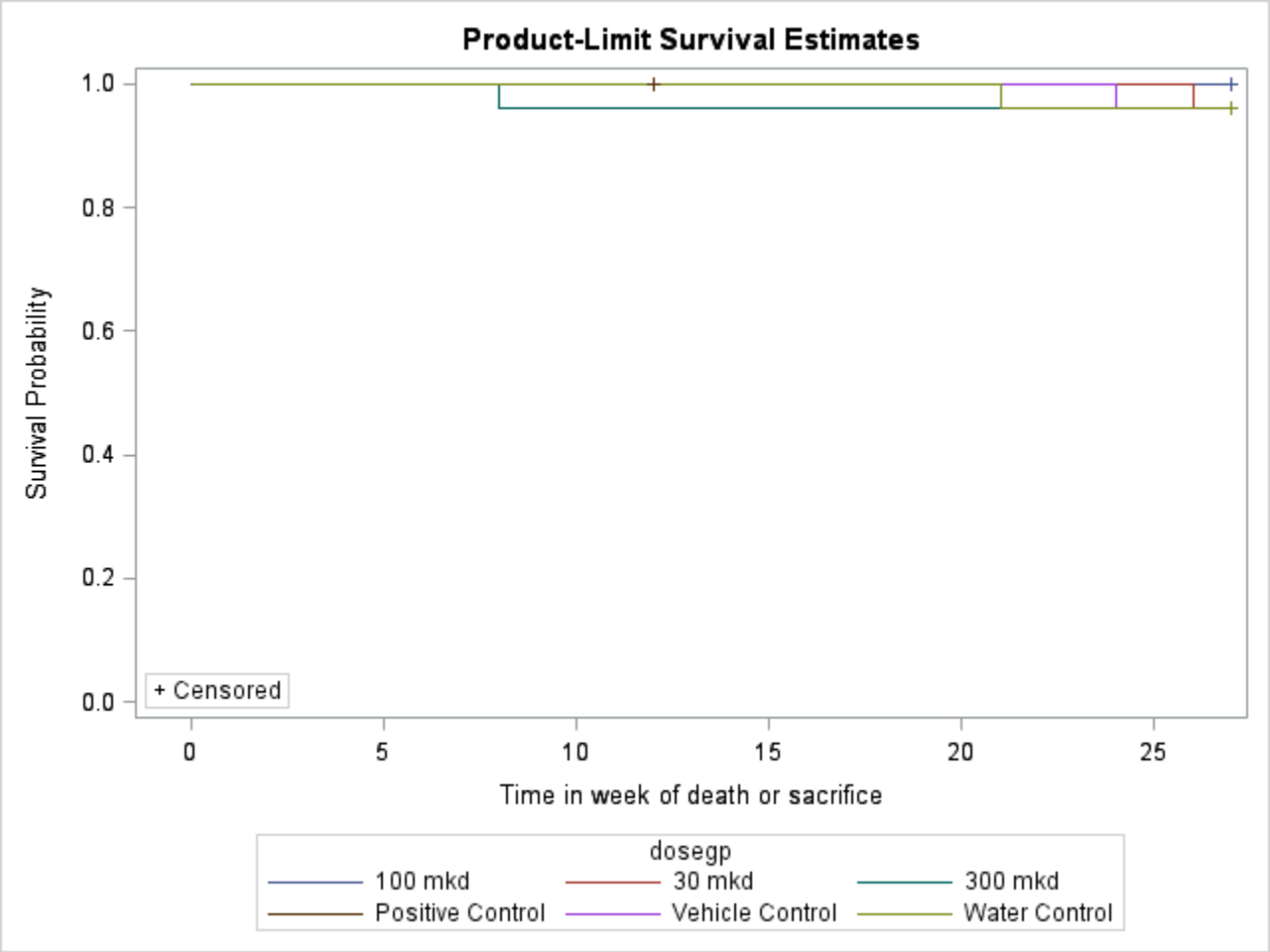
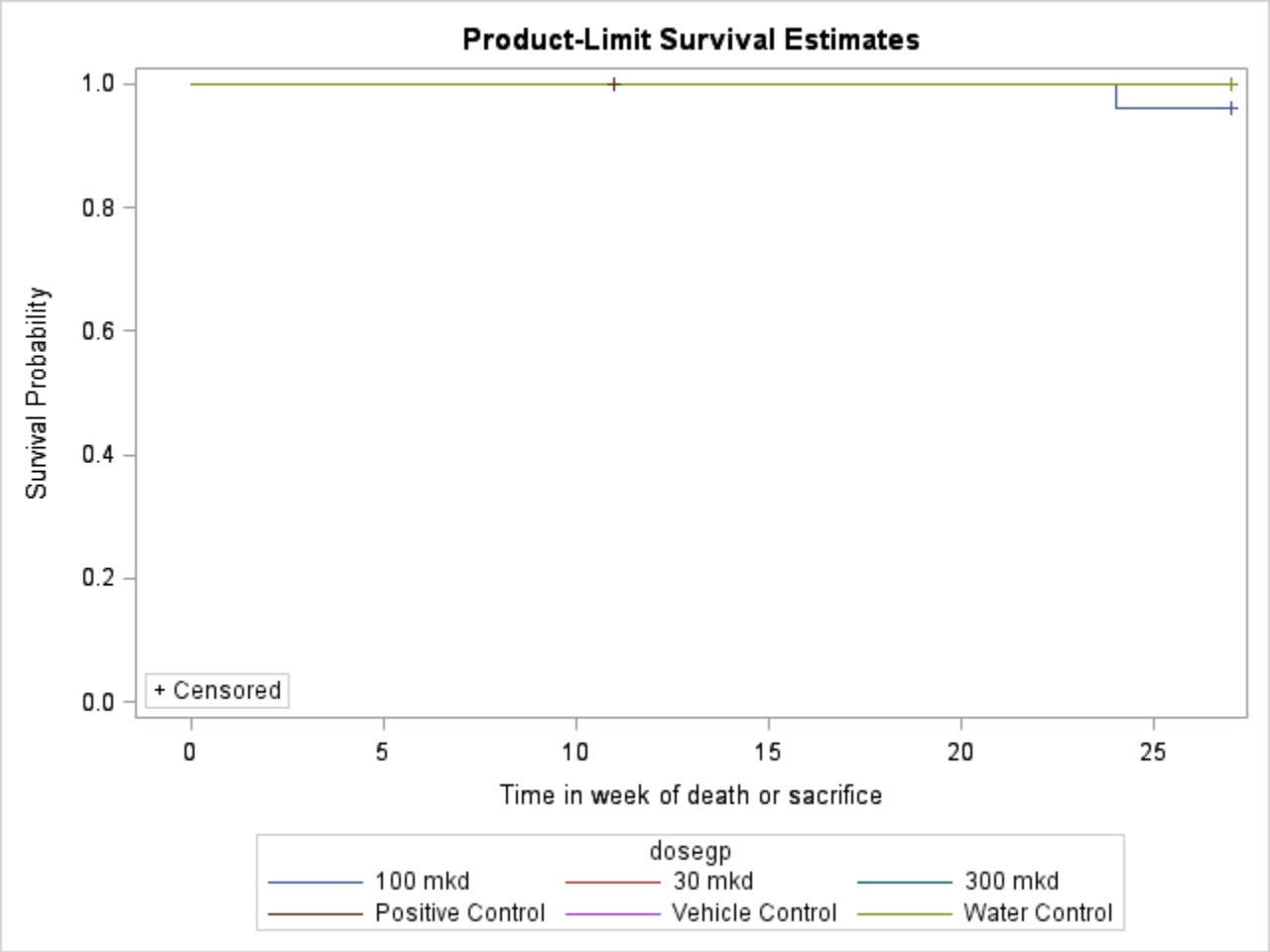


Figure 4: Kaplan-Meier Survival Functions for Female Mice



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/s/

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02/26/2020 02:12:15 PM
placed in DARRTS on behalf of Zhuang Miao, Ph.D., Statistical Reviewer

FENG ZHOU
02/26/2020 02:48:43 PM

KARL K LIN
02/26/2020 02:52:23 PM
Concur with review.

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 212728 / Serial Number 0001 -
Drug Name:	Rimegepant 75 mg ODT (Orally Disintegrating Tablet)
Indication(s):	Acute Migraine with or without Aura in Adults
Applicant:	Biohaven
Date(s):	June 27, 2019 (date received by CDER) February 27, 2020(PDUFA Goal Date)
Review Priority:	Priority (Voucher)
Biometrics Division:	Division of Biometrics 1
Statistical Reviewer:	Jinnan Liu, Ph.D., Statistical Reviewer
Concurring Reviewers:	Kun Jin, Ph.D., Statistical Team Leader Hsien Ming Hung, Ph.D., Division Director
Medical Division:	Division of Neurology Products
Clinical Team:	Laura Jawidzik, M.D., Clinical Reviewer Heather Fitter, M.D., Clinical Team Leader Nicholas Kozauer, M.D., Associate Director Eric Bastings, M.D., Deputy Director Billy Dunn, M.D., Division Director
Project Manager:	Lana Chen, Pharm D

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1 EXECUTIVE SUMMARY

This submission of NDA 212728 is to obtain marketing authorization for Rimegapant 75 mg ODT (Orally Disintegrating Tablet) in the treatment of acute migraine in adults. The efficacy evidence for the Rimegepant 75 mg ODT in NDA 212728 is from one Phase III study BHV3000-303.

1.1 Conclusions and Recommendations

The one pivotal study BHV3000-303 in patients with acute migraine presented a statistical evidence that Rimegapant at 75 mg ODT is efficacious for the treatment of acute migraine based on increased rate of pain freedom and MBS (Most Bothersome Symptom) freedom at two hours post dose.

1.2 Brief Overview of Clinical Study BHV3000-303

Study 303 (BHV3000-303) is a study for acute migraine with one dose level 75 mg in the form of ODT. Study 303 is multi-center, randomized, double-blinded, parallel group and placebo controlled.

1.3 Statistical Issues and Findings

No major statistical issues were found.

2 INTRODUCTION

The pivotal study BHV3000-303 is included in this statistical review for the efficacy evaluation.

2.1 Overview

Rimegepant (BHV-3000) is a calcitonin gene-related peptide (CGRP) receptor antagonist in development for the treatment of migraine.

Table 1 List of All Studies included in Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
BHV-3000-303	MC, R, DB, PG, PC	Placebo/ 682 Drug 75 mg ODT / 669	Free from headache pain at 2 hours post first dose Most Bothersome Symptom free at 2 hours post first dose	21.2% in 75 mg ODT group 10.9% in placebo with p- value < 0.0001 35.1% in 75 mg ODT group 26.8% in placebo with p-value 0.0009

*MC: multi-center, R: randomized, DB: double-blinded, PG: parallel group, PC: placebo controlled.
(Source: Sponsor' result, replicated but not verified by the reviewer at the time of Filing review.)

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form.

Please note that the data files for study 303 is in the cross-referenced NDA (b) (4)
NDA 212728 module 5 contains literature only.

At the time of review the following is the link to the EDR Location:
\\CDSESUB1\evsprod\NDA (b) (4)\0001

Additional patient level flags were provided with updated datasets to identify patients with missing data potentially caused by the e-dairy device software issue for study 1 and 2.
\\CDSESUB1\evsprod\NDA (b) (4)\0007

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There are some minor issues with the study conduct: mainly the sample size planning and the documentation process.

(1) There were two major changes to the study protocol and SAP (Statistical Analysis Plan) after the study start date:

- Change to the list of secondary endpoints and the order of the testing.
- Increase of sample size.

The issue of multiple changes to the secondary endpoints was resolved by the clinical review team providing a list of secondary endpoints overriding the sponsor's plan.

The issue of unplanned sample size increase remains. Please note this was a study with no interim analyses planned nor performed as reported by the sponsor. Sample size was increased by about 37% from 380 to 600 per group in the protocol amendments from the version 2 to the version 3. The sponsor simply said the increase of sample size was to ensure study power. However, the effect size was never clearly specified in the sample size calculation section in any version of the protocol (nor SAP) for this study 303. One possible reason for sponsor to increase the sample size could be that the treatment effects in the completed studies 301 and 302 turned out to be smaller than expected from the Phase2b study. However, if this were the reason, then the protocol for study 303 should have been planned as using the sample size of 600 per group in the version 01. This reflects poorly on the study planning and the documentation process.

The two tables below list the important study dates and document dates for all 3 studies. The final date of the protocol and the SAP was before the "Unblinding dates" of the study by a merely 8 days.

Table 2 Important Study Dates for All 3 Studies

Study	BHV3000-301	BHV3000-302	BHV3000-303
First Patient First Visit	18-July-2017	27-July-2017	27-February-2018
Last Patient Last Visit	26-January-2018	31-January-2018	15-October-2018
Database Lock	01-March-2018	06-March-2018	21-November-2018
Unblinding Dates	01-March-2018	07-March-2018	23-November-2018

(Source: Cover Letter by sponsor submitted on 12/4/2019 under SN 24 of NDA (b) (4)

Table 3 Important Study Documents Dates for All 3 Studies

Study	BHV3000-301	BHV3000-302	BHV3000-303
Protocol v1	12-April-2017	12-April-2017	03-January-2018
Protocol v2	11-July-2017	11-July-2017	06-March-2018
Protocol v3	06-October-2017	06-October-2017	03-May-2018
Protocol v4	23-January-2018	23-January-2018	25-July-2018
SAP v1	28-February-2018	05-March-2018	02-October-2018
SAP v2	20-June-2018	20-June-2018	15-November-2018
CSR	22-Mar-2019	22-Mar-2019	16-April-2019

(Source: reviewer's own analysis using submission history.)

(2) This study appears to be overpowered by design.

A planned sample size of 108 per group will have power > 80% to detect the effect size "from 15% to 31% for pain free at 2 hours", as observed in the Phase 2b study.

A planned sample size of 380 per group will have power >.999.
A planned sample size of 600 per group will have power >.999.

The sample size of 600 per group will have power 81.6% to detect an effect size "from 15% to 21.5% for pain free at 2 hours". Please note that the 6.5% increase is far smaller than the 16% as expected based on Phase 2b study.

We are concerned that:

- An overpowered trial can detect smaller but statistically significant differences that may or may not be clinically significant.
- An overpowered study has too large a sample size and wastes resources.

We defer to the clinical review team to comment on the clinically meaningful effect size.

(3) There was a study site (002) with multiple problems discovered by the sponsor at its own internal auditing which initiated around July 6, 2018 and ended November 1, 2018 which uncovered issues dated back to May of 2018. In the letter submitted by the sponsor on 09-Nov-2018, the problems described included the following:

- One study personnel could not produce a proper medical license.
- The study drug was not properly stored that it should be stored at a place climate - controlled (temperature and humidity) but it was left in a metal cabinet during the summer months in Nashville, TN.
- Some consent forms were dated after the study procedure.
- Several subjects did not have reliable vital signs data, medical history data which were part of the screening and inclusion/exclusion criteria.
- There were data entered into the EDC software system for Biohaven study with no paper forms to substantiate.
- The audit trails in the EDC system for Biohaven study presented different entry dates from the visit dates in the EMR -eClinic system.
- Underreporting and late reporting of protocol deviations to the IRB by the site investigator.

As a result, the site was put on enrollment hold on July 11, 2018. No further subjects were enrolled at this site. Statistically, removal of this site had no effect on the efficacy results. Please refer to the clinical review for more details about the problems with this site.

In summary, the above issues with the study conduct and data quality do not seem to affect the results of primary analyses.

3.2 Evaluation of Efficacy Study – 303

3.2.1 Description of the Study

This study had its first subject enrolled on 27 February 2018, and the last subject completed on 15 October 2018.

The study was conducted at 69 centers in the United States of America.

The purpose of this study was to evaluate the effect of Rimegapant 75 mg ODT compared to placebo on the rates of pain freedom at 2 hours and MBS freedom at 2 hours in subjects with acute migraine.

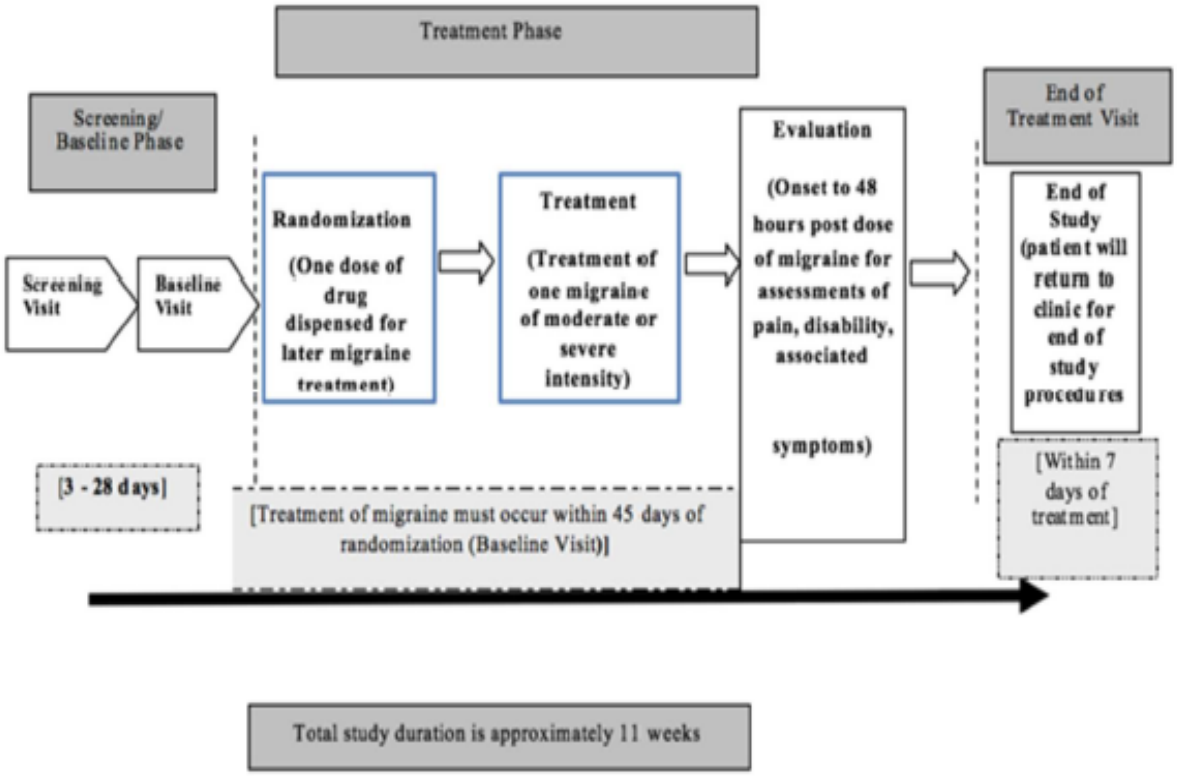
Eligible subjects were adults 18 years of age or above with history of migraine for at least 1 year, migraine if untreated lasting about 4 to 72 hours on average, 2 to 8 attacks of moderate or severe intensity per month within the last 3 months, < 15 headache days per month in the last 3 months, with migraine onset before the age of 50 years.

The total duration of the study was up to 11 weeks. This included a 3- to 28-day screening period, an acute treatment phase that could last up to 45 days or until the subject had a migraine that reached moderate or severe intensity, and an end-of-treatment visit 7 days after the administration of the study medication.

Headache pain-freedom was defined as a reduction in headache severity from moderate (2), or severe (3) at baseline to none (0) at the 2 hours post dose timepoint.

After completion of all screening evaluations, all eligible subjects were randomized in a 1:1 ratio to the Rimegepant or placebo treatment groups. The randomization was stratified by the usage of prophylactic migraine medications (yes or no).

Figure 1 Study Design Diagram – Study BHV3000-303



(Source: study protocol.)

3.2.2 Efficacy Variables

3.2.2.1 Primary Endpoints

The two co-primary endpoints for this study were rates of pain freedom at 2 hours and MBS freedom at 2 hours post the initial dose of the study drug (or placebo) as assigned treating a qualifying acute migraine attack during the double-blind treatment phase. The MBS was decided before the dosing.

3.2.2.2 Secondary Endpoints

1. Pain relief at 2 hours.
2. Sustained pain free from 2 to 24 hours.
3. Use of Rescue Medication.
4. Functional Disability at 2 hours.

Please refer to the clinical review for more details on the rationales behind the selection of the above 4 secondary endpoints and the order of them.

Both the list of secondary endpoints and the hierarchical testing order of these endpoints changed throughout the 4 versions of the protocol, with the final version (version 4) of the protocol listed a total of 21 secondary endpoints. But we will only review the above 4 considered as most clinically relevant by the clinical reviewer.

3.2.3 Statistical Analysis Methods

Efficacy analyses were based on the mITT population, which included subjects who had a qualified migraine attack and took the investigational product and completed at least 1 evaluable post baseline efficacy data point. Subjects were grouped based on the assigned treatment. Efficacy analyses were based on the initial dose.

For the two co-primary endpoints, the between-group difference in the percentage of pain free subjects or MBS (Most Bothersome Symptom) free subjects at 2 hours post dose was assessed by using Cochran-Mantel-Haenszel (CMH) weights (sample size weights), stratified by prophylactic migraine medication use.

Subjects who took rescue medication were considered as failures for any efficacy evaluations that are coincident or follow the time of the rescue medication.

Subjects that recorded their MBS (Most Bothersome Symptom) after taking the investigation product (IP), or who did not provide an MBS, were considered failures for the analysis of MBS.

Missing data at 2 hours post-dose will be imputed as failures (NC=F). If a stratum (prophylactic medication use: yes or no) has sparse data (less than 5 subjects), then the strata will be pooled.

For treatment comparisons, an estimate of the rate of achieving a response, as well as the corresponding p-value, will be computed.

3.2.3.1 Multiplicity Adjustment

The multiplicity adjustment method was pre-specified and deemed to be adequate.

If the primary endpoint tests were both significant, then the secondary endpoints were evaluated using a fixed sequence hierarchical gate-keeping procedure, with each test in the hierarchy conducted at $p = 0.05$.

If one of the analyses was not statistically significant, then all subsequent analyses would be exploratory rather than confirmatory. The 4 secondary endpoints would be testing one by one in the order as described in the above section.

3.2.4 Patient Results

3.2.4.1 Patient Disposition

A total of 1811 subjects were enrolled.

A total of 1466 subjects were randomized: 732 subjects to receive BHV3000 and 734 to Placebo.
A total of 1375 subjects used at least 1 dose of the study drug were analyzed for safety.
A total of 1351 subjects treated a qualifying migraine attack and provided at least 1 post dose assessment and were included in the mITT population: 669 for BHV3000 and 682 for placebo.

Of the 91 (6.2%) subjects who were randomized but not treated, 53 subjects never experienced migraine of moderate or severe intensity, 16 subjects were lost to follow-up, 12 subjects withdrew consent. Other reasons include pregnancy (2 subjects), and other (5 subjects), adverse event (1 subject), non-compliance with study drug (1 subject) and protocol deviation (1 subject).

Of the 1375 treated subjects, 1368 (99.5%) completed the acute phase of the study. Of the 7 (0.5%) subjects who did not complete the acute phase, 4 subjects were lost to follow-up (3 BHV3000 subjects and 1 placebo subjects), 1 placebo subject had a protocol deviation, and 2 placebo subjects withdrew from the study.

Table 4 Patient Disposition - Study BHV-3000-303

Analysis Populations, n	**BHV3000 (75 mg)**	**Placebo**	**All Subjects**
ITT population (randomized)	732	734	1466
Safety Population (treated)	682	693	1375
mITT Population	669	682	**1351**

(Source: modified from the Table 10-1 in the sponsor's study report, verified by the statistical reviewer.)

3.2.4.2 Patient Demographics

Of the 1351 subjects in the mITT population, majority were women (84.9%), white (75.3%), and the mean age was 39.3 (18 to 76) years. The treatment groups were balanced for these baseline demographic characteristics.

Table 5 Patient Baseline Demographics – mITT – Study BHV-3000-303

	BHV3000 (75 mg) N=669	Placebo N=682	All Subjects N=1351
Age (years), n	669	682	1351
Mean (SD)	40.29 (12.08)	40.03 (11.87)	40.16 (11.97)
Median	39.7	38.9	39.3
Minimum	18	18	18
Maximum	76	72	76
Gender, n (%)	669	682	1351
Female	568 (84.9%)	579 (84.9%)	1147 (84.9%)
Male	101 (15.1%)	103 (15.1%)	204 (15.1%)
Race, n (%)	669	682	1351
American Indian or Alaska Native	4 (0.6%)	3 (0.4%)	7 (0.5%)
Asian	8 (1.2%)	19 (2.8%)	27 (2.0%)
Black or African American	141 (21.1%)	125 (18.3%)	266 (19.7%)
Native Hawaiian or other Pacific Islander	11 (1.6%)	5 (0.7%)	16 (1.2%)
White	496 (74.1%)	521 (76.4%)	1017 (75.3%)
Multiple	7 (1.0%)	9 (1.3%)	16 (1.2%)
Unknown	2 (0.3%)	0	2 (0.1%)
BMI (kg/m2), n	668	680	1348
Mean (SD)	31.12(8.17)	30.64 (8.03)	30.88 (8.10)
Median	29.85	29.25	29.55
Minimum	16.5	15.1	15.1
Maximum	63.8	69.7	69.7

BMI = body mass index
(Source: modified from the Table 10-2 in the sponsor's study report, verified by the statistical reviewer.)

3.2.4.3 Patient Baseline Disease Characteristics

Baseline disease characteristics were consistent with a migraine population and well balanced across the treatment groups.

The mean (SD) age at migraine onset was 20.9 (10.23) and 21.1 (10.22) in the BHV 3000 and the placebo groups, respectively.

The mean (SD) migraine per month was 4.6 (1.80) and 4.5 (1.78) respectively.

Table 6 Patient Baseline Disease Characteristics - mITT - Study 303

	BHV3000 (75 mg)	Placebo	All Subjects
Age at Migraine Disease Onset (Years)			
N	669	682	1351
Mean (SD)	20.9 (10.23)	21.1 (10.22)	21.0 (10.22)
Median	19.0	19.0	19.0
Min, Max	2, 49	3, 49	2, 49
Number of Moderate to Severe Migraines per Month			
N	669	682	1351
Mean (SD)	4.6 (1.80)	4.5 (1.78)	4.6 (1.79)
Median	4.0	4.0	4.0
Min, Max	2, 8	2, 8	2, 8
Average Duration of Untreated Migraine Attacks (Hours)			
N	669	682	1351
Mean (SD)	28.7 (21.50)	30.4 (21.69)	29.5 (21.60)
Median	24.0	24.0	24.0
Min, Max	4, 72	4, 72	4, 72
Historically/typically Migraine MBS, n (%)	669	682	1351
Photophobia (sensitivity to light)	394 (58.89%)	376 (55.13%)	770 (56.99%)
Phonophobia (sensitivity to sound)	125 (18.68%)	136 (19.94%)	261 (19.32%)
Nausea	148 (22.12%)	169 (24.78%)	317 (23.46%)
Migraine with Aura, n (%)	224 (33.48%)	256 (37.54%)	480 (35.53%)
Use of Prophylactic Medication, n (%)	93 (13.90%)	94 (13.78%)	187 (13.84%)
Triptan Use	669	682	1351
Historic Use of Triptans, n (%)	214 (31.99%)	226 (33.14%)	440 (32.57%)
Current Use of Triptans, n (%)	186 (27.80%)	198(29.03%)	384 (28.42%)
Cardiac and Other Risk Factors	669	682	1351
Family History of Coronary Artery Disease, n (%)	135 (20.18%)	136 (19.94%)	271 (20.04%)
Treatment for Hypertension	89 (13.30%)	68 (9.97%)	157 (11.62%)
Current Smoker	86 (12.86%)	73 (10.70%)	159 (11.77%)

(Source: Reviewer's own analysis.)

3.2.5 Results and Conclusions

3.2.5.1 Efficacy Results of the Primary Endpoints

The results reported by the sponsor were confirmed.

Table 7 Primary Endpoint Analyses- Study 303

	mITT	
	BHV 3000 (75 mg ODT)	**Placebo**
Pain Freedom at 2 Hours		
N	669	682
n	142	74
% Responders	21.23%	10.85%
Difference from Placebo	10.38%	-
p-value	<.0001	-
Freedom from MBS at 2 Hours		
N	669	682
n	235	183
% Responders	35.12%	26.83%
Difference from Placebo	8.29%	-
p-value	.0009	-

N = total patients; n = number of responders.
Risks (percentages) were calculated using CMH(Cochran-Mantel-Haenszel) weights, stratified by use of prophylactic migraine medication.
(Source: reviewer's own analysis and sponsor's analysis Table 11-1 verified by the reviewer.)

The primary analysis for Pain Freedom at 2 hours included 1351 patients. There was a statistically significant ($p < 0.0001$) increase in the rate of pain freedom at 2 hours without rescue medication from 10.85% in the placebo group to 21.23% in the BHV 3000 (75 mg ODT) group. The primary analysis for Freedom from MBS at 2 hours included 1351 patients. There was a statistically significant increase ($p = 0.0009$) in the rate of MBS free at 2 hours without rescue medication from 26.83% in the placebo group to 35.12% in the BHV 3000 (75 mg ODT) group. Patients with missing data at 2-hour time point were counted as treatment failures. As a clinical rule, patients with rescue medication use prior to the 2-hour time point were considered as treatment failures.

The MBS had to be identified before the subject took study medication. Patients who identified the MBS after taking the study medication were counted as treatment failures.

3.2.5.2 Missing Data and Sensitivity Analyses

The overall missing rate was relatively low for this study and were similar among the groups as can be seen from the following table which shows the missing data patient counts for each group.

If the subject did not record a pain severity at the time of dosing, then this subject was not included in the analysis. If the subject did not record a pain severity rating at 2 hours post dosing, then this subject's pain free status at 2 hours was set as missing.

Table 8 Patient Counts at Time of Dosing and Two Hours (rescue*= failure)– Study 303

	Pain at Time 0	Pain at 2 Hours	Missing n	Missing %	MBS at Time 0	MBS at 2 Hours	Missing n	Missing %
75 mg ODT	669	649	20	2.99%	669	636	33	4.93%
placebo	682	654	28	4.11%	682	645	37	5.43%

(Source: Reviewer's own analysis.)

If the subject failed to identify a symptom as the MBS before dosing, then this subject's MBS status at 2 hours was set as treatment failure. There was only one such patient.

As a clinical rule, if the subject took any recue medication prior to the 2 hours timepoint, then this patient was considered as treatment failure.

In the primary efficacy analysis, subjects with missing data at 2 hours timepoint were counted as treatment failures.

The next table shows the breakdown of patient counts with or without actual efficacy measurements at 2 hours (Yes/No/Missing).

Table 9 Descriptive Patient Counts for Data Status at 2 Hours – mITT- Study 303

		Pain			**MBS**	
75 mg ODT	669	142	Yes	669	237	Yes
		507	No		399	No
		20	2-Hour missing		33	2-Hour Missing
Placebo	682	75	Yes	682	186	Yes
		579	No		459	No
		28	2-Hour missing		37	2-Hour Missing

(Source: Reviewer's own analysis.)

The following table shows the distribution of the rescue medication use for treatment groups.

Table 10 Descriptive Patient Counts for Rescue Meds before 2-hours – mITT- Study 303

		Pain			**MBS**	
75 mg ODT	5	0	Yes	5	2	Yes
		5	No		3	No
		0	2-Hour missing		0	2-Hour missing
Placebo	10	1	Yes	10	2	Yes
		9	No		8	No
		0	2-Hour missing		0	2-Hour missing

(Source: Reviewer's own analysis.)

The table below shows the patient efficacy results after applying the clinical rule of rescue medication use before 2 hours = failure. Please note 1 patient in the placebo group did not identify

the MBS before taking the treatment and was set as treatment failure even though the observed data showed that this patient was free of the MBS at 2 hours post dosing in the e-Dairy.

Table 11 Counts for Patients' Data Status at 2H (rescue* = failure) – mITT- Study 303

			Pain			MBS
75 mg ODT	669	142	Yes	669	235	Yes
		507	No		401	No
		20	2-Hour Missing		33	2-Hour Missing
Placebo	682	74	Yes	682	183	Yes
		580	No		462	No (Note:1 patient did not identify the MBS before taking the treatment and was set as treatment failure.)
		28	2-Hour Missing		37	2-Hour Missing

(Source: Reviewer's own analysis.)

In the sensitivity analyses performed by the sponsor, missing data at 2 hours post-dose was imputed using LAV (Last Available Value). Additional sensitivity analysis used only data from complete cases (data present at baseline and 2 hours).

Results for both sensitivity analyses were consistent with those observed for the primary analysis.

Table 12 Sensitivity Analyses – Study 303

	mITT		mITT - LAV		Complete Case	
	BHV 3000 (75 mg ODT)	Placebo	BHV 3000 (75 mg ODT)	Placebo	BHV 3000 (75 mg ODT)	Placebo
Pain Free 2H						
N	669	682	669	682	649	654
n	142	74	145	77	142	74
% Responders	21.23%	10.85%	21.7%	11.3%	21.9%	11.3%
Difference from Placebo	10.38%	-	10.38%	-	10.58%	-
p-value	<.0001	-	<.0001	-	<.0001	-
MBS Free 2H						
N	669	682	669	682	636	645
n	235	183	240	189	235	183
% Responders	35.1%	26.8%	36.5%	28.1%	37.0%	28.4%
Difference from Placebo	8.29%	-	8.4%	-	8.6%	-
p-value	.0009	-	.0010	-	.0010	-

N = total patients; n = number of responders.
LAV = Last Available Value NS = Not Significant.
(Source: reviewer's analysis, Table 11-1, Table 14.2.1.1.4.1, Table 14.2.1.1.4.2, Table 14.2.1.2.4.1 and Table 14.2.1.2.4.2 from the study report, verified by the reviewer.)

3.2.5.3 Efficacy Results of the Secondary Endpoints

Pain Relief at 2 hours

Pain relief was defined as a reduction in pain severity from moderate (2) or severe (3) at the time of dosing to mild (1) or none (0) at the indicated assessment time, with no rescue medication before the 2 hours timepoint. The mITT population was used for the analysis. The proportions of subjects with pain relief at 2 hours were 59.3%, and 43.3% for the 75 mg and placebo groups, respectively ($p < .0001$ versus placebo).

Table 13 Responder Rate: Pain Relief at 2 Hours – mITT Population - Study 303

	75 mg ODT	**Placebo**
N	669	682
Pain Relief at 2 hours, n (%)	397 (59.3%)	295 (43.3%)
Difference from Placebo	16.09%	
p-value vs Placebo	<.0001	

N = total patients; n = number of responders.
(Source: Table 14.2.2.6.2 in study report, verified by the reviewer.)

Sustained Pain Freedom at 24 hours

Sustained pain-free at 24 hours was defined as pain-free at 2 hours after first dose and at the 24 hours, having not used any medications after the first dose. The proportions of subjects with sustained pain free at 24 hours were 15.7% and 5.6% for the 75 mg and placebo groups, respectively ($p < .0001$ versus placebo).

Table 14 Responder Rate: Sustained Pain Free at 24 Hours – mITT - Study 303

	75 mg ODT	**Placebo**
N	669	682
Sustained Pain Free at 24 hours, n (%)	105 (15.7%)	38 (5.6%)
Difference from Placebo	10.12%	
p-value vs Placebo	<.0001	

N = total patients; n = number of responders.
(Source Table 14.2.2.11.1 in study report, verified by the reviewer).

Use of Rescue Medication within 24 Hours

The proportions of subjects used rescue medication within 24 hours were 14.2% and 29.2% for the 75 mg and placebo groups, respectively (p <.0001 versus placebo).

Table 15 Responder Rate: Use of Rescue Mediations within 24 Hours – mITT - Study 303

	75 mg ODT	Placebo
N	669	682
Use of Rescue Mediations within 24 Hours, n (%)	95 (14.2%)	199 (29.2%)
Difference from Placebo	-14.98%	
p-value vs Placebo	<.0001	

N = total patients; n = number of responders.
(Source Table 14.2.2.7.1 in study report, verified by the reviewer).

Freedom from Functional Disability at 2 hours

The impact of treatment on functional disability was assessed using a single-question scale. Subjects rated the level of disability they perceived as a result of their migraine in performing normal actions. This was to be done in the e-Diary using a 4-point numeric rating scale (normal function, mild impairment, severe impairment, required bedrest).

The proportions of subjects achieving freedom from functional disability at 2 hours were 38.1% and 25.8% for the 75 mg and placebo groups, respectively (p <.0001 versus placebo).

Table 16 Responder Rate: Freedom from Functional Disability at 2 Hours – mITT - Study 303

	75 mg ODT	Placebo
N	669	682
Freedom from Functional Disability at 2 hours, n (%)	255 (38.1%)	176 (25.8%)
Difference from Placebo	12.31%	
p-value vs Placebo	< .0001	

N = total patients; n = number of responders.
(Source: Table 14.2.2.10.2 in study report, verified by the reviewer).

3.3 Evaluation of Safety

Please refer to the clinical review for details on safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age and Geographic Region – Study 303

In the study 303, the median age of the subjects was about 40 years, with the percentage of female as 85%, and the majority being either black or white, with the percentage of being white 74% and 76%, being black as 21% and 18% for the 75 mg ODT group and the placebo group respectively.

There is no need to subgroup by region, since the entire study was conducted in the US.

Table 17 Age, Gender, and Race Summaries by Treatment Group - Study 303

	Age (Median)	Gender (%F)	Race (%White)	Race (%Black)
75 mg ODT	40	84.9	74.1	21.1
Placebo	39	84.9	76.4	18.3
Overall	40	84.9	75.3	19.7

(Reviewer's result.)

For study 303, analyses for the treatment effect across clinically meaningful subgroups such as age, gender, and race were performed.

The trend in treatment success appears to be similar across subgroups.

Table 18 Findings in Subgroup Populations – Age, Gender and Race – Study 303

Pain Free 2 hours	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate
	Age < 40			**Age >= 40**					
75 mg ODT	341	72	21.1%	328	70	21.4%			
Placebo	368	42	11.5%	314	32	10.2%			
	Gender = Female			**Gender = Male**					
75 mg ODT	568	128	22.6%	101	14	13.9%			
Placebo	579	62	10.7%	103	12	11.7%			
	Race = White			**Race = Black**			**Race = All Other**		
75 mg ODT	496	105	21.2%	141	33	23.3%	30	4	13.3%
Placebo	521	54	10.4%	125	16	12.9%	36	4	11.1%
MBS Free 2 hours	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate	Total Patient	Success Count	Success Rate
	Age < 40			**Age >= 40**					
75 mg ODT	341	118	34.6%	328	117	35.7%			
Placebo	368	103	28.0%	314	80	25.5%			
	Gender = Female			**Gender = Male**					
75 mg ODT	568	206	36.3%	101	29	28.8%			
Placebo	579	161	27.8%	103	22	21.6%			
	Race = White			**Race = Black**			**Race = All Other**		
75 mg ODT	496	170	34.3%	141	57	40.2%	30	8	26.7%
Placebo	521	135	25.9%	125	37	29.6%	36	11	30.6%

(Sponsor's result verified by the reviewer.)

4.2 Other Special/Subgroup Populations

None.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The one pivotal study provided statistical evidence that Rimegapant 75 mg ODT is effective in treating patients with acute migraine.

No major statistical issues were identified.

5.2 Conclusions and Recommendations

The efficacy results obtained from the statistical analyses of the one pivotal study support the conclusion that Rimegapant 75 mg ODT is effective in treating patients with acute migraine.

5.3 Labeling Recommendations

Table 19 Efficacy Result from Study 303 – mITT population

	mITT	
	BHV 3000 (75 mg ODT)	**Placebo**
Pain Freedom at 2 Hours		
N	669	682
n	142	74
% Responders	21.23%	10.85%
Difference from Placebo	10.38%	-
p-value	<.0001	-
Freedom from MBS at 2 Hours		
N	669	682
n	235	183
% Responders	35.12%	26.83%
Difference from Placebo	8.29%	-
p-value	.0009	-

N = total patients; n = number of responders.
Risks (percentages) were calculated using CMH(Cochran-Mantel-Haenszel) weights, stratified by use of prophylactic migraine medication.
(Source: reviewer's own analysis and sponsor's analysis Table 11-1 verified by the reviewer.)

6 REFERENCES

[1] FDA Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. http://www fda.gov/cder/guidance/1397fnl.pdf

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/s/

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01/21/2020 03:38:03 PM

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01/21/2020 05:37:05 PM
I concur with the review.

HSIEN MING J HUNG
01/22/2020 09:33:25 AM