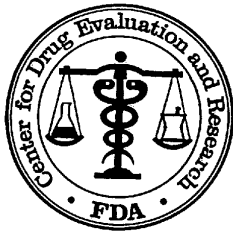


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216386Orig1s000

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 216386
Drug Name:	Zavzapret (zavegepant)- BHV-3500
Indication(s):	for the acute treatment of migraine, with or without aura, in adults
Studies	One Two-Year Intranasal Carcinogenicity Study of BHV-3500 in Rats and One Six-Month Carcinogenicity Study of BHV-3500 by Intranasal Administration in CByB6F1/Tg rasH2 Hemizygous Mice
Applicant:	Sponsor: Biohaven Pharmaceutical Holding Co Ltd 215 Church St New Haven, Connecticut 06510, USA
	Test facility for rat study: (b) (4)
	Test facility for mouse study: (b) (4)
	(b) (4)
Documents Reviewed:	Electronic submission, dated: May 3 rd , 2022, via SN0102 Electronic data submitted March 9 th , 2022, via SN0001.
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Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Pharm/Tox for Neuroscience
Reviewing Pharmacologist:	Elizabeth, Khoury, Ph.D.
Project Manager:	Lana Chen, RPM, DN2.
Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the potential carcinogenicity of BHV-3500, for the treatment of migraines, when administered intranasally at appropriate drug levels for about 104 weeks in rats and 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Khoury.

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

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups, one saline control group and one vehicle control group. Three hundred and twenty-five Sprague Dawley rats of each sex were assigned to three treated groups, one saline control group and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 65 animals, as indicated in Table 1. The dose levels for the three treated groups were 2, 9, and 18.8 mg/kg/day for both male and female rats, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The saline control group received (0.9% sodium chloride), the vehicle control consisted of a solution of (b) (4) mM succinic acid and (b) (4) % (w/v) (b) (4) dextrose, USP, in Sterile Water for Injection, USP; the final pH of the vehicle was adjusted to 5.8 and 6.2 as necessary, administered intranasally for about 104 weeks in the same manner as the treated groups. Due to survival rates, both male and female groups were terminated prior to the protocol scheduled terminal sacrifice. Female groups were sacrificed beginning on day 582 (week 84). Male groups were sacrificed beginning on day 665 (week 95).

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal ^a	
		Male	Female	Males	Females
Saline controls	1	0	0	65/65	65/65
Vehicle Control	2	0	0	65/65	65/65
Low	3	2	2	65/61	65/64
Medium	4	9	9	65/59	65/65
High	5	18.8	18.8	65/65	65/65

^a number of animals for which survival data was available / number of animals for which at least one organ was examined.

Female groups were sacrificed beginning on day 582 (week 84). Male groups were sacrificed beginning on day 665 (week 95).

During the study period all animals were observed for general health/mortality and moribundity twice daily (a.m. and p.m.), abnormal findings were recorded throughout the study. Animals were not removed from cage during observation, unless necessary for identification or confirmation of possible findings. Detailed clinical observation was conducted at least once every 2 weeks beginning during Week -2, and weekly during the study period. Abnormal findings or an indication of normal was recorded. In addition, for each grossly visible or palpable mass, the time of onset, location, size, appearance, and progression was recorded. Any animal showing signs of severe debility or intoxication, and if determined to suffer excessively was euthanized. Observations will include, but will not be limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals in Groups 1 (sterile saline

control), 2 (vehicle control), and 5 (high dose) and from all main study rats found dead or killed moribund or sacrificed at the end of the experiment.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's analysis, the tests for survival comparisons were performed separately for each sex. The survival function of each group was estimated using the Kaplan-Meier product-limit method applied on daily intervals. The log-rank test was used to make pairwise comparisons of each treated group (low, mid, and high doses [Groups 3, 4, and 5, respectively]) with each control group (saline control [Group 1] and vehicle control [Group 2]). All tests were 2-sided and conducted at the 0.05 significance level.

The time to death or sacrifice (in weeks, calculation detailed in the following) was the dependent variable. The test article-treated groups were included as the strata. Any animal with accidental injury that caused its death, or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day.

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy were 23 (35%), 18 (28%), 20 (31%), 20 (31%), and 22 (34%), in the saline control, vehicle control, low, medium, and high dose groups, in male rats, respectively, and 23 (35%), 20 (31%), 23 (35%), 27 (42%), and 29 (45%), in the saline control, vehicle control, low, medium, and high dose groups, in female rats, respectively. The sponsor's report showed, there were no statistically significant findings among males or females for survival rates.

2.1.2. Tumor data analysis

The statistical evaluation of tumor data was done separately for each sex, the incidence of tumors was analyzed by Peto's mortality-prevalence method (Peto, 1980) without continuity correction, incorporating the context (incidental or fatal) in which tumors were observed. 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.

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 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 saline 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 incidence. The analysis of tumors was based on the following fixed time intervals: weeks 0-50, 51-end of study (up to but excluding terminal sacrifice), and terminal sacrifice for females and weeks 0-50, 51-80, 81-end of study (up to but excluding terminal sacrifice), and terminal sacrifice for males. The actual dose levels were used as the scores in the analyses.

Adjustment for the multiplicity:

Following FDA draft Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (May 2001); trend tests were conducted at the 0.01 and 0.05 significance levels for common and rare tumors, respectively (this is one two-year carcinogenicity study). Pairwise comparisons with the control groups were conducted at the 0.05 significance level for both common and rare tumors. A rare tumor was defined as one in which the spontaneous tumor rate was less than 1%. The spontaneous tumor rate was determined based on the concurrent control groups and historical control data of the conducting laboratory and animal supplier, as available.

Sponsor's findings:

Following the multiple testing adjustment method described above, the sponsor's report concluded that there were no statistically significant tumor findings among males or females.

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on March 9th, 2022, via SN0001.

The tumor.xpt file does not contain all animal information it has contained data of animals for which at least one organ was examined, therefore for survival analysis this reviewer included the missing animals' survival data obtained from the Send dataset.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female rats separately. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 23 (35%), 18 (28%), 20 (31%), 20 (31%), and 22 (34%), in the saline control, vehicle control, low, medium, and high dose groups, in male rats, respectively, and 23 (35%), 20 (31%), 23 (35%), 27 (42%), and 29 (45%), in the saline control, vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons also, showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of rats.

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups 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 with development of the tumor type being tested gets a score of $s_h = 1$. An animal that dies at Week w_h without development of the given tumor type 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 $\sum s_h$. 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 $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of $k=3$ is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used $k=3$ for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 105 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with (0, 2, 9, and 18.8 for both male and female rats) as scores. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

Following the FDA draft guidance for the carcinogenicity study design and data analysis 2001, for the two-year rat study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate in the historical data provided in the study report or the spontaneous rate of the vehicle control is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons
Treated Groups and Control Group in Rats

Sex	Organ Name	Tumor Name	0 mg Vehicle Cont (N=65) P - Trend	0 mg Saline Cont (N=65) P - VC vs. SC	2 mg Low (N=61) P - VC vs. L	9 mg Med (N=59) P - VC vs. M	18.8 mg High (N=65) P - VC vs. H
Male	brain	astrocytoma, malignant	1/65 (33) 0.0300@	0/65 (31) NC	0/51 (21) 1.0000	0/52 (23) 1.0000	4/65 (34) 0.1873

Sex	Organ Name	Tumor Name	0 mg Vehicle Cont (N=65) P - Trend	0 mg Saline Cont (N=65) P - VC vs. SC	2 mg Low (N=61) P - VC vs. L	9 mg Med (N=59) P - VC vs. M	18.8 mg High (N=65) P - VC vs. H
	gland, thyroid	c-cell adenoma	0/65 (33) 0.4633	1/65 (31) NC	0/45 (16) NC	3/45 (19) 0.0438*	0/65 (32) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

*: Statistically significant at 0.05 level for rare tumors for pairwise comparison.

@: Not statistically significant at 0.005 level for common tumor for tests of dose response relationship.

Following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased BHV-3500. The pairwise comparisons showed a statistically significant increase at 5% level, in the medium dose group, for the incidences of c-cell adenoma in the thyroid, in male rats, when compared to the vehicle control group (p-value = 0.0438), if this tumor type was considered as rare tumor.

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one saline control, one vehicle control group, and one positive control group. One hundred and forty hemizygous transgenic RasH2 mice of each sex were assigned randomly to one of the six groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals, except the positive control group which had 15 animals. The dose levels for the three treated groups were 0.3, 0.8, and 2.5 mg/day for both male and female mice, for up to 26 weeks, as indicated in Table 3. The positive control article is N-methyl-N-nitrosourea (MNU), also known as N-nitroso-N-methylurea, by intraperitoneal (IP) injection on Day 1 at a dose of 75 mg/kg. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. The saline control group received (0.9% sodium chloride), the vehicle control consisted of a solution of (b) (4) mM succinic acid and (b) (4) % (w/v) (b) (4) dextrose, USP, in Sterile Water for Injection, USP; the final pH of the vehicle was adjusted to 5.8 and 6.2, administered intranasally for about 26 weeks in the same manner as the treated groups.

Table 3: Experimental Design in Mouse Study

Group Name	Group No.	Dose Level (mg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	25	25
saline Control	2	0	0	25	25
Low	3	0.3	0.3	25	25
Medium	4	0.8	0.8	25	25
High	5	2.5	2.5	25	25
Positive control	6	75 NMU	75 NMU	15	15

The positive control was administered with 1 intraperitoneal (i.p.) injections of urethane in saline on Days 1.

During the study period all animals were observed for general health/mortality and moribundity twice daily (morning and afternoon) beginning upon arrival through termination, abnormal findings were recorded throughout the study. Animals were not removed from cage during observation, unless necessary for identification or confirmation of possible findings. Detailed clinical observation was conducted weekly beginning during Week -1. Abnormal findings or an indication of normal was recorded. In addition, for each grossly visible or palpable mass, the time of onset, location, size,

appearance, and progression was recorded. Any animal showing signs of severe debility or intoxication, and if determined to suffer excessively was euthanized. Observations will include, but will not be limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body weights were recorded weekly beginning during Week -1, starting during Day 8. Terminal body weights were not collected from animals found dead or euthanized moribund.

3.1. Sponsor's analyses

3.1.1 Survival analysis

In the sponsor's analysis, the tests for survival comparisons excluding the positive control group (Group 6), were performed separately for each sex and all statistical tests were conducted at the 5% significance level. The survival function of each group was estimated using the Kaplan-Meier product-limit method applied on daily intervals. The log-rank test was applied to all groups (Groups 1 to 5) in order to assess the significance of the overall group effect on mortality data. If this test was found to be significant, then the significance of an overall dose-related trend in mortality across the control article group (Group 1) and the 3-test article-treated groups (Groups 3, 4, and 5), and the comparison between Group 1 and the saline control group (Group 2) were evaluated using Peto's two-sided test.

When the statistical result revealed significant difference between Groups 1 and 2, then each of Groups 3, 4, and 5 were compared to each of Groups 1 and 2. Otherwise, each of Groups 3, 4, and 5 were only compared to Group 1. These pairwise comparisons were conducted using Peto's two-tailed test.

The time to death or sacrifice (in weeks, calculation detailed in the following) was the dependent variable. The test article-treated groups were included as the strata. Any animal with accidental injury that caused its death, or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day.

Sponsor's findings:

Sponsor's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 23 (92%), 25 (100%), 25 (100%), and 22 (88%), in vehicle control, saline control, low, medium, and high dose groups in male mice, respectively, and 23 (92%), 23 (92%), 24 (96%), 24 (96%), and 24 (96%), in female mice, respectively.

The significance of an overall dose-related trend in mortality across all groups was assessed via Peto's two-tailed test. The results were not found to be significant for the males or the females, with respective p-values of 0.1726 and 0.9317. Therefore, the overall dose-related trend test and the pairwise comparisons were not conducted for both sexes.

3.1.2 Tumor data analysis

The statistical evaluation of tumor data excluding the positive control group (Group 6), was done separately for each sex, with all statistical tests conducted at the 5% significance level and was limited to subcutis and hemolymphoreticular tissue using all study animals, and to the combination of hemangiosarcoma findings across whole body.

For each dataset of interest within each sex, the significance of an overall linear dose-related increase in tumor incidence rate, across Groups 1, 3, 4, and 5 will be evaluated using Cochran-Armitage's one-sided exact test. Furthermore, Groups 1 and 2 will be compared using Fisher's exact two-sided test. If the result reveals significant difference between Groups 1 and 2, then Fisher's exact one-sided test will be used in order to assess significance of tumor rate increase in each of Groups 3, 4, and 5 when compared to each of Groups 1 and 2. Otherwise, Fisher's exact one-sided test will be used in order to assess significance of tumor rate increase in each of Groups 3, 4, and 5 when only compared to Group 1.

Multiple testing adjustment:

All statistical tests were conducted at the 5% significance level.

Sponsor's findings:

the sponsor's report revealed no significant trend for female datasets using either control group, or for the male dataset using the vehicle control Group 1. The significance of an overall linear dose-related increase in tumor incidence rate and pairwise comparisons of interest were assessed using Cochran-Armitage's and Fisher's exact one-sided exact tests, respectively. The results of the overall and pairwise comparisons tests were not found to be significant for any data sets.

3.2 Reviewer's analyses

Similar to the rat study, this reviewer independently performed the survival and tumor data analyses of the mouse study. For the analysis of the survival data and the tumor data of the mouse study, this reviewer used similar methodologies that were used for the analyses of the survival and tumor data of the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1 Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 23 (92%), 25 (100%), 25 (100%), and 22 (88%), in vehicle control, saline control, low, medium, and high dose groups in male mice, respectively, and 23 (92%), 23 (92%), 24 (96%), 24 (96%), and 24 (96%), in female mice, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of mice. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of mice.

For both males and females, the positive control group had a statistically significant increase ($p < 0.001$) in unscheduled death compared with the vehicle control group.

3.2.2 Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and the pairwise comparisons of the vehicle controls and treated groups are given in Table 6A and 6B in the appendix for male and female mice, respectively.

Multiple testing adjustment:

For multiplicity testing adjustment in a transgenic mouse study, this reviewer used the level of significance of 0.05 for tests of positive dose responses and for pairwise increase comparisons for both common and rare tumor types.

Reviewer's findings:

Following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased BHV-3500 dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in BHV-3500 treated groups, when compared to the vehicle control group in either male or female mice.

Also, this reviewer's analyses showed Statistically significant in positive control group for the incidences of malignant lymphoma in the hemolymphoreticular tissue, papilloma in the skin and papilloma in the stomach, compared to the vehicle control group in male mice ($P < 0.0001$, $= 0.0010$, and < 0.0001 , respectively). Also, the incidence of adenoma, in harderian gland, malignant lymphoma in the hemolymphoreticular tissue, papilloma, in the skin, papilloma in the stomach, and endometrial stromal polyp in uterus/cervix, were statistically higher, when compared to the vehicle control group in female mice ($P = 0.0452$, < 0.0001 , $= 0.0019$, < 0.0001 , and $= 0.0019$, respectively).

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the potential carcinogenicity of BHV-3500, for the treatment of migraines, when administered intranasally at appropriate drug levels for about 104 weeks in rats and 26 weeks in mice.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups, one saline control group and one vehicle control group. Three hundred and twenty-five Sprague Dawley rats of each sex were assigned to three treated groups, one saline control group and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 65 animals, as indicated in Table 1. The dose levels for the three treated groups were 2, 9, and 18.8 mg/kg/day for both male and female rats, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The saline control group received (0.9% sodium chloride), the vehicle control consisted of a solution of (b) (4) mM succinic acid and (b) (4) % (w/v) (b) (4) dextrose, USP, in Sterile Water for Injection, USP; the final pH of the vehicle was adjusted to 5.8 and 6.2 as necessary, administered intranasally for about 104 weeks in the same manner as the treated groups. Due to survival rates, both male and female groups were terminated prior to the protocol scheduled terminal sacrifice. Female groups were sacrificed beginning on day 582 (week 84). Male groups were sacrificed beginning on day 665 (week 95).

The tumor.xpt file does not contain all animal information it has contained data of animals for which at least one organ was examined, therefore for survival analysis this reviewer included the missing animals' survival data obtained from the Send dataset.

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 23 (35%), 18 (28%), 20 (31%), 20 (31%), and 22 (34%), in the saline control, vehicle control, low, medium, and high dose groups, in male rats, respectively, and 23 (35%), 20 (31%), 23 (35%), 27 (42%), and 29 (45%), in the saline control, vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons also, showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of rats.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased BHV-3500. The pairwise comparisons showed a statistically significant increase at 5% level, in the medium dose group, for the incidences of c-cell adenoma in the thyroid, in male rats, when compared to the vehicle control group (p-value = 0.0438), if this tumor type was considered as rare tumor.

Mouse Study:

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one saline control, one vehicle control group, and one positive control group. One hundred and forty hemizygous transgenic RasH2 mice of each sex were assigned randomly to one of the six groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals, except the positive control group which had 15 animals. The dose levels for the three treated groups were 0.3, 0.8, and 2.5 mg/day for both male and female mice, for up to 26 weeks, as indicated in Table 3. The positive control article is N-methyl-N-nitrosourea (MNU), also known as N-nitroso-N-methylurea, by intraperitoneal (IP) injection on Day 1 at a dose of 75 mg/kg. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. The saline control group received (0.9% sodium chloride), the vehicle control consisted of a solution of (b) (4) mM succinic acid and (b) (4) % (w/v) (b) (4) dextrose, USP, in Sterile Water for Injection, USP; the final pH of the vehicle was adjusted to 5.8 and 6.2, administered intranasally for about 26 weeks in the same manner as the treated groups.

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 23 (92%), 25 (100%), 25 (100%), and 22 (88%), in vehicle control, saline control, low, medium, and high dose groups in male mice, respectively, and 23 (92%), 23 (92%), 24 (96%), 24 (96%), and 24 (96%), in female mice, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of mice. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of mice.

For both males and females, the positive control group had a statistically significant increase (p<0.001) in unscheduled death compared with the vehicle control group.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased BHV-3500 dose. The pairwise comparisons also showed no tumor types with a statistically

significant increase in tumor incidences in BHV-3500 treated groups, when compared to the vehicle control group in either male or female mice.

Also, this reviewer's analyses showed Statistically significant in positive control group for the incidences of malignant lymphoma in the hemolymphoreticular tissue, papilloma in the skin and papilloma in the stomach, compared to the vehicle control group in male mice ($P < 0.0001$, $= 0.0010$, and < 0.0001 , respectively). Also, the incidence of adenoma, in harderian gland, malignant lymphoma in the hemolymphoreticular tissue, papilloma, in the skin, papilloma in the stomach, and endometrial stromal polyp in uterus/cervix, were statistically higher, when compared to the vehicle control group in female mice ($P = 0.0452$, < 0.0001 , $= 0.0019$, < 0.0001 , and $= 0.0019$, respectively).

Malick Mbodj, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI

cc:

Archival NDA 216386 - BHV-3500

Dr. Tsong	Dr. Lin
Dr. Khoury	Lana Chen
Dr. Rahman	Dr. Collins

5. Appendix

Table1A: Intercurrent Mortality Rate

Male Rats

Week	0 mg/kg/day Vehicle		0 mg/kg/day Saline		2 mg/kg/day Low		9 mg/kg/day Med		18.8mg/kg/day High	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 50	2	3.08	8	12.31	4	6.15	8	12.31	8	12.31
51 - 80	24	40.00	23	47.69	27	47.69	17	38.46	20	43.08
81 - 96	19	69.23	9	61.54	13	67.69	18	66.15	12	61.54
ADD	2	3.08	2	3.08	1	1.54	2	3.08	3	4.62
Ter. Sac.	18	27.69	23	35.38	20	30.77	20	30.77	22	33.85
Total	65	100.00	65	100.00	65	100.00	65	100.00	65	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded. sacrifice beginning on day 665 (week 95).

ADD: accidental death

Table1B: Intercurrent Mortality Rate

Female Rats

Week	0 mg/kg/day Vehicle		0 mg/kg/day Saline		2 mg/kg/day Low		9mg/kg/day Med		18.8mg/kg/day High	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 50	5	7.69	4	6.15	6	9.23	4	6.15	5	7.69
51 - 80	35	61.54	31	53.85	33	60.00	30	52.31	29	52.31
81 - 84	5	69.23	7	64.62	3	64.62	4	58.46	2	55.38
Ter. Sac.	20	30.77	23	35.38	23	35.38	27	41.54	29	44.62
Total	65	100.00	65	100.00	65	100.00	65	100.00	65	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	P-value for Vehicle Cont. vs Saline	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.7860	0.5398	0.9578	0.7776	0.6247
Homogeneity (Log-Rank)	0.7839	0.9380	0.9573	0.7752	0.6212

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	P-value for Vehicle Cont. vs Saline	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.6253	0.1521	0.8712	0.2754	0.2134
Homogeneity (Log-Rank)	0.6177	0.4991	0.8685	0.2661	0.2037

Table3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Organ Name	Tumor Name	Male Rats Poly-3 Test				
		0 mg Vehicle Cont (N=65) P - Trend	0 mg Saline Cont. (N=65) P - VC vs. SC	2 mg Low(N=61) P - VC vs. L	9 mg Med (N=59) P - VC vs. M	18.8 mg High (N=65) P - VC vs. H
Body Cavity, Nasal	Odontoma	0/64 (33) 0.3265	0/65 (31) NC	0/45 (16) NC	0/44 (17) NC	1/65 (32) 0.4923
Brain	Astrocytoma, Malignant	1/65 (33) 0.0300	0/65 (31) NC	0/51 (21) 1.0000	0/52 (23) 1.0000	4/65 (34) 0.1873
Eye	Schwannoma, Malignant	0/65 (33) NC	1/65 (32) NC	0/45 (16) NC	0/45 (18) NC	0/64 (32) NC
Gland, Adrenal	Cortical Adenoma	0/65 (33) 0.5051	1/65 (31) NC	0/45 (16) NC	1/45 (18) 0.3529	0/65 (32) NC
	Pheochromocytoma, Benign	4/65 (35) 0.5770	3/65 (32) NC	1/45 (17) 0.8751	1/45 (18) 0.8869	3/65 (33) 0.7610
	Pheochromocytoma, Malignant	0/65 (33) 0.6325	0/65 (31) NC	1/45 (17) 0.3400	1/45 (18) 0.3529	0/65 (32) NC
	Pheochromocytoma, Benign / Malignant	4/65 (35) 0.6395	3/65 (32) NC	2/45 (17) 0.6492	2/45 (18) 0.6748	3/65 (33) 0.7610
Gland, Parathyroid	Adenoma	1/54 (26) 0.7469	0/55 (26) NC	0/39 (15) 1.0000	1/35 (14) 0.5833	0/54 (26) 1.0000
Gland, Pituitary	Adenoma, Pars Distalis	51/63 (57) 0.9786	37/65 (48) NC	35/54 (41) 0.8226	36/54 (41) 0.7222	38/64 (51) 0.9895
	Adenoma, Pars Intermedia	0/63 (32) NC	2/65 (32) NC	0/54 (24) NC	0/54 (25) NC	0/64 (32) NC
	Carcinoma, Pars Distalis	0/63 (32) 0.5088	0/65 (31) NC	0/54 (24) NC	1/54 (26) 0.4483	0/64 (32) NC
Gland, Salivary	Fibroma	1/64 (33) 1.0000	0/65 (31) NC	0/44 (16) 1.0000	0/45 (18) 1.0000	0/65 (32) 1.0000
Gland, Thyroid	C-Cell Adenoma	0/65 (33) 0.4633	1/65 (31) NC	0/45 (16) NC	3/45 (19) 0.0438*	0/65 (32) NC
	Follicular Cell Adenoma	1/65 (33) 0.5661	4/65 (33) NC	1/45 (17) 0.5690	1/45 (18) 0.5859	1/65 (33) 0.7538
Gland, Zymbals	Acinar Adenoma	0/64 (33) 0.6598	0/64 (30) NC	1/44 (17) 0.3400	0/42 (16) NC	0/62 (31) NC
	Carcinoma	1/64 (33) 1.0000	0/64 (30) NC	0/44 (16) 1.0000	0/42 (16) 1.0000	0/62 (31) 1.0000
Hemolymphoretic ular Tissue	Histiocytic Sarcoma	1/3 (2) 0.6071	0/1 (0) NC	2/3 (3) 0.7000	1/2 (1) 0.6667	1/2 (2) 0.8333
	Lymphoma, Malignant	2/3 (2) 0.8571	1/1 (1) NC	1/3 (2) 1.0000	1/2 (1) NC	1/2 (2) 1.0000
Large Intestine, Cecum	Adenocarcinoma	0/65 (33) 0.3232	0/65 (31) NC	0/45 (16) NC	0/45 (18) NC	1/64 (32) 0.4923
Lung	Bronchioloalveolar Carcinoma	1/65 (34) 0.5446	0/65 (31) NC	0/46 (17) 1.0000	0/45 (18) 1.0000	1/65 (33) 0.7463
Pancreas	Acinar Adenoma	1/63 (32) 1.0000	0/63 (31) NC	0/43 (16) 1.0000	0/41 (16) 1.0000	0/63 (31) 1.0000
	Islet Cell Adenoma	3/63 (32) 0.3675	4/63 (32) NC	0/43 (16) 1.0000	1/41 (17) 0.8303	3/63 (32) 0.6641
Skin	Basal Cell Tumor, Malignant	1/64 (33) 0.7430	1/63 (31) NC	0/52 (22) 1.0000	1/48 (21) 0.6310	0/65 (32) 1.0000

Male Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=65) P - Trend	0 mg Saline Cont. (N=65) P - VC vs. SC	2 mg Low(N=61) P - VC vs. L	9 mg Med (N=59) P - VC vs. M	18.8 mg High (N=65) P - VC vs. H
	Fibroma	1/64 (33) 0.4043	4/63 (32) NC	2/52 (22) 0.3493	2/48 (21) 0.3330	2/65 (33) 0.5000
	Fibrosarcoma	1/64 (33) 0.7229	1/63 (31) NC	3/52 (24) 0.1960	1/48 (21) 0.6310	1/65 (32) 0.7462
	Fibroma / Fibrosarcoma	2/64 (33) 0.5975	5/63 (32) NC	5/52 (24) 0.1030	3/48 (21) 0.2909	3/65 (33) 0.5000
	Hemangiosarcoma	0/64 (33) 0.4907	0/63 (31) NC	0/52 (22) NC	1/48 (21) 0.3889	0/65 (32) NC
	Hibernoma, Malignant	0/64 (33) 0.3056	0/63 (31) NC	0/52 (22) NC	0/48 (20) NC	1/65 (33) 0.5000
	Lipoma	0/64 (33) 0.7392	2/63 (31) NC	2/52 (23) 0.1643	1/48 (21) 0.3889	0/65 (32) NC
	Liposarcoma	1/64 (33) 1.0000	0/63 (31) NC	0/52 (22) 1.0000	0/48 (20) 1.0000	0/65 (32) 1.0000
	Papilloma	1/64 (33) 0.5804	2/63 (31) NC	1/52 (22) 0.6444	0/48 (20) 1.0000	1/65 (32) 0.7462
	Sarcoma	0/64 (33) NC	1/63 (31) NC	0/52 (22) NC	0/48 (20) NC	0/65 (32) NC
	Schwannoma, Malignant	1/64 (33) 0.5346	1/63 (32) NC	1/52 (23) 0.6571	1/48 (21) 0.6310	1/65 (32) 0.7462
	Squamous Cell Carcinoma	0/64 (33) 0.4907	2/63 (31) NC	0/52 (22) NC	1/48 (21) 0.3889	0/65 (32) NC
Spinal Cord	Ependymoma, Malignant	1/65 (34) 1.0000	0/65 (31) NC	0/45 (16) 1.0000	0/45 (18) 1.0000	0/65 (32) 1.0000
Testis	Interstitial (Leydig) Cell Adenoma	1/65 (33) 0.4549	1/65 (31) NC	0/48 (19) 1.0000	1/51 (23) 0.6571	1/65 (33) 0.7538
Thymus	Thymoma, Benign	0/58 (30) 0.4944	0/56 (28) NC	0/41 (15) NC	1/40 (16) 0.3478	0/58 (28) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

*: Statistically significant at 0.05 level for rare tumors for pairwise comparison.

Table3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=65) P - Trend	0 mg Saline Cont. (N=65) P - VC vs. SC	2 mg Low(N=64) P - VC vs. L	9 mg Med (N=65) P - VC vs. M	18.8 mg High (N=65) P - VC vs. H
Artery, Aorta	Hibernoma, Benign	0/65 (23) 0.5211	0/65 (24) NC	0/42 (11) NC	1/39 (12) 0.3429	0/65 (25) NC
Bone, Sternum	Osteosarcoma	0/65 (23) 0.6761	0/65 (24) NC	1/42 (12) 0.3429	0/38 (11) NC	0/65 (25) NC
Brain	Pinealoma, Benign	0/65 (23) 0.5432	0/65 (24) NC	0/48 (14) NC	1/52 (19) 0.4524	0/65 (25) NC
Cervix	Granular Cell Tumor, Benign	0/64 (23) NC	1/65 (25) NC	0/42 (11) NC	0/37 (11) NC	0/65 (25) NC
	Granular Cell Tumor, Malignant	0/64 (23) 0.6714	0/65 (24) NC	1/42 (11) 0.3235	0/37 (11) NC	0/65 (25) NC
	Hemangioma	0/64 (23) 0.5143	0/65 (24) NC	0/42 (11) NC	1/37 (11) 0.3235	0/65 (25) NC
Gland, Adrenal	Cortical Adenoma	1/65 (24) 0.6138	0/65 (24) NC	1/44 (12) 0.5619	0/42 (13) 1.0000	1/65 (25) 0.7653
	Pheochromocytoma, Benign	1/65 (24) 1.0000	1/65 (25) NC	0/44 (12) 1.0000	0/42 (13) 1.0000	0/65 (25) 1.0000
Gland, Mammary	Adenocarcinoma	13/64 (32) 0.5421	10/61 (28) NC	15/56 (28) 0.2287	16/59 (32) 0.3080	15/64 (34) 0.4851
	Adenocarcinoma Arising In Fibroadenoma	0/64 (23) 0.1302	2/61 (24) NC	2/56 (20) 0.2104	3/59 (23) 0.1167	3/64 (26) 0.1411
	Adenoma	0/64 (23) NC	2/61 (24) NC	0/56 (18) NC	0/59 (22) NC	0/64 (24) NC
	Fibroadenoma	21/64 (36) 0.3271	26/61 (39) NC	19/56 (29) 0.3696	25/59 (36) 0.2310	24/64 (37) 0.3696
	Adenocarcinoma / arising in fibroadenoma / adenoma / fibroadenoma	27/64 (40) 0.4237	33/61 (43) NC	29/56 (36) 0.1516	35/59 (42) 0.0787	30/64 (41) 0.3763
Gland, Pituitary	Adenoma, Pars Distalis	56/65 (59) 0.7274	59/65 (61) NC	50/58 (52) 0.5601	57/63 (59) 0.5000	55/65 (59) 0.7806
	Carcinoma, Pars Distalis	1/65 (24) 0.2889	1/65 (25) NC	1/58 (21) 0.7212	0/63 (24) 1.0000	2/65 (26) 0.5306
	Adenoma / Carcinoma, pars distalis	57/65 (60) 0.7205	60/65 (62) NC	51/58 (53) 0.5590	57/63 (59) 0.5080	57/65 (61) 0.7736
Gland, Thyroid	C-Cell Adenoma	0/65 (23) 0.5143	1/65 (25) NC	0/42 (11) NC	1/38 (11) 0.3235	0/65 (25) NC
	C-Cell Carcinoma	1/65 (24) 1.0000	0/65 (24) NC	0/42 (11) 1.0000	0/38 (11) 1.0000	0/65 (25) 1.0000
	Follicular Cell Adenoma	1/65 (24) 0.7606	0/65 (24) NC	0/42 (11) 1.0000	1/38 (11) 0.5361	0/65 (25) 1.0000

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=65) P - Trend	0 mg Saline Cont. (N=65) P - VC vs. SC	2 mg Low(N=64) P - VC vs. L	9 mg Med (N=65) P - VC vs. M	18.8 mg High (N=65) P - VC vs. H
Gland, Zymbals	Carcinoma	0/64 (23) 0.3424	0/64 (24) NC	1/41 (11) 0.3235	0/36 (10) NC	1/63 (24) 0.5106
Heart	Mesothelioma, Benign	0/65 (23) NC	1/65 (25) NC	0/42 (11) NC	0/38 (11) NC	0/65 (25) NC
Kidney	Adenoma	0/65 (23) 0.6761	0/65 (24) NC	1/42 (12) 0.3429	0/39 (11) NC	0/65 (25) NC
	Amphophilic Vacuolar Tubular Adenoma	1/65 (24) 0.8320	1/65 (25) NC	1/42 (12) 0.5619	1/39 (12) 0.5619	0/65 (25) 1.0000
Liver	Hepatocellular Adenoma	1/65 (24) 0.5646	0/65 (24) NC	0/44 (12) 1.0000	0/42 (13) 1.0000	1/65 (25) 0.7653
Ovary	Adenoma	0/65 (23) 0.6892	0/65 (24) NC	1/45 (13) 0.3611	0/42 (13) NC	0/65 (25) NC
	Mixed Sex Cord Stromal Tumor, Benign	0/65 (23) 0.4977	2/65 (25) NC	2/45 (14) 0.1366	1/42 (14) 0.3784	1/65 (25) 0.5208
Pancreas	Islet Cell Adenoma	1/64 (24) 1.0000	0/65 (24) NC	0/41 (10) 1.0000	0/37 (11) 1.0000	0/65 (25) 1.0000
Skin	Fibrosarcoma	2/65 (25) 1.0000	0/64 (24) NC	0/57 (19) 1.0000	0/56 (20) 1.0000	0/64 (24) 1.0000
	Lipoma	1/65 (24) 0.4343	0/64 (24) NC	0/57 (19) 1.0000	1/56 (21) 0.7212	1/64 (25) 0.7653
	Liposarcoma	1/65 (24) 1.0000	0/64 (24) NC	0/57 (19) 1.0000	0/56 (20) 1.0000	0/64 (24) 1.0000
	Papilloma	1/65 (24) 0.9279	0/64 (24) NC	1/57 (20) 0.7082	0/56 (20) 1.0000	0/64 (24) 1.0000
Thymus	Lymphoma, Malignant	0/63 (23) 0.3582	0/60 (22) NC	0/38 (10) NC	0/37 (10) NC	1/60 (24) 0.5106
Uterus	Endometrial Stromal Polyp	1/65 (24) 0.0890	2/65 (25) NC	2/45 (14) 0.3020	0/39 (11) 1.0000	5/65 (28) 0.1344
	Schwannoma, Malignant	0/65 (23) 0.6005	0/65 (24) NC	0/45 (12) NC	2/39 (13) 0.1238	0/65 (25) NC
Vagina	Endometrial Stromal Polyp	0/64 (23) 0.5143	0/65 (24) NC	0/42 (11) NC	1/37 (11) 0.3235	0/65 (25) NC
	Granular Cell Tumor, Benign	0/64 (23) NC	2/65 (25) NC	0/42 (11) NC	0/37 (10) NC	0/65 (25) NC
	Leiomyosarcoma	0/64 (23) 0.6714	0/65 (24) NC	1/42 (12) 0.3429	0/37 (10) NC	0/65 (25) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

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

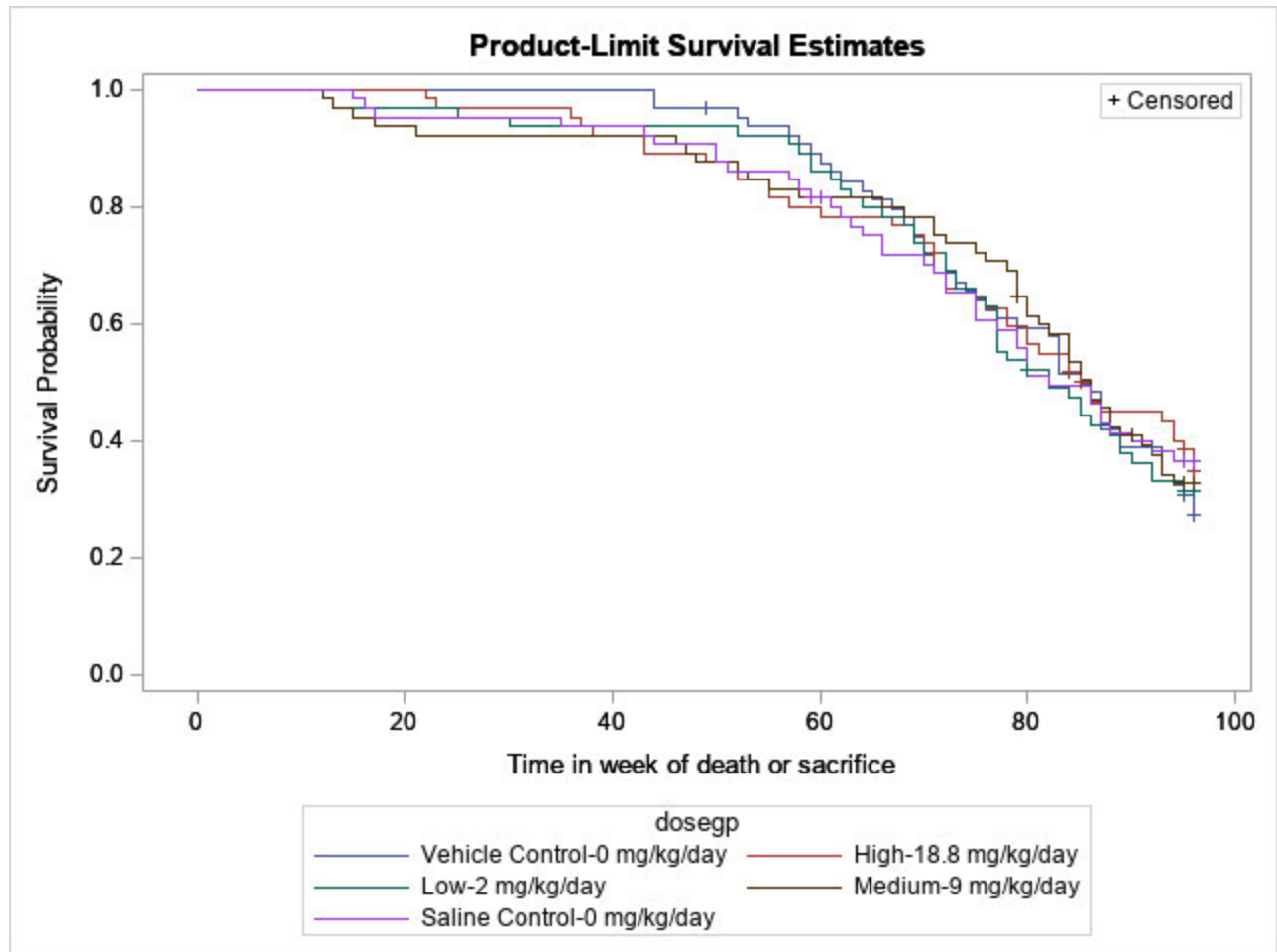


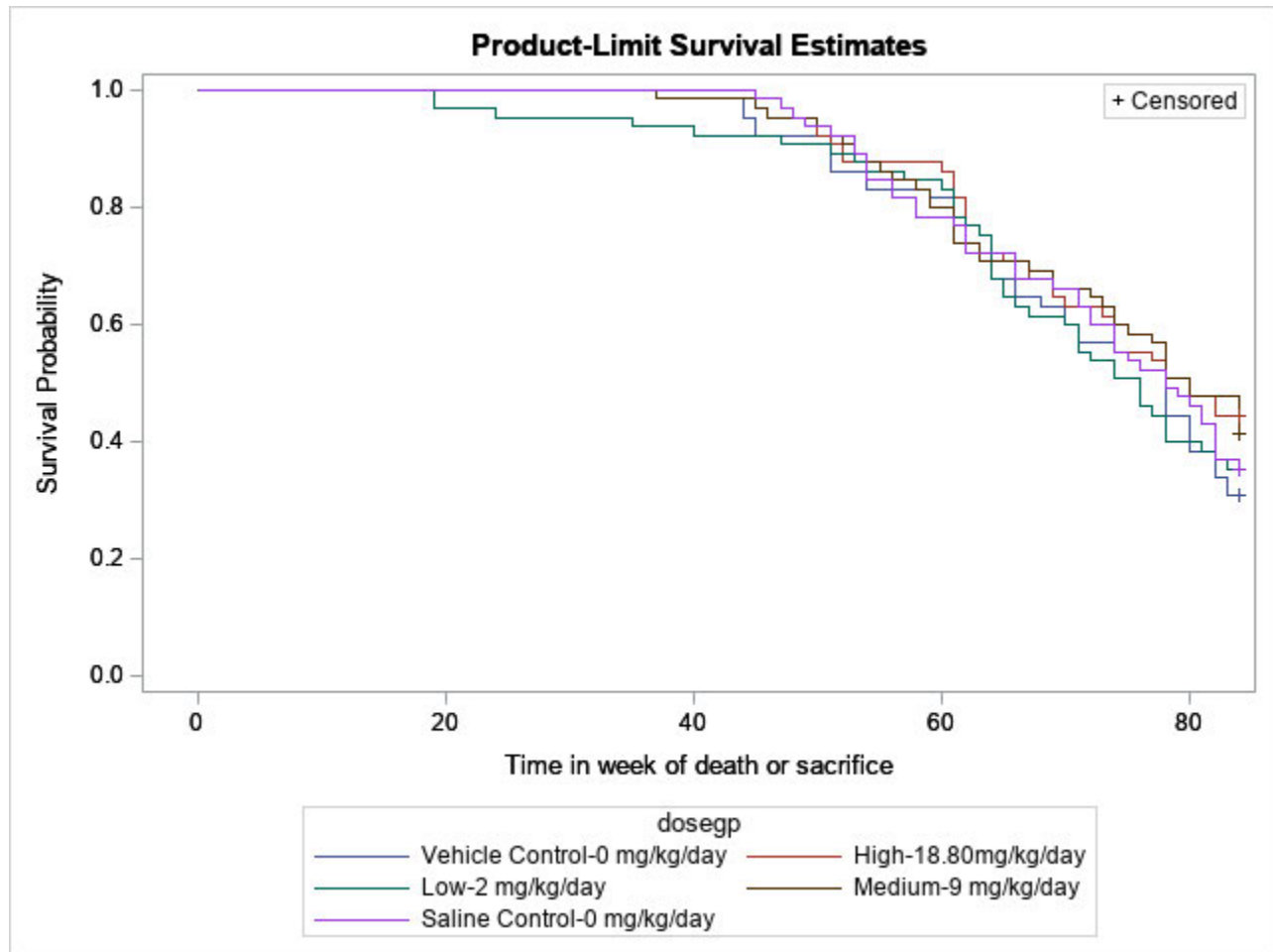
Figure 1B: Kaplan-Meier Survival Curves for
Female Rats

Table4A: Intercurrent Mortality Rate
Male Mice

	0mg/kg/day Vehicle		0 mg/kg/day Saline		0.3 mg/kg/day Low		0.8mg/kg/day Medium		2.5mg/kg/day High		75mg/kg/day Positive	
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	.	.	.	.	.	.	1	4.00	.	.
14 - 27	.	.	2	8.00	.	.	.	.	2	12.00	13	86.67
Ter. Sac.	24	96.00	23	92.00	25	100.00	25	100.00	22	88.00	2	13.33
Total	25	100.00	25	100.00	25	100.00	25	100.00	25	100.00	15	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded

Table4B: Intercurrent Mortality Rate
Female Mice

	0mg/kg/day Vehicle		0mg/kg/day Saline		0.3mg/kg/day Low		0.8mg/kg/day Medium		2.5mg/kg/day High		75mg/kg/day Positive	
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	1	6.67
14 - 27	2	8.00	2	8.00	1	4.00	1	4.00	.	.	12	86.67
Ter. Sac.	23	92.00	23	92.00	24	96.00	24	96.00	24	96.00	2	13.33
Total	25	100.00	25	100.00	25	100.00	25	100.00	25	100.00	15	100.00

Animals were assigned to the terminal sacrifice strata based on the sacrifice status recorded

Table 5A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	P-value for Vehicle Control Low, Med, high	P-value for Vehicle Control vs Saline	P-value for Vehicle Control vs Low	P-value for Vehicle Control vs Med	P-value for Vehicle Control vs High	P-value for Vehicle Control vs Positive
Dose-Response (Likelihood Ratio)	0.0550	0.5678	0.2390	0.2390	0.2968	<.0001*
Homogeneity (Log-Rank)	0.1004	0.5717	0.3173	0.3173	0.3073	<.0001*

Table 5B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	P-value for Vehicle Control Low, Med, high	P-value for Vehicle Control vs Saline	P-value for Vehicle Control vs Low	P-value for Vehicle Control vs Med	P-value for Vehicle Control vs High	P-value for Vehicle Control vs Positive
Dose-Response (Likelihood Ratio)	0.6845	0.9668	0.5757	0.5757	0.5757	<.0001*
Homogeneity (Log-Rank)	0.9057	0.9664	0.5770	0.5770	0.5770	<.0001*

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise Comparisons

Male Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=25) P - Trend	0 mg Saline Cont (N=25) P - VC vs. SC	0.3 mg Low(N=21) P - C vs. L	0.8 mg Med(N=25) P - VC vs. M	2.5 mg High (N=25) P - VC vs. H	75 mg Posi (N=15) P - VC vs. PC
Body Cavity, Nasal	Hemangiosarcoma	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (23) NC	1/15 (7) 0.2258
	Papilloma	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (23) NC	1/15 (7) 0.2258
Epididymis	Carcinoma	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (23) NC	1/15 (7) 0.2258
Gland, Harderian	Adenoma	2/25 (24) 0.2906	2/25 (25) NC	0/25 (25) 1.0000	1/25 (25) 0.8901	2/25 (24) 0.6957	0/15 (7) 1.0000
Gland, Thyroid	Follicular Cell Adenoma	1/25 (24) 1.0000	0/25 (25) NC	0/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000	0/15 (7) 1.0000
Hemolymphoretic ular Tissue	Lymphoma, Malignant	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (23) NC	13/15 (15) <0.0001*
Kidney		0/25 (24) 0.7526	0/25 (25) NC	1/25 (25) 0.5102	0/25 (25) NC	0/25 (23) NC	0/15 (7) NC
Lung	Bronchioloalveolar Adenoma	3/25 (24) 0.5154	2/25 (25) NC	1/25 (25) 0.9498	2/25 (25) 0.8384	2/25 (23) 0.8130	4/15 (9) 0.0683
	Bronchioloalveolar Carcinoma	0/25 (24) 0.2371	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	1/25 (23) 0.4894	0/15 (7) NC
	Bronchioloalveolar Adenoma/ Carcinoma	3/25 (24) 0.2967	2/25 (25) NC	1/25 (25) 0.9498	2/25 (25) 0.8384	3/25 (23) 0.6460	4/15 (9) 0.0683
Skin	Hemangiosarcoma	0/25 (24) 0.2449	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	1/25 (24) 0.5000	0/15 (7) NC
	Papilloma	1/25 (24) 1.0000	0/25 (25) NC	0/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (23) 1.0000	6/15 (10) 0.0010*
	Squamous Cell Carcinoma	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (23) NC	1/15 (8) 0.2500
Small Intestine, Jejunum	Adenocarcinoma	0/25 (24) NC	0/23 (23) NC	0/25 (25) NC	0/25 (25) NC	0/25 (23) NC	1/14 (6) 0.2000
Spleen	Hemangiosarcoma	0/25 (24) 0.8119	2/25 (25) NC	2/25 (25) 0.2551	0/25 (25) NC	0/25 (23) NC	1/15 (7) 0.2258
Stomach	Papilloma	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (23) NC	15/15 (15) <0.0001*
	Squamous Cell Carcinoma	0/25 (24) 0.2449	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	1/25 (24) 0.5000	0/15 (7) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

NC = Not calculable

*: Statistically significant at levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and The pairwise comparisons
Female Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=25) P - Trend	0 mg Saline Cont (N=25) P - VC vs. SC	0.3 mg Low (N=21) P - C vs. L	0.8 mg Med (N=25) P - VC vs. M	2.5 mg High (N=25) P - VC vs. H	75 mg Posi (N=15) P - VC vs. PC
Body Cavity, Nasal		0/25 (24) 0.7500	0/25 (23) NC	1/25 (24) 0.5000	0/25 (24) NC	0/25 (24) NC	0/15 (6) NC
Gland, Harderian	Adenoma	0/25 (24) 0.6289	0/25 (23) NC	1/24 (23) 0.4894	1/25 (24) 0.5000	0/25 (24) NC	2/15 (7) 0.0452*
Gland, Mammary	Adenocarcinoma	0/25 (24) NC	0/25 (23) NC	0/25 (24) NC	0/25 (24) NC	0/25 (24) NC	1/15 (6) 0.2000
Gland, Salivary, Mandibular	Adenocarcinoma	0/25 (24) NC	0/25 (23) NC	0/24 (23) NC	0/25 (24) NC	0/25 (24) NC	1/14 (6) 0.2000
Hemolymphoretic Tissue	Lymphoma, Malignant	0/25 (24) 0.5052	0/25 (23) NC	0/25 (24) NC	1/25 (25) 0.5102	0/25 (24) NC	10/15 (12) <0.0001*
Lung	Bronchioloalveolar Adenoma	3/25 (24) 0.1277	3/25 (23) NC	3/25 (24) 0.6669	0/25 (24) 1.0000	5/25 (24) 0.3504	5/15 (8) 0.0115
	Bronchioloalveolar Carcinoma	2/25 (25) 0.5911	1/25 (24) NC	0/25 (24) 1.0000	0/25 (24) 1.0000	1/25 (25) 0.8827	1/15 (6) 0.4883
	Bronchioloalveolar Adenoma/Carcinoma	5/25 (25) 0.1740	4/25 (24) NC	3/25 (24) 0.8636	0/25 (24) 1.0000	6/25 (25) 0.5000	6/15 (9) 0.0173
Skin	Hemangioma	1/25 (24) 1.0000	0/25 (23) NC	0/25 (24) 1.0000	0/25 (24) 1.0000	0/25 (24) 1.0000	0/15 (6) 1.0000
	Papilloma	0/25 (24) NC	1/25 (23) NC	0/25 (24) NC	0/25 (24) NC	0/25 (24) NC	4/15 (8) 0.0019*
	Sarcoma	0/25 (24) 0.2500	0/25 (23) NC	0/25 (24) NC	0/25 (24) NC	1/25 (24) 0.5000	0/15 (6) NC
Small Intestine, Duodenum	Adenocarcinoma	0/25 (24) NC	0/25 (23) NC	0/25 (24) NC	0/25 (24) NC	0/25 (24) NC	1/15 (6) 0.2000
Spleen	Hemangioma	0/25 (24) NC	1/25 (23) NC	0/25 (24) NC	0/25 (24) NC	0/25 (24) NC	0/15 (6) NC
	Hemangiosarcoma	0/25 (24) 0.5000	1/25 (23) NC	0/25 (24) NC	1/25 (24) 0.5000	0/25 (24) NC	0/15 (6) NC
Stomach	Papilloma	0/25 (24) 0.8132	0/25 (23) NC	2/25 (24) 0.2447	0/25 (24) NC	0/25 (24) NC	13/15 (14) <0.0001*
	Squamous Cell Carcinoma	0/25 (24) NC	0/25 (23) NC	0/25 (24) NC	0/25 (24) NC	0/25 (24) NC	1/15 (6) 0.2000
Uterus/Cervix	Endometrial Stromal Polyp	0/25 (24) NC	0/25 (23) NC	0/25 (24) NC	0/25 (24) NC	0/24 (24) NC	4/15 (8) 0.0019*
	Squamous Cell Carcinoma	0/25 (24) NC	0/25 (23) NC	0/25 (24) NC	0/25 (24) NC	0/24 (24) NC	1/15 (7) 0.2258

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ= total number of animals observed;

NC = Not calculable;

*: Statistically significant at levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons

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

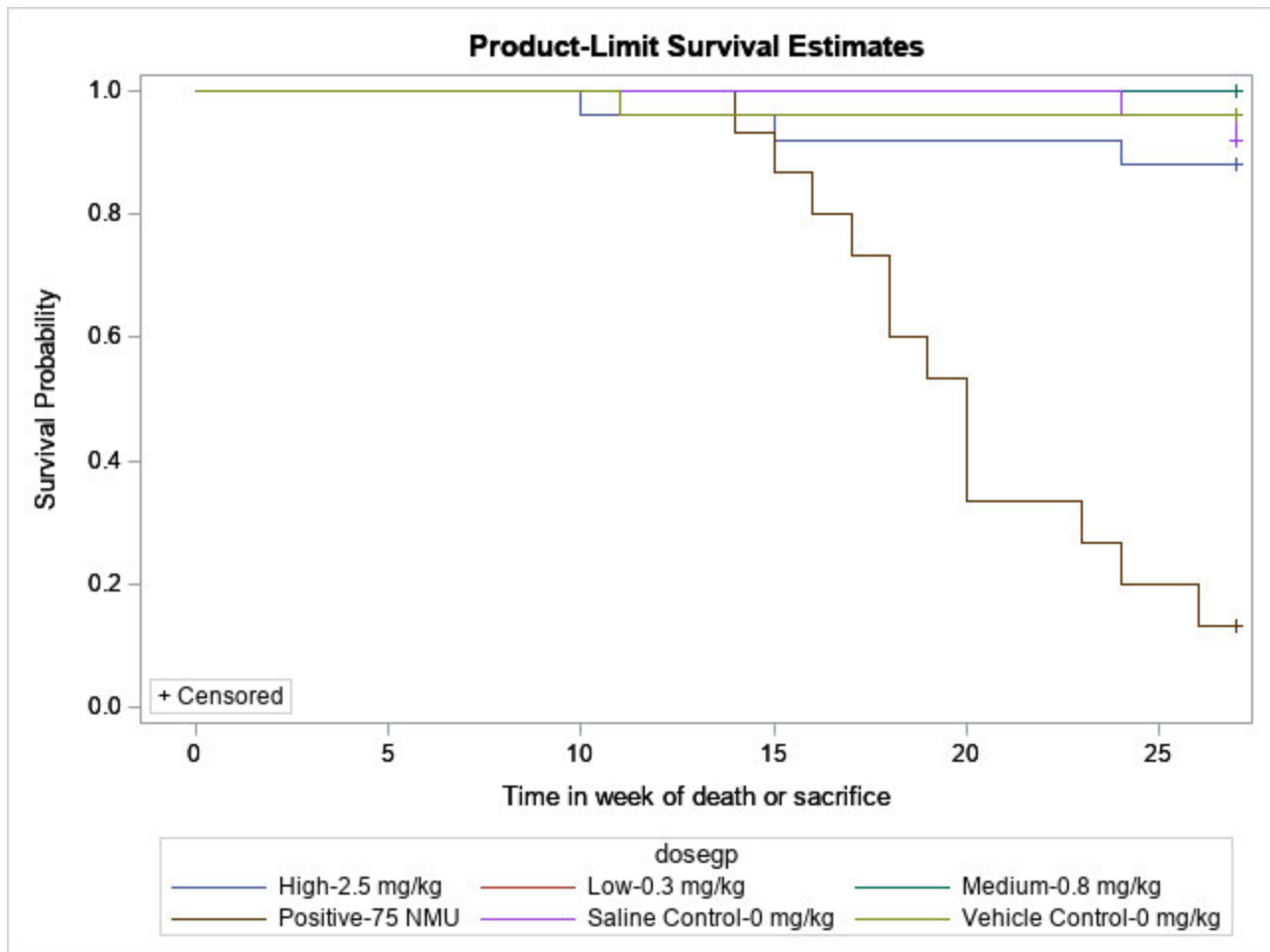
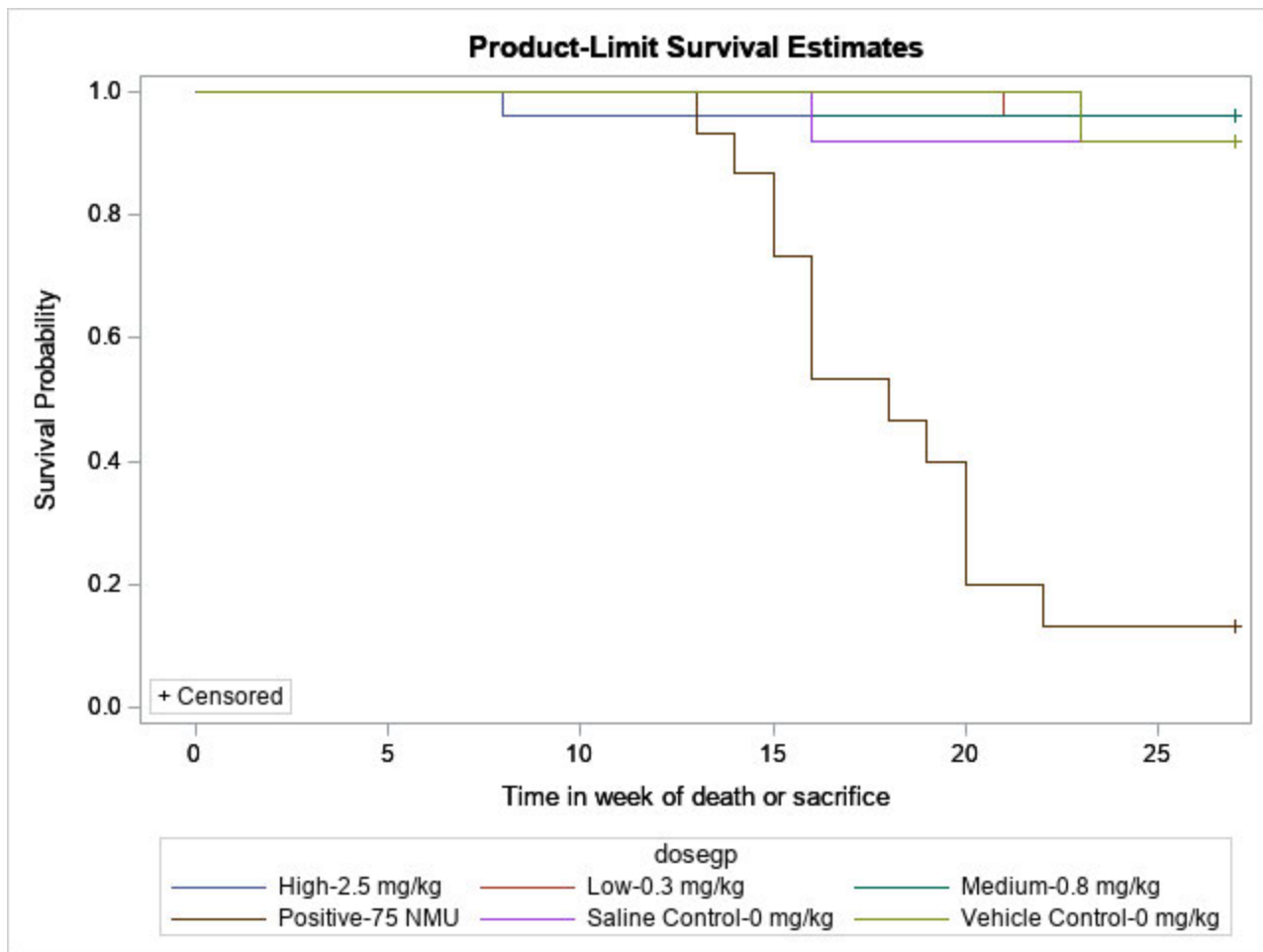


Figure 2B: Kaplan-Meier Survival Curves for
Female Mice



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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 #: NDA216386

Supplement #:

Drug Name: Zavegepant, Nasal spray, 10 mg

Indication(s): Acute treatment of migraine

Applicant: Biohaven Pharmaceutical Holding co ltd

Date(s): Submission date: 03/09/2022
Due date: 03/09/2023

Review Priority: Standard

Biometrics Division: Division of Biometrics I, Office of Biostatistics

Statistical Reviewer: Ye Li

Concurring Reviewers: John Lawrence, Team Leader
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1 EXECUTIVE SUMMARY

The efficacy of zavegepant (BHV-3500) was studied in two pivotal placebo-controlled trials in the acute treatment of migraine: Study 201 and Study 301. Study 201 investigated three dose levels of zavegepant, 5 mg, 10 mg, 20 mg and demonstrated efficacy of zavegepant 10 mg and zavegepant 20 mg. Study 301 only investigated the zavegepant 10 mg dose.

Both Study 201 and Study 301 demonstrated a statistically significant effect of zavegepant 10 mg in the treatment of acute migraine. For the co-primary efficacy endpoint of pain freedom at 2 hours post-dose, there was a 7% therapeutic gain (percentage difference) in the zavegepant 10 mg group over placebo group in Study 201 and an 8.8% therapeutic gain for zavegepant 10 mg over placebo group in Study 301. For co-primary endpoint of most bothersome symptom (MBS), there was an 8.3% therapeutic gain in the zavegepant 10 mg group over placebo group in Study 201 and an 8.7% therapeutic gain for zavegepant 10 mg over placebo group in Study 301. The efficacy on therapeutic gain was robust, supported by sensitivity analyses and subgroup analyses.

Study 301 showed significant efficacy effect of zavegepant 10 mg on the following key secondary endpoints: pain relief at 2 hours post-dose, the patient's ability to function normally at 2 hours post-dose according to the Functional Disability scale (FDS), freedom from photophobia at 2 hours post-dose, freedom from phonophobia at 2 hours post-dose, sustained pain freedom from 2 to 48 hours post-dose. These key secondary endpoints were not considered significant for any zavegepant dose group versus placebo in Study 201.

2 INTRODUCTION

2.1 Overview

Zavegepant has been developed under Investigational New Drug (IND) application 134120 for the treatment of acute migraine. The clinical efficacy program consisted of two pivotal studies. Study 201 was a phase II/III, double-blind, randomized, placebo controlled, dose-ranging study that compared three different doses of zavegepant (zavegepant 5 mg, zavegepant 10 mg, zavegepant 20 mg) to placebo in the acute treatment of migraine. The total duration of Study 201 was approximately 11 weeks. Study 301 was a phase III, double-blind, randomized, placebo-controlled study comparing zavegepant 10 mg to placebo in the acute treatment of migraine. The total duration of Study 301 was up to 11 weeks.

Table 1: Overview of Pivotal Clinical Studies

	Number of patients randomized /in mITT dataset (Efficacy dataset)	Primary endpoints
Study 201	Total 1673/1581 Zavegepant 5 mg 418/387 Zavegepant 10 mg 417/391 Zavegepant 20 mg 418/402 Placebo 420/401	Co-primary endpoint1: pain freedom at 2 hours post-dose Co-primary endpoint2: MBS freedom at 2 hours post-dose
Study 301	Total 1405/1269 Zavegepant 10 mg 703/623 Placebo 702/646	

2.2 Data Sources

Materials reviewed for this application including the clinical study reports, raw and derived datasets, statistical analysis plans, and documents of regulatory communications are located in the following directories:

<\\CDSESUB1\evsprod\nda216386\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\acute-migraine\5351-stud-rep-contr>

<\\CDSESUB1\evsprod\NDA216386\0001\m5\datasets>

<\\CDSESUB1\evsprod\nda216386\0001\m1\us\163-fda-corr-initial.pdf>

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

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

There were programming errors that caused the following sensitivity analysis of co-primary endpoints in Study 201 and Study 301 to include/exclude incorrect subjects in the analysis: varying response rate imputation for the co-primary endpoint of MBS pain freedom at 2 hours post-dose in Study 201, varying response rate imputation for the co-primary endpoint of pain freedom at 2 hours post-dose in Study 301, multiple imputation for the co-primary endpoint of MBS freedom at 2 hours post-dose in Study 301, varying response rate imputation for the co-primary endpoint of MBS freedom at 2 hours post-dose in Study 301. An information request letter was sent to the Applicant on 07/12/2022 and response from the Applicant was received by the Agency on 07/24/2022 including corrected analysis results conducted with the correct subjects following the SAP. The updates in the corrected sensitivity analyses results were minor and did not change the conclusions of these analyses.

The Applicant used CMH test to evaluate efficacy of co-primary endpoints in subgroup analyses of Study 201 and Study 301. FDA reviewer used the CMH test stratified by prophylactic migraine medication use at randomization (yes, no) to evaluate the efficacy of co-primary endpoints in subgroup analyses for Study 201 and Study 301 because the efficacy analyses on co-primary endpoints and key secondary endpoints used the CMH test stratified by prophylactic migraine medication use at randomization. The differences between the subgroup analysis results from the Applicant and the FDA reviewer were minor and did not change the conclusions of these analyses.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 201 was initiated on March 25, 2019 and completed on November 11, 2019. Study 201 final database lock occurred on December 11, 2019. The final version of the protocol of Study 201 was dated August 08, 2019. The final version of Statistical Analysis Plan (SAP) of Study 201 was dated November 15, 2019.

Study 301 was initiated on October 27, 2020 and completed on October 22, 2021. Study 301 final database lock occurred on November 12, 2021. The final version of the protocol of Study 301 was dated June 02, 2021. The final version of SAP of Study 301 was dated September 15, 2021.

Study Design

Study 201 was a double-blind, randomized, placebo-controlled, dose-ranging, multicenter, outpatient study in patients with moderate or severe migraine. Subjects were randomized in a 1:1:1:1 ratio to receive zavegepant 5 mg, zavegepant 10 mg, zavegepant 20 mg and placebo. The total duration of Study 201 was approximately 11 weeks. Study 201 included the screening phase (lasting 3 to 28 days) and the treatment phase (consisting of a randomization/baseline visit up to 45 days or until a subject experienced a migraine attack of moderate or severe intensity), followed by an end of treatment (EOT) visit.

Study 301 was a double-blind, randomized, placebo-controlled, multicenter, outpatient study in patients with moderate or severe migraine. Subjects were randomized in a 1:1 ratio to receive zavegepant 10 mg and placebo. The total duration of the study was up to 11 weeks. Study 301

included a 3- to 28-day Screening Phase, a Treatment Phase that could last up to 45 days or until the subject had a migraine that reached moderate or severe intensity, and an EOT Visit 7 (+ 2) days after the administration of the study drug.

Efficacy Endpoints

Study 201 and Study 301 had the same co-primary endpoints and key secondary endpoints. The first co-primary endpoint was pain freedom at 2 hours post-dose, defined as percentage of subjects with a pain intensity of none at 2 hours post-dose. Pain intensity was measured on a 4-point numeric rating scale (0=none, 1=mild, 2=moderate, 3=severe). The second co-primary endpoint was MBS freedom at 2 hours post-dose, defined as percentage of subjects with MBS reported on study before dosing that was absent at 2 hours post-dose. The MBS on study before dosing was reported as nausea, phonophobia, or photophobia. Symptom status was reported post-dose as present or absent for each symptom (nausea, phonophobia, and photophobia).

The key secondary endpoints were the following for both Study 201 and Study 301:

- Pain relief at 2 hours post-dose
- Return to normal function at 2 hours post-dose
- Sustained pain freedom from 2 to 48 hours post-dose
- Phonophobia freedom at 2 hours post-dose
- Photophobia freedom at 2 hours post-dose

3.2.2 Statistical Methodologies

Analysis Population

The modified intent-to-treat population was the primary efficacy population and included subjects in the randomized analysis set who 1) were randomized only once, 2) had a migraine of moderate or severe pain intensity at the time of dosing, 3) took study drug, and 4) had post-dose efficacy data.

Multiple Testing Procedure

To control Type I error rate, the Applicant implemented the following strategy: if the co-primary endpoint tests were both significant for zavegepant versus placebo, the secondary endpoints were tested for zavegepant versus placebo using a hierarchical gate-keeping procedure, with each test in the hierarchy conducted at a 2-sided alpha level 0.0167 in Study 201 and at a 2-sided alpha level 0.05 in Study 301, respectively.

Analysis Methods

Co-primary endpoints: Pain freedom at 2 hours post-dose and MBS freedom at 2 hours post-dose

The co-primary endpoints were analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by prophylactic migraine medication use at randomization (yes, no). Subjects with rescue

medication taken at or before 2 hours post-dose and subjects with missing response status at 2 hours post-dose were classified as failures for both co-primary endpoints.

The following sensitivity analyses were planned for co-primary endpoints.

1. Complete case analysis: the primary analysis was repeated excluding subjects with missing response status in the 2-hour post-dose analysis window.
2. Multiple imputation: the primary analysis was repeated using the copy from reference multiple imputation approach with m=20 imputations to impute missing response status at 2 hours post-dose. The fully conditional specification (FCS) method was used with a generalized logit distribution. Covariates included prophylactic migraine medication use at randomization (yes or no), sex, pain intensity at the time of dosing (moderate or severe), historical number of moderate to severe migraine attacks per month (< median, >= median), and MBS on study before dosing (nausea, phonophobia, or photophobia).
3. Hypothetical success rate imputation: the primary analysis was repeated by imputing response status at 2 hours post-dose in each treatment group with varying response rates over the range of 0%, 10%, 20% and 30%.

Key Secondary endpoints

Key secondary endpoints were analyzed using Cochran-Mantel-Haenszel (CMH) tests stratified by prophylactic migraine medication use at randomization (yes, no). Subjects with rescue medication taken and subjects with missing response status were classified as failures.

Additionally, for secondary endpoint sustained pain freedom from 2 to 48 hours post-dose, subjects with missing response status at more than 1 time point were classified as failures.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In Study 201, a total of 1673 subjects were randomized, of whom 1588 subjects were treated and 1581 treated subjects were included in the mITT population sample. Among randomized subjects in the zavegepant dose groups, the percentages of being treated were similar (92.8%, 94.5% and 96.4%, respectively) and the percentages of being included in the mITT population sample were similar (92.6%, 93.8% and 96.2%, respectively). (Table 2)

Table 2: Study 201 Subject Disposition

	Zavegepant 5 mg Group (N=418)	Zavegepant 10 mg Group (N=417)	Zavegepant 20 mg Group (N=418)	All Zavegepant Group (N=1,253)	Placebo Group (N=420)	Overall (N=1,673)
Disposition: n (%)						
Reason: n (%)						
Treated	388 (92.8)	394 (94.5)	403 (96.4)	1,185 (94.6)	403 (96.0)	1,588 (94.9)
Not treated	30 (7.2)	23 (5.5)	15 (3.6)	68 (5.4)	17 (4.0)	85 (5.1)
Adverse event	1 (0.2)	1 (0.2)	0	2 (0.2)	0	2 (0.1)
Lost to follow-up	6 (1.4)	5 (1.2)	1 (0.2)	12 (1.0)	3 (0.7)	15 (0.9)
Never treated migraine	19 (4.5)	17 (4.1)	13 (3.1)	49 (3.9)	12 (2.9)	61 (3.6)
Pregnancy	1 (0.2)	0	0	1 (0.1)	0	1 (0.1)
Protocol deviation	2 (0.5)	0	0	2 (0.2)	2 (0.5)	4 (0.2)
Withdrawal by subject	0	0	1 (0.2)	1 (0.1)	0	1 (0.1)
Other	1 (0.2)	0	0	1 (0.1)	0	1 (0.1)
Included in mITT population sample	387 (92.6)	391 (93.8)	402 (96.2)	1,180 (94.2)	401 (95.5)	1,581 (94.5)
Excluded from mITT population sample	31 (7.4)	26 (6.2)	16 (3.8)	73 (5.8)	19 (4.5)	92 (5.5)
Treated	1 (0.2)	3 (0.7)	1 (0.2)	5 (0.4)	2 (0.5)	7 (0.4)
Pain level at on-study migraine attack onset						
Mild	0	0	0	0	0	0
None	0	0	0	0	0	0
Not reported	0	3 (0.7)	0	3 (0.2)	1 (0.2)	4 (0.2)
Randomized more than once	0	0	0	0	0	0
No post-baseline efficacy data	1 (0.2)	3 (0.7)	1 (0.2)	5 (0.4)	2 (0.5)	7 (0.4)
Not treated	30 (7.2)	23 (5.5)	15 (3.6)	68 (5.4)	17 (4.0)	85 (5.1)

Source: Study 201 CSR Table 9-3, confirmed by FDA reviewer

In Study 301, a total of 1405 subjects were randomized, of whom 1282 subjects were treated and 1269 subjects are included in the efficacy analysis set. 6 subjects of the 1269 subjects in the efficacy analysis set did not complete the study due to lost to follow-up. (Table 3)

Table 3: Study 301 Subject Disposition

	Zavegepant 10 mg N = 623	Placebo N = 646	Overall N = 1269
Disposition: n (%)			
Reason: n (%)			
Completed the study	617 (99.0)	646 (100.0)	1263 (99.5)
Did not complete the study	6 (1.0)	0	6 (0.5)
Lost to follow-up	6 (1.0)	0	6 (0.5)
Terminated the study prematurely due to COVID-19	0	0	0

Source: Study 301 CSR Table 14.1.3.1D Subject Disposition from Treatment to End of Study Efficacy Analysis Set, confirmed by FDA reviewer

Demographics were generally balanced among the zavegepant dose groups for Study 201 and between the treatment groups for Study 301. Most patients were female and white, with a median age 40 or 39 years in Study 201 and with a median age 40 years in Study 301. Study 201 and Study 301 were conducted in US sites only. (Table 4 and Table 5)

Table 4: Study 201 mITT Patient Demographics

	BHV3500-201			
	BHV-3500 10 mg N=391	BHV-3500 20 mg N=402	BHV-3500 5 mg N=387	Placebo N=401
Sex, n (%)				
Female	333 (85.2)	344 (85.6)	336 (86.8)	338 (84.3)
Male	58 (14.8)	58 (14.4)	51 (13.2)	63 (15.7)
Age at informed consent, years				
Mean (SD)	41.4 (12.94)	40.0 (12.96)	41.9 (12.59)	39.9 (12.00)
Median	40.0	39.0	40.0	39.0
IQR	31.0, 51.0	29.0, 50.0	32.0, 52.0	31.0, 48.0
Min, Max	18.0, 74.0	18.0, 74.0	18.0, 70.0	18.0, 79.0
Race, n (%)				
AMERICAN INDIAN OR ALASKA NATIVE	0	3 (<1)	2 (<1)	1 (<1)
ASIAN	13 (3.3)	15 (3.7)	17 (4.4)	13 (3.2)
BLACK OR AFRICAN AMERICAN	72 (18.4)	62 (15.4)	65 (16.8)	58 (14.5)
MULTIPLE	9 (2.3)	7 (1.7)	4 (1.0)	1 (<1)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (<1)	0	0	0
WHITE	296 (75.7)	315 (78.4)	299 (77.3)	328 (81.8)

Abbreviations: IQR = interquartile range, mITT = modified Intention-to-treat population, SD = standard deviation

Source: Reviewer generated analysis based on applicant submitted data adsl.xpt

Table 5: Study 301 mITT Patient Demographics

	Placebo N=646	Zavegepant 10 mg N=623	Total N=1269
Sex, n (%)			
Female	546 (84.5)	506 (81.2)	1052 (82.9)
Male	100 (15.5)	117 (18.8)	217 (17.1)
Age at informed consent, years			
Mean (SD)	40.8 (13.46)	40.9 (13.22)	40.8 (13.34)
Median	40.0	40.0	40.0
IQR	29.0, 51.0	30.0, 51.0	30.0, 51.0
Min, Max	18.0, 76.0	18.0, 73.0	18.0, 76.0
Race, n (%)			
AMERICAN INDIAN OR ALASKA NATIVE	2 (<1)	0	2 (<1)
ASIAN	15 (2.3)	20 (3.2)	35 (2.8)
BLACK OR AFRICAN AMERICAN	83 (12.8)	85 (13.6)	168 (13.2)
MULTIPLE	5 (<1)	5 (<1)	10 (<1)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (<1)	2 (<1)	3 (<1)
WHITE	540 (83.6)	511 (82.0)	1051 (82.8)

Abbreviations: IQR = interquartile range, mITT = modified Intention-to-treat population, SD = standard deviation

Source: Reviewer generated analysis based on applicant submitted data adsl.xpt

Baseline disease characteristics were generally balanced among the zavegepant dose groups for Study 201 and between the treatment groups for Study 301. In these two studies, the most common MBS reported before dosing was photophobia, followed by nausea, and phonophobia. (Table 6 and Table 7)

Table 6: Study 201 Baseline Disease Characteristics

	BHV3500-201			
	BHV-3500 10 mg N=391	BHV-3500 20 mg N=402	BHV-3500 5 mg N=387	Placebo N=401
Prophylactic Medication Use at Randomization, n (%)				
No	341 (87.2)	345 (85.8)	333 (86.0)	347 (86.5)
Yes	50 (12.8)	57 (14.2)	54 (14.0)	54 (13.5)
MBS at Onset of Migraine during Study, n (%)				
nausea	129 (33.0)	140 (34.8)	111 (28.7)	118 (29.4)
not reported	5 (1.3)	3 (<1)	3 (<1)	2 (<1)
phonophobia	54 (13.8)	63 (15.7)	67 (17.3)	65 (16.2)
photophobia	203 (51.9)	196 (48.8)	206 (53.2)	216 (53.9)

Source: Reviewer generated analysis based on applicant submitted data adsl.xpt, adsb.xpt, adsymp.xpt

Table 7: Study 301 Baseline Disease Characteristics

	Placebo N=646	Zavegepant 10 mg N=623	Total N=1269
Triptan Non-Responder, n (%)			
No	627 (97.1)	611 (98.1)	1238 (97.6)
Yes	19 (2.9)	12 (1.9)	31 (2.4)
Cardiovascular Risk Counter Indicating Triptans, n (%)			
No	643 (99.5)	619 (99.4)	1262 (99.4)
Yes	2 (<1)	3 (<1)	5 (<1)
not reported	1 (<1)	1 (<1)	2 (<1)
Prophylactic Medication Use at Randomization, n (%)			
No	564 (87.3)	535 (85.9)	1099 (86.6)
Yes	82 (12.7)	88 (14.1)	170 (13.4)
Non-study Stable Prophylactic Migraine Medication use through Randomization, n (%)			
No	575 (89.0)	540 (86.7)	1115 (87.9)
Yes	71 (11.0)	83 (13.3)	154 (12.1)
MBS at Onset of Migraine during Study, n (%)			
nausea	175 (27.1)	177 (28.4)	352 (27.7)
not reported	8 (1.2)	3 (<1)	11 (<1)
phonophobia	115 (17.8)	89 (14.3)	204 (16.1)
photophobia	348 (53.9)	354 (56.8)	702 (55.3)

Source: Reviewer generated analysis based on applicant submitted data adsl.xpt, adsb.xpt, adsymp.xpt

3.2.4 Results and Conclusions

3.2.4.1 Study 201

Co-primary endpoints

The percentage of subjects with pain freedom at 2 hours post-dose was 19.6% in zavegepant 5 mg group with a 4.2% therapeutic gain over placebo group ($p=0.1214$), 22.5% in zavegepant 10 mg group with a 7.0% therapeutic gain over placebo group ($p=0.0113$) and 23.1% in zavegepant 20 mg group with a 7.7% therapeutic gain over placebo group ($p=0.0055$). (Table 8) Results of all the pre-specified sensitivity analyses were consistent with that of the primary analysis for the co-primary endpoint of pain freedom at 2 hours post-dose in favoring zavegepant 10 mg and 20 mg over placebo.

Table 8: Study 201 Primary Efficacy Analysis: Pain Freedom at 2 Hours Post-dose

	Zavegepant 5 mg N=387	Zavegepant 10 mg N=391	Zavegepant 20 mg N=402	Placebo N=401
Responder ¹ , n (%)	76 (19.6)	88 (22.5)	93 (23.1)	62 (15.5)
Stratified Difference (98.3% CI) in Percentages	4.2 (-2.3, 10.7)	7.0 (0.4, 13.7)	7.7 (1.1, 14.3)	-
Stratified CMH p-value	0.1214	0.0113	0.0055	-

Abbreviations: CI = confidence interval

¹ Responder: No pain at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose.

Source: Reviewer generated analysis based on applicant submitted data adpain.xpt for NDA 216386.

The percentage of subjects with MBS pain freedom at 2 hours post-dose was 39.0% in zavegepant 5 mg group with a 5.4% therapeutic gain over placebo group ($p=0.1162$), 41.9% in zavegepant 10 mg group with an 8.3% therapeutic gain over placebo group ($p=0.0155$) and 42.5% in zavegepant 20 mg group with an 8.9% therapeutic gain over placebo group ($p=0.0094$). (Table 9)

Results of sensitivity analyses with complete cases and with multiple imputation were consistent with that of the primary analysis for the co-primary endpoint of MBS freedom at 2 hours post-dose in favoring zavegepant 10 mg and 20 mg over placebo. Results of sensitivity analysis with hypothetical success rate imputation consistently favored zavegepant 10 mg and 20 mg over placebo at a hypothetical success rate of 30% for subjects in zavegepant group at any hypothetical success rate for subjects in placebo group.

Table 9: Study 201 Primary Efficacy Analysis: MBS Freedom at 2 Hours Post-dose

	Zavegepant 5 mg N=387	Zavegepant 10 mg N=391	Zavegepant 20 mg N=402	Placebo N=401
Responder ¹ , n (%)	151 (39.0)	164 (41.9)	171 (42.5)	135 (33.7)
Stratified Difference (98.3% CI) in Percentages	5.4 (-2.8, 13.6)	8.3 (0.1, 16.5)	8.9 (0.7, 17.0)	-
Stratified CMH p-value	0.1162	0.0155	0.0094	-

Abbreviations: CI = confidence interval

¹ Responder: MBS reported at on study migraine attack onset before taking study drug, MBS absent at 2 hours post-dose,

and no intervening rescue medication taken at or before 2 hours post-dose.

Source: Reviewer generated analysis based on applicant submitted data adsymp.xpt for NDA 216386.

Key secondary endpoints

The secondary endpoints were tested hierarchically at a 2-sided 0.0167 significance level and the first secondary endpoint, pain relief at 2 hours post-dose, was not significant for any zavegepant dose group. All secondary endpoints listed after the secondary endpoint of pain relief at 2 hours post-dose were considered not significant.

Table 10: Study 201 Secondary Efficacy Analysis: Pain Relief at 2 Hours Post-dose

	Zavegepant 5 mg N=387	Zavegepant 10 mg N=391	Zavegepant 20 mg N=402	Placebo N=401
Responder ¹ , n (%)	224 (57.9)	237 (60.6)	246 (61.2)	215 (53.6)
Stratified Difference (98.3% CI) in Percentages	4.2 (-4.2, 12.7)	7.1 (-1.3, 15.4)	7.5 (-0.8, 15.9)	-
Stratified CMH p-value	0.2296	0.0439	0.0302	-

Abbreviations: CI = confidence interval

¹ Responder: Mild or no pain at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose

Source: Reviewer generated analysis based on applicant submitted data adpain.xpt for NDA 216386.

Table 11: Study 201 Secondary Efficacy Analysis: Return to Normal Function at 2 Hours Post-dose

	Zavegepant 5 mg N=363	Zavegepant 10 mg N=354	Zavegepant 20 mg N=372	Placebo N=369
Responder ¹ , n (%)	115 (31.7)	122 (34.5)	129 (34.7)	101 (27.4)
Stratified Difference (98.3% CI) in Percentages	4.3 (-3.8, 12.3)	7.1 (-1.1, 15.3)	7.3 (-0.8, 15.4)	-
Stratified CMH p-value	0.2039	0.0389	0.0305	-

Abbreviations: CI = confidence interval

¹ Responder: Normal at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose

Source: Reviewer generated analysis based on applicant submitted data adfds.xpt for NDA 216386.

Table 12: Study 201 Secondary Efficacy Analysis: Photophobia Freedom at 2 Hours Post-dose

	Zavegepant 5 mg N=337	Zavegepant 10 mg N=340	Zavegepant 20 mg N=354	Placebo N=358
Responder ¹ , n (%)	118 (35.0)	121 (35.6)	134 (37.9)	109 (30.4)
Stratified Difference (98.3% CI) in Percentages	4.6 (-3.9, 13.1)	5.1 (-3.4, 13.6)	7.4 (-1.0, 15.9)	-
Stratified CMH p-value	0.1986	0.1494	0.0352	-

Abbreviations: CI = confidence interval

¹ Responder: Photophobia absent at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose

Source: Reviewer generated analysis based on applicant submitted data adsymp.xpt for NDA 216386.

Table 13: Study 201 Secondary Efficacy Analysis: Phonophobia Freedom at 2 Hours Post-dose

	Zavegepant 5 mg N=260	Zavegepant 10 mg N=239	Zavegepant 20 mg N=263	Placebo N=276
Responder ¹ , n (%)	115 (44.2)	107 (44.8)	114 (43.3)	94 (34.1)
Stratified Difference (98.3% CI) in Percentages	10.1 (0.1, 20.1)	10.8 (0.6, 21.1)	9.3 (-0.6, 19.3)	-
Stratified CMH p-value	0.0161	0.0115	0.0249	-

Abbreviations: CI = confidence interval

¹ Responder: Phonophobia absent at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose

Source: Reviewer generated analysis based on applicant submitted data adsymp.xpt for NDA 216386.

Table 14: Study 201 Secondary Efficacy Analysis: Sustained Pain Freedom From 2 to 48 Hours Post-dose

	Zavegepant 5 mg N=387	Zavegepant 10 mg N=391	Zavegepant 20 mg N=402	Placebo N=401
Responder ¹ , n (%)	50 (12.9)	54 (13.8)	53 (13.2)	30 (7.5)
Stratified Difference (98.3% CI) in Percentages	5.5 (0.3, 10.6)	6.3 (1.1, 11.6)	5.7 (0.6, 10.8)	-
Stratified CMH p-value	0.0111	0.0038	0.0075	-

Abbreviations: CI = confidence interval

¹ Responder: No pain at all time points from 2 to 48 hours post-dose, missing data at ≤ 1 time point from 3 to 8 hours post-dose, and no intervening rescue medication taken at or before 48 hours post-dose

Source: Reviewer generated analysis based on applicant submitted data adpain.xpt for NDA 216386.

3.2.4.1 Study 301

Co-primary endpoints

The percentage of subjects with pain freedom at 2 hours post-dose was 23.6% in zavegepant 10 mg group with an 8.8% therapeutic gain over placebo group (p<0.001). (Table 15)

Results of all the pre-specified sensitivity analyses were consistent with that of the primary analysis for the co-primary endpoint of pain freedom at 2 hours post-dose in favoring zavegepant 10 mg over placebo.

Table 15: Study 301 Primary Efficacy Analysis: Pain Freedom at 2 Hours Post-dose

	Zavegepant 10 mg N=623	Placebo N=646
Responder ¹ , n (%)	147 (23.6)	96 (14.9)
Stratified Difference (95% CI) in Percentages	8.8 (4.5, 13.1)	-
Stratified CMH p-value	<0.001	-

Abbreviations: CI = confidence interval

¹ Responder: Pain intensity of none at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose.

Source: Reviewer generated analysis based on applicant submitted data adpain.xpt for NDA 216386.

The percentage of subjects with MBS freedom at 2 hours post-dose was 39.6% in zavegepant 10 mg group with an 8.7% therapeutic gain over placebo group (p=0.0012). (Table 16)

Results of all the pre-specified sensitivity analyses were consistent with that of the primary analysis for the co-primary endpoint of MBS freedom at 2 hours post-dose in favoring zavegepant 10 mg over placebo.

Table 16: Study 301 Primary Efficacy Analysis: MBS Freedom at 2 Hours Post-dose

	Zavegepant 10 mg N=623	Placebo N=646
Responder ¹ , n (%)	247 (39.6)	201 (31.1)
Stratified Difference (95% CI) in Percentages	8.7 (3.4, 13.9)	-
Stratified CMH p-value	0.0012	-

Abbreviations: CI = confidence interval

¹ Responder: MBS reported at on study before dosing, MBS absent at 2 hours post-dose, and no intervening rescue medication taken at or before 2 hours post-dose.

Source: Reviewer generated analysis based on applicant submitted data adsymp.xpt for NDA 216386.

Key secondary endpoints

The secondary endpoints were tested hierarchically at a 2-sided 0.05 significance level. The key secondary endpoints were all with significant results in the hierarchically testing.

The percentage of subjects with pain relief at 2 hours post-dose was 58.7% in zavegepant 10 mg group with a 9.0% therapeutic gain over placebo group (p=0.0012). (Table 17)

Table 17: Study 301 Secondary Efficacy Analysis: Pain Relief at 2 Hours Post-dose

	Zavegepant 10 mg N=623	Placebo N=646
Responder ¹ , n (%)	366 (58.7)	321 (49.7)
Stratified Difference (95% CI) in Percentages	9.0 (3.6, 14.5)	-
Stratified CMH p-value	0.0012	-

Abbreviations: CI = confidence interval

¹ Responder: Pain intensity of mild or none at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose

Source: Reviewer generated analysis based on applicant submitted data adpain.xpt for NDA 216386.

The percentage of subjects returning to normal function at 2 hours post-dose was 35.8% in zavegepant 10 mg group with a 10.2% therapeutic gain over placebo group (p=0.0001). (Table 18)

Table 18: Study 301 Secondary Efficacy Analysis: Return to Normal Function at 2 Hours Post-dose

	Zavegepant 10 mg N=570	Placebo N=593
Responder ¹ , n (%)	204 (35.8)	152 (25.6)
Stratified Difference (95% CI) in Percentages	10.2 (5.0, 15.5)	-
Stratified CMH p-value	0.0001	-

Abbreviations: CI = confidence interval

¹ Responder: Normal level at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose

Source: Reviewer generated analysis based on applicant submitted data adfds.xpt for NDA 216386.

The percentage of subjects with sustained pain freedom from 2 to 48 hours post-dose was 12.4% in zavegepant 10 mg group with a 3.7% therapeutic gain over placebo group (p=0.0308). (Table 19)

Table 19: Study 301 Secondary Efficacy Analysis: Sustained Pain Freedom from 2 to 48 Hours Post-dose

	Zavegepant 10 mg N=623	Placebo N=646
Responder ¹ , n (%)	77 (12.4)	56 (8.7)
Stratified Difference (95% CI) in Percentages	3.7 (0.3, 7.1)	-
Stratified CMH p-value	0.0308	-

Abbreviations: CI = confidence interval

¹ Responder: No pain at all time points from 2 to 48 hours post-dose, missing data at ≤ 1 time point from 3 to 8 hours post-dose, and no intervening rescue medication taken at or before 48 hours post-dose

Source: Reviewer generated analysis based on applicant submitted data adpain.xpt for NDA 216386.

The percentage of subjects with phonophobia freedom at 2 hours post-dose was 41.0% in zavegepant 10 mg group with an 8.3% therapeutic gain over placebo group (p=0.0123). (Table 20)

Table 20: Study 301 Secondary Efficacy Analysis: Phonophobia Freedom at 2 Hours Post-dose

	Zavegepant 10 mg N=407	Placebo N=425
Responder ¹ , n (%)	167 (41.0)	139 (32.7)
Stratified Difference (95% CI) in Percentages	8.3 (1.8, 14.9)	-
Stratified CMH p-value	0.0123	-

Abbreviations: CI = confidence interval

¹ Responder: Phonophobia absent at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose

Source: Reviewer generated analysis based on applicant submitted data adsymp.xpt for NDA 216386.

The percentage of subjects with photophobia freedom at 2 hours post-dose was 37.1% in zavegepant 10 mg group with an 8.6% therapeutic gain over placebo group (p=0.0018). (Table 21)

Table 21: Study 301 Secondary Efficacy Analysis: Photophobia Freedom at 2 Hours Post-dose

	Zavegepant 10 mg N=558	Placebo N=585
Responder ¹ , n (%)	207 (37.1)	167 (28.5)
Stratified Difference (95% CI) in Percentages	8.6 (3.2, 14.1)	-
Stratified CMH p-value	0.0018	-

Abbreviations: CI = confidence interval

¹ Responder: Photophobia absent at 2 hours post-dose and no intervening rescue medication taken at or before 2 hours post-dose

Source: Reviewer generated analysis based on applicant submitted data adsymp.xpt for NDA 216386.

3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The subgroup analyses to evaluate the efficacy of co-primary endpoints for Study 201 and Study 301 were conducted by the FDA reviewer using the CMH test stratified by prophylactic migraine medication use at randomization (yes, no) to be consistent with the stratified CMH methodology applied in primary efficacy analyses of the co-primary endpoints and secondary efficacy analyses of the key secondary endpoints.

Subgroup analysis results using the CMH test stratified by prophylactic migraine medication use at randomization (yes, no) for the co-primary endpoint of pain freedom at 2 hours post-dose for Study 201 are shown in Table 22. Zavegepant 10 mg and 20 mg showed a therapeutic gain over placebo across the subgroups except for small subgroups of race.

Table 22: Study 201 Subgroup Analysis: Pain Freedom in 2 Hours Post-dose

	Zavegepant 5 mg N=387	Zavegepant 10 mg N=391	Zavegepant 20 mg N=402	Placebo N=401
Age (years): <40				
n/N (%)	29/181 (16.0)	51/186 (27.4)	49/208 (23.6)	29/203 (14.3)
Stratified Difference (98.3% CI) in Percentages	1.9 (-6.9, 10.6)	12.9 (3, 22.7)	9.3 (0.1, 18.4)	-
Age (years): ≥ 40				
n/N (%)	47/206 (22.8)	37/205 (18.0)	44/194 (22.7)	33/198 (16.7)
Stratified Difference (98.3% CI) in Percentages	6.1 (-3.3, 15.6)	1.3 (-7.7, 10.3)	6 (-3.6, 15.6)	-
Sex: Female				
n/N (%)	67/336 (19.9)	78/333 (23.4)	82/344 (23.8)	54/338 (16.0)
Stratified Difference (98.3% CI) in Percentages	4 (-3.1, 11)	7.4 (0.1, 14.7)	7.9 (0.6, 15.1)	-
Sex: Male				
n/N (%)	9/51 (17.6)	10/58 (17.2)	11/58 (19.0)	8/63 (12.7)
Stratified Difference (98.3% CI) in Percentages	4.9 (-11.2, 21)	4.2 (-11, 19.3)	6.3 (-9.6, 22.1)	-
Race: White				
n/N (%)	55/299 (18.4)	61/296 (20.6)	71/315 (22.5)	51/328 (15.5)
Stratified Difference (98.3% CI) in Percentages	2.9 (-4.3, 10.1)	5.1 (-2.3, 12.4)	7 (-0.4, 14.4)	-
Race: Black or African American				
n/N (%)	19/65 (29.2)	25/72 (34.7)	17/62 (27.4)	8/58 (13.8)
Stratified Difference (98.3% CI) in Percentages	15.7 (-1.5, 33)	21.2 (4, 38.4)	15.7 (-1.9, 33.4)	-
Race: Other including Asian				
n/N (%)	2/23 (8.7)	2/23 (8.7)	5/25 (20.0)	3/15 (20.0)
Stratified Difference (98.3% CI) in Percentages	-10.8 (-39.1, 17.6)	-12.1 (-40.4, 16.3)	0.1 (-30.5, 30.8)	-
Race: Asian				
n/N (%)	1/17 (5.9)	1/13 (7.7)	3/15 (20.0)	3/13 (23.1)
Stratified Difference (98.3% CI) in Percentages	-19.1 (-52, 13.8)	-15.4 (-48.2, 17.4)	-3.3 (-40.3, 33.6)	-

Abbreviations: CI = confidence interval

Source: Reviewer generated analysis based on applicant submitted data adpain.xpt for NDA 216386.

Subgroup analysis results using the CMH test stratified by prophylactic migraine medication use at randomization (yes, no) for the co-primary endpoint of MBS freedom at 2 hours post-dose for Study 201 are shown in Table 23. Zavegepant 10 mg and 20 mg showed a therapeutic gain over placebo across the subgroups except for small subgroups of race and sex.

Table 23: Study 201 Subgroup Analysis: MBS Freedom in 2 Hours Post-dose

	Zavegepant 5 mg N=387	Zavegepant 10 mg N=391	Zavegepant 20 mg N=402	Placebo N=401
Age (years): <40				
n/N (%)	67/181 (37.0)	79/186 (42.5)	84/208 (40.4)	71/203 (35.0)
Stratified Difference (98.3% CI) in Percentages	2 (-9.7, 13.8)	7.3 (-4.5, 19.2)	5.4 (-6, 16.7)	-
Age (years): ≥ 40				
n/N (%)	84/206 (40.8)	85/205 (41.5)	87/194 (44.8)	64/198 (32.3)
Stratified Difference (98.3% CI) in Percentages	8.4 (-3, 19.7)	9 (-2.5, 20.3)	12.6 (0.9, 24.2)	-
Sex: Female				
n/N (%)	134/336 (39.9)	145/333 (43.5)	151/344 (43.9)	114/338 (33.7)
Stratified Difference (98.3% CI) in Percentages	6.2 (-2.7, 15)	9.9 (0.9, 18.8)	10.2 (1.3, 19)	-
Sex: Male				
n/N (%)	17/51 (33.3)	19/58 (32.8)	20/58 (34.5)	21/63 (33.3)
Stratified Difference (98.3% CI) in Percentages	0 (-20.9, 20.9)	-0.6 (-20.7, 19.5)	1.2 (-19.3, 21.7)	-
Race: White				
n/N (%)	113/299 (37.8)	126/296 (42.6)	137/315 (43.5)	110/328 (33.5)
Stratified Difference (98.3% CI) in Percentages	4.3 (-4.9, 13.4)	9 (-0.2, 18.3)	10 (0.9, 19.1)	-
Race: Black or African American				
n/N (%)	30/65 (46.2)	32/72 (44.4)	26/62 (41.9)	20/58 (34.5)
Stratified Difference (98.3% CI) in Percentages	11.8 (-9.3, 32.8)	9.8 (-10.7, 30.3)	8.7 (-12.9, 30.2)	-
Race: Other including Asian				
n/N (%)	8/23 (34.8)	6/23 (26.1)	8/25 (32.0)	5/15 (33.3)
Stratified Difference (98.3% CI) in Percentages	1 (-36.3, 38.3)	-7.5 (-43.6, 28.6)	-0.8 (-36.4, 34.8)	-
Race: Asian				
n/N (%)	6/17 (35.3)	3/13 (23.1)	4/15 (26.7)	5/13 (38.5)
Stratified Difference (98.3% CI) in Percentages	-6.4 (-50.3, 37.6)	-15.4 (-57.2, 26.5)	-12.2 (-53.6, 29.3)	-

Abbreviations: CI = confidence interval

Source: Reviewer generated analysis based on applicant submitted data adpain.xpt for NDA 216386.

Subgroup analysis results using the CMH test stratified by prophylactic migraine medication use at randomization (yes, no) for the co-primary endpoint of pain freedom in 2 hours post-dose for Study 301 are shown in Table 24. Zavegepant 10 mg showed a therapeutic gain over placebo across the subgroups except for small subgroups of race.

Table 24: Study 301 Subgroup Analysis: Pain Freedom in 2 Hours Post-dose

	Zavegepant 10 mg N=623	Placebo N=646
Age (years): <40		
n/N (%)	78/299 (26.1)	52/319 (16.3)
Stratified Difference (98.3% CI) in Percentages	9.8 (3.4, 16.3)	-
Age (years): ≥ 40		
n/N (%)	69/324 (21.3)	44/327 (13.5)
Stratified Difference (98.3% CI) in Percentages	7.8 (2, 13.5)	-
Sex: Female		
n/N (%)	117/506 (23.1)	75/546 (13.7)
Stratified Difference (98.3% CI) in Percentages	9.4 (4.8, 14.1)	-
Sex: Male		
n/N (%)	30/117 (25.6)	21/100 (21.0)
Stratified Difference (98.3% CI) in Percentages	4.5 (-6.7, 15.7)	-
Race: White		
n/N (%)	109/511 (21.3)	70/540 (13.0)
Stratified Difference (98.3% CI) in Percentages	8.5 (4, 13.1)	-
Race: Black or African American		
n/N (%)	29/85 (34.1)	16/83 (19.3)
Stratified Difference (98.3% CI) in Percentages	14.9 (1.6, 28.2)	-
Race: Other including Asian		
n/N (%)	9/27 (33.3)	10/23 (43.5)
Stratified Difference (98.3% CI) in Percentages	-7.3 (-34.6, 20.1)	-
Race: Asian		
n/N (%)	6/20 (30.0)	6/15 (40.0)
Stratified Difference (98.3% CI) in Percentages	-7.8 (-39.2, 23.7)	-

Abbreviations: CI = confidence interval

Source: Reviewer generated analysis based on applicant submitted data adpain.xpt for NDA 216386.

Subgroup analysis results using the CMH test stratified by prophylactic migraine medication use at randomization (yes, no) for the co-primary endpoint of MBS freedom in 2 hours post-dose for Study 301 are shown in Table 25. Zavegepant 10 mg showed a therapeutic gain over placebo across the subgroups.

Table 25: Study 301 Subgroup Analysis: MBS Freedom in 2 Hours Post-dose

	Zavegepant 10 mg N=623	Placebo N=646
Age (years): <40		
n/N (%)	122/299 (40.8)	92/319 (28.8)
Stratified Difference (98.3% CI) in Percentages	12.1 (4.6, 19.5)	-
Age (years): ≥ 40		
n/N (%)	125/324 (38.6)	109/327 (33.3)
Stratified Difference (98.3% CI) in Percentages	5.1 (-2.2, 12.4)	-
Sex: Female		
n/N (%)	205/506 (40.5)	172/546 (31.5)
Stratified Difference (98.3% CI) in Percentages	9.2 (3.4, 15)	-
Sex: Male		
n/N (%)	42/117 (35.9)	29/100 (29.0)
Stratified Difference (98.3% CI) in Percentages	6.7 (-5.7, 19.1)	-
Race: White		
n/N (%)	201/511 (39.3)	165/540 (30.6)
Stratified Difference (98.3% CI) in Percentages	9.1 (3.3, 14.8)	-
Race: Black or African American		
n/N (%)	35/85 (41.2)	28/83 (33.7)
Stratified Difference (98.3% CI) in Percentages	6.5 (-8.2, 21.3)	-
Race: Other including Asian		
n/N (%)	11/27 (40.7)	8/23 (34.8)
Stratified Difference (98.3% CI) in Percentages	4.6 (-23.1, 32.2)	-
Race: Asian		
n/N (%)	8/20 (40.0)	5/15 (33.3)
Stratified Difference (98.3% CI) in Percentages	4.9 (-27.2, 36.9)	-

Abbreviations: CI = confidence interval

Source: Reviewer generated analysis based on applicant submitted data adpain.xpt for NDA 216386.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and collective Evidence

The efficacy of zavegepant was studied in 2 pivotal trials in subjects with acute migraine: Study 201, a double-blind, randomized, placebo-controlled, dose-ranging study, and study 301, a double-blind, randomized, placebo-controlled, safety and efficacy study. Study 201 investigated three doses and results demonstrated that zavegepant 10 mg was the lowest dose with significant efficacy on co-primary endpoints, pain freedom at two hours post-dose and MBS at 2 hours post-dose. Study 301 only investigated zavegepant 10 mg. The discussion below only refers to the zavegepant 10 mg dose unless otherwise stated.

Both study 201 and study 301 demonstrated a statistically significant effect of zavegepant on the treatment of acute migraine. On the co-primary endpoint of pain freedom at 2 hours post-dose, there was a 7.0% therapeutic gain over placebo group ($p=0.0113$) in Study 201 and an 8.8% therapeutic gain over placebo group ($p<0.001$) in Study 301. On the co-primary endpoint of MBS pain freedom at 2 hours post-dose, there was an 8.3% therapeutic gain over placebo group ($p=0.0155$) in Study 201 and an 8.7% therapeutic gain over placebo group ($p=0.0012$) in Study 301. The efficacy on both co-primary endpoints was robust, supported by sensitivity analyses and subgroup analyses.

Only Study 301 showed statistically significant therapeutic gain on the following key secondary endpoints: pain relief at 2 hours post-dose, return to normal function at 2 hours post-dose, sustained pain freedom from 2 to 48 hours post-dose, phonophobia freedom at 2 hours post-dose, photophobia freedom at 2 hours post-dose.

In Study 301, there was a 9.0% therapeutic gain over placebo group in pain relief at 2 hours post-dose ($p=0.0012$), a 10.2% therapeutic gain over placebo group in return to normal function at 2 hours post-dose ($p=0.0001$), a 3.7% therapeutic gain over placebo group in sustained pain freedom from 2 to 48 hours post-dose ($p=0.0308$), an 8.3% therapeutic gain over placebo group in phonophobia freedom at 2 hours post-dose ($p=0.0123$) and an 8.6% therapeutic gain over placebo group in photophobia freedom at 2 hours post-dose ($p=0.0018$).

5.2 Conclusions and Recommendations

The data overall provides adequate evidence to support the efficacy of zavegepant 10 mg in treatment of acute migraine.

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