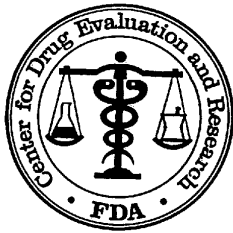


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208854Orig1s000

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 STUDIES

IND/NDA Number: NDA-208854

Drug Name: S-297995 (Symproic™)

Indication: Treatment of opioid-induced constipation (OIC) in subjects with chronic non-cancer pain opioid therapy.

Studies: 104 Week Carcinogenicity Studies in Rats and Mice

Applicant: Sponsor:
Shionogi Inc
300 Campus Dr
Florham Park, New Jersey 07932
United States

Testing Facility: (b) (4)

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to evaluate the carcinogenic potential of S-297995 when administered daily via oral gavage to rats and mice separately for at least 104 weeks.

In this review the phrase "dose response relationship" refers to the linear component (trend) 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

Two separate experiments, one in male rats and one in female rats were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups and one vehicle control group. Two hundred sixty rats of each sex were assigned randomly to the treated and control groups in equal size of 65 CD rats per group. The dose levels for treated groups were 10, 30, and 100 mg/kg/day for both male and female rats. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The rats in the vehicle control group were administrated with the vehicle [0.5% w/v methylcellulose aqueous solution (0.5% w/v MC)], and handled for the same duration and in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	65	65	Vehicle control	0	0
2	65	65	S-297995 low	10	10
3	65	65	S-297995 mid	30	30
4	65	65	S-297995 high	100	100

Animals were inspected visually at least twice daily for evidence of ill-health or reaction to treatment. Cages were inspected daily for evidence of animal ill-health amongst the occupants. Any deviation from normal was recorded at the time in respect of nature and severity, date and time of onset, duration and progress of the observed condition, as appropriate. In conjunction with the weekly physical examination, palpation was performed on all animals. New masses were recorded at detection in respect of mass number and location, date, size and description. A viability check was performed near the start and end of each working day. All animals were subject to a detailed necropsy. After a review of the history of each animal, a full macroscopic examination of the tissues was performed. All external features and orifices were examined visually. Any abnormality in the appearance or size of any organ and tissue (external and cut surface) was recorded and the required tissue samples preserved in appropriate fixative.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor analyzed the number of animal deaths during the study, up to terminal sacrifice using the log-rank tests for a trend across the groups. The numbers of animal deaths during the study were presented as life-tables and Kaplan-Meier survival curves. Two statistical tests were

carried out, including a two-tailed test for a trend across the groups, and a two-tailed pairwise comparison test of each treatment group against the control group. Where the test for trend was statistically significant, the highest dose group was excluded and the trend test repeated using a one-tailed test in the direction identified with all groups included, until the test was no longer statistically significant. As a check, tests for non-linearity (not presented) were carried out. In this study, the non-linearity tests were not statistically significant at the 1% level, and thus the results of the trend tests are to be preferred.

Sponsor's findings:

The sponsor's analysis showed that the numbers of rats surviving to their terminal necropsy were 29 (44.62%), 32 (49.23%), 26 (40.00%), and 28 (43.08%) in Groups 1, 2, 3, and 4 for male rats, respectively, and 15 (23.08%), 19 (29.23%), 19 (29.23%), and 17 (26.15%) for female rats respectively. The sponsor reported that for both male and female rats, the trend tests were not statistically significant when all groups were included in the analysis ($p=0.839$ and 0.563 , respectively), and no statistically significant pairwise comparisons were noted.

2.1.2. Tumor data analysis

The sponsor analyzed tumors from tissues listed in the protocol for all animals. Tumor types were selected for full statistical analysis where at least two tumors were observed in treated groups for which all animals were examined.

For non-palpable tumors, each tumor was categorized as non-incidental if the tumor was a factor contributing towards the death of the animal, incidental otherwise. For statistical purposes, all animals that died after terminal sacrifice commenced (Week 105 for males and from Week 103 for females) were considered terminal and the tumors observed in these animals were categorized as incidental. For palpable tumors, each tumor was classified as non-incidental if it was palpable before death and before the terminal sacrifice commenced, or, if it was a factor contributing towards the death of the animal. The tumor was classified as incidental, if the tumor was first found after death and was not a factor contributing towards the death of the animal, or if it was first found in or after the first week of the terminal sacrifice.

The sponsor used the life-table analysis to indicate the number of animals with a specific tumor and the number of animals at risk for the incidental tumors in the following fixed time strata, 1-52, 53-78, 79-92, 93-104 weeks and terminal sacrifice for males, and 1-52, 53-78, 79-92, 93-103 weeks and terminal sacrifice for females, respectively. For the non-incidental tumors, the strata are defined as those weeks during which there were deaths.

The sponsor used the time-to-tumor log-rank analysis to analyze the number of animals with tumors across treatment groups. The two χ^2 statistical tests were carried out, including a one-tailed test for a trend using nominal dose levels, with the control group, and a one-tailed pairwise comparison test of each treatment group against the control group. Where the test for trend was statistically significant, the highest dose group was excluded and the trend test was repeated using a one-tailed test until the test was no longer statistically significant. The significance levels were adjusted using a continuity correction where there was one degree of freedom. As a check, tests for non-linearity were carried out (not presented). For all analyses the non-linearity tests were not statistically significant at the 1 % level, hence the trend tests are to be preferred.

Where there were fewer than ten observed tumors, exact one-tailed p-values were calculated using permutation tests for stratified contingency tables, to test for trend and for pairwise comparisons of each treatment group against the control group.

Adjustment for multiple testing:

The sponsor adopted the rules described in Lin (Lin, 2000) to summarize the statistical results. These rules require an initial designation of tumor-types into "common" or "rare".

- Tumors with historical frequency greater than 1% were designated as being "common". A significance level of 0.005 was used for the trend tests, and 0.01 for each pairwise test.
- Tumors with historical frequency less than or equal to 1% were designated as being "rare". A significance level of 0.025 was used for the trend tests, and 0.05 for each pairwise test.

The classification of tumors was carried out based upon the overall incidence in historical control data from eight 104 week CD rat studies (The sponsor did not mention in their report whether these data were from the same laboratory or not). The tumors in the following list were considered to be "rare" tumors, all other tumors in this report were considered to be "common" tumors.

Males

Pancreas - Malignant Islet cell carcinoma

Thyroids - Malignant C-cell carcinoma

Pituitary (pars distalis) - Malignant carcinoma

Skin - Benign sebaceous cell adenoma

Skin - Benign sebaceous cell adenoma and malignant sebaceous cell carcinoma combined

Skin - Malignant fibro sarcoma, pleomolphic

Haematopoietic tumor - Malignant lymphoma

Females

Liver - Benign cholangioma

Thymus - Malignant thymoma

Thyroids - Malignant follicular cell carcinoma

Thyroids - Malignant C-cell carcinoma

Parathyroids - Benign chief cell adenoma

Mammary areas - Malignant adenocarcinoma arising in adenoma

Skin - Malignant fibrosarcoma

Brain - Malignant astrocytoma

Ovaries - Benign sex cord stromal mixed tumor

Ovaries - Benign sex cord stromal mixed tumor and malignant granulosa cell tumor combined

Uterine cervix - Malignant schwannoma

Sponsor's findings:

The sponsor reported a statistically significant trend in malignant lymphoma of haematopoietic tumor in male rats when all groups were included in the analysis ($p=0.024$). Upon exclusion of 100 mg/kg/day treated group the trend test was no longer significant ($p=0.128$). None of the pairwise comparisons were statistically significant for male rats. No statistically significant findings were noted for female rats.

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of rats in all four groups (Groups 1, 2, 3, and 4) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across Groups 1, 2, 3, and 4 using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all four groups in male and female rats, respectively. The intercurrent mortality data of all four groups, and the results of the tests for dose response relationship and homogeneity of survivals for Groups 1, 2, 3, and 4 are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 29 (44.62%), 32 (49.23%), 26 (40.00%), and 28 (43.08%) in Groups 1, 2, 3, and 4 for male, respectively, and 15 (23.08%), 19 (29.23%), 19 (29.23%), and 17 (26.15%) for female, respectively. No statistically significant findings in mortality was noted in for both male and female rats.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across Groups 1, 2, 3, and 4, and pairwise comparisons of each of the three treated groups (Groups 2, 3, and 4) against the vehicle control group (Group 1), using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the poly-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the i -th treatment group R^*_i is defined as $R^*_i = \sum w_{ij}$ where w_{ij} is the weight for the j -th animal in the i -th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w_{ij} as follows:

$w_{ij} = 1$ to animals dying with the tumor, and

$w_{ij} = (t_{ij} / t_{sacr})^3$ to animals dying without the tumor,

where t_{ij} is the time of death of the j -th animal in the i -th treatment group, and t_{sacr} is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned $w_{ij} = 1$ since $t_{ij} = t_{sacr}$.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the t_{sacr} should not be affected by the unplanned early terminations. The t_{sacr} should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than t_{sacr} , regardless their actual terminal sacrifice time, t_{sacr} was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data.

Multiple testing adjustment:

For the adjustment of multiple testing this reviewer used the methodologies suggested in the FDA guidance for statistical design and analysis of carcinogenicity studies (2001). For dose response relationship tests, the guidance suggests the use of test levels of $\alpha=0.005$ for common tumors and $\alpha=0.025$ for rare tumors for a submission with two species where both are two-years studies, in order to keep the false-positive rate at the nominal level of approximately 10%. For multiple pairwise comparisons of treated group with control, the guidance suggests the use of test levels of $\alpha=0.01$ for common tumors and $\alpha=0.05$ for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 2.

Table 2. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Rats

Organ name	Tumor name	0 mg	10 mg	30 mg	100 mg
		Vehicle (C) P - Trend	Low (L) P - C vs. L	Mid (M) P - C vs. M	High (H) P - C vs. H
Male: H-Poietic Tumor	Malignant Lymphoma	0/48 (65)	0/50 (65)	2/49 (65)	3/48 (65)
		0.0227 \$	NC	0.2526	0.1211
Male: Liver	Hepatocellular Adenoma/ Hepatocellular Carcinoma	0/48 (65)	0/50 (65)	1/49 (65)	3/47 (65)
		0.0170 @	NC	0.5052	0.1171

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

\$ = Statistically significant at 0.025 level in rare tumor for test of dose response relationship;

@ = Not statistically significant at 0.005 level in common tumor for test of dose response relationship;

NC = Not calculable.

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis

showed that a statistically significant positive trend ($p = 0.0227$) for the incidence rates of malignant lymphoma in haematopoietic (H-poietic) tumor in male rats, if this tumor was considered to be rare; while no statistically significant pairwise comparisons were noted for this tumor. A p -value of 0.0170 was noted for the dose response relationship of the combined adenoma and carcinoma hepatocellular in live for male rats. However, this trend was not statistically significant as this tumor was considered to be common based on the historical control data provided by the sponsor. No other statistically significant findings were noted for male and female rats.

3. Mouse Study

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 3. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred forty Crl:CD1(ICR) mice of each sex were assigned randomly to the treated and control groups in equal size of 60 mice per group. The dose levels for treated groups were 10, 30, and 100 mg/kg/day for both male and female mice. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The mice in the vehicle control group were administered with the vehicle [0.5% w/v methylcellulose aqueous solution (0.5% w/v MC)], and handled for the same duration and in the same manner as the treated groups.

Table 3. Experimental Design in Mouse Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	60	60	Vehicle control	0	0
2	60	60	S-297995 low	10	10
3	60	60	S-297995 mid	30	30
4	60	60	S-297995 high	100	100

Animals were inspected visually at least twice daily for evidence of ill-health or reaction to treatment. Cages were inspected daily for evidence of animal ill-health amongst the occupants. Any deviation from normal was recorded at the time in respect of nature and severity, date and time of onset, duration and progress of the observed condition, as appropriate. In conjunction with the weekly physical examination, palpation was performed on all animals. New masses were recorded at detection in respect of mass number and location, date, size and description. A viability check was performed near the start and end of each working day. All animals were subject to a detailed necropsy. After a review of the history of each animal, a full macroscopic examination of the tissues was performed. All external features and orifices were examined visually. Any abnormality in the appearance or size of any organ and tissue (external and cut surface) was recorded and the required tissue samples preserved in appropriate fixative.

3.1. Sponsor's analyses

3.1.1. Survival analysis

The sponsor used similar methodologies to analyze the mouse survival data as those used to analyze the rat survival data.

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 28 (46.67%), 26, (43.33%), 30 (50.00%), and 23 (38.33%) in Groups 1, 2, 3, and 4 for male, respectively, and 23 (38.33%), 20 (33.33%), 23 (38.33%), and 26, (43.33%) for female, respectively. The sponsor reported that for both male and female mice, the trend tests were not statistically significant when all groups were included in the analysis ($p=0.321$ and 0.538 , respectively), and no statistically significant pairwise comparisons were noted.

3.1.2. Tumor data analysis

The sponsor used similar methodologies to analyze the mouse tumor data as those used to analyze the rat tumor data.

The classification of mouse tumors was carried out based upon the overall incidence in historical control data. The tumors in the following list were considered to be "rare", all other tumors in this report were considered to be "common".

Males

Spleen - Malignant haemangiosarcoma
Thyroids - Benign follicular cell adenoma
Adrenals - Malignant pheochromocytoma
Pituitary (pars distalis) - Benign adenoma
Skin - Benign papilloma and malignant squamous cell carcinoma combined
Haematopoietic tumor - Malignant myeloid cell leukemia
Liver - Malignant haemangiosarcoma
Pancreas - Benign Islet cell adenoma
Mesenteric lymph node - Benign haemangioma and malignant haemangiosarcoma combined

Females

Gall bladder - Benign adenoma
Skin - Malignant fibrosarcoma
Uterus - Malignant leiomyosarcoma
Uterus - Malignant schwannoma
Liver - Benign haemangioma
Pancreas - Benign Islet cell adenoma
Mesenteric lymph node - Benign haemangioma

Sponsor's findings:

The sponsor's analysis showed no significant findings for neoplastic lesions in for both male and female mice.

3.2. Reviewer's analyses

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

For the analysis of both the survival data and the tumor data, this reviewer used similar methodologies that were used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data, and the results of the tests for dose response relationship and homogeneity of survivals for the combined vehicle control, low, mid, and high dose groups were given in Tables 3A and 3B in the appendix for male and female mice, respectively.

Reviewer's findings:

In the reviewer's analysis, the numbers of mice surviving to their terminal necropsy were 28 (46.67%), 26, (43.33%), 30 (50.00%), and 23 (38.33%) in Groups 1, 2, 3, and 4 for male, respectively, and 23 (38.33%), 20 (33.33%), 23 (38.33%), and 26, (43.33%) for female, respectively. No statistically significant difference across all dosing groups in mortality was noted in for both male and female mice.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tested tumor types are given in Tables 4A and Table 4B in the appendix, for male and female mice, respectively.

Reviewer's findings:

The reviewer's analysis showed no significant dose response relationship or pairwise comparisons in both male and female mice.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to evaluate the carcinogenic potential of S-297995 when administered daily via oral gavage to both rats and mice for at least 104 weeks.

Rat Study:

Two separate experiments, one in male rats and one in female rats were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups and one vehicle control group. Two hundred sixty rats of each sex were assigned randomly to the treated and control groups in equal size of 65 CD rats per group. The dose levels for treated groups were 10, 30, and 100 mg/kg/day for both male and female rats. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The rats in the vehicle control group were administered with the vehicle [0.5% w/v methylcellulose aqueous solution (0.5% w/v MC)], and handled for the same duration and in the same manner as the treated groups.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 29 (44.62%), 32 (49.23%), 26 (40.00%), and 28 (43.08%) in Groups 1, 2, 3, and 4 for male,

respectively, and 15 (23.08%), 19 (29.23%), 19 (29.23%), and 17 (26.15%) for female, respectively. No statistically significant findings in mortality was noted in for both male and female rats.

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed that a statistically significant positive trend ($p = 0.0227$) for the incidence rates of malignant lymphoma in haematopoietic (H-poietic) tumor in male rats, if this tumor was considered to be rare; while no statistically significant pairwise comparisons were noted for this tumor. No other statistically significant findings were noted for male and female rats.

Mouse Study:

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 3. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred forty Crl:CD1(ICR) mice of each sex were assigned randomly to the treated and control groups in equal size of 60 mice per group. The dose levels for treated groups were 10, 30, and 100 mg/kg/day for both male and female mice. In this review these dose groups were referred to as the low (Group 2), mid (Group 3), and high (Group 4) dose groups, respectively. The mice in the vehicle control group were administrated with the vehicle [0.5% w/v methylcellulose aqueous solution (0.5% w/v MC)], and handled for the same duration and in the same manner as the treated groups.

In the reviewer's analysis, the numbers of mice surviving to their terminal necropsy were 28 (46.67%), 26, (43.33%), 30 (50.00%), and 23 (38.33%) in Groups 1, 2, 3, and 4 for male, respectively, and 23 (38.33%), 20 (33.33%), 23 (38.33%), and 26, (43.33%) for female, respectively. No statistically significant difference across all dosing groups in mortality was noted in for both male and female mice.

The reviewer's analysis showed no significant dose response relationship or pairwise comparisons in both male and female mice.

Hepei Chen.
Mathematical Statistician

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

Cc: Archival NDA 208854

Dr. Tracy Behrsing
Dr. Lillian Patrician
Dr. Mohammad Atiar Rahman

5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

Week / Type of Death	0 mg/kg/day Vehicle Control		10 mg/kg/day Low		30 mg/kg/day Mid		100 mg/kg/day High	
	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	Cum %
0 - 52	3	4.62	1	1.54	2	3.08	5	7.69
53 - 78	12	23.08	10	16.92	10	18.46	7	18.46
79 - 92	8	35.38	8	29.23	11	35.38	10	33.85
93 - 104	13	20.00	13	20.00	16	24.62	13	20.00
Accidental Death			1	1.54			2	3.08
Terminal sacrifice	29	44.62	32	49.23	26	40.00	28	43.08
Total	65		65		65		65	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.8320	0.4625	0.7225	0.9396
Homogeneity (Log-Rank)	0.7271	0.4587	0.7201	0.9392

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 1B: Intercurrent Mortality Rate in Female Rats

Week / Type of Death	0 mg/kg/day Vehicle Control		10 mg/kg/day Low		30 mg/kg/day Mid		100 mg/kg/day High	
	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	Cum %
0 - 52	2	3.08	1	1.54	2	3.08	3	4.62
53 - 78	15	26.15	15	24.62	18	30.77	19	33.85
79 - 92	20	56.92	17	50.77	10	46.15	18	61.54
93 - 103	13	20.00	13	20.00	16	24.62	8	12.31
Terminal sacrifice	15	23.08	19	29.23	19	29.23	17	26.15
Total	65		65		65		65	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.5649	0.5028	0.3997	0.8534
Homogeneity (Log-Rank)	0.6921	0.4960	0.3917	0.8510

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	0 mg	10 mg	30 mg	100 mg
		Vehicle (C) P - Trend	Low (L) P - C vs. L	Mid (M) P - C vs. M	High (H) P - C vs. H
Adrenals	Cortical Adenoma	0/48 (65) 0.1826	0/49 (64) NC	1/49 (65) 0.5052	1/47 (65) 0.4947
	Cortical Carcinoma	0/48 (65) 0.4922	1/50 (64) 0.5102	0/48 (65) NC	0/47 (65) NC
	Cortical Adenoma/ Cortical Carcinoma	0/48 (65) 0.2884	1/50 (64) 0.5102	1/49 (65) 0.5052	1/47 (65) 0.4947
	Phaeochromocytoma	6/48 (65) 0.0886	2/49 (64) 0.8726	6/49 (65) 0.3944	8/47 (65) 0.3702
	Malignant Phaeochromocytoma	2/48 (65) 0.5058	0/49 (64) 0.7577	1/49 (65) 0.5078	1/47 (65) 0.4920
	Malignant Phaeochromocytoma/ Phaeochromocytoma	8/48 (65) 0.1209	2/49 (64) 0.9577	7/49 (65) 0.5175	9/48 (66) 0.5000
Brain	Astrocytoma	2/49 (65) 0.5834	1/50 (65) 0.5077	2/50 (65) 0.3163	1/47 (65) 0.4842
	Meningioma	1/49 (65) 0.7474	0/50 (65) 0.5051	0/48 (65) 0.4948	0/47 (65) 0.4896
	Mixed Glioma	0/48 (65) 0.2474	0/50 (65) NC	0/48 (65) NC	1/48 (65) 0.5000
Epididymides	Mesothelioma	0/48 (65) 0.2435	0/50 (65) NC	1/48 (65) 0.5000	0/47 (65) NC
Eyes	Malignant Schwannoma	1/48 (65) 0.7513	0/50 (64) 0.5102	0/48 (65) 0.5000	0/47 (65) 0.4947
H-Poietic Tumor	Histiocytic Sarcoma	1/48 (65) 0.5685	2/51 (65) 0.5230	0/48 (65) 0.5000	1/48 (65) NC
	Malignant Lymphoma	0/48 (65) 0.0227 \$	0/50 (65) NC	2/49 (65) 0.2526	3/48 (65) 0.1211
	Myeloid Cell Leukaemia	0/48 (65) 0.2435	0/50 (65) NC	0/48 (65) NC	1/47 (65) 0.4947
Harderian Glands	Adenoma	1/48 (65) 0.7513	0/50 (65) 0.5102	0/48 (65) 0.5000	0/47 (65) 0.4947
	Squamous Cell Carcinoma	0/48 (65) 0.4922	1/50 (65) 0.5102	0/48 (65) NC	0/47 (65) NC

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

\$ = Statistically significant at 0.025 level in rare tumor for test of dose response relationship;

NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	10 mg Low (L) P - C vs. L	30 mg Mid (M) P - C vs. M	100 mg High (H) P - C vs. H
Head	Sebaceous Gland Carcinoma,	0/0 (1)	0/1 (1)	1/2 (2)	0/3 (4)
	Zymbal_s Gland	0.5000	NC	NC	NC
	Squamous Cell Carcinoma	1/1 (1)	1/1 (1)	1/1 (2)	3/3 (4)
		NC	NC	NC	NC
Kidneys	Renal Liposarcoma	0/48 (65)	1/51 (65)	0/48 (65)	0/47 (65)
		0.4897	0.5152	NC	NC
	Tubular Adenoma	0/48 (65)	0/50 (65)	1/49 (65)	0/47 (65)
		0.2423	NC	0.5052	NC
	Tubular Carcinoma	2/48 (65)	0/50 (65)	0/48 (65)	0/47 (65)
		0.9391	0.7627	0.7526	0.7474
	Tubular Adenoma/ Tubular Carcinoma	2/48 (65)	0/50 (65)	1/49 (65)	0/47 (65)
		0.8269	0.7627	0.5078	0.7474
Liver	Hepatocellular Adenoma	0/48 (65)	0/50 (65)	1/49 (65)	1/47 (65)
		0.1808	NC	0.5052	0.4947
	Hepatocellular Carcinoma	0/48 (65)	0/50 (65)	0/48 (65)	2/47 (65)
		0.0583	NC	NC	0.2421
	Hepatocellular Adenoma/ Hepatocellular Carcinoma	0/48 (65)	0/50 (65)	1/49 (65)	3/47 (65)
		0.0170 @	NC	0.5052	0.1171
Ln Lumbar	Haemangiosarcoma	0/6 (6)	0/5 (6)	1/3 (3)	0/3 (4)
		0.3529	NC	0.3333	NC
Ln Mesenteric	Haemangioma	1/49 (65)	1/48 (62)	3/49 (65)	1/46 (64)
		0.4700	0.7474	0.3086	0.7366
Mammary Areas	Mammary Adenocarcinoma	1/47 (64)	0/50 (64)	0/48 (65)	0/47 (65)
		0.7552	0.5155	0.5053	0.5000
	Mammary Adenoma	0/47 (64)	0/50 (64)	0/48 (65)	1/47 (65)
		0.2448	NC	NC	0.5000
	Mammary Fibroadenoma	1/47 (64)	0/50 (64)	1/48 (65)	1/47 (65)
		0.3830	0.5155	0.2526	NC

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

@ = Not statistically significant at 0.005 level in common tumor for test of dose response relationship;

NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg	10 mg	30 mg	100 mg
		Vehicle (C) P - Trend	Low (L) P - C vs. L	Mid (M) P - C vs. M	High (H) P - C vs. H
Pancreas	Acinar Cell Adenoma	1/48 (65) 0.8220	2/50 (65) 0.5155	1/48 (64) NC	0/47 (65) 0.4947
	Islet Cell Adenoma	5/49 (65) 0.2567	6/51 (65) 0.5285	5/48 (64) 0.6166	7/48 (65) 0.3649
	Islet Cell Carcinoma	2/48 (65) 0.6182	1/50 (65) 0.5155	0/47 (64) 0.7474	1/47 (65) 0.4920
	Islet Cell Adenoma/I slet Cell Carcinoma	7/49 (65) 0.3198	7/51 (65) 0.4187	5/48 (64) 0.6056	8/48 (65) 0.4825
Parathyroids	Chief Cell Adenoma	2/44 (60) 0.4984	0/48 (62) 0.7740	3/49 (65) 0.5514	1/43 (59) 0.4913
Paws	Keratoacanthoma	0/9 (9) 0.2116	1/9 (10) 0.5000	0/5 (6) NC	1/5 (5) 0.3571
	Osteoma	0/9 (9) 0.5952	2/9 (10) 0.2353	0/5 (6) NC	0/5 (5) NC
Pituitary	Adenoma, Pars Distalis	22/54 (65) 0.8078	24/55 (65) 0.4554	22/54 (65) NC	18/52 (64) 0.6734
	Adenoma, Pars Intermedia	1/49 (65) 0.8063	1/50 (65) 0.2525	0/48 (65) 0.4948	0/47 (64) 0.4896
	Adenoma, Pars Distalis/ Adenoma, Pars Intermedia	23/55 (65) 0.8477	25/55 (65) 0.4238	22/54 (65) 0.4680	18/52 (64) 0.7144
Prostate	Adenocarcinoma	0/48 (65) 0.4897	1/51 (65) 0.5152	0/48 (65) NC	0/47 (65) NC

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

NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg	10 mg	30 mg	100 mg
		Vehicle (C) P - Trend	Low (L) P - C vs. L	Mid (M) P - C vs. M	High (H) P - C vs. H
Skin	Basal Cell Carcinoma	0/48 (65) 0.2423	0/50 (65) NC	1/49 (65) 0.5052	0/47 (65) NC
	Basal Cell Tumor	1/48 (65) 0.6205	0/50 (65) 0.5102	1/49 (65) 0.2526	0/47 (65) 0.4947
	Basal Cell Carcinoma/ Basal Cell Tumor	1/48 (65) 0.6316	0/50 (65) 0.5102	2/49 (65) 0.5078	0/47 (65) 0.4947
	Fibroma	6/49 (65) 0.2639	9/50 (65) 0.3030	9/49 (65) 0.2880	9/47 (65) 0.2581
	Fibrosarcoma	2/49 (65) 0.8471	5/51 (65) 0.2349	3/49 (65) 0.5000	1/47 (65) 0.4842
	Fibrosarcoma, Pleomorphic	0/48 (65) 0.7057	2/51 (65) 0.2628	2/50 (65) 0.2577	0/47 (65) NC
	Fibrosarcoma/ Fibrosarcoma, Pleomorphic	2/49 (65) 0.9041	7/52 (65) 0.0948	5/50 (65) 0.2264	1/47 (65) 0.4842
	Haemangioma	1/48 (65) 0.7513	0/50 (65) 0.5102	0/48 (65) 0.5000	0/47 (65) 0.4947
	Keratoacanthoma	5/48 (65) 0.7664	5/50 (65) 0.3967	4/49 (65) 0.5132	3/48 (65) 0.6428
	Lipoma	2/49 (65) 0.6814	2/50 (65) 0.3163	3/49 (65) 0.5000	1/47 (65) 0.4842
	Osteosarcoma	0/48 (65) 0.4922	1/50 (65) 0.5102	0/48 (65) NC	0/47 (65) NC
	Schwannoma	0/48 (65) 0.0603	0/50 (65) NC	0/48 (65) NC	2/48 (65) 0.2474
	Sebaceous Cell Adenoma	0/48 (65) 0.1801	0/50 (65) NC	1/48 (65) 0.5000	1/47 (65) 0.4947
	Sebaceous Cell Carcinoma	1/48 (65) 0.7513	0/50 (65) 0.5102	0/48 (65) 0.5000	0/47 (65) 0.4947
	Sebaceous Cell Adenoma/ Sebaceous Cell Carcinoma	1/48 (65) 0.3799	0/50 (65) 0.5102	1/48 (65) NC	1/47 (65) 0.7474
	Squamous Cell Papilloma	0/48 (65) 0.1816	2/50 (65) 0.2577	0/48 (65) NC	2/47 (65) 0.2421
	Tumor Hair Follicle	2/48 (65) 0.2894	0/50 (65) 0.7627	2/49 (65) 0.3164	2/47 (65) 0.6835

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

NC = Not calculable.

**Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	10 mg Low (L) P - C vs. L	30 mg Mid (M) P - C vs. M	100 mg High (H) P - C vs. H
Spinal C. Thor.	Meningeal Sarcoma	1/49 (65) 0.7448	0/50 (65) 0.5051	0/48 (65) 0.4948	0/45 (63) 0.4787
Spleen	Haemangiosarcoma	1/49 (65) 0.6152	0/50 (65) 0.5051	1/48 (65) 0.7474	0/47 (65) 0.4896
	Splenic Sarcoma Nos	0/48 (65) 0.4896	1/50 (65) 0.5102	1/48 (65) 0.5000	0/47 (65) NC
Tail	Haemangioma	0/1 (1) 0.3636	0/9 (9) NC	0/4 (5) NC	1/8 (8) 0.8889
Testes	Haemangioma	1/48 (65) 0.7513	0/50 (65) 0.5102	0/48 (65) 0.5000	0/47 (65) 0.4947
	Interstitial (Leydig) Cell Adenoma	3/48 (65) 0.1403	3/50 (65) 0.3585	8/51 (65) 0.1198	6/47 (65) 0.2324
Thyroids	C-Cell Adenoma	8/49 (65) 0.4077	5/51 (65) 0.7488	6/49 (65) 0.6131	7/47 (63) 0.4646
	C-Cell Carcinoma	1/48 (65) 0.4965	1/50 (65) 0.2577	1/49 (65) 0.2526	1/46 (63) 0.7419
	C-Cell Adenoma/ C-Cell Carcinoma	9/49 (65) 0.4061	6/51 (65) 0.7400	7/49 (65) 0.6073	8/47 (63) 0.4619
	Follicular Cell Adenoma	1/48 (65) 0.3502	0/50 (65) 0.5102	2/48 (65) 0.5000	1/46 (63) 0.7419
	Follicular Cell Carcinoma	0/48 (65) 0.4896	1/50 (65) 0.5102	0/48 (65) NC	0/46 (63) NC
	Follicular Cell Adenoma/ Follicular Cell Carcinoma	1/48 (65) 0.4179	1/50 (65) 0.2577	2/48 (65) 0.5000	1/46 (63) 0.7419
Tongue	Squamous Cell Papilloma	1/48 (65) 0.7513	0/50 (65) 0.5102	0/48 (65) 0.5000	0/47 (65) 0.4947

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

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	0 mg	10 mg	30 mg	100 mg
		Vehicle (C) P - Trend	Low (L) P - L vs. C	Mid (M) P - M vs. C	High (H) P - H vs. C
Adrenals	Cortical Adenoma	1/42 (64)	1/44 (65)	0/44 (65)	3/40 (65)
		0.0779	0.2588	0.5116	0.2895
	Pheochromocytoma	0/42 (64)	1/44 (65)	0/44 (65)	2/40 (65)
		0.0976	0.5116	NC	0.2349
	Malignant Pheochromocytoma	1/42 (64)	0/44 (65)	1/45 (65)	0/39 (65)
		0.6140	0.5116	0.2646	0.4815
Brain	Malignant Pheochromocytoma/ Pheochromocytoma	1/42 (64)	1/44 (65)	1/45 (65)	2/40 (65)
		0.2371	0.2588	0.2646	0.4815
	Astrocytoma	1/42 (65)	0/44 (65)	2/44 (65)	1/39 (65)
		0.3407	0.5116	0.5176	0.7343
	Malignant Granular Cell Tumor	0/42 (65)	0/44 (65)	0/44 (65)	1/39 (65)
		0.2308	NC	NC	0.4815
Femur Inc. Joint	Osteosarcoma	0/42 (65)	0/44 (65)	1/44 (65)	0/39 (65)
		0.2308	NC	0.5116	NC
Kidneys	Nephroblastoma	0/42 (65)	0/44 (65)	0/44 (65)	1/40 (65)
		0.2353	NC	NC	0.4878
	Renal Liposarcoma	1/42 (65)	0/44 (65)	0/44 (65)	0/39 (65)
		0.7515	0.5116	0.5116	0.4815
	Tubular Carcinoma	0/42 (65)	1/44 (65)	0/44 (65)	0/39 (65)
		0.4911	0.5116	NC	NC
Liver	Cholangioma	1/42 (65)	1/44 (65)	1/45 (64)	0/39 (65)
		0.7212	0.2588	0.2646	0.4815
Ln Mesenteric	Haemangioma	1/42 (65)	0/44 (65)	0/43 (64)	0/39 (64)
		0.7500	0.5116	0.5059	0.4815
Lungs + Bronchi	Bronchiolo-Alveolar Adenocarcinoma	0/42 (65)	1/44 (65)	0/44 (65)	0/39 (65)
		0.4911	0.5116	NC	NC

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

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	10 mg Low (L) P - L vs. C	30 mg Mid (M) P - M vs. C	100 mg High (H) P - H vs. C
Mammary Areas	Carcinosarcoma	0/41 (64) 0.2367	0/44 (65) NC	0/44 (65) NC	1/40 (65) 0.4938
	Mammary Adenocarcinoma	17/49 (64) 0.5690	21/52 (65) 0.3506	20/50 (65) 0.3679	16/45 (65) 0.5508
	Mammary Adenocarcinoma Arising In Mammary Adenoma	1/41 (64) 0.5093	4/45 (65) 0.2105	4/45 (65) 0.2105	2/40 (65) 0.4906
	Mammary Adenocarcinoma/ Mammary Adenocarcinoma Arising In Mammary Adenoma	18/49 (64) 0.6205	25/54 (67) 0.2171	24/54 (68) 0.2764	18/47 (66) 0.5208
	Mammary Adenoma	2/42 (64) 0.3278	2/44 (65) 0.3259	5/45 (65) 0.2463	3/41 (65) 0.4884
	Mammary Fibroadenoma	29/46 (64) 0.3584	36/55 (65) 0.4820	35/54 (65) 0.5094	35/52 (65) 0.4087
	Mixed Tumor	0/41 (64) 0.2321	0/44 (65) NC	0/44 (65) NC	1/39 (65) 0.4875
Ovaries	Malignant Granulosa Cell Tumor	0/42 (65) 0.2308	0/44 (65) NC	1/44 (65) 0.5116	0/39 (65) NC
	Tumor, Sex Cord Stromal, Mixed	0/42 (65) 0.4136	2/44 (65) 0.2588	2/44 (65) 0.2588	1/40 (65) 0.4878
	Yolk Sac Tumor	0/42 (65) 0.2308	0/44 (65) NC	1/44 (65) 0.5116	0/39 (65) NC
Pancreas	Islet Cell Adenoma	1/41 (64) 0.3798	0/43 (64) 0.5119	3/44 (65) 0.3352	1/39 (65) 0.7405
Parathyroids	Chief Cell Adenoma	0/40 (63) 0.5530	0/40 (59) NC	4/43 (63) 0.0672	0/37 (62) NC
Pituitary	Adenoma, Pars Distalis	46/57 (65) 0.6762	51/58 (65) 0.2092	44/57 (64) 0.5906	45/56 (64) 0.4245
	Carcinoma, Pars Distalis	0/42 (65) 0.0522	0/44 (65) NC	0/44 (64) NC	2/39 (64) 0.2287
	Adenoma, Pars Distalis/ Carcinoma, Pars Distalis	46/57 (65) 0.5493	51/58 (65) 0.2092	44/57 (64) 0.5906	47/57 (64) 0.5000

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

NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats
(Continued)**

Organ name	Tumor name	0 mg	10 mg	30 mg	100 mg
		Vehicle (C) P - Trend	Low (L) P - L vs. C	Mid (M) P - M vs. C	High (H) P - H vs. C
Skin	Basal Cell Tumor	0/41 (64)	1/44 (65)	0/44 (65)	0/39 (65)
		0.4940	0.5176	NC	NC
	Fibroma	4/42 (64)	1/44 (65)	2/45 (65)	2/41 (65)
		0.6013	0.8342	0.6944	0.6505
	Fibrosarcoma	0/41 (64)	1/44 (65)	2/45 (65)	0/39 (65)
		0.5652	0.5176	0.2709	NC
	Fibrosarcoma, Pleomorphic	1/42 (64)	0/44 (65)	0/44 (65)	1/40 (65)
		0.4163	0.5116	0.5116	0.7407
	Fibrosarcoma/ Fibrosarcoma, Pleomorphic	1/42 (64)	1/44 (65)	2/45 (65)	1/40 (65)
		0.4769	0.2588	0.5262	0.7407
	Keratoacanthoma	0/41 (64)	0/44 (65)	0/44 (65)	1/40 (65)
		0.2367	NC	NC	0.4938
	Squamous Cell Papilloma	0/41 (64)	1/44 (65)	0/44 (65)	0/39 (65)
		0.4940	0.5176	NC	NC
	Haemangioma	1/42 (65)	0/44 (65)	0/44 (64)	0/39 (65)
		0.7515	0.5116	0.5116	0.4815
	Liposarcoma	1/3 (3)	0/4 (4)	0/2 (2)	0/3 (3)
		0.7500	0.5714	0.4000	0.5000
	Thymoma	0/40 (63)	1/43 (63)	2/45 (65)	1/40 (65)
		0.3113	0.5181	0.2773	0.5000
Thymus	Thymoma	0/40 (63)	0/43 (63)	0/44 (65)	2/40 (65)
		0.0563	NC	NC	0.2468
	Thymoma/Thymoma	0/40 (63)	1/43 (63)	2/45 (65)	3/40 (65)
		0.0488	0.5181	0.2773	0.1203

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

NC = Not calculable.

**Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats
(Continued)**

Organ name	Tumor name	0 mg	10 mg	30 mg	100 mg
		Vehicle (C) P - Trend	Low (L) P - L vs. C	Mid (M) P - M vs. C	High (H) P - H vs. C
Thyroids	C-Cell Adenoma	3/42 (65)	6/45 (65)	2/45 (65)	8/42 (65)
		0.0562	0.2779	0.5331	0.0972
	C-Cell Carcinoma	0/42 (65)	1/44 (65)	1/45 (65)	0/39 (65)
		0.4762	0.5116	0.5172	NC
	C-Cell Adenoma/ C-Cell Carcinoma	0/42 (65)	1/44 (65)	1/45 (65)	0/39 (65)
		0.4762	0.5116	0.5172	NC
	Follicular Cell Adenoma	1/42 (65)	1/44 (65)	0/44 (65)	1/40 (65)
		0.5125	0.2588	0.5116	0.7407
	Follicular Cell Carcinoma	1/42 (65)	1/44 (65)	0/44 (65)	1/40 (65)
		0.5125	0.2588	0.5116	0.7407
Uterine Cervix	Granular Cell Tumor	2/43 (65)	2/44 (65)	0/44 (65)	2/40 (65)
		0.4286	0.3168	0.7586	0.6642
	Schwannoma	0/42 (65)	0/43 (64)	1/44 (65)	0/39 (65)
		0.2321	NC	0.5116	NC
	Schwannoma	1/42 (65)	1/43 (64)	0/44 (65)	1/40 (65)
		0.5141	0.2529	0.5116	0.7407
Uterus	Endometrial Adenocarcinoma	2/43 (65)	0/44 (65)	0/44 (65)	0/39 (65)
		0.9371	0.7586	0.7586	0.7281
	Endometrial Polyp	1/42 (65)	4/45 (65)	3/45 (65)	2/40 (65)
		0.4849	0.2024	0.3347	0.4815
	Endometrial Adenocarcinoma/ Endometrial Polyp	3/43 (65)	4/45 (65)	3/45 (65)	2/40 (65)
		0.6844	0.5257	0.3602	0.4653
Vagina	Granular Cell Tumor	0/42 (65)	1/44 (65)	0/44 (65)	0/39 (65)
		0.4911	0.5116	NC	NC

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

NC = Not calculable.

Table 3A: Intercurrent Mortality Rate in Male Mice

Week / Type of Death	0 mg/kg/day Vehicle Control		10 mg/kg/day Low		30 mg/kg/day Mid		100 mg/kg/day High	
	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	Cum %
0 - 52	6	10.00	3	5.00	4	6.67	6	10.00
53 - 78	10	26.67	11	23.33	5	15.00	14	33.33
79 - 92	8	40.00	11	41.67	13	36.67	7	45.00
93 - 104	8	13.33	9	15.00	7	11.67	10	16.67
Accidental Death					1	1.67		
Terminal sacrifice	28	46.67	26	43.33	30	50.00	23	38.33
Total	60		60		60		60	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.3248	0.8017	0.5011	0.3702
Homogeneity (Log-Rank)	0.4793	0.8007	0.4987	0.3672

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 3B: Intercurrent Mortality Rate in Female Mice

Week / Type of Death	0 mg/kg/day Vehicle Control		10 mg/kg/day Low		30 mg/kg/day Mid		100 mg/kg/day High	
	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	Cum %
0 - 52	9	15.00	4	6.67	6	10.00	9	15.00
53 - 78	5	23.33	9	21.67	12	30.00	8	28.33
79 - 92	11	41.67	10	38.33	6	40.00	8	41.67
93 - 104	11	18.33	16	26.67	13	21.67	8	13.33
Accidental Death	1	1.67	1	1.67			1	1.67
Terminal sacrifice	23	38.33	20	33.33	23	38.33	26	43.33
Total	60		60		60		60	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.5322	0.9090	0.9838	0.6764
Homogeneity (Log-Rank)	0.9325	0.9081	0.9837	0.6740

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	10 mg Low (L) P - C vs. L	30 mg Mid (M) P - C vs. M	100 mg High (H) P - C vs. H
Adipose Tissue	Lipoma	1/2 (3) 0.3333	0/1 (2) 0.3333	0/0 (1) NC	0/0 (1) NC
Adrenals	Cortical Adenoma	0/42 (59) 0.5000	1/43 (59) 0.5059	0/45 (58) NC	0/40 (60) NC
	Malignant Phaeochromocytoma	0/42 (59) 0.2993	1/43 (59) 0.5059	0/45 (58) NC	1/40 (60) 0.4878
	Phaeochromocytoma	1/42 (59) 0.5200	1/43 (59) 0.2529	0/45 (58) 0.5172	1/41 (60) 0.7470
	Subcapsular Cell Adenoma	1/42 (59) 0.1217	1/43 (59) 0.2529	8/45 (58) 0.0194	4/41 (60) 0.1723
Caecum	Adenoma	0/43 (60) 0.5000	1/43 (60) 0.5000	0/46 (60) NC	0/40 (60) NC
Duodenum	Adenocarcinoma	0/43 (60) 0.5000	1/43 (60) 0.5000	0/46 (60) NC	0/40 (59) NC
Femur Inc. Joint	Haemangiosarcoma	0/43 (60) 0.2326	0/43 (60) NC	1/46 (60) 0.5169	0/40 (60) NC
Gall Bladder	Adenoma	2/42 (59) 0.8310	0/43 (59) 0.7588	1/46 (59) 0.5345	0/40 (60) 0.7407
H-Poietic Tumor	Histiocytic Sarcoma	1/43 (60) 0.6185	0/43 (60) 0.5000	1/47 (60) 0.2699	0/40 (60) 0.4819
	Malignant Lymphoma	9/46 (60) 0.2304	9/47 (60) 0.4167	13/50 (60) 0.3071	11/43 (60) 0.3352
	Malignant Mast Cell Tumor	0/43 (60) 0.2326	0/43 (60) NC	0/46 (60) NC	1/40 (60) 0.4819
	Myeloid Cell Leukaemia	1/44 (60) 0.3787	0/43 (60) 0.4943	1/47 (60) 0.2640	1/41 (60) 0.7350
Harderian Glands	Adenoma	5/44 (60) 0.1075	2/44 (60) 0.7832	8/47 (60) 0.3202	7/41 (60) 0.3286
Jejunum	Adenocarcinoma	1/43 (60) 0.7500	0/43 (60) 0.5000	0/46 (60) 0.5169	0/40 (60) 0.4819

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

NC = Not calculable.

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	10 mg Low (L) P - C vs. L	30 mg Mid (M) P - C vs. M	100 mg High (H) P - C vs. H
Kidneys	Tubular Adenoma	0/43 (60) 0.2326	0/43 (60) NC	0/46 (60) NC	1/40 (60) 0.4819
	Tubular Carcinoma	1/43 (60) 0.7500	0/43 (60) 0.5000	0/46 (60) 0.5169	0/40 (60) 0.4819
	Tubular Adenoma /Tubular Carcinoma	1/43 (60) 0.4121	0/43 (60) 0.5000	0/46 (60) 0.5169	1/40 (60) 0.7346
Liver	Haemangioma	0/43 (60) 0.1274	1/43 (60) 0.5000	2/46 (60) 0.2643	2/41 (60) 0.2352
	Haemangiosarcoma	0/43 (60) 0.1101	1/43 (60) 0.5000	1/47 (60) 0.5222	2/41 (60) 0.2352
	Haemangioma/ Haemangiosarcoma	0/43 (60) 0.0473	2/43 (60) 0.2471	3/47 (60) 0.1380	4/42 (60) 0.0553
	Hepatocellular Adenoma	4/44 (60) 0.0674	8/45 (60) 0.1874	10/47 (60) 0.0926	10/41 (60) 0.0532
	Hepatocellular Carcinoma	0/43 (60) 0.5480	0/43 (60) NC	3/47 (60) 0.1380	0/40 (60) NC
	Hepatocellular Adenoma/ Hepatocellular Carcinoma	4/44 (60) 0.0803	8/45 (60) 0.1874	13/48 (61) 0.0239	10/41 (60) 0.0532
Ln Mesenteric	Haemangioma	0/43 (60) 0.2353	0/41 (58) NC	1/46 (60) 0.5169	0/40 (60) NC
	Haemangiosarcoma	0/43 (60) 0.2339	0/41 (58) NC	1/47 (60) 0.5222	0/40 (60) NC
	Haemangioma/ Haemangiosarcoma	0/43 (60) 0.4142	0/41 (58) NC	2/47 (60) 0.2699	0/40 (60) NC
Lungs + Bronchi	Bronchiolo-Alveolar Adenoma	21/46 (60) 0.8632	9/44 (60) 0.9900	21/50 (60) 0.5614	11/42 (60) 0.9534
	Bronchiolo-Alveolar Carcinoma	9/45 (60) 0.9705	9/44 (60) 0.5829	6/47 (60) 0.7440	3/41 (60) 0.9182
	Bronchiolo-Alveolar Adenoma/ Bronchiolo-Alveolar Carcinoma	30/51 (63) 0.9834	18/44 (60) 0.9379	27/54 (63) 0.7614	14/43 (60) 0.9905
Pancreas	Islet Cell Adenoma	0/43 (60) 0.5686	1/43 (60) 0.5000	2/46 (60) 0.2643	0/40 (60) NC

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

NC = Not calculable.

**Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	10 mg Low (L) P - C vs. L	30 mg Mid (M) P - C vs. M	100 mg High (H) P - C vs. H
Pituitary	Adenoma, Pars Distalis	1/41 (57) 0.5197	1/42 (57) 0.2530	0/44 (58) 0.5176	1/40 (57) 0.7469
	Adenoma, Pars Intermedia	0/41 (57) 0.2349	0/42 (57) NC	0/44 (58) NC	1/39 (57) 0.4875
	Adenoma, Pars Distalis/ Adenoma, Pars Intermedia	1/41 (57) 0.2223	1/42 (57) 0.2530	0/44 (58) 0.5176	2/40 (57) 0.4906
Seminal Vesicles	Adenoma	0/43 (60) 0.4971	1/43 (60) 0.5000	0/45 (59) NC	0/40 (60) NC
	Granular Cell Tumor	0/43 (60) 0.2339	0/43 (60) NC	1/45 (59) 0.5114	0/40 (60) NC
	Leiomyosarcoma	0/43 (60) 0.4971	1/43 (60) 0.5000	0/45 (59) NC	0/40 (60) NC
Skin	Fibroma	1/44 (60) 0.7457	0/43 (60) 0.4943	0/46 (60) 0.5111	0/40 (60) 0.4762
	Fibrosarcoma	8/46 (60) 0.9406	4/45 (60) 0.8124	5/48 (60) 0.7514	2/41 (60) 0.9342
	Fibroma/ Fibrosarcoma	9/46 (60) 0.9606	4/45 (60) 0.8764	5/48 (60) 0.8302	2/41 (60) 0.9613
	Lipoma	2/43 (60) 0.9386	0/43 (60) 0.7529	0/46 (60) 0.7694	0/40 (60) 0.7346
	Papilloma	0/43 (60) 0.2326	0/43 (60) NC	1/46 (60) 0.5169	0/40 (60) NC
	Sebaceous Cell Adenoma	0/43 (60) 0.2326	0/43 (60) NC	0/46 (60) NC	1/40 (60) 0.4819
	Squamous Cell Carcinoma	0/43 (60) 0.2326	0/43 (60) NC	1/46 (60) 0.5169	0/40 (60) NC
Spleen	Haemangiosarcoma	0/43 (60) 0.2861	1/43 (60) 0.5000	1/47 (60) 0.5222	1/41 (60) 0.4881
Stomach	Squamous Cell Papilloma	1/43 (60) 0.6170	0/43 (60) 0.5000	1/46 (60) 0.2643	0/40 (60) 0.4819
Testes	Interstitial (Leydig) Cell Adenoma	0/43 (60) 0.2859	1/43 (60) 0.5000	1/46 (60) 0.5169	1/41 (60) 0.4881

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

**Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice
(Continued)**

Organ name	Tumor name	0 mg	10 mg	30 mg	100 mg
		Vehicle (C) P - Trend	Low (L) P - C vs. L	Mid (M) P - C vs. M	High (H) P - C vs. H
Thyroids	C-Cell Adenoma	0/41 (58)	1/43 (60)	0/45 (58)	0/40 (60)
		0.5030	0.5119	NC	NC
	Follicular Cell Adenoma	0/41 (58)	0/43 (60)	1/46 (58)	1/41 (60)
		0.1862	NC	0.5287	0.5000
	C-Cell Adenoma/ Follicular Cell Adenoma	0/41 (58)	1/43 (60)	1/46 (58)	1/41 (60)
		0.2941	0.5119	0.5287	0.5000

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

NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	10 mg Low (L) P - L vs. C	30 mg Mid (M) P - M vs. C	100 mg High (H) P - H vs. C
Adipose Tissue	Osteosarcoma	0/4 (6) 0.5000	1/2 (4) 0.3333	0/2 (4) NC	0/4 (5) NC
Adrenals	Subcapsular Cell Adenoma	0/41 (60) 0.6694	1/43 (60) 0.5119	3/42 (59) 0.1249	0/41 (60) NC
Duodenum	Adenoma	0/41 (59) 0.2470	0/42 (59) NC	0/42 (60) NC	1/41 (60) 0.5000
Gall Bladder	Adenoma	0/41 (60) 0.4272	2/43 (59) 0.2590	0/42 (60) NC	1/40 (57) 0.4938
H-Poietic Tumor	Histiocytic Sarcoma	1/41 (60) 0.2705	3/43 (60) 0.3262	3/43 (60) 0.3262	3/41 (60) 0.3078
	Malignant Lymphoma	21/48 (60) 0.2111	16/50 (60) 0.8391	18/45 (60) 0.5618	22/48 (60) 0.5000
	Myeloid Cell Leukaemia	0/41 (60) 0.2500	0/43 (60) NC	0/42 (60) NC	1/42 (60) 0.5060
Harderian Glands	Adenoma	3/41 (60) 0.7321	4/43 (60) 0.5270	5/42 (60) 0.3700	2/41 (60) 0.5000
Jejunum	Adenocarcinoma	0/41 (60) 0.4970	1/43 (60) 0.5119	0/42 (60) NC	0/41 (60) NC
Liver	Haemangioma	0/41 (60) 0.3106	1/43 (60) 0.5119	0/42 (60) NC	1/41 (60) 0.5000
	Hepatocellular Carcinoma	0/41 (60) 0.2455	0/43 (60) NC	0/42 (60) NC	1/41 (60) 0.5000
Ln Mesenteric	Haemangioma	0/41 (60) 0.3159	1/43 (59) 0.5119	0/42 (60) NC	1/42 (60) 0.5060
Ln Renal	Haemangioma	0/6 (11) 0.2400	0/4 (9) NC	0/9 (13) NC	1/6 (10) 0.5000

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

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	10 mg Low (L) P - L vs. C	30 mg Mid (M) P - M vs. C	100 mg High (H) P - H vs. C
Lungs + Bronchi	Bronchiolo-Alveolar Adenoma	11/44 (60) 0.6461	7/43 (60) 0.7697	11/43 (60) 0.5728	8/43 (60) 0.6775
	Bronchiolo-Alveolar Carcinoma	2/41 (60) 0.5470	3/43 (60) 0.5229	3/43 (60) 0.5229	2/41 (60) NC
	Bronchiolo-Alveolar Adenoma/ Bronchiolo-Alveolar Carcinoma	13/45 (60) 0.6791	10/44 (60) 0.6630	14/45 (61) 0.5000	10/44 (61) 0.6630
Mammary Areas	Adenosquamous Carcinoma	1/41 (60) 0.7545	0/43 (60) 0.5119	0/42 (60) 0.5060	0/41 (60) 0.5000
	Mammary Adenoma	0/41 (60) 0.2455	0/43 (60) NC	0/42 (60) NC	1/41 (60) 0.5000
	Mammary Adenocarcinoma	6/42 (60) 0.5623	3/43 (60) 0.7702	2/42 (60) 0.8677	4/42 (60) 0.6310
	Mammary Adenocarcinoma/ Mammary Adenoma	6/42 (60) 0.4151	3/43 (60) 0.7702	2/42 (60) 0.8677	5/42 (60) 0.5000
	Mammary Adenomyoepithelioma	1/41 (60) 0.7545	0/43 (60) 0.5119	0/42 (60) 0.5060	0/41 (60) 0.5000
Ovaries	Cystadenoma	1/41 (60) 0.7530	0/42 (59) 0.5060	0/42 (60) 0.5060	0/41 (60) 0.5000
	Granulosa Cell Tumor	0/41 (60) 0.2470	0/42 (59) NC	0/42 (60) NC	1/41 (60) 0.5000
	Malignant Granulosa Cell Tumor	1/41 (60) 0.7530	0/42 (59) 0.5060	0/42 (60) 0.5060	0/41 (60) 0.5000
	Granulosa Cell Tumor/ Malignant Granulosa Cell Tum	1/41 (60) 0.4341	0/42 (59) 0.5060	0/42 (60) 0.5060	1/41 (60) NC
	Haemangioma	0/41 (60) 0.2470	0/42 (59) NC	0/42 (60) NC	1/41 (60) 0.5000
	Luteoma	0/41 (60) 0.4364	2/42 (59) 0.2530	0/42 (60) NC	1/41 (60) 0.5000
	Mixed Stromal Tumor, Malignant	0/41 (60) 0.5000	1/42 (59) 0.5060	0/42 (60) NC	0/41 (60) NC
	Tubulostromal Adenoma	0/41 (60) 0.2470	0/42 (59) NC	0/42 (60) NC	1/41 (60) 0.5000
Pancreas	Islet Cell Adenoma	0/41 (60) 0.1054	1/43 (60) 0.5119	0/42 (60) NC	2/41 (60) 0.2469

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

NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	10 mg Low (L) P - L vs. C	30 mg Mid (M) P - M vs. C	100 mg High (H) P - H vs. C
Pituitary	Adenoma, Pars Distalis	3/41 (58) 0.9850	0/42 (59) 0.8840	0/42 (60) 0.8840	0/38 (57) 0.8652
	Carcinoma, Pars Intermedia	1/41 (58) 0.7485	0/42 (59) 0.5060	0/42 (60) 0.5060	0/38 (57) 0.4810
	Adenoma, Pars Distalis/ Carcinoma, Pars Intermedia	4/41 (58) 0.9964	0/42 (59) 0.9449	0/42 (60) 0.9449	0/38 (57) 0.9326
Skeletal Muscle	Fibrosarcoma	1/42 (60) 0.7500	0/43 (60) 0.5059	0/42 (60) 0.5000	0/41 (60) 0.4940
Skin	Fibrosarcoma	1/42 (60) 0.5701	5/45 (60) 0.1177	1/42 (60) NC	2/42 (60) 0.5000
	Haemangiosarcoma	1/41 (60) 0.7545	0/43 (60) 0.5119	0/42 (60) 0.5060	0/41 (60) 0.5000
Spleen	Haemangiosarcoma	2/41 (60) 0.9408	0/43 (60) 0.7648	0/42 (60) 0.7590	0/41 (60) 0.7531
Thyroids	Follicular Cell Adenoma	0/40 (59) 0.5030	1/42 (59) 0.5122	0/42 (60) NC	0/41 (60) NC
Uterine Cervix	Granular Cell Tumor	0/41 (60) 0.2485	0/42 (59) NC	0/41 (59) NC	1/41 (60) 0.5000

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

NC = Not calculable.

**Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice
(Continued)**

Organ name	Tumor name	0 mg Vehicle (C) P - Trend	10 mg Low (L) P - L vs. C	30 mg Mid (M) P - M vs. C	100 mg High (H) P - H vs. C
Uterus	Deciduoma	0/41 (60) 0.2470	0/42 (59) NC	0/42 (60) NC	1/41 (60) 0.5000
	Endometrial Adenocarcinoma	1/41 (60) 0.8144	1/42 (59) 0.2530	0/42 (60) 0.5060	0/41 (60) 0.5000
	Endometrial Adenoma	0/41 (60) 0.2470	0/42 (59) NC	0/42 (60) NC	1/41 (60) 0.5000
	Endometrial Adenocarcinoma/ Endometrial Adenoma	1/41 (60) 0.5307	1/42 (59) 0.2530	0/42 (60) 0.5060	1/41 (60) NC
	Endometrial Polyp	10/42 (60) 0.9235	12/44 (59) 0.4524	7/43 (60) 0.7243	6/43 (60) 0.8116
	Endometrial Stromal Cell Sarcoma	0/41 (60) 0.2470	0/42 (59) NC	1/42 (60) 0.5060	0/41 (60) NC
	Endometrial Polyp/ Endometrial Stromal Cell Sarcoma	10/42 (60) 0.9249	12/44 (59) 0.4524	8/43 (60) 0.6260	6/43 (60) 0.8116
	Granular Cell Tumor	0/41 (60) 0.2470	0/42 (59) NC	1/42 (60) 0.5060	0/41 (60) NC
	Haemangioma	1/41 (60) 0.4341	0/42 (59) 0.5060	0/42 (60) 0.5060	1/41 (60) NC
	Haemangiosarcoma	1/41 (60) 0.6258	0/42 (59) 0.5060	1/42 (60) 0.2530	0/41 (60) 0.5000
	Haemangioma/ Haemangiosarcoma	2/41 (60) 0.5126	0/42 (59) 0.7590	1/42 (60) 0.5091	1/41 (60) 0.5000
	Leiomyoma	1/41 (60) 0.4354	3/44 (59) 0.3352	1/42 (60) 0.2530	2/41 (60) 0.5000
	Leiomyosarcoma	0/41 (60) 0.4319	0/42 (59) NC	2/43 (60) 0.2590	0/41 (60) NC
	Leiomyoma/ Leiomyosarcoma	1/41 (60) 0.4574	3/44 (59) 0.3352	3/43 (60) 0.3262	2/41 (60) 0.5000
	Malignant Schwannoma	0/41 (60) 0.1856	0/42 (59) NC	1/42 (60) 0.5060	1/41 (60) 0.5000

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

NC = Not calculable.

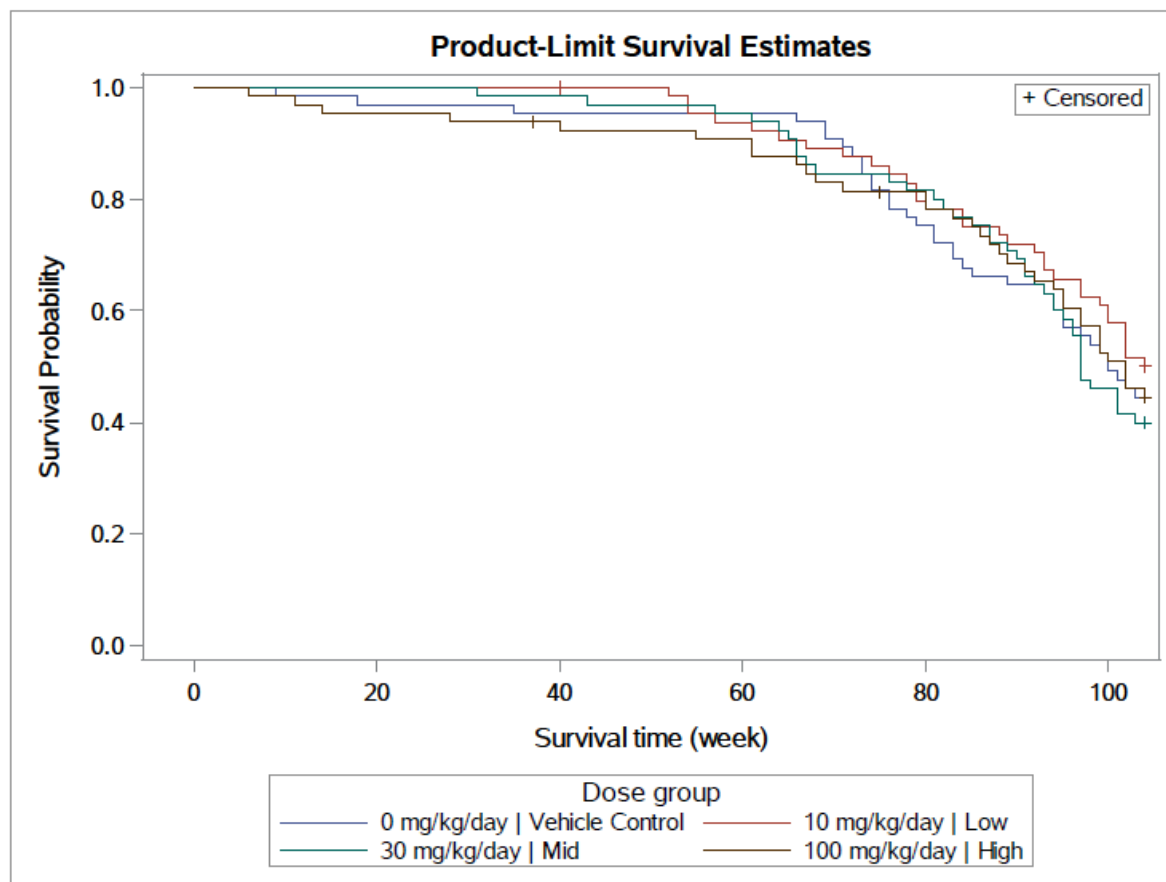
Figure 1A: Kaplan-Meier Survival Functions for Male Rats

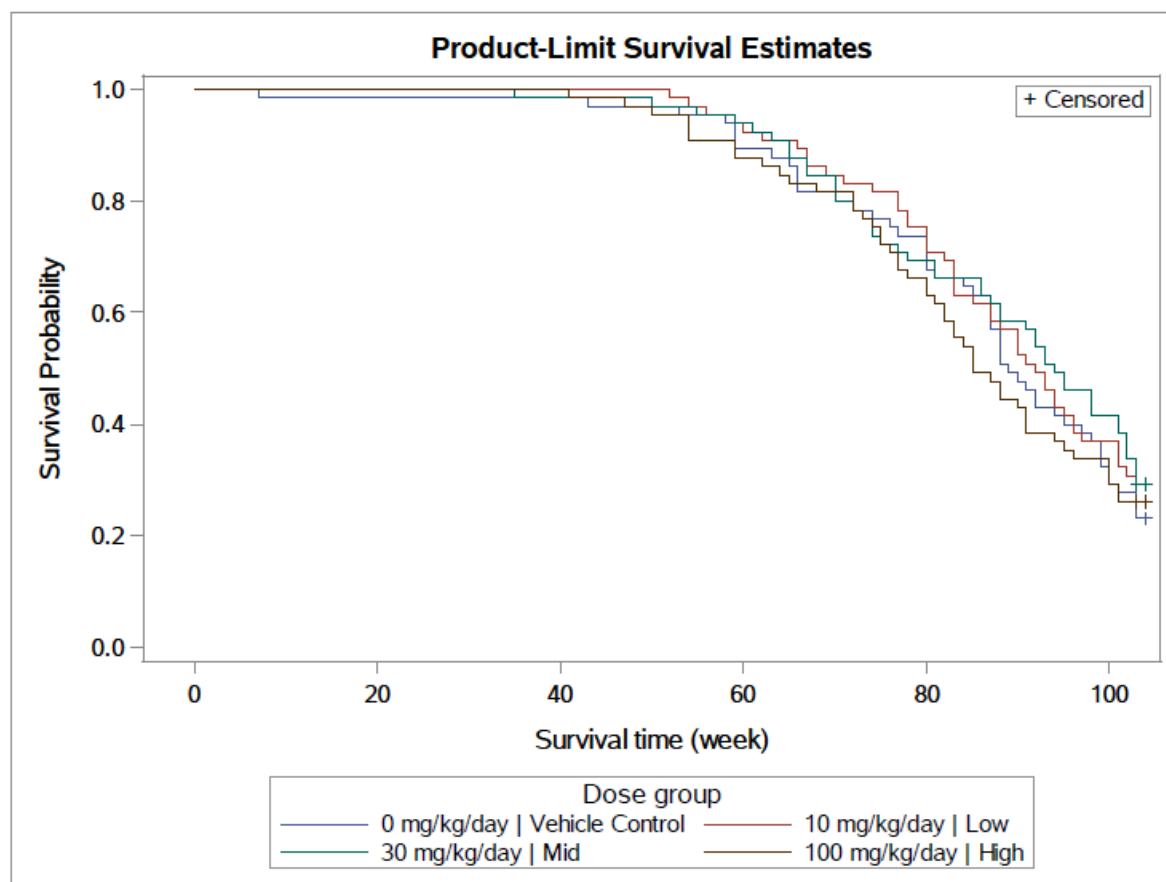
Figure 1B: Kaplan-Meier Survival Functions for Female Rats

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

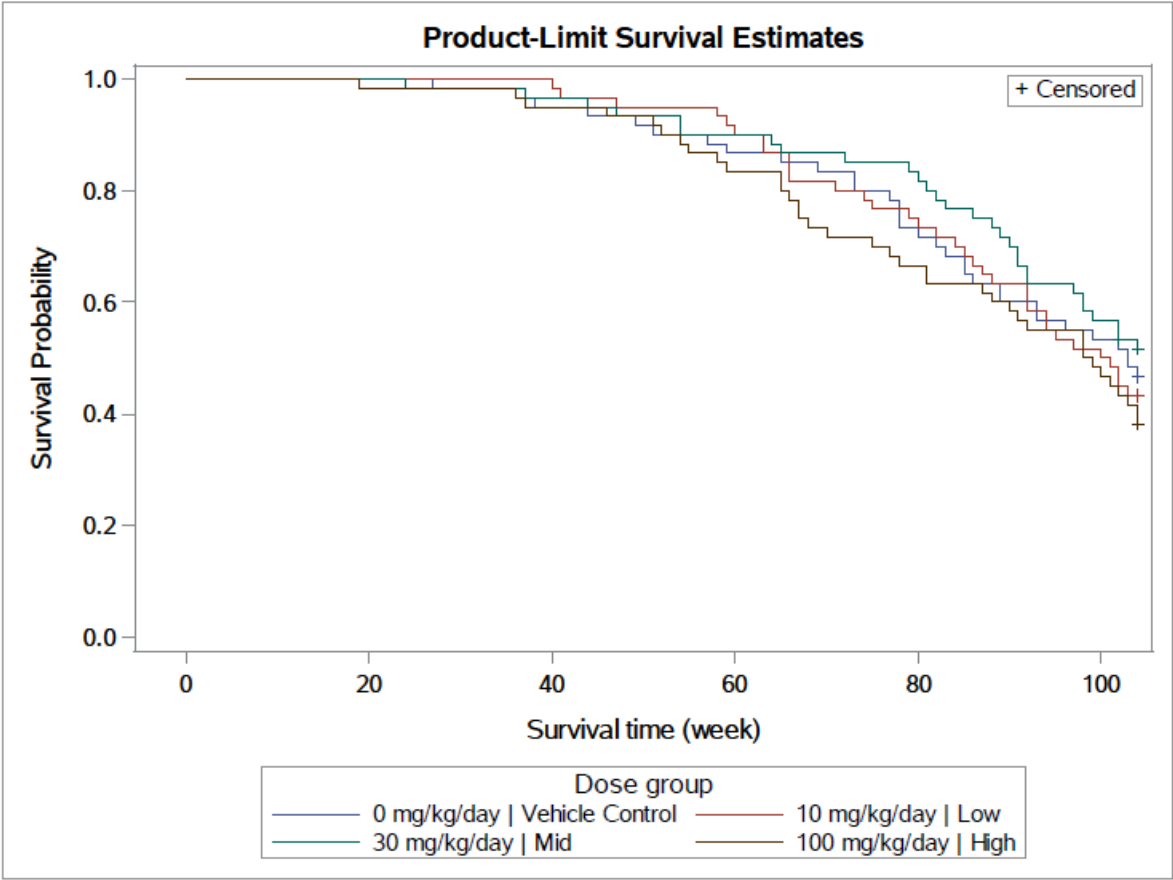
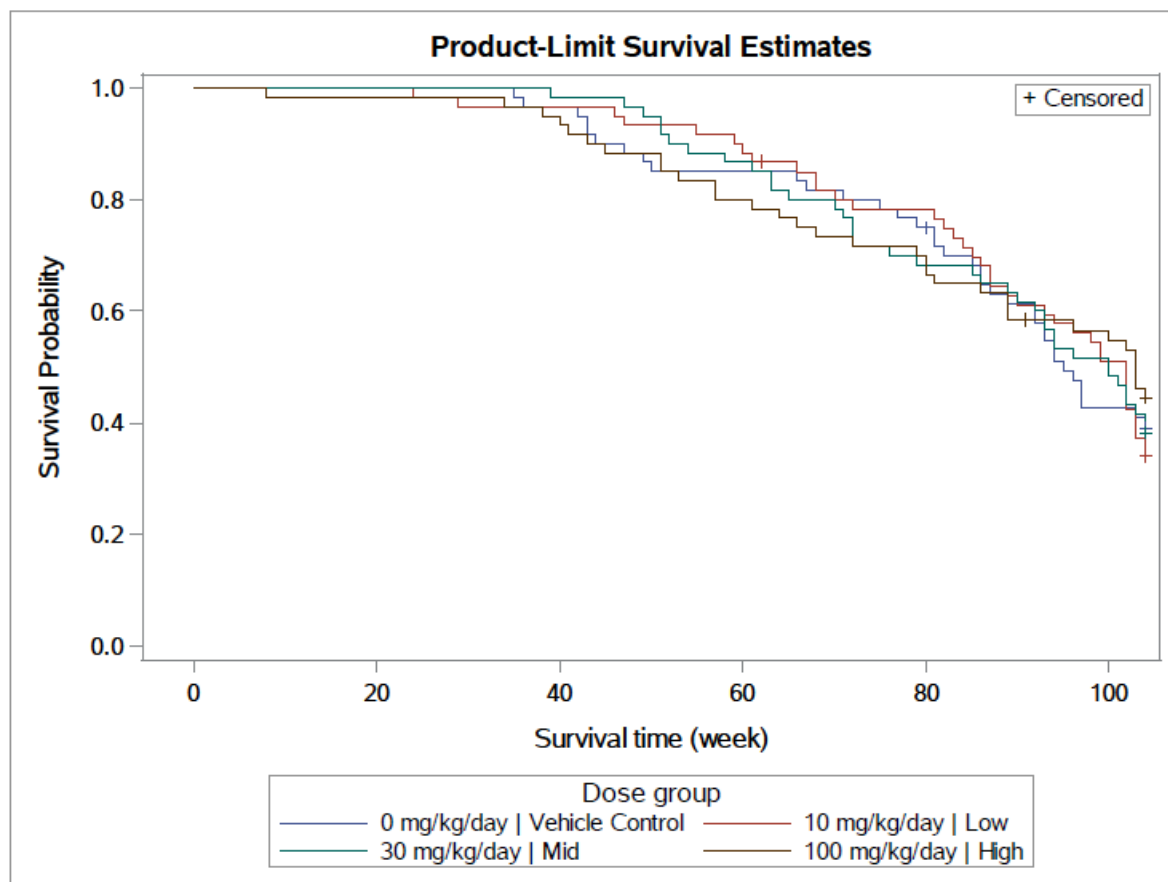


Figure 2B: Kaplan-Meier Survival Functions for Female Mice

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HEPEI CHEN
12/14/2016

KARL K LIN
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Concur with review



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

STATISTICAL REVIEW AND EVALUATION

NDA/BLA #: 208-854
Supplement #: 000
Related IND #: 107,475
Product Name: Symproic (naldemedine) Oral Tablets 0.2 mg
Indication(s): Opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain
Applicant: Shionogi Inc.
Dates: Date Submitted: March 23, 2016
PDUFA Due Date: March 23, 2017
Review Priority: Standard
Biometrics Division: DBIII
Statistical Reviewer: George Kordzakhia, Ph.D.; Ling Lan, Ph.D.
Concurring Reviewers: Yeh-Fong Chen, Ph.D. (Statistical Team Leader).
Medical Division: DGIEP
Clinical Team: Lauren Weintraub, M.D.
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1 EXECUTIVE SUMMARY

The sponsor submitted the original New Drug Application (NDA) for naldemedine oral tablets 0.2 mg for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

The efficacy of naldemedine 0.2 mg QD versus placebo in the treatment of OIC is supported by two positive phase 3, short-term randomized, placebo-controlled, parallel-group studies with 12-week double-blind treatment period.

Based on the pre-specified primary statistical analysis, Cochran Mantel Haenszel test adjusted by the opioid dose strata, naldemedine 2mg QD demonstrated efficacy compared to placebo in both trials as measured by the primary endpoint, proportion of spontaneous bowel movement (SBM) responders.

Besides the primary endpoint, there were four key-secondary efficacy endpoints: changes in the frequency of SBMs per week, complete SBMs per week, and SBMs without straining per week from baseline to the last two weeks of the Treatment Period; and change in the frequency of SBMs per week from baseline to Week 1 in both studies. Compared to placebo, naldemedine 0.2 mg showed statistically significant improvement in all key-secondary measures.

The safety of naldemedine 0.2 mg QD on major adverse cardiovascular events (MACE; including cardiovascular death, myocardial infarction and stroke) was also assessed in this review. Our finding concludes that it not evident compared to the placebo arm with 11 events among 2328 subjects with OIC and chronic non-cancer pain. The conclusion is based on the evaluation of the two aforementioned short-term Phase 3 studies and one long-term randomized Phase 3, placebo-controlled, parallel-group study with 52-week double blinded treatment. These Phase 3 studies showed similar incidences and incidence rates in both naldemedine and placebo arms during the first 12-week treatment period and cross overall study period.

2 INTRODUCTION

2.1 Overview

Naldemedine is a peripherally-acting μ -opioid receptor antagonist (PAMORA) being developed as a once daily treatment for opioid-induced constipation (OIC) in a population of chronic non-cancer pain subjects. The sponsor submitted two Phase 3 studies, 1314V9231 and 1315V9232 (hereafter referred to as V9231 and V9232) to demonstrate the naldemedine's efficacy and also safety. For safety evaluation, in addition to the above two studies, the submission also included one long-term randomized, placebo-controlled, parallel-group safety Phase 3 study, 1326V9235 (hereafter referred to as V9235), with 52-week double-blinded treatment of OIC in subjects with chronic non-cancer pain.

Of note, for this statistical review, Dr. George Kordzakhia focused on the evaluation of the drug efficacy and Dr. Ling Lan focused on the evaluation for the drug safety, especially on major adverse cardiovascular events (MACE; including cardiovascular death, myocardial infarction and stroke).

2.2 Data Sources

The clinical study reports and data sets were submitted electronically. The network path for the submission is: [\\CDSESUB1\evsprod\NDA208854\0000](#). Primary analysis data sets are located at [\\CDSESUB1\evsprod\NDA208854\0000\m5\datasets](#).

Safety data sets included the primary analysis data sets and 120 day safety update data sets located at [\\CDSESUB1\evsprod\NDA208854\0009\m5\datasets\1326v9235-sr\analysis\adam\datasets](#).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewers found the quality and integrity of the submitted data acceptable.

3.2 Evaluation of Efficacy

Two clinical study reports (Studies V9231 and V9232) were included for demonstrating the efficacy and safety of naldemedine 0.2 mg QD for the treatment of OIC in patients with non-malignant chronic pain receiving a stable opioid regimen for >1 month. Studies V9231 and V9232 were conducted globally (North America and Europe) with 68 and 69 sites involved, respectively.

3.2.1 Study Description for V9231 and V9232

3.2.1.1 Study Design and Endpoints

The primary objective for clinical studies V9231 and V9232 was to evaluate the efficacy of naldemedine 0.2 mg QD compared to placebo without concomitant laxative treatment. The studies used an identical randomized, double-blind, placebo-controlled design which was composed of 3 periods: Screening Period (2-4 weeks); a double-blind and placebo-controlled Treatment Period (12 weeks); and a Follow-up Period (4 weeks).

Enrollment criteria

Subjects had to meet the following 3 criteria based on the Bowel Movement and Constipation Assessment (BMCA) log collected via electronic Diary (eDiary) over a 14-consecutive-day qualifying period during the Screening Period:

- a) No more than 4 SBMs total over the 14-consecutive-day qualifying period. In addition, no more than 3 SBMs in a given week of the qualifying period.
- b) Experienced ≥ 1 of the following bowel symptoms in $\geq 25\%$ of BMs:
 1. Presence of straining
 2. Lumpy or hard stools
 3. Sensation of incomplete evacuation
 4. Sensation of anorectal obstruction/blockage
- c) Had $\geq 78\%$ compliance with daily completion of eDiary entries (i.e., made 11 of 14 eDiary completions) during the 14-consecutive-day qualification period.

Treatment Arms and Randomization

In both studies, eligible subjects were randomized in a 1:1 ratio to receive a single tablet of either 0.2 mg of naldemedine or placebo. Subjects were stratified at randomization based on their documented opioid use (average total daily dose (TDD) during the 14-consecutive-day qualifying period) as follows:

- 30 to 100 mg equivalents of oral morphine sulfate (average TDD)
- 100 mg equivalents of oral morphine sulfate (average TDD).

The Primary Efficacy Endpoint was the proportion of SBM responders. A responder was defined as a subject with a positive-response week in at least 9 out of the 12 weeks and in at least 3 of the last 4 weeks of the 12-week treatment period. A positive-response week was defined as a week with ≥ 3 SBMs per week and an increase from baseline ≥ 1 SBM. Any subject who had less than 4 days of diary entries (related to BMs) for a week, was treated as “non-responder” for that week.

The sponsor also pre-specified four Key-Secondary Efficacy Endpoints:

1. Change in the frequency of SBMs per week from baseline to the last 2 weeks of the Treatment Period;
2. Change in the frequency of SBMs per week from baseline to Week 1 of the Treatment Period;
3. Change in the frequency of complete spontaneous bowel movements (CSBMs) per week from baseline to the last 2 weeks of the Treatment Period;

4. Change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the Treatment Period.

The frequency of SBMs/CBMS per week for the last two weeks was defined as: (Total number of SBMs in the last two weeks) $\times 7 /$ (Number of days of observation related to defecation in the last two weeks). Similarly, the frequency of SBMs per week for Week 1 was defined as: (Total number of SBMs for Week 1) $\times 7 /$ (Number of days of observation related to defecation for Week 1).

3.2.1.2 Statistical Methodologies

Analysis Population

The intention-to-treat (ITT) population is defined as all randomized subjects. All efficacy analyses will be based on this population. This population will be analyzed as randomized.

Analysis of the Primary Endpoint

The primary efficacy endpoint, the proportion of SBM responders, was analyzed by the Cochran Mantel Haenszel test adjusted by the opioid dose strata for the comparison between naldemedine and placebo. The confidence intervals for proportion of responders by treatment group were calculated with the Clopper-Pearson method. Difference in the responder proportion between naldemedine and placebo was adjusted by the opioid dose strata and derived using the estimator given by Koch et al [“Categorical Data Analysis” (1990)]. The respective 95% confidence intervals were calculated using normal approximation.

Sensitivity Analysis

The sponsor pre-specified several sensitivity analyses with respect to missing diary entries including:

- Worst Case Analysis: If subjects had missing diary entries related to defecation at any day in a week, that week would be considered as a non-response week.
- Modified Worst Case Analysis: If subjects have no entries related to defecation at a day, the number of SBM at the day will be considered as worst value (i.e. 0 SBM). If a subject has less than 4 days of diary in a particular week, that week will be treated as a “non-response” week.

Analyses of the Key Secondary Endpoints

Each of the key secondary endpoints was tested based on an analysis of covariance method using the treatment arm and opioid dose strata as factors.

Multiple Testing

The primary and the 4 key secondary endpoints were tested at 5% in a predefined hierarchical order to control the overall Type 1 error.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Study V9231 was conducted at 68 sites in North America and Europe: Austria (2), Czech Republic (4), Germany (2), Poland (3), Spain (1), United Kingdom (8), and the United States (48). Of the 547 randomized subjects, 471 (86.1 %) patients completed the double-blind treatment period. Most subjects were randomized from the United States.

Study V9232 randomized patients at 69 sites in North America and Europe: Austria (1), Czech Republic (6), Germany (4), Poland (3), Spain (1), and the United States (54). Of the 553 randomized subjects, 469 (84.8 %) patients completed the double-blind treatment period. Most subjects were randomized from the United States.

Subject disposition is summarized by treatment group in Table 1. In both studies the incidence of discontinuations was similar in the placebo and in the naldemedine groups. The ITT population was defined as all randomized subjects. However, several subjects randomized in studies V9231 and V9232 were subsequently randomized in a different naldemedine trial (study V9235). These subjects were excluded from the ITT population.

Table 1. Subject Disposition: Number of Patients by Treatment Group

	Naldemedine 0.2 mg	Placebo
Study V9231	N (%)	N (%)
Patients Randomized	274 (100%)	273 (100%)
Intent-to-treat	273 (99.6%)	272 (99.6%)
Patients Completed	233 (85.0%)	238 (87.2%)
Discontinued	41 (15.0%)	35 (12.8%)
Study V9232		
Patients Randomized	277 (100%)	276 (100%)
Intent-to-treat	276 (99.6%)	274 (99.2%)
Patients Completed	237 (85.6%)	232 (84.1%)
Discontinued	40 (14.4%)	44 (15.9%)

N=number of patients; percentages are relative to the number of randomized patients;

Source: Clinical Study Report (CSR) V9231 Figures 10-1, 10.2 (pg. 61, 65), CSR V9232 Figure 10-1, 10-2 (pg. 63, 67)

The main reasons for discontinuation in all randomized subjects were subject withdrawal and adverse events. Discontinuation rates are summarized by treatment arms and by reasons in Appendix A. In both studies, the higher rate of adverse events was observed in the naldemedine treatment arms. The higher rates of withdrawal were observed in the placebo arms.

Demographic and Baseline Characteristics

The demographic and baseline characteristics for studies V9231 and V9232 are summarized by study and by treatment group in Table 2. In both studies, the majority of the patients were female ($\geq 60\%$) and white ($\geq 80\%$). The mean age was approximately 53 years, ranging from 19 to 79 years, and the mean weight was approximately 90 kg, ranging from 47 kg to 188 kg. The demographic and baseline characteristics were generally similar across treatment groups.

Table 2. Demographic and Baseline Characteristics by Study (ITT Population)

	Study V9231		Study V9232	
	Naldemedine 0.2mg N=273	Placebo N=272	Naldemedine 0.2mg N=276	Placebo N=274
Age (years): Mean (SD)	53.3 (10.4)	53.4 (11.0)	54.1 (10.5)	52.9 (11.4)
Gender				
Male	112 (41.0%)	104 (38.2%)	111(40.2%)	106 (38.7%)
Female	161 (59.0%)	168 (61.8%)	165 (59.8%)	168 (61.3%)
Race				
White	216 (79.1%)	220 (80.9%)	222 (80.4%)	227 (82.8%)
Black	53 (19.4%)	48 (17.6%)	49 (17.8%)	39 (14.2%)
Other	4 (1.5%)	4 (1.5%)	5 (1.8%)	8 (3.0%)
Weight (kg): Mean (SD)	89.7 (23.8)	90.2 (23.0)	89.2 (21.2)	89.1 (22.2)
BMI: Mean (SD)	31.4 (7.4)	31.3 (6.8)	31.4 (7.0)	31.3 (7.5)
SBM per Week Mean (SD)	1.31 (0.75)	1.30 (0.71)	1.16 (0.76)	1.17 (0.73)

N=number of patients; Percentages are relative to the number of randomized patients; SD=Standard Deviation
Source: CSR V9231 Table 10-2 (pg. 67-70) and CSR V9232 Table 10-2 (pg. 69-72)

3.2.3 Efficacy Results and Conclusions

3.2.3.1 Primary Efficacy Endpoint: Proportion of Spontaneous Bowel Movement Responders

The primary efficacy endpoint, the proportion of SBM responders, was analyzed by the Cochran Mantel Haenszel test adjusted by the opioid dose strata. The sponsor's results for the primary efficacy endpoint based on the ITT population are displayed in Table 3. In both studies V9231 and V9232, statistically significantly higher proportions of SBM responders were observed in the naldemedine group relative to the placebo group (respective p-values of 0.002 and <0.0001). The observed differences between the treatment groups in the proportion of SBM responders were 13% in study V9231 and 19% in study V9232. These results were confirmed by the statistical reviewer.

Table 3 Sponsor's Primary Analysis: Proportion of SBM Responders (ITT Population)

Study	Primary Endpoint	Naldemedine 0.2 mg	Placebo
V9231		N=273	N=272
	Proportion of Responders (95% CI)*	47.6% (41.6%, 53.7%)	34.6% (28.9%, 40.5%)
	Difference of Proportions (95% CI)	13.0% (4.8%, 21.3%)	--
	p-value	0.0020	--
V9232		N=276	N=274
	Proportion of Responders (95% CI)	52.5% (46.5%, 58.6%)	33.6% (28.0%, 39.5%)
	Difference of Proportions (95% CI)	18.9% (10.8%, 27.0%)	--
	p-value	<0.0001	--

*Confidence Interval.

Source: CSR 1314V9231 Table 11-1 (pg. 77), CSR V9232 Table 11-1 (pg. 79)

Sensitivity Analyses

Table 4 and Table 5 present sponsor’s “worst case” and “modified worst case” sensitivity analyses to missing data for ITT population. In the worst case sensitivity analysis, if subjects had missing diary entries related to defecation at any day in a week, that week would be considered as a non-response week. In modified worst case analysis, if subjects have no entries related to defecation at a day, the number of SBM at the day will be considered as worst value (i.e. 0 SBM). If a subject has less than 4 days of diary in a particular week, that week will be treated as a “non-response” week. Conclusions of both analyses were consistent with those of the primary analysis, which were confirmed by the statistical reviewer.

Table 4. Sponsor’s Worst Case Sensitivity Analysis: Proportion of SBM Responders (ITT Population).

Study	Primary Endpoint	Naldemedine 0.2 mg	Placebo
V9231		N=273	N=272
	Proportion of Responders (95% CI*)	40.3% (34.4%, 46.4%)	30.9% (25.4%, 36.7%)
	Difference of Proportions (95% CI)	9.4% (1.4%, 17.4%)	--
	p-value	0.022	--
V9232		N=276	N=274
	Proportion of Responders (95% CI)	43.8% (37.9%, 49.9%)	29.9 % (24.6%, 35.7%)
	Difference of Proportions (95% CI)	13.9% (5.9%, 21.8%)	--
	p-value	0.0007	--

* Confidence Interval.

Source: CSR 1314V9231 Table 14.2-1.2.3 (pg. 399), CSR V9232 Table 14.2-1.2.3 (pg. 441)

Table 5. Sponsor’s Modified Worst Case Sensitivity Analysis: Proportion of SBM Responders (ITT Population).

Study	Primary Endpoint	Naldemedine 0.2 mg	Placebo
V9231		N=273	N=272
	Proportion of Responders (95% CI*)	47.3% (41.2%, 53.4%)	34.6% (28.9%, 40.5%)
	Difference of Proportions (95% CI)	12.7% (4.5%, 20.9%)	--
	p-value	0.0026	--
V9232		N=276	N=274
	Proportion of Responders (95% CI)	52.5% (46.5%, 58.6%)	33.2% (27.7%, 39.1%)
	Difference of Proportions (95% CI)	19.3% (11.2%, 27.4%)	--
	p-value	<0.0001	--

* Confidence Interval.

Source: CSR V9231 Table 14.2-1.2.4 (pg. 400), CSR V9232 Table 14.2-1.2.4 (pg. 442)

3.2.3.2 Key Secondary Efficacy Endpoints

There were four pre-specified key secondary efficacy endpoints in both studies:

- Change in the frequency of SBMs per week from baseline to the last two weeks of the Treatment Period
- Change in the frequency of SBMs per week from baseline to Week 1
- Change in the frequency of complete spontaneous bowel movements (CSBM) per week from baseline to the last two weeks of the Treatment Period

- Change in the frequency of SBMs without straining (straining score of 0) per week from baseline to the last two weeks of the Treatment Period.

The key-secondary endpoints were analyzed using ANCOVA models with factors treatment and opioid dose strata. In both studies, naldemedine group was statistically significantly better than placebo group in all four endpoints (see Table 6, Table 7, Table 8, Table 9) which was confirmed by the statistical reviewer. Mean changes from baseline by treatment groups and treatment differences were generally consistent in the two studies. However, magnitudes of treatment differences were relatively small. In particular, for change in frequency of SBMs without straining, least squares estimates of treatment effect in both studies were less than 1 (i.e. 0.75 in study V9231 and 0.73 in study V9232). Also, the key secondary endpoints measuring frequency changes from baseline to the last two weeks of double-blind phase are closely related and appear to be possibly redundant since they measure the same domain of disease at the same time point.

Table 6. Sponsor's Analysis of Change in the Frequency of Spontaneous Bowel Movement per Week from Baseline to the Last Two Weeks

Study	1 st Key Secondary Endpoint	Naldemedine 0.2 mg	Placebo
V9231		N=273	N=272
	Baseline: Mean (SD [*])	1.31 (0.75)	1.30 (0.71)
	Change from Baseline: LS Mean (SE [#])	3.42 (0.19)	2.12 (0.19)
	Treatment Difference: LS Mean (SE)	1.30 (0.27)	--
	p-value	<0.0001	--
V9232		N=276	N=274
	Baseline: Mean (SD)	1.16 (0.76)	1.17 (0.73)
	Change from Baseline: LS Mean (SE)	3.56 (0.17)	2.16 (0.17)
	Treatment Difference: LS Mean (SE)	1.40 (0.24)	--
	p-value	<0.0001	--

*Standard Deviation, #Standard Error.

Source: CSR V9231 Table 11-4 (pg. 82), CSR V9232 Table 11-4 (pg. 84)

Table 7. Sponsor's Analysis of Change in the Frequency of Spontaneous Bowel Movement per Week from Baseline to Week 1

Study	2 nd Key Secondary Endpoint	Naldemedine 0.2 mg	Placebo
V9231		N=273	N=272
	Baseline: Mean (SD [*])	1.31 (0.75)	1.30 (0.71)
	Change from Baseline: LS Mean (SE [#])	3.48 (0.19)	1.36 (0.18)
	Treatment Difference: LS Mean (SE)	2.11 (0.26)	--
	p-value	<0.0001	--
V9232		N=276	N=274
	Baseline: Mean (SD)	1.16 (0.76)	1.17 (0.73)
	Change from Baseline: LS Mean (SE)	3.86 (0.20)	1.69 (0.20)
	Treatment Difference: LS Mean (SE)	2.17 (0.28)	--
	p-value	<0.0001	--

*Standard Deviation, #Standard Error.

Source: CSR V9231 Table 11-5 (pg. 84), CSR V9232 Table 11-5 (pg. 86)

Table 8. Sponsor's Analysis of Change in the Frequency of Complete Spontaneous Bowel Movement per Week from Baseline to the Last Two Weeks

Study	3 rd Key Secondary Endpoint	Naldemedine 0.2 mg	Placebo
V9231		N=273	N=272
	Baseline: Mean (SD [*])	0.40 (0.60)	0.38 (0.57)
	Change from Baseline: LS Mean (SE [#])	2.58 (0.17)	1.57 (0.17)
	Treatment Difference: LS Mean (SE)	1.01 (0.24)	--
	p-value	<0.0001	--
V9232		N=276	N=274
	Baseline: Mean (SD)	0.35 (0.51)	0.40 (0.56)
	Change from Baseline: LS Mean (SE)	2.77 (0.17)	1.62 (0.17)
	Treatment Difference: LS Mean (SE)	1.15 (0.23)	--
	p-value	<0.0001	--

*Standard Deviation, #Standard Error.

Source: CSR V9231 Table 11-6 (pg. 86), CSR V9232 Table 11-6 (pg. 88)

Table 9. Sponsor's Analysis of Change in the Frequency of Spontaneous Bowel Movement without Straining per Week from Baseline to the Last Two Weeks

Study	4 th Key Secondary Endpoint	Naldemedine 0.2 mg	Placebo
V9231		N=273	N=272
	Baseline: Mean (SD [*])	0.11 (0.31)	0.08 (0.30)
	Change from Baseline: LS Mean (SE [#])	1.46 (0.14)	0.73 (0.14)
	Treatment Difference: LS Mean (SE)	0.73 (0.20)	--
	p-value	0.0003	--
V9232		N=276	N=274
	Baseline: Mean (SD)	0.08 (0.27)	0.13 (0.38)
	Change from Baseline: LS Mean (SE)	1.85 (0.16)	1.10 (0.16)
	Treatment Difference: LS Mean (SE)	0.75 (0.23)	--
	p-value	0.0011	--

*Standard Deviation, #Standard Error.

Source: CSR V9231 Table 11-7 (pg. 88), CSR V9232 Table 11-7 (pg. 90)

3.3 Evaluation of Safety

The sponsor reported clinical safety findings in the integrated safety summary (ISS) and Summary of Clinical Safety (SCS). Safety analyses were based on dataset from one long-term study V9235 and a pooled dataset of studies V9231 and V9232 by data cutoff date of 24 June 2015. This safety review accessed MACE using data during 1) first 12-week common treatment period in three Phase 3 studies to summarize short-term MACE risk, and 2) Day 1 to end of all studies to examine overall risk in MACE. Exposure time adjusted MACE incidence rate (IR) was examined in this review instead of the follow-up time adjusted IR from the sponsor. The submission did not include last day on study for each subject therefore follow-up time adjusted IR is not reproducible.

3.3.1 Study Design and Endpoints

Study design and endpoints of trials V9231 and V9232 refer to section 3.2.1.1. Study V9235 is a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel group (1:1) study to evaluate the long-term safety and tolerability of naldemedine 0.2 mg QD versus placebo for the treatment of OIC in subjects with non-malignant chronic pain who received a stable opioid regimen for >1 month.

The study included a 28-day screening period, a 52-week double-blind, placebo-controlled treatment period, and a 14-day follow-up period. Subject enrollment criteria were similar to studies V9231 and V9232 (section 3.2.1.1).

In total 1246 subjects (1:1) were stratified at randomization based on their documented opioid use (TDD during the 14-consecutive-day qualifying period) as follows:

- 30 to 100 mg equivalents of oral morphine sulfate (average TDD)
- 100 mg equivalents of oral morphine sulfate (average TDD).

Primary safety endpoints were summary measures of treatment emergent adverse events. MACE was adjudicated by an adjudication committee

3.3.2 Statistical Methodologies

The safety population was defined as all subjects randomized and received at least one dose of naldemedine. Safety analyses on MACE were based on this population. MACE incidence and IR adjusted by follow-up time was calculated by the sponsor used data up to the cut-off date of 24 June 2015 with subjects having at least 24 weeks and up to 52 weeks of exposure in Study V9235. All remaining data were summarized in the 120 day safety update report. No statistical test was planned for comparison of MACE risks between two treatment arms.

3.3.3 Patient Demographics and baseline Characteristics (V9235)

This study was conducted in 195 sites in North America, Europe, and Asia Pacific and majority of the subjects were from the United States (133). The demographic and baseline characteristics for study V9235 are summarized by treatment group in Table 10 for 1240 subjects in the safety population. The majority of the patients were female ($\geq 60\%$) and white ($\geq 79\%$). The mean age was approximately 53 years, ranging from 20 to 80 years, and the mean weight was approximately 90 kg, ranging from 40 kg to 201 kg. The demographic and baseline characteristics were generally similar between treatment groups.

The reviewer's calculation found 620 subjects received naldemedine as opposed to 621 in naldemedine arm reported in Table 10 by the sponsor. Patients' demographics and characteristics were similar between reviewer's analyses and the sponsor's summary in Table 10.

Note that the ITT population and safety population in the three Phase 3 studies are close (safety vs ITT: V9231: 543 vs 545, V9232: 545 vs 550, and V9235: 1240 vs 1241). As a result, patients' demographics and characteristics were similar in ITT and safety populations.

Table 10. Demographic and Baseline Characteristics for Study V9235 (Safety population)

	Naldemedine 0.2mg N=621	Placebo N=619
Age (years):		
Mean (SD)	53.4 (11.7)	52.7 (10.5)
Gender		
Male	238 (38%)	217 (35%)
Female	383 (62%)	402 (65%)
Race		
White	492 (79%)	496 (80%)
Black	120 (19%)	108 (17%)
Other	9 (2%)	15 (3%)
Weight (kg):		
Mean (SD)	90.6 (23.6)	90.3 (24.2)
BMI: Mean (SD)	31.7 (7.6)	31.5 (7.6)
SBM per Week		
Mean (SD)	1.6 (0.7)	1.6 (0.6)

N=number of patients; Percentages are relative to the number of patients received at least one dose of treatment; SD=Standard Deviation

Source: CSR V9235 Table 10-1 (pg. 74-75) and Table 10-2 (pg. 76)

3.3.4 MACE Results and Conclusions

The statistical reviewer confirmed MACE incidence reported in ISS and SCS (Appendix B). The follow-up time adjusted MACE IR could not be calculated based on the submitted data. Table 11 summarized incidence of MACE during the first 12 weeks of treatment, and Table 12 reported the overall MACE incidence and exposure time adjusted IR for all studies.

For the first 12-week treatment period, the incidences of MACE were similar in both treatment arms, 0.2% (2/1163) in naldemedine arm and 0.3% (3/1165) in placebo arm. By the end of all phase 3 studies, MACE incidences and exposure time adjusted IRs remained comparable between two treatment arms (naldemedine: 0.4%, 8.3 per 1000 subject-years; placebo: 0.5%, 9.9 per 1000 subject years).

Table 11 Reviewer's Analyses: Incidence of MACE during the first 12 weeks of Phase 3 safety population

MACE N (%)	V9231 + V9232		V9235		Overall	
	Naldemedine N=542	Placebo N=546	Naldemedine N=621	Placebo N=619	Naldemedine N=1163	Placebo N=1165
Total	1 (0.2)	1 (0.2)	1 (0.2)	2(0.3)	2 (0.2)	3 (0.3)
Cardiovascular Death	0	0	0	0	0	0
Myocardial Infarction	1 (0.2)	1 (0.2)	1 (0.2)	2(0.3)	2 (0.2)	3 (0.3)
Stroke	0	0	0	0	0	0

Table 12 Reviewer's Analyses: MACE incidence and exposure time adjusted incidence rate from Day 1 to end of study in safety population

MACE N (%)	V9231 + V9232		V9235		Overall	
	Naldemedine N=542	Placebo N=546	Naldemedine N=621	Placebo N=619	Naldemedine N=1163	Placebo N=1165
Total	1 (0.2)	1 (0.2)	4 (0.6)	5 (0.8)	5 (0.4)	6 (0.5)
Cardiovascular death	0	0	1 (0.2)	3 (0.5)	1 (0.1)	3 (0.3)
Myocardial infarction	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.3)	2 (0.2)	3 (0.3)
Stroke	0	0	2 (0.3)	0	2 (0.2)	0
Exposure time (subject years)					603.4	603.7
Incidence rate per 1000 subject-years					8.3	9.9

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

This section contains reviewer's exploratory summary of the proportion of SBM responders by gender, race, and age subgroups and by geographic region (US, non-US). As presented in Table 13, we observed quite consistent findings between different subgroups in both studies. In particular, patients treated with naldemedine had higher percentage of responders than those treated with placebo in all investigated subgroups except black racial subgroup in study V9232.

Table 13 Reviewer's Subgroup Summary: Proportion of Responders by Gender, Race, Age, and Geographic Region Subgroups

	Study V9231		Study V9232	
	Naldemedine 0.2mg	Placebo	Naldemedine 0.2mg	Placebo
Gender				
Male	55.4% (62/112)	34.6% (36/104)	56.8% (63/111)	39.6% (42/106)
Female	42.2% (68/161)	34.5% (58/168)	49.7% (82/165)	29.8% (50/168)
Race				
Black	49.1% (26/53)	41.7% (20/48)	40.8% (20/49)	46.2% (18/39)
White	47.2 % (102/216)	33.2% (73/220)	54.5% (121/222)	31.3% (71/227)
Age				
< 65 years	48.7% (114/234)	35.6% (80/225)	50.9% (118/232)	31.4% (74/236)
≥ 65 years	41.0% (16/39)	29.8% (14/47)	61.4% (27/44)	47.4% (18/38)
Region				
US	45.2% (104/230)	34.9% (80/229)	53.9% (130/241)	32.6% (78/239)
Non-US	60.5% (26/43)	32.6% (14/43)	42.9% (15/35)	40.0% (14/35)

N=number of patients; SE=Standard Error

Reviewer's Note: Given the small number of MACE, incidence of MACE by the aforementioned demographic subgroups was not warranted.

4.2 Other Special/Subgroup Populations

This section includes exploratory summary of proportion of responders by opioid dose strata (30-10mg, >100mg). In both opioid dose strata, naldemedine arms had numerically higher proportion of responders compared with placebo arm (displayed in Table 14).

Table 14. Reviewer's Subgroup Analysis by Geographic Region (US, non-US)

Opioid Dose Strata	Study V9231		Study V9232	
	Naldemedine 0.2mg	Placebo	Naldemedine 0.2mg	Placebo
30-100 mg	49.0% (76/155)	35.9% (55/153)	57.4% (97/169)	38.9% (65/167)
>100 mg	45.8% (54/118)	32.8% (39/119)	44.9 % (48/107)	25.2% (27/107)

N=number of patients; SE=Standard Error

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Statistical efficacy and safety analyses were pre-specified by the sponsor in the clinical study protocols. No major issues with the sponsor's statistical methods were identified by statistical reviewers.

The primary efficacy endpoint, proportion of SBM responders, was analyzed by the Cochran Mantel Haenszel test adjusted by the opioid dose. Naldemedine 0.2mg/ day was statistically superior to placebo in both studies. The pairwise comparisons versus placebo adjusted by the opioid dose strata, and their 95% confidence intervals are summarized in Table 15. The reported treatment differences in proportions in studies V9231 and V9232 were 13% (nominal p=0.002) and 18.9% (nominal p<0.0001) respectively.

Table 15. Collective Evidence for Primary Endpoint

	Study V9231		Study V9232	
	Naldemedine 0.2mg N=273	Placebo N=272	Naldemedine 0.2mg N=276	Placebo N=274
Proportion of Responders (95% CI)*	47.6% (41.6%, 53.7%)	34.6% (28.9%, 40.5%)	52.5% (46.5%, 58.6%)	33.6% (28.0%, 39.5%)
Difference of Proportions (95% CI)	13.0% (4.8%, 21.3%)	--	18.9% (10.8%, 27.0%)	--
p-value	0.0020	--	<0.0001	--

* Confidence Interval.

Source: CSR V9231 Table 11-1 (pg. 77), CSR V9232 Table 11-1 (pg.79)

Results confirmed by the reviewer

Efficacy results for the key secondary endpoints summarized in Table 16 support primary efficacy findings. In both studies, in comparison with placebo, naldemedine 0.2mg/ day had statistically significant improvement from baseline to the last two weeks of the double-blind treatment period in daily frequencies of SBM, complete SBM and SBM without straining. Naldemedine 0.2 mg was also superior to placebo in improving SBM frequency from Baseline to Week 1. The magnitudes of treatment differences were relatively small. In particular, for the change in the frequency of SBMs without straining, least squares estimates of treatment effects

in both studies were less than 1 (i.e. 0.75 in study V9231 and 0.73 in study V9232). Whether the observed treatment differences are clinically meaningful is deferred to the clinical review team. Also, the key secondary endpoints measuring frequency changes from baseline to the last two weeks are closely related and appear to be possibly redundant since they measure the same domain of disease at the same time point.

Table 16. Collective Evidence for Key Secondary Endpoints

	Study V9231		Study V9232	
	Naldemedine 0.2mg	Placebo	Naldemedine 0.2mg	Placebo
	Change in SBM from Baseline to the Last Two Weeks of DBT			
LS Mean (SE)	3.42 (0.19)	2.12 (0.19)	3.56 (0.17)	2.16 (0.17)
Treatment Difference: LS Mean (SE)	1.30 (0.27) ***	--	1.40 (0.24) ***	--
	Change in SBM from Baseline to Week 1 of DBT			
LS Mean (SE)	3.48 (0.19)	1.36 (0.18)	3.86 (0.20)	1.69 (0.20)
Treatment Difference: LS Mean (SE)	2.11 (0.26) ***	--	2.17 (0.28) ***	--
	Change in CSBM from Baseline to the Last Two Weeks of DBT			
LS Mean (SE)	2.58 (0.17)	1.57 (0.17)	2.77 (0.17)	1.62 (0.17)
Treatment Difference: LS Mean (SE)	1.01 (0.24) ***	--	1.15 (0.23) ***	--
	Change in SBM without straining from Baseline to the Last Two Weeks of DBT			
LS Mean (SE)	1.46 (0.14)	0.73 (0.14)	1.85 (0.16)	1.10 (0.16)
Treatment Difference: LS Mean (SE)	0.73 (0.20) **	--	0.75 (0.23) *	--

LS=Least Squares; SE=Standard Error

***p-value<0.0001; **p-value<0.001; *p-value<0.01

Source: CSR V9231 Table 11-4 (pg. 82), Table 11-5 (pg. 84), Table 11-6 (pg. 86), and Table 11-7 (pg. 88);

CSR V9232 Table 11-4 (pg. 84), Table 11-5 (pg. 86), Table 11-6 (pg. 88), and Table 11-7 (pg. 90)

For the first 12-week treatment period, the incidences of MACE were similar in both treatment arms, 0.2% (2/1163) in naldemedine arm and 0.3% (3/1165) in placebo arm. By the end of all phase 3 studies, MACE incidences and exposure time adjusted IRs remained comparable between two treatment arms (naldemedine: 0.4%, 8.3 per 1000 subject-years; placebo: 0.5%, 9.9 per 1000 subject years).

5.2 Conclusions and Recommendations

Based on the results for the primary endpoint of proportion of spontaneous bowel movement (SBM) in two positive phase 3 studies, Naldemedine 0.2mg/day was statistically superior to placebo as a treatment of opioid-induced constipation in subjects with non-malignant chronic pain receiving opioid therapy. Although the sponsor's results for the four pre-specified key secondary endpoints were all positive, we noted that the treatment differences for all of these continuous endpoints were small. It is not clear whether these small changes are clinical meaningful.

In terms of safety evaluation for the MACE outcome, we found that there was no evident risk associated with naldemedine 0.2mg/day treatment compared to placebo in non-malignant chronic pain patients with OIC.

APPENDIX A. Reasons for Discontinuation

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Table 17. Study V9231 Discontinuation Rates by Reasons and by Treatment Group

	Naldemedine 0.2 mg N=274 n (%)	Placebo N=273 n (%)
Subjects Completed	233 (85.0)	238 (87.2)
Subjects Discontinued	41 (15.0)	35 (12.8)
Primary Reason for Discontinuation		
- Adverse Event	14 (5.1)	5 (1.8)
- Pregnancy	0	0
- Withdrawal by Subject	16 (5.8)	24 (8.8)
- Lost to Follow-up	7 (2.6)	5 (1.8)
- Protocol Violation	1 (0.4)	1 (0.4)
- Study Terminated by Sponsor	0	0
- Other	3 (1.1)	0

Source: V9231 Table 14.1-1.2 (pg. 165)

Table 18. Study V9232 Discontinuation Rates by Reasons and by Treatment Group

	Naldemedine 0.2 mg N=277 n (%)	Placebo N=276 n (%)
Subjects Completed	237 (85.6)	232 (84.1)
Subjects Discontinued	40 (14.4)	44 (15.9)
Primary Reason for Discontinuation		
- Adverse Event	16 (5.8)	11 (4.0)
- Pregnancy	0	0
- Withdrawal by Subject	15 (5.4)	19 (6.9)
- Lost to Follow-up	2 (0.7)	5 (1.8)
- Protocol Violation	5 (1.8)	8 (2.9)
- Study Terminated by Sponsor	0	0
- Death	1 (0.4)	0
- Other	1 (0.4)	1 (0.4)

Source: Source: CSR V9232 Table 14.1-1.2 (pg. 195)

APPENDIX B. MACE Outcome

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Table 19. MACE incidence by type in Study V9235

MACE Type	V9231 + V9232		V9235		Overall	
	Naldemedine	Placebo	Naldemedine	Placebo	Naldemedine	Placebo
	0.2 mg N=542 n (%)	N=546 n (%)	0.2 mg N=621 n (%)	N=619 n (%)	0.2 mg N=1163 n (%)	N=1165 n (%)
Subjects with MACE	1 (0.2)	1 (0.2)	2 (0.3)	5 (0.8)	3 (0.3)	6 (0.5)
- Cardiovascular Death	0	0	0	3 (0.5)	0	3 (0.3)
- Myocardial Infarction	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.3)	2 (0.2)	3 (0.3)
- Cerebrovascular Accident (Stroke)	0	0	1 (0.2)	0	1 (0.1)	0

Source: Sponsor's summary of clinical safety (Page 65)

Table 20. MACE follow-up adjusted incidence rate by type in Study V9235

	Naldemedine 0.2 mg N=1163	Placebo N=1165
Number of Subjects with Events	3	6
Subject-years	601.0	598.5
Incidence Rate [a]	5.0	10.0
Difference of Incidence Rate (SE)	-5.0 (5.00)	
95% CI for Difference	-14.84, 4.77	

[a] $1000 * (\text{Number of Subjects with Events}) / (\text{Subject-years})$

V9231, V9232 and V9235 were pooled.

Source: Sponsor's SCS (Page 65)

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/s/

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