CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES- ADDENDUM

NDA:	**204063**
Drug Name:	**BG00012 (Dimethyl Fumarate) delayed action capsule**
Indications:	**Multiple Sclerosis**
Applicants:	**Sponsor: Biogen Idec, Inc.** **14 Cambridge Center, Cambridge, MA 02142** (b) (4) [redacted]
Date:	**To Reviewer: 16 January 2013**
Review Priority:	**Standard**
Biometrics Division:	**Division 6**
Statistical Reviewer:	**Steve Thomson**
Concurring Reviewers:	**Karl Lin, Ph.D.**
Medical Division:	**Neurology Products**
Toxicologist Team:	**Melissa Banks-Muckenfuss, Ph.D.**
Project Manager:	**Nicole Bradley, Pharm.D.**

Keywords: Carcinogenicity, Cochran-Armitage test, Poly-k test, Trend test

The original submissions for this carcinogenicity study involved two standard two year studies, in rats and mice. [redacted] (b) (4) . The study report and data for the rat study were originally submitted with IND 73061 from the same Sponsor. The results of the FDA analysis of the rat study are summarized in the statistical carcinogenicity review dated 22 April 2008. The data for the mice were submitted later, and the data for both species were reanalyzed in a review dated 28 September 2012.

After completion and posting of these reviews the Sponsor submitted new data for the renal data in both rats and mice. The table below indicates the changes in reported tumor incidence:

Table Add 1. Kidney Tumor Incidence (Adenomas and Carcinomas Only)

	Original Incidence					Revised Incidence				
Animal-Tumor	Veh-icle	Low	Med-ium	High-Med	High	Veh-icle	Low	Med-ium	High-Med	High
Male Rats – Adenomas	0	0	1	1	4	0	0	1	1	**0**
Female Rats– Adenomas	1	0	0	0	2	1	0	**1**	0	2
Carcinomas	0	0	0	2	4	0	0	0	**0**	**1**
Male Mice – Adenomas	1	2	0	5	3	**2**	2	0	5	3
Carcinomas	0	0	2	4	3	0	0	2	4	3
Female Mice–Adenomas	0	0	0	2	4	0	0	0	2	4
Carcinomas	0	0	0	0	1	0	0	0	0	1

All these changes in incidence tend to reduce any apparent dose related indication of carcinogenicity in kidneys. This caused some concern to this reviewer, but the toxicology reviewer noted that: "An expert in rat renal histopathology conducted a re-evaluation of the original renal findings in the carcinogenicity assays. His re-evaluation was conducted to identify the nature of the reported lesions, taking into account histopathological events that would yield information about the mode of renal tumor formation. In his analysis of the rat renal data, he discovered that three of the identified renal tumors were of non-renal origin and that a number of others were of a particular morphology now known to be of spontaneous origin in rats. These alterations in the interpretation of the findings produced a substantially different renal tumor incidence in rats." (personal communication)

For incidence only data, the typical analysis is based on a so-called Cochran-Armitage test of trend, which basically does a regression type analysis of the incidence of the event under study, in this case the development of a specific organ tumor combination, regressed on dose. Each animal at each dose level is treated as being equally likely to develop the tumor. But in practice some animals die early and it may not be appropriate to consider those animals as having the same chance of developing the tumor as those animals in the same dose group that survive to the end of the study. The usual FDA analysis for carcinogenicity uses the so-called poly-k modification of the Cochran-Armitage test of trend where the risk set for the specific organ tumor combination is reduced by animals that die early in the study without the tumor..

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Inspecting a large number of studies, Bailer and Portier (1988) noted that survival time seemed to fit a Weibull distribution, generally with a shape parameter of between 1 and 5, with 3 a typical value. With t_{max} denoting the maximal time to terminal sacrifice and t_{obs} the time to death of the animal, they proposed weighting the animal by $(t_{obs}/t_{max})^k$, so that an animal that survives for say 52 weeks in 104 week study without the tumor being analyzed is counted as $(1/2)^k$ of an animal when computing the size of the risk set for that tumor. For k = 3, that means that particular animal would count as 1/8 of an animal in the Cochran-Armitage analysis of that tumor. Further, the k = 3 specification seems to represent tumor incidence where some animals are perhaps more sensitive and respond earlier to the insult than the remaining animals. Under this structure, time to incidence would tend to follow a cubic expression. Thus an animal with the specific tumor being studied or who survives to terminal sacrifice without the tumor will be given a weight of 1 when counting the number of animals at risk. However, animals that die early without the tumor are down weighted when counting the number of animals in the risk set for that specific tumor. With differential mortality, this can mean a substantial reduction in the size of that risk set. This seems to be an appropriate adjustment whenever there is differential mortality across dose groups. The report of the Society of Toxicological Pathology "town hall" meeting in June 2001 recommended the use of this poly-k modification of the so-called Cochran-Armitage tests of trend.

As transmitted to this reviewer the data consisted only of revised tumor incidence without the attendant mortality data. Under some circumstances, this could present a problem, and requesting original data was considered. However, it seems clear that in this case imputing a few new values will have no particular effect upon conclusions. In particular, data values were recoded as discussed below:

1. In the original data, the high dose group in male rats included four rats identified with adenomas in the kidneys. The Sponsor's reanalysis deleted all four of these adenomas. Note that this change is unique in the sense that we know exactly which animals should have the tumor incidence changed, and hence the computed p-values would be remain the same if the Sponsor had provided the corrected data.

2. In female rats, one adenoma was added to control group totals, the tumors assigned to the original two identified carcinomas in the high medium dose group were deleted (animals E660 and E663) as in 1. above. Further, three of the four carcinomas in the high dose group were deleted. Since animals that die early are downweighted, and thus reduce the size of the risk set, choosing a control group animal that survived to the end of the study will have the smallest effect. This was done for the single imputed adenoma in the control. Among the four animals originally identified with carcinomas in the high dose group, retention of the highest surviving animal will be least favorable for the Sponsor and thus is used here. Any other choice would increase the size of the risk set, thus decreasing statistical significance.

3. In male mice, one adenoma was added to the control group. An animal with the least effect on the overall risk set was selected (animal 43 with survival to day 735). Again, this choice would be least favorable to the Sponsor.

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4. In female mice, the tumor reanalysis had no effect on tumor incidence and hence results are unchanged.

Using these imputed values allows one to use the poly-k methodology and adjust for differences in mortality. Note that in cases 2. and 3. above, these imputations will increase uncertainty and thus actual variance in results. But it was felt that this increase in "noise" would be difficult to assess, should be conservative, and did not warrant actual adjustment of results.

In the following tables, for each species by gender the number of animals analyzed and used in the statistical tests is presented first. The entry for each tumor is preceded by the adjusted number of animals at risk for that tumor. It seems clear that an animal that dies early without a tumor reduces the size of the risk set for that getting that particular umor. The poly-k test down weights such animals, and the sum of these poly-k weights seems to be a better estimate of the number of animals at risk of getting that tumor. This sum is given in the row labeled "Adjusted # at risk". Tumor incidence is presented next, with the significance levels of the tests of trend, and the results of pairwise tests between the high, high-medium, low-medium, and low dose groups versus vehicle. For this analysis, incidence in the vehicle group is used to assess background tumor incidence, and thus whether a tumor is considered to be rare (background incidence <1%) or common. Finally, the significance level of the original Cochran-Armitage test of trend over all five dose groups, with no poly-k adjustment for mortality, is presented under the heading for trend, below the corresponding poly-k trend result. Please note that the poly-k results are strongly recommended, but the Cochran-Armitage test does not depend upon the imputed incidence cited in 2. and 3. above.

To adjust for the multiplicity of tests the so-called Haseman-Lin-Rahman (HLR) rules are often applied. That is, when testing for trend over dose groups and the difference between the highest dose group with a control group, to control the overall Type I error rate to roughly 10% for a standard two species, two sex study, one compares the unadjusted significance level of the trend test to 0.005 for common tumors and 0.025 for rare tumors, and the pairwise test to 0.01 for common tumors and 0.05 for rare tumors. Using these adjustments for other tests, like testing the comparisons between the low, medium, and medium-high dose groups versus vehicle can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the nominal 10% rate.

Table Add. 2. Kidney Tumors in Rats

Gender/Tumor	Incidence					Significance Levels				
	Veh	Low	Med-ium	MedHi	High	Trend	Hi vs Veh	MedHi vsVeh	Medvs Veh	Low vsVeh
Male Rats										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.7	25.9	22.2					
RENAL TUBULE- ADENOMA	0	0	1	1	0	.3026	.	.3378	.4494	.
Cochran-Armitage test						.4802				

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Table Add. 2. (cont.) Kidney Tumors in Rats

Gender/Tumor	Incidence					Significance Levels				
	Veh	Low	Med-ium	MedHi	High	Trend	Hi vs Veh	MedHi vsVeh	Medvs Veh	Low vsVeh
Female Rats										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.9	53.2	48.7	48.1	52.0					
RENAL TUBULE- ADENOMA	1	0	1	0	1	.5055	.7429	1	.7222	1
Cochran-Armitage test						.5200				
Adjusted # at risk	54.9	53.2	48.7	48.1	52.0					
Overall Adenoma	1	0	1	0	2	.2330	.4857	1	.7222	1
Cochran-Armitage test						.2422				
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
RENAL TUBULE-CARCINOMA	0	0	0	0	1	.2008	.4857	.	.	.
Cochran-Armitage test						.2000				
Adjusted # at risk	54.9	53.2	48.7	48.1	52.0					
Overall Adenoma/Carc.	1	0	1	0	3	.0923	.2947	1	.7222	1
Cochran-Armitage test						.0969				

In either gender in rats, none of these tests in kidneys achieved the nominal 0.05 level of statistical significance, let alone any of the the multiplicity adjusted HLR levels. One female rat in the high dose group was identified with a “Pelvis- Transitional Epithelium Adenoma” in the kidney. It is added to the overall adenomas, but the latter still shows no statistically significant tests of trend or pairwise differences.

Table Add. 3. Kidney Tumors in Mice

Gender/Tumor	Incidence					Significance Levels				
	Veh	Low	Med-ium	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
Male Mice										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	48.7	22.1					
Adenoma	2	2	0	5	3	.0163	.1811	.2264	1	.7286
Cochran-Armitage test						.1373				
Adjusted # at risk	47.5	52.1	50.7	47.7	22.0					
Carcinoma	0	0	2	4	3	.0015	.0265	.0585	.2631	.
Cochran-Armitage test						.0280				
Adjusted # at risk	47.5	52.1	50.7	49.3	22.8					
Adenoma/Carcinoma	2	2	2	8	5	.0008	.0298	.0525	.7145	.7286
Cochran-Armitage test						.0407				
Female Mice										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.1	51.8	29.1					
Adenoma	0	0	0	2	4	.0002	.0117	.2248	.	.
Cochran-Armitage test						.0024				
Adjusted # at risk	56.6	52.9	52.1	51.8	27.6					
Carcinoma	0	0	0	0	1	.1134	.3253	.	.	.
Cochran-Armitage test						.2000				
Adjusted # at risk	56.6	52.9	52.1	51.8	29.1					
Adenoma/Carcinoma	0	0	0	2	4	.0002	.0117	.2248	.	.
Cochran-Armitage test						.0024				

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In male mice, using the HLR rules, the tests of trend in carcinoma and pooled adenoma and carcinoma were statistically significant ($p = 0.0015 < 0.025$ and $p = 0.0008 < 0.005$, respectively). Continuing in male mice, the pairwise test between the high dose and vehicle in carcinomas would be statistically significant ($p = 0.0265 < 0.05$) while the pairwise test between the high dose and vehicle pooled adenoma and carcinoma would be somewhat close to statistically significant ($p = 0.0298 > 0.01$). In female mice, the tests of trend in carcinoma and pooled carcinoma and adenoma of the kidneys were identical (since the only animal with a carcinoma of the kidneys also was identified with an adenoma). Both tests were statistically significant (both $p = 0.0002 < 0.025$ and $p = 0.0117 < 0.025$, respectively).

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/s/

STEVEN F THOMSON
02/20/2013
Addendum to Statistical Carcinogenicity Review

KARL K LIN
02/21/2013
Concur with review

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

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA:	**204063**
Drug Name:	**BG00012 (Dimethyl Fumarate) delayed action capsule**
Indications:	**Multiple Sclerosis**
Applicants:	**Sponsor: Biogen Idec, Inc.** **14 Cambridge Center, Cambridge, MA 02142** (b) (4)
Date(s):	**Submitted: 27 February 2012** **To Reviewer: 30 July 2012**
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Biometrics Division:	**Division 6**
Statistical Reviewer:	**Steve Thomson**
Concurring Reviewers:	**Karl Lin, Ph.D.**
Medical Division:	**Neurology Products**
Toxicologist Team:	**Melissa Banks-Muckenfuss, Ph.D.**
Project Manager:	**Nicole Bradley, Pharm.D.**

Keywords: Bayesian analysis, Carcinogenicity, Cox regresson, Kaplan-Meier product limit, Survival analysis, Trend test

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1. EXECUTIVE SUMMARY

Reports and data from two studies, in rats and mice, were provided. [redacted] (b) (4) The study report and data for the rat study were originally submitted with IND 73061 from the same Sponsor. The results of the FDA analysis of the rat study are summarized in the statistical carcinogenicity review dated 22 April 2008. Although the current analysis of the rat study is slightly different, only the new mouse study contains completely new results.

According to the mouse report provided by the Sponsors: "The purpose of this study was to evaluate the potential carcinogenicity of BG00012 following once daily oral gavage to CD-1 mice for at least 104 weeks and toxicokinetics following once daily oral gavage for 180 days." (page 18 of report) The objective of the rat report is expressed similarly. Each study included five treatment groups, as described below.

1.1. Conclusions and Recommendations

The Sponsor describes the drug vehicle as hydroxypropylmethylcellulose (HPMC) or hypromellose (3,500-5,600 cps), 0.8% w/v in reverse osmosis deionized water. For each study, in each gender, there are five treatment groups. Animals were dosed once daily by oral gavage. Gross aspects of the study designs for the main study animals are summarized in Tables 1 and 2 below:

Table 1. Design of Rat Study (75 animals per main study group/gender)

Treatment Group	Vehicle or Test Article	BG00012 Dosage (mg/kg/day)	Dose Volume (mL/kg)	Dosing Concentration[a]
1. Vehicle	HPMC[a]	0	10	0
2. Low	BG00012	25	10	2.5
3. Medium	BG00012	50	10	5
4. Med-High[b]	BG00012	100	10	10
5. High[b]	BG00012	150	10	15

[a] Hydroxypropylmethylcellulose or Hypromellose (3,500-5,600 cps), 0.8% w/v in reverse osmosis deionized water.
[b] Due to mortality, the High dose group (150 mg/kg/day, Group 5) males were terminated during Week 86 and the Medium-High (100 mg/kg/day,Group 4) males were terminated during Week 88.

Table 2. Design of Mouse Study (75 animals per main study group/gender)

Treatment Group	Vehicle or Test Article	BG00012 Dosage (mg/kg/day)	Dose Volume (mL/kg)	Dosing Concentration[a]
1. Vehicle[a]	HPMC	0	10	0
2. Low	BG00012	25	10	2.5
3. Medium	BG00012	75	10	7.5
4. Med-High	BG00012	200	10	20
5. High	BG00012	600/400[b]	10	60/40[b]

[a] Hydroxypropylmethylcellulose or Hypromellose (3,500-5,600 cps), 0.8% w/v in reverse osmosis deionized water.
[b] Due to mortality observed in the high-dose group, beginning on Day 9,.the dose level for Group 5 was decreased from 600 mg/kg/day to 400 mg/kg/day (40 mg/mL) . For tests it is treated as dosage at 400 mg/kg/day.

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More detailed descriptions of the studies are provided in Section 3.2.1 and 3.2.2 below. In this report the vehicle group is sometimes referred to as the "HPMC" or "control group" while the other dose groups are referred to as "actual dose groups", and, purposes of assessing trend, the Vehicle, Low, Medium, Medium-High, and High dose groups (i.e., Groups 1-5) as "treated groups." Simple summary life tables in mortality are presented in the report in these sections of this report. Also, because early very high mortality in the mice study, on day 9 dosage was reduced from 600 mg/kg/day to 400 mg/kg/day. On all tests used in the FDA analysis it is treated as the 400 mg/kg/day.

In Appendix 1, Figures A.1.1 and A.1.2 for rats display Kaplan-Meier estimated survival curves for each study group for each gender. Two sets of plots are displayed for mice. Figures A.1.3 and A.1.4 for mice display the Kaplan-Meier estimated survival curves for gender using the original data while Figures A.1.5 and A.1.6 display the corresponding plots deleting those animals that died before day 9, because of initial high mortality. Results of tests on survival in rats and mice are summarized below:

Table 3. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Rat Study

Hypothesis Tested	Males [a]		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Rat Homogeneity over Groups 1-5	< 0.0001	< 0.0001	0.4421	0.2737
Homogeneity over Groups 1-4	< 0.0001	< 0.0001	0.2904	0.1602
Homogeneity over Groups 1-3	0.0292	0.0153	0.2090	0.1594
No trend over Groups 1-5	< 0.0001	< 0.0001	0.3427	0.2033
No trend over Groups 1-4	< 0.0001	< 0.0001	0.1345	0.0389
No trend over Groups 1-3	0.0169	0.0119	0.1386	0.0734
No Difference Between Groups 1 vs 5	< 0.0001	< 0.0001	0.4943	0.3229
No Difference Between Groups 1 vs 4	< 0.0001	< 0.0001	0.2503	0.0931
No Difference Between Groups 1 vs 3	0.0180	0.0142	0.1205	0.0613

[a] Due to mortality, the High dose group (150 mg/kg/day, Group 5) males were terminated during Week 86 and the Medium-High (100 mg/kg/day,Group 4) males were terminated during Week 88.

From Figure A.1.1, in male rats, the HPMC vehicle and Low dose group are largely intertwined, with the highest survival, while the Medium dose group has the next highest survival, and the Medium-High and High dose groups having the lowest but quite close survival over the study period. Note these groups were sacrificed early due to low survival, but in the analysis such deaths are considered as censored times, not deaths. This is sufficient to cause significant tests of lack of homogeneity, no trend, and no difference between the highest doses and vehicle in groups 1-4 and groups 1-5 (all 12 $p < 0.0001$, usually much less than the 0.0001 level). Even the seperation of the Medium dose group from the Vehicle and Low dose is sufficient to result in consistently statistically significant results (all six $p \leq 0.0292$). The situation in female rats is quite different. From Figure A.1.2, in female rats, although the HPMC vehicle seems to have slightly highest survival, the survival curves of the other four dose groups are generally quite close and are largely intertwined. While this is not strong evidence of no

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differences, it is evidence of no strong differences when comparing all five groups plus the High dose to HPMC (all six $p \geq 0.2033$). Results of the tests using treatment subgroups 1-4 and 1-3 are primarily included to match those for male rats. Note that the Wilcoxon test is more sensitive to early differences in survival and the corresponding test of lack of trend is barely statistically significant at the usual level (i.e., Wilcoxon $p = 0.0389$), but this conclusion is not supported by the Logrank test ($p = 0.1386$).

Table 4. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Mouse Study

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Mouse Homogeneity over Groups 1-5 [a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Homogeneity over Groups 1-4	0.1115	0.3129	0.4603	0.5208
No trend over Groups 1-5 [a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
No trend over Groups 1-4	0.1119	0.3181	0.1847	0.2348
No Difference Between Groups 1 vs 5[a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
No Difference Between Groups 1 vs 4	0.4876	0.7711	0.1099	0.1322

[a] Printed P-value bounds are identical whether one conditions on survival to day 9 or not.

Figures A.1.3 and A.1.4, in Appendix 1, display the gender specific survival curves over the five dose groups in mice. Note that in both genders the High dose group is clearly separated from the remaining dose groups. This is sufficient to result in the highly statistically significant tests of homogeneity, lack of trend, and no difference between the High dose and the vehicle dose group (for each gender all six $p < 0.0001$). One might speculate that the separation of the High dose from the other dose groups may be due solely to the early deaths in the High dose group, reflected in the initial drop in the Kaplan-meier curve apparent in the figures. Figures A.1.5 and A.1.6 in the appendix display the survival curves over the five dose groups conditional upon animals surviving to at least until day 9. Even with this criterion, the High dose remains seperated from the remaining dose groups. While the actual values of the significance levels for the tests of homogeneity and trend over groups 1-5, and the pairwise comparison between the High dose and vehicle are larger (and thus less statistically significant), the printed values remain the same (i.e., all tests still have all six $p < 0.0001$).

In both sets of plots, for both genders, the survival curves for the dose groups 1-4 are more or less closely intertwined, but with much higher survival than that in the High dose group. This is consistent with the tests of survival completely deleting the High dose group, i.e., none of the tests of homogeneity, lack of trend, and no difference between the next highest dose and the Vehicle dose group were particularly statistically significant, at least at the usual 0.05 level (Males: all six $p \geq 0.1115$, Females all six $p \geq 0.1009$). This suggests that differences in survival are largely due to differences in the High dose from the remaining dose groups.

Of course in a carcinogenicity study, primary interest is on the occurrence of cancers. The statistical analysis of tumors compares tumor incidence over dose groups. Complete tumor

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incidence tables for each organ listed by the Sponsor in the submitted data sets and those combined by this reviewer are provided in Tables A.2.3 through A.2.6 in Appendix 3. For each species by gender by organ the number of animals analyzed and used in the statistical tests is presented first. The tumor incidence for each organ is presented next, with the significance levels of the tests of trend, and the results of pairwise tests between the high, medium, and low dose groups. These statistical tests are supposed to be conditioned on the animals actually evaluated, ignoring those not analyzed. In other words, animals not analyzed are treated as being not at risk.

To adjust for the multiplicity of tests the so-called Haseman-Lin-Rahman rules discussed in Section 1.3.1.5, below, are often applied. That is, when testing for lack of trend in carcinogencity over dose and no difference between the highest dose group with a control group using Peto or poly-k tests, to control the overall Type I error rate to roughly 10% for a standard two species, two sex study, one compares the unadjusted significance level of the trend test to 0.005 for common tumors (incidence > 1%) and 0.025 for rare tumors, and the pairwise test to 0.01 for common tumors and 0.05 for rare tumors. As also discussed in section 1.3.1.5, `employing these adjustments for other than the overall trend and the comparison between the High dose group and vehicle can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than this nominal rate.

The following tables, Tables 5-8, display those organ tumor combinations that had at least one comparison statistically significant at the "usual" 0.05 level (but not adjusted for multiplicity). . As discussed in section 1.3.1.3 below, the adjusted number at risk seems to be a more appropriate denominator than the actual number evaluated when assessing tumor rates.

Table 5. Potentially Statistically Significant Neoplasms in Male Rats

organ tumor	Incidence Veh	Low	Med	MedHi	High	Significance Levels Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
BRAIN										
# Evaluated	73	75	75	75	74					
Adjusted # at risk	49.5	48.6	40.3	25.3	23.1					
CEREBRUM-GRANULAR CELL TMR	0	0	0	0	2	.0149	.0990	.	.	.
KIDNEYS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.7	25.9	25.2					
RENAL TUBULE- ADENOMA	0	0	1	1	4	.0006	.0110	.3378	.4494	.
LIVER										
# Evaluated	75	74	75	75	75					
Adjusted # at risk	50.1	49.9	42.2	25.3	22.2					
Hepato. Adenoma/Carcinoma	2	8	5	0	0	.9542	1	1	.1520	.0426
PARATHYROID										
# Evaluated	68	64	70	71	70					
Adjusted # at risk	44.5	42.8	38.7	23.8	21.5					
ADENOMA	0	0	1	0	2	.0251	.1010	.	.4634	.
Adjusted # at risk	44.5	42.8	38.7	23.8	22.3					
Adenoma, any	0	0	1	0	3	.0049	.0337	.	.4634	.

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Table 5. (cont.) Potentially Statistically Significant Neoplasms in Male Rats

organ tumor	Incidence Veh	Low	Med	MedHi	High	Trend	Significance Levels Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
SKIN										
# Evaluated	75	74	75	74	75					
Adjusted # at risk	50.8	51.2	41.4	28.7	27.4					
KERATOACANTHOMA	8	8	9	7	9	.0256	.0736	.2494	.3236	.6237
Adjusted # at risk	49.6	48.9	40.3	24.7	23.6					
SUBCUT TISS.-FIBROSARCOMA	0	1	0	0	2	.0357	.0990	.	.	.4948
Adjusted # at risk	51.2	52.1	42.1	30.9	29.7					
Sq.Cell Pap./Carc./Kerato.	11	11	10	10	12	.0136	.0532	1825	.4950	.6147
STOMACH										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	49.2	50.1	60.0	61.3					
NONGLAND.- SQUAMOUS CELL CARCINOMA	0	5	18	51	58	<.0001	<.0001	<.0001	<.0001	.0281
Adjusted # at risk	49.6	53.5	51.4	55.7	58.4					
NONGLAND.- SQ. CELL PAP.	0	22	24	46	49	<.0001	<.0001	<.0001	<.0001	<.0001
Adjusted # at risk	49.6	53.5	55.3	70.9	71.1					
Nongland.Sq.Cell Pap./Carc.	0	22	34	68	70	<.0001	<.0001	<.0001	<.0001	<.0001
TESTES										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	50.3	49.0	41.4	30.2	32.8					
INTERSTITIAL CELL- ADENOMA	3	3	2	9	17	<.0001	<.0001	.0053	.7514	.6415
Adjusted # at risk	49.6	48.6	40.3	25.3	23.5					
INTERSTITIAL CELL- ADENOMA, BILATERAL	0	0	0	0	2	.0149	.0990	.	.	.
Adjusted # at risk	50.3	49.0	41.4	30.2	34.0					
Intersit. Adenoma, any	3	3	2	9	19	<.0001	<.0001	.0053	.7514	.6415

In male rats, even adjusting for multiplicity (please see Section 1.3.1.4), the tests of no trend and no differences in all pairwise comparisons of the four treated groups to HPMC vehicle in nonglandular squamous cell papilloma and pooled papilloma and carcinoma were all highly statistical significant (all $p<0.0001$, with both trend < 0.025 and pairwise tests < 0.05 since the tumors are categorized as rare). The same holds for nonglandular squamous cell carcinoma except that the comparison between the low dose group and vehickle was just statistically significant ($p = 0.0281 < 0.05$). The tests of trend and pairwise differences between the high dose and vehicle in interstial cell adenoma of the testes were both highly statistically significant ($p < 0.0001 < 0.005$ and 0.1, respectively, since the tumor would be categorized as common). Accepting the increase in probable error from including other tests, the pairwise comparison between the medium dose group and vehicle would also be classified as statistically significant ($p = 0.0053 < 0.01$). Since adding the interstial cell carcinoma only affects incidence in the high dose group, the tests for pooled interstitial cell adenoma and carcinoma are, at least to the printed significance levels, identical to those for carcinoma are identical to those for interstial cell adenoma alone. In this organ, the simple test of trend in interstial cell bilateral adenoma was also statistically significant ($p = 0.0149 < 0.025$), though not extremely. The test of trend in renal tubule adenoma of the kidneys was also statistically significant ($p = 0.0006 < 0.025$), as were the tests of granular cell tumor of the brain ($p = 0.0149 < 0.025$) and the test of pooled adenomas of the parathyroid ($p = 0.0049 < 0.025$). The test of trend in simple adenoma of the

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parathyroid was close to statistical significance (p= 0.0251 > 0.025). No other test achieved the multiplicity adjusted levels of statistical significance.

Table 6. Potentially Statistically Significant Neoplasms in Female Rats

organ tumor	Incidence Veh	Low	Med	MedHi	High	Significance Levels Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
CAVITY, ABDOMINAL										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.9					
HISTIOCYTIC SARCOMA	0	0	0	0	2	.0397	.2335	.	.	.
KIDNEYS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.9					
RENAL TUBULE-CARCINOMA	0	0	0	2	4	.0015	.0523	.2190	.	.
Adjusted # at risk	54.9	53.2	48.7	48.1	52.4					
Renam Tub. Adenoma/Carc.	1	0	0	2	5	.0033	.0942	.4555	1	1
MAMMARY GLAND										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	57.8	56.6	52.7	50.3	56.8					
CARCINOMA	10	13	13	8	19	.0688	.0372	.6800	.2364	.3036
STOMACH										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	49.6	56.6	65.8					
NONGLANDULAR-SQUAMOUS CELL CARCINOMA	0	1	4	30	48	<.0001	<.0001	<.0001	.0479	.4953
Adjusted # at risk	54.8	55.0	53.7	56.4	61.2					
NONGLANDULAR- SQUAMOUS CELL PAPILLOMA	0	11	21	31	24	<.0001	<.0001	<.0001	<.0001	.0003
Adjusted # at risk	54.8	55.0	54.3	61.1	69.3					
Nongland. Sq, Pap./Carc.	0	11	23	48	58	<.0001	<.0001	<.0001	<.0001	.0003
VAGINA										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	52.2					
Endo. Stromal polyp/sarcoma	0	0	0	1	2	.0314	.2383	.4706	.	.

Results in female rats are rather similar. In female rats, the tests of trend and all pairwise comparisons between the high, medium high, and medium dose groups with vehicle in nonglandular squamous cell papilloma and pooled papilloma and carcinoma were all highly statistical significant (all $p < 0.0001$, with both trend < 0.025 and pairwise tests < 0.05) even adjusting for multiplicity. For both of these the comparison between the low dose and vehicle was also statistically significant (for both tumors, $p = 0.0003 < 0.05$). These results also hold for the tests of trend and pairwise comparisons between the high and medium high dose groups in nonglandular squamous cell carcinoma ($p < 0.0001$, with both trend < 0.025 and pairwise tests < 0.05). The comparison between the medium dose and vehicle was barely statistically significant ($p = 0.0479 < 0.05$). The test of trend in renal tubule carcinoma of the kidneys was also statistically significant ($p = 0.0015 < 0.025$), as was the test of pooled adenoma and carcinoma ($p = 0.0033 < 0.005$). Again, no other test achieved the multiplicity adjusted levels of statistical significance, although several were somewhat close.

A Bayesian analysis of carcinogenicity in rats, as originally presented in the review for IND 73061, is given in Appendix 3. This Bayesian analysis is also generally consistent with the

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analysis above. Although it is hardly surprising given the incidence, in both male and female rats the posterior probability that there is no effect of increasing dose on nonglandular squamous cell papilloma and carcinoma are both essentially zero to a number of decimal places. In females, the posterior probabilities of no differences between the high dose group and controls in these tumors is similar, as well as for nonglandular squamous cell carcinoma in males. In males the posterior probability that there is no difference between nonglandular squamous cell papilloma is actually 0.0002 (so the estimated probability that there is difference is about 1 - 0.0002 = 0.9998), i.e., almost certainly. In male rats the estimated posterior probability that there is no trend in interstitial cell adenoma in the testes is also 0.0 to a number of decimal places, while the corresponding probability that there is no difference between the high dose group and control is 0.091 (so the estimated probability of a difference is 1 - 0.091 = 0.909). In male rats the estimated posterior probability that there is no trend in renal tubule adenoma in the kidneys is essentially 0.086 (so the probability there is a difference in 1 - 0.086 = 0.914), while in female rats the estimated posterior probability that there is no trend in renal tubule carcinoma in the kidneys is essentially 0.0074 (with 1- 0.0074 = 0.9926). More details are included in the appendix.

Results in mice are given below:

Table 7. Potentially Statistically Significant Neoplasms in Male Mice

organ tumor	Incidence Veh	Low	Med	MedHi	High	Significance Levels Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
KIDNEY										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	48.7	22.1					
Adenoma	1	2	0	5	3	.0074	.0922	.1067	1	.5382
Adjusted # at risk	47.5	52.1	50.7	49.3	22.8					
Adenoma/Carcinoma	1	2	2	8	5	.0003	.0109	.0179	.5234	.5382
Adjusted # at risk	47.5	52.1	50.7	47.7	22.0					
Carcinoma	0	0	2	4	3	.0015	.0265	.0585	.2631	.
LUNG WITH BRONCHI										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	50.0	53.9	52.5	51.4	23.2					
Bronchiolo-Alveolar Adenocarcinoma	6	6	5	11	5	.0411	.2292	.1541	.7598	.6607
STOMACH										
# Evaluated	74	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	47.1	23.0					
Leiomyosarcoma	0	0	0	0	3	.0010	.0324	.	.	.
Adjusted # at risk	47.5	52.5	51.1	50.0	30.5					
Papilloma	0	1	3	12	14	<.0001	<.0001	.0002	.1369	.5253
Adjusted # at risk	47.5	52.4	50.6	47.7	22.3					
Squamous Cell Carcinoma	0	1	0	2	6	<.0001	.0006	.2473	.	.5253

As with rats, in male mice, the test of trend and pairwise comparisons between the High dose group with HPMC Vehicle in papilloma of the stomach was highly statistical significant (both $p < 0.0001$, with trend < 0.025 and pairwise test < 0.05) even adjusting for multiplicity. The pairwise test between the Medium High dose and vehicle was also statistically significant ($p = 0.0002 < 0.05$). The tests of trend and pairwise comparison of the High dose to vehicle in

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terms of squamous cell carcinoma of the stomach were also statistically significant ($p < 0.0001 < 0.025$ and $p = 0.0006 < 0.05$, respectively), as were the tests of Leiomysarcoma ($p < 0.0010 < 0.025$ and $p = 0.0324 < 0.05$, respectively). In the kidneys the tests of trend in carcinoma and pooled carcinoma and adenoma were also statistically significant ($p = 0.0015 < 0.025$ and $0.0003 < 0.005$, respectively). Again, although a couple of tests were close, no other test achieved the multiplicity adjusted levels of statistical significance.

Table 8. Potentially Statistically Significant Neoplasms in Female Mice

organ tumor	Incidence Veh	Low	Med	MedHi	High	Significance Levels Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
HEMOLYMPHORETICULAR										
# Evaluated	23	18	20	19	12					
Adjusted # at risk	15.7	12.4	14.6	10.3	6.0					
Leukemia	1	0	0	0	2	.0269	.1404	1	1	1
KIDNEY										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.1	51.8	29.1					
Adenoma	0	0	0	2	4	.0002	.0117	.2248	.	.
Adjusted # at risk	56.6	52.9	52.1	51.8	29.1					
Adenoma/Carcinoma	0	0	0	2	4	.0002	.0117	.2248	.	.
LUNG WITH BRONCHI										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	58.6	56.9	54.6	55.8	31.8					
Bronchiolo-Alv. Adenoma	12	14	9	20	10	.0372	.1714	.0503	.7839	.3725
STOMACH										
# Evaluated	75	75	74	75	75					
Adjusted # at risk	56.6	52.9	52.0	51.8	28.2					
Fibrosarcoma	0	0	0	0	2	.0134	.1084	.	.	.
Adjusted # at risk	56.6	52.9	52.0	51.8	29.9					
Leiomyoma/Leiomysarcoma	0	0	0	0	3	.0016	.0370	.	.	.
Adjusted # at risk	56.6	52.9	52.0	51.8	29.9					
Leiomyosarcoma	0	0	0	0	3	.0016	.0370	.	.	.
Adjusted # at risk	56.6	52.9	52.6	53.4	37.0					
Papilloma	1	0	3	6	16	<.0001	<.0001	.0483	.2815	1
Adjusted # at risk	56.6	53.2	52.2	52.7	33.1					
Squamous Cell Carcinoma	0	1	1	5	12	<.0001	<.0001	.0233	.4815	.4862
UTERUS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	57.4	56.3	55.1	54.4	30.3					
Endometrial Stromal Polyp	6	9	14	11	8	.0597	.0529	.1197	.0340	.2776

As with rats, results in female mice are similar to those in male mice. The tests of trend and pairwise comparison between the high dose group with vehicle in squamous cell carcinoma of the stomach was highly statistical significant (both $p < 0.0001$, with trend < 0.025 and pairwise test < 0.05) even adjusting for multiplicity. Results are similar for papilloma of the stomach with a significant test of trend ($p < 0.0001 < 0.005$) and a comparison between the High dose and vehicle ($p < 0.0001 < 0.01$). The comparison to vehicle of the Medium High dose was also barely statistically significant ($p = 0.0233 < 0.025$) in stomach squamous cell carcinoma. The tests of trend and pairwise comparison of the high dose to vehicle in terms of Leiomysarcoma were statistically significant ($p = 0.0016 < 0.025$ and $p = 0.0370 < 0.05$, respectively). In the kidneys the tests of trend in carcinoma and pooled carcinoma and adenoma were identical, and were also statistically significant (both $p = 0.0002 < 0.025$ and $0.0117 <$

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0.025, respectively). Again, although several were close, no other test achieved the multiplicity adjusted levels of statistical significance.

Complete incidence tables in each species by gender combination are presented in Appendix 2.

1.2. Brief Overview of the Studies

This submission had a rat study:

Study P00012-04-11 A Two Year Oral (Gavage) Carcinogenicity Study in Rats with BG00012,

and a very similar, mouse study:

Study P00012-05-03 Two-Year Oral (Gavage) Carcinogenicity Study in Mice with BG00012.

(b) (4) Fairly detailed descriptions of these studies are available in Sections 3.2.1 and 3.2.2, below.

1.3. Statistical Issues and Findings

1.3.1. Statistical Issues

In this section, several issues, typical of statistical analyses of these studies, are considered. These issues include details on the survival analyses, tests on tumorigenicity, multiplicity of tests on neoplasms, and the validity of the designs.

1.3.1.1. Survival Analysis:

The survival analyses presented here are based on both the log rank test and the Wilcoxon test comparing survival curves. The log rank tests tend to put higher weight on later events, while the Wilcoxon test tends to weight events more equally, and thus is more sensitive to earlier differences in survival. The logrank test is most powerful when the survival curves track each other, and thus the hazards, i.e., the conditional probability of the event in the next infinitesimal interval, would be roughly proportional. This is the test used by the Sponsor in both studies and seems to be the test usually recommended by statisticians. In the FDA analysis, both tests were used to test both homogeneity of survival among the treatment groups and the effect of dose on trend in survival. Appendix 1 reviews the specific animal survival analyses in more detail. The results of the Sponsor's analysis are summarized in Sections 3.2.1.1 and 3.2.2.1.

1.3.1.2. Multiplicity of Tests on Survival:

Using both the logrank and Wilcoxon tests, for each gender in rats there are 18 tests of survival differences. In mice there are 12 log rank and Wilcoxon tests of survival in each

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gender. Assuming tests within each set were independent, but that there actually were no differences in survival across groups, the probability of at least one statistically significant result, at the usual 0.05 level, for each gender inn rats is about 0.60 in rats, and about 0.46 in mice. These bounds assume the tests are independent, which they clearly are not, but these values can give bounds on the probability of at least result significant at the 0.05 level. This can give some idea of the possible price paid for the multiplicity of hypothesis tests in the statistical frequentist paradigm.

1.3.1.3. Tests on Neoplasms:

The Sponsor's analyses of tumorigenicity are Peto tests (Peto *et al*, 1980). The Cochran-Armitage test is designed to test for trend or pairwise differences in event incidence, weighted by dose. However it ignores differential mortality across dose groups. Inspecting a large number of studies, Bailer and Portier (1988) noted that survival time seemed to fit a Weibull distribution, generally with a shape parameter of between 1 and 5, with 3 a typical value. With t_{max} denoting the maximal time to terminal sacrifice and t_{obs} the time to death of the animal, they propose weighting the animal by $(t_{obs}/t_{max})^k$, so that an animal that survives for say 52 weeks in 104 week study without the tumor being analyzed is counted as $(1/2)^k$ of an animal. For k = 3, that means that animal would count as 1/8 of an animal. Further, the k = 3 specification seems to represent tumor incidence where some animals are perhaps more sensitive and respond earlier to the insult than the remining animals. Under this structure time to incidence would tend to follow a cubic expression. Thus an animal with the specific tumor being studied or who survives to terminal sacrifice without the tumor will be given a weight of 1 when counting the number of animals at risk. However, animals that die early without the tumor are down weighted when counting the number of animals in the risk set for that specific tumor. With differential mortality, as observed in male rats, this can mean a substantial reduction in the size of that risk set. Note this seems to be an appropriate adjustment for dose groups that are terminated early as in the rats study. In the tumor incidence tables the effective size of the risk set for each tumor is listed in the row labeled "Adjusted # at risk", and seems to be a more appropriate denominator when comparing incidence rates than the simple unadjusted number evaluated.

Note that the report of the Society of Toxicological Pathology "town hall" meeting in June 2001 recommeded the use of this poly-k modification of the Cochran-Armitage tests of trend over the corresponding Peto tests.

1.3.1.4. Multiplicity of Tests on Neoplasms:

Frequentist hypothesis testing involves accepting or rejecting hypotheses about the parameters of interest on the basis of the values of some statistic. If one does not provide some sort of multiplicity adjustment to the significance level, the chances of rejecting one or more true null hypothesis increases as the number of such tests increases. To avoid this, it is common to adjust for multiplicity in hypothesis testing resulting in an adjustment in experiment-wise Type I error (i.e., the probability of rejecting a true null hypothesis and thus concluding there is an effect when in fact there is none). Based on his extensive experience with such carcinogenicity analyses in standard laboratory rodents, for pairwise tests between the highest dose group and controls in two species, Haseman (1983) claimed that for a roughly 0.10 (10%)

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overall false positive error rate, rare tumors should be tested at a 0.05 (5%) level, and common tumors (with a historical control incidence greater than 1%) at a 0.01 level. Similarly, Lin and Rahman (1998) showed that tests of trend over all dose groups should be tested at about a 0.025 level for rare tumors and 0.005 for common tumors. This approach is intended to balance both Type I error and Type II error (i.e., the error of concluding there is no evidence of a relation to tumorgenicity when there actually is such a relation). Because of the possibility of genetic drift, or differences in treatment, in this study the vehicle group is used to determine if the tumor is classified as rare or common.

Significance levels of the pairwise tests between the Vehicle group and the other dose groups are also provided. Including these tests can be expected to increase the overall type I error rate to some level above the rough 10% level associated with the Haseman-Lin-Rahman multiplicity adjustment cited above, possibly considerably larger.

1.3.1.5. Validity of the Designs:

When determining the validity of designs there are two key points:

1) adequate drug exposure,
2) tumor challenge to the tested animals.

1) is related to whether or not sufficient animals survived long enough to be at risk of forming late-developing tumors and 2) is related to the Maximum Tolerated Dose (MTD), designed to achieve the greatest likelihood of tumorigenicity.

Lin and Ali (2006), quoting work by Haseman, have suggested that in standard laboratory rodent species, a survival rate of about 25 animals, out of 50 or more animals (i.e. 50%), between weeks 80-90 of a two-year study may be considered a sufficient number of survivors as well as one measure of adequate exposure. Note that as a percentage of the High dose group animals that survived to week 91, this criterion does seem to be satisfied in female rats, but clealy not in male rats, or somewhat less clearly in both mouse genders, even if one adjusts for early mortality during the short 600 mg/kg/day dosing period (Please see Tables 17 and 18 on pages 21 and 22, and Tables 25 and 26 on page 31). Like the other comments in this section this requires the expertise of the toxicologist, but may suggest that the MTD was exceeded in at least three of four the species-gender combinations.

The mean weight values used to derive differences and ratios in the following tables were taken directly from the Sponsor's reports (Rat Appendix 8, pages 2661-2758, and Mouse Appendix 8, pages 2228-2324). The change from baseline in the table below is the simple difference between the means at the specified dates, and thus animals that die are only counted at the study initiation, not at the end of the study.

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Table 9. Mean Weights and Changes (in g) in Male Rats

Dose Group	Dose mg/kg/day	Week		Change from Baseline	% change relative to vehicle	Week	Change from baseline	% change relative to vehicle
		1	85			104		
1. Vehicle	0	219	772	553		726	507	
2. Low	25	217	744	527	95.3%	697	480	94.7%
3. Medium	50	216	750	534	96.6%	668	452	89.2%
4. Med-High	100	217	643	426	77.0%			
5. High	150	216	640	424	76.7%			

Table 10. Mean Weights and Changes (in g) in Female Rats

Dose Group	Dose mg/kg/day	Week		Change from baseline	% change relative to vehicle
		1	104		
1. Vehicle	0	164	493	329	
2. Low	25	164	498	334	101.5%
3. Medium	50	162	500	338	102.7%
4. Med-High	100	164	465	301	91.5%
5. High	150	164	432	268	81.5%

Table 11. Mean Weights and Changes (in g) in Male Mice

Dose Group	Dose mg/kg/day	Week		Change from baseline	% change relative to vehicle
		1	104		
1. Vehicle	0	31.2	40.0	8.8	
2. Low	25	30.9	39.7	8.8	100.0%
3. Medium	75	31.3	40.7	9.4	106.8%
4. Med-High	200	31.3	39.4	8.1	92.0%
5. High	600/400	31.4	38.7	7.3	83.0%

Table 12. Mean Weights and Changes (in g) in Female Mice

Dose Group	Dose mg/kg/day	Week		Change from baseline	% change relative to vehicle
		1	84		
1. Vehicle	0	25.5	36.7	11.2	
2. Low	25	25.3	35.9	10.6	94.0%
3. Medium	75	25.6	36.9	11.3	100.9%
4. Med-High	200	25.4	35.6	10.2	91.1%
5. High	600/400	25.8	36.3	10.5	93.8%

Chu, Ceuto, and Ward (1981), citing earlier work by Sontag *et al* (1976) recommend that the MTD "is taken as 'the highest dose that causes no more than a 10% weight decrement as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span' " From Table 9 and 10 above, the

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weight decrement criterion is clearly exceeded in both the Medium-High and High dose groups in male rats and the High dose group in female rats. From Table 11 it is exceded in the High dose in male mice, but it is not exceeded in female mice. Again, although this requires the expertise of the toxicologist, this may be evidence that the MTD was exceeded in male and female rats, and possibly male mice.

The Sponsor summarizes effects on weight gain in rats as fillows: "There were clear test article-related effects on body weight gain throughout the study in males and females.

"Most test article-treated males generally had lower body weights than controls, and this effect exhibited a dose-related trend. With the exception of Weeks 93-101, the 25 mg/kg/day (Group 2) males were generally within ± 5.0% of the control mean body weights. The 50 mg/kg/day (Group 3) males had lower body weights than controls throughout the study, with only sporadic statistically significant differences that represented decreases generally less than 10% compared to controls. The 100 mg/kg/day (Group 4) males began to show significantly lower body weights from Weeks 57 through 85, with a difference of greater than 10% compared to controls from Weeks 61 through 85. The 150 mg/kg/day (Group 5) males had significantly lower body weights compared to control (Group 1) males from Week 2 until early termination, with a difference of greater than 10% from Weeks 37 through 85.

"Test article-related effects on body weight gains were less pronounced in females. Females administered BG00012 at 25 mg/kg/day (Group 2) or at 50 mg/kg/day (Group 3) had body weights that were generally comparable to controls. The 100 mg/kg/day females had body weights that were generally comparable to controls during Weeks 1 through 69, but had body weights that were 3.5% to 8.3% less than controls from Weeks 73 through 104. The 150 mg/kg/day females had body weights within 2% of controls from Weeks 1-5, body weights that were 2.3% to 9.4% less than controls from Weeks 6-65, and body weights that ranged from 11.9% to 17.0% less than controls from Weeks 69-104." (page 38-39 of rat report)

Dosing related weight differences in the mouse study are summarized by the Sponsor as follows: 'The only statistically significant differences in body weights that appeared to be test article-related occurred in Week 2, when the body weights of Group 5 animals were significantly lower (5.0 to 7.3%) than those of controls. Following a brief dosing holiday (*i.e.*, Days 6-8) and the resumption of dosing at a lower dose (400 mg/kg/day), body weights of Group 5 animals were more comparable to those of controls. With the exception of the Group 5 females, which weighed 4.3 to 8.7% more than controls from Weeks 3-49, other statistically significant differences in body weights or body weight changes in treated groups did not exhibit consistent trends, and were considered incidental." (page 37 of mouse report)

The Sponsor summarizes food consumption during the rat study as follows: "Food consumption was generally comparable in test article-treated groups and controls. With a few exceptions, food consumption differences between test article-treated animals and controls were ± 10%." (page 39 of rat report) Results in the mouse study are summarized as follows: "Food consumption was reduced in 600 mg/kg/day (Group 5) males and females from Weeks 1 to 2.

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Following the dosing holiday and reduction of the dose from 600 to 400 mg/kg/day, food consumption in Group 5 animals was generally slightly greater than that of controls. Other differences were not regarded as meaningful." (page 37 of mouse report)

Again from 2) above, excess mortality not associated with any tumor or sacrifice in the higher dose groups might suggest that the MTD was exceeded. This suggests that a useful way to assess whether or not the MTD was achieved is to measure early mortality not associated with any identified tumor. If this is high in the higher dose groups it suggests that animals tend to die before having time to develop tumors. Tables 13 and 14, below, display the number of animals in each dose group that died of a natural death or moribund sacrifice, but did not show any tumors (i.e., the "Event"):

Table 13. Natural Death with No Identified Tumor in Rats (Male/Female)

	1. Vehicle	2. Low	3. Medium	4. Med-High	5. High
Males Event	13	12	11	2	4
No event	62	63	64	73	71
Females Event	4	5	5	5	2
No event	71	70	70	70	73

In female rats there is no evidence of dose related differences in the mortality without tumors. This result is exemplified by the chi-square test of homogeneity ($p \leq 0.7880$), and the Cochran-Armitage test of no trend ($p \leq 0.4281$). It appears that in male rats there is strong evidence of a dose related trend over the five treatment groups as confirmed by the chi-square test of homogeneity ($p \leq 0.0088$), and even further by the Cochran-Armitage test of no trend ($p \leq 0.0010$). However, this trend is associated with an actual decreased incidence of death without tumor. Thus in both genders there is no evidence of an increasing incidence of death without tumor over increasing dose.

Table 14. Natural Death with No Identified Tumor in Mice (Male/Female)

	1. Vehicle	2. Low	3. Medium	4. Med-High	5. High
Males Event	15	23	29	23	34
No event	60	52	46	52	41
Females Event	10	12	12	10	28
No event	65	63	63	65	47

Results in mice are much more clear and consistent. The chi-square tests of homogeneity were statistically significant (Males $p = 0.0150$, Females $p = 0.0005$), as were the Cochran-Armitage test of no trend (Males $p = 0.0074$, Females $p = 0.0001$). However, when deleting the early deaths in the high dose in mice, the chi-square tests of homogeneity were no longer statistically significant (Males $p = 0.1766$, Females $p = 0.4324$), as were the Cochran-Armitage test of no trend (Males $p = 0.4757$, Females $p = 0.1327$).

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Thus, in rats there is no evidence of a dose related effect on mortality without tumor. In mice there is such evidence, but it seems to be primarily due to the 600 mg/kg/day dose during the first week. Ignoring those early deaths during the first week and reducing the dosage to 400 mg/kg/day there is no evidence of a lack of homogeneity or a trend in dose.

Once again, like the other observations above, these require the expertise of the toxicologist, but these tests do not seem to provide evidence that the MTD was exceeded in rats. However in mice there is evidence that it was exceded with the original 600 mg/kg/day dosage in the High dose group, but was not exceded when this dose was reduced to 400 mg/kg/day.

Combining these rather inconsistent observations into a valid assessment of the MTD requires the expertise of the toxicologist.

1.3.2. Statistical Findings

Please see Section 1.1 above.

2. INTRODUCTION

2.1. Overview

This submission summarizes the results of two year rat and mouse studies to assess the carcinogenic potential carcinogenic potential of the test article, BG00012 (Dimethyl Fumarate), with daily gavage dosing. Both studies were actually conducted, starting in 2004, (b) (4)

2.2. Data Sources

The Sponsor provided three SAS transport files. In rats, these were:

eba00009-male-tumor.xpt	containing	male.sas7bdat
eba00009-female-tumor.xpt		female.sas7bdat

In mice, this was:

eba00124-tumor.xpt	containing	alldata.sas7bdat

Note these contained sufficient survival and tumorigencity data to conduct the primary analyses in this report.

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

NA

3.2. Evaluation of Safety

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3.2.1. Study P00012-04-11 A Two Year Oral (Gavage) Carcinogenicity Study in Rats with BG00012.

STUDY DURATION: 104 Weeks (two male dose groups terminated early)
STARTING DOSING DATE: October 26, 2004.
TERMINAL SACRIFICE (NECROPSY) DATE: October 27, 2006.
STUDY ENDING DATE (Final Report dated): February 28, 2008.
RAT STRAIN: Sprague Dawley Crl:CD(SD)IGS BR Rats.
ROUTE: Daily Oral Gavage

Five treatment groups, Groups 1-5, were formed for each of the male and female Sprague Dawley rats (75/gender in each group) as described in Table 15, below (partly a repeat of Table 1 above) The Sponsor states that "The dose levels were selected in an attempt to produce graded responses to the test article. The high-dose level was expected to produce toxic effects, but not excessive lethality. The mid-dose levels were expected to produce no or minimal to mild observable effects. The low-dose level was expected to produce no observable effects, if possible." (page 27 of rat report)

Table 15. Design of Rat Study

Treatment Group	# animals (TK Satellite Animals)[a]		Vehicle or Test Article	BG00012 Dosage (mg/kg/day)	Dose Volume (mL/kg)	Dosing Concen-tration[a]
	Males	Females				
1. Vehicle[b]	75 (15)	75 (15)	HPMC	0	10	0
2. Low	75 (15)	75 (15)	BG00012	25	10	2.5
3. Medium	75 (15)	75 (15)	BG00012	50	10	5
4. Med-High	75 (15)	75 (15)	BG00012	100	10	10
5. High	75 (15)	75 (15)	BG00012	150	10	15

[a] Toxicokinetic phase animals began dosing during Week 24 of the carcinogenicity phase. The first day of dosing was designated Day 1. The duration of the toxicokinetic phase was a minimum of 180 days.
[b] Hydroxypropylmethylcellulose or Hypromellose (3,500-5,600 cps), 0.8% w/v in reverse osmosis deionized water (HPMC)

During the initial acclimation animals were housed two or three together, but were housed individually prior to actually initiating the study. An additional 15 rats per sex and group were used for toxicokinetic phase with the same mode of administration. The report indicates that detailed clinical signs were checked weekly, including a palpation for tissue masses. The Sponsor states that food and water was available *ad libitum* throughout the study. The report indicates that: "The treatment duration for this study was intended to be a minimum of 104 weeks. However, prior to Week 100, dosing of any treatment group of either sex was discontinued if the number of survivors in that sex/group reached 20 or less (the target of 20 animals/sex/group was exceeded if multiple animals in a group died in a single day). Treatment of other groups continued. Any given treatment group of either sex was terminated and subjected to necropsy if the number of surviving animals in that sex/group declined to 10. These measures were implemented based upon FDA guidance to the Sponsor (Protocol Amendment No. 6.) Therefore, dosing was discontinued on Day 547 (Week 80) for males in Group 5 and on Day 564

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(Week 82) for males in Group 4. Group 5 males were subsequently euthanized on Week 86 and Group 4 males were subsequently euthanized on Week 88." (page 28 of rat report)

The Sponsor indicates that "a simple randomization procedure" was used to assign animals to the control and treatment groups, but details are not apparent. Animals were housed individually with food and water available *ad libitum*, although food was with held during "designated periods".

3.2.1.1. Sponsor's Results and Conclusions

This section will present a summary of the Sponsor's analysis on survivability and tumorigenicity in rats.

Survival analysis:

The Sponsor provided the following summary of the results on survival as assessed by log rank tests on survival:

Table 16: Sponsor's Analysis of Survival

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Kaplan-Meier Estimates of Survival

		Deaths[a] / At Risk[b]				
Sex	Interval (Weeks)	Vehicle Control	25 mg/kg/day	50 mg/kg/day	100 mg/kg/day	150 mg/kg/day
Male	0 – 50	3/75 (96)	6/75 (92)	5/75 (93)	12/75 (84)	17/75 (77)
	51 – 85	27/72 (60)	21/69 (64)	37/69 (43)	47/63 (21)	47/58 (15)
	86 – EOS	22/45 (31)	27/47 (27)	19/32 (18)	6/16 (13)	1/11 (13)
	Term.	23	20	13	10	10
	p-value	<0.0001* (T)	0.9225	0.0196*	<0.0001*	<0.0001*
Female	0 – 50	4/75 (95)	2/75 (97)	2/75 (97)	2/75 (97)	3/75 (96)
	51 – 85	14/71 (76)	24/73 (65)	27/73 (61)	31/73 (56)	24/72 (64)
	86 – EOS	32/57 (33)	21/49 (37)	26/46 (27)	20/42 (29)	25/48 (31)
	Term.	25	28	20	22	23
	p-value	0.3372 (T)	0.7308	0.0613	0.0931	0.3229

[a]Deaths = Number of natural deaths or moribund sacrifices. Does not include accidental deaths.
[b]At Risk = Number of animals at risk (on study) at start of interval. Does not include accidental deaths that occurred in previous interval(s).
EOS = end of study (up to terminal sacrifice).
Term. = Number of animals surviving until terminal sacrifice.
p-values: (T) = Dose response trend test. Listed under individual treatment groups are pairwise comparisons with control.
*Statistically significant at the defined significance level (trend test and pairwise comparisons with control: significance level = 0.05).

(page 44 of rat report)

According to the Sponsor: "Among males, there was a statistically significant decreasing dose-response trend in the survival rates. In pair-wise comparisons, the survival rate of the male 50 mg/kg/day, 100 mg/kg/day, and 150 mg/kg/day groups were significantly less than that in the

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control group. Female survival was not significantly impacted by BG00012 administration at doses up to 150 mg/kg/day. ” (page 43 of rat report)

In male rats the tests of trend over all doses and the comparisons of the 100 mg/kg/day (Medium-High) and 150 mg/kg/day (High) dose groups to control were all highly statistically significant (all three $p<0.0001$), indicating there was heterogeneity in survival over dose groups. The test comparing the 50 mg/kg/day (Medium) dose group to control in males was also statistically significant ($p = 0.0196$), while comparison between the 25 mg/kg/day (Low) dose group to the control was not statistically significant ($p = 0.9225$). Strictly, in female rats the test of trend and none of the the comparisons between the treatment groups and control were statistically significant at the usual 0.05 level

Tumorigenicity analysis:

The Sponsor summarizes carcinogenicity results as follows: “In males, there was a statistically significant dose-related increasing trend in the onset of benign cerebral granular cell tumors, although the study pathologist did not regard these tumors as treatment related. In the [redacted] (b) (4) historical control dataset . . , in those studies in which granular cell tumors were observed in male control animals, the incidence was as high as 2.0% for benign tumors or 2.86% for malignant tumors.

“In males, there was a statistically significant dose-related increasing trend in the onset of renal tubule adenoma in the kidneys; pairwise comparisons between each dose group and its respective control group did not demonstrate statistical significance at any of the dose levels evaluated.

“In males, there were also statistically significant dose-related increasing trends in the onset of squamous cell papilloma, squamous cell carcinoma, and squamous cell papilloma/carcinoma in the nonglandular stomach. In addition, the pairwise comparisons with control were significant for all male dose groups.

“Parathyroid adenomas did not show a statistically significant trend in onset, nor were pairwise comparisons with control significant for any male dose groups.

“There was a statistically significant dose-related increasing trend in the onset of interstitial cell adenoma in the testes. In addition, the pairwise comparisons with control were significant for the 100 and 150 mg/kg/day dose groups. There were no other statistically significant tumor findings among males.

“In females, there were statistically significant dose-related increasing trends in the onset of renal tubule carcinoma and renal tubule adenoma/carcinoma in the kidneys. In addition, the pairwise comparison with control was significant for the 150 mg/kg/day group for the renal tubule carcinoma.

“In females, there were also statistically significant dose-related increasing trends in the onset of squamous cell papilloma, squamous cell carcinoma, and squamous cell papilloma/carcinoma in the nonglandular stomach. In addition, the pairwise comparisons with control were significant in

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all dose groups for the nonglandular squamous cell papilloma and nonglandular squamous cell papilloma/carcinoma, and in the 100 and 150 mg/kg/day groups for the nonglandular squamous cell carcinoma. There were no other statistically significant tumor findings among females. (pages 45-46 rat of report)

3.2.1.2. FDA Reviewer's Results

This section will present the Agency findings on survival and tumorigenicity in male and female rats.

Survival analysis:

The following tables (Table 17 for male rats, Table 18 for females) summarize the mortality results for the study groups. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent that survived at the end of the interval. In these tables the terminal period only includes those animals were sacrificed. Rats that died of other causes during the terminal period are included in the preceding, overlapping time period. The Kaplan-Meier survival plots in Appendix 1 provide a more detailed picture of the profile of mortality losses.

Table 17. Summary of Male Rats Survival (dose label/dose/weeks dosing)

Period (Weeks)	HPMC 0/ 1-105	Low 25/ 1- 105	Medium 50/ 1- 105	Med- High[4] 100/ 1- 105	High[4] 150/ 1-105
1-52	4/75[1] 94.7%[2]	6/75 92.0%	7/75 90.7%	12/754 84.0%	19/75 74.7%
53-78	18/71 70.7%	10/69 78.7%	21/68 62.7%	37/63 34.7%	34/56 29.3%
79-91	16/53 49.3%	26/59 44.0%	23/47 32.0%	16/26 13.3%	12/22 13.3%
92-105	14/37 30.7%	13/33 26.7%	11/24 17.3%		
Terminal [3,4] 105 (88,86)	23	20	13	10[4]	10[4]

[1] number of deaths / number at risk
[2] overall per cent survival to end of period.
[3] number of animals that survived to terminal sacrifice
[4] Group 4, Med-High dose, terminated in Week 88, Group 5, High dose, in Week 86

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Table 18. Summary of Female Rats Survival (dose label/dose/weeks dosing)

Period (Weeks)	HPMC 0/ 1-105	Low 25/ 1- 105	Medium 50/ 1- 105	Med- High 100/ 1- 105	High 150/ 1-105
1-52	4/75[1] 94.7%[2]	2/75 97.3%	3/75 96.0%	2/75 97.3%	3/75 96.0%
53-78	8/71 84.0%	10/73 84.0%	12/72 80.0%	22/73 68.0%	18/72 72.0%
79-91	17/63 61.3%	22/63 54.7%	29/60 41.3%	14/51 49.3%	15/54 72.0%
92-105	21/46 33.3%	13/41 37.3%	11/31 26.7%	15/37 29.3%	16/39 30.7%
Terminal [3] 105	25	28	20	22	23

[1] number of deaths / number at risk
[2] overall per cent survival to end of period.
[3] number of animals that survived to terminal sacrifice.

Table 19 below provides the significance levels of the tests of homogeneity and trend over dose groups as proposed in Section 1.3.1.1 above (and is a repeat of Table 3 above and Table A.1.1 in Appendix 1).

Table 19. Statistical Significances of Tests of Homogeneity and Trend in Survival in Rats

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Rat Homogeneity over Groups 1-5	< 0.0001	< 0.0001	0.4421	0.2737
Homogeneity over Groups 1-4	< 0.0001	< 0.0001	0.2904	0.1602
Homogeneity over Groups 1-3	0.0292	0.0153	0.2090	0.1594
No trend over Groups 1-5	< 0.0001	< 0.0001	0.3427	0.2033
No trend over Groups 1-4	< 0.0001	< 0.0001	0.1345	0.0389
No trend over Groups 1-3	0.0169	0.0119	0.1386	0.0734
No Difference Between Groups 1 vs 5	< 0.0001	< 0.0001	0.4943	0.3229
No Difference Between Groups 1 vs 4	< 0.0001	< 0.0001	0.2503	0.0931
No Difference Between Groups 1 vs 3	0.0180	0.0142	0.1205	0.0613

From Figure A.1.1 in Appendix 1, in male rats, the HPMC vehicle and Low dose group are largely intertwined, with the highest survival, while the Medium dose group has the next highest survival, and the Medium-High and High dose groups having the lowest but quite close survival over the study period. These groups were sacrificed early due to low survival. Although the early sacrifices are treated as censored, not deaths, this difference is sufficient to cause significant tests of lack of homogeneity, no trend, and no difference between the highest doses and vehicle in groups 1-4 and groups 1-5 (all 12 $p < 0.0001$, usually much less than the 0.0001 level). Even the seperation of the Medium dose group from the Vehicle and Low dose is sufficient to result in consistently statistically significant results (all six $p \leq 0.0292$). The situation in female rats is quite different. From Figure A.1.2, in female rats, although the HPMC vehicle seems to have slightly the highest survival, the survival curves of the other dose groups

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are generally quite close and are largely intertwined. While this is not strong evidence of no differences it is evidence of no strong differences (all six $p \geq 0.2033$). Results of the tests using treatment subgroups 1-4 and 1-3 are mostly included to balance those of for male rats. Note that the Wilcoxon test is more sensitive to early differences in survival and the corresponding test of lack of trend is barely statistically significant at the usual level (i.e., Wilcoxon $p = 0.0389$), but this conclusion is not supported by the Logrank test ($p = 0.1386$).

Tumorigenicity analysis:

As discussed in Section 1.3.1.5, the Haseman-Lin-Rahman rules for adjusting for multiplicity in a single species study specify that for a very rough 0.10 (10%) overall false positive error rate, both overall trend and the comparison between control and the high dose should be tested at a 0.05 (5%) level in rare tumors (background incidence 1% or less) and at 0.01 (1%) level in common tumors. In this analysis we use the incidence in the HPMC vehicle control group to specify whether a tumor is treated as common or rare. Note that the period '.' in the table denotes the p-values of tests of dose groups with none of the particular tumors the specified groups.

The following table 20 is a repeat of tables 5 and 6, above.

Table 20. Potentially Statistically Significant Neoplasms in Rats

gender organ tumor	Incidence Veh	Low	Med	MedHi	High	Significance Levels Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
Male Rats										
BRAIN										
# Evaluated	73	75	75	75	74					
Adjusted # at risk	49.5	48.6	40.3	25.3	23.1					
CEREBRUM- GRANULAR CELL TUMOR	0	0	0	0	2	.0149	.0990	.	.	.
KIDNEYS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.7	25.9	25.2					
RENAL TUBULE- ADENOMA	0	0	1	1	4	.0006	.0110	.3378	.4494	.
LIVER										
# Evaluated	75	74	75	75	75					
Adjusted # at risk	50.1	49.9	42.2	25.3	22.2					
Hepato. Adenoma/Carcinoma	2	8	5	0	0	.9542	1	1	.1520	.0426
PARATHYROID										
# Evaluated	68	64	70	71	70					
Adjusted # at risk	44.5	42.8	38.7	23.8	21.5					
ADENOMA	0	0	1	0	2	.0251	.1010	.	.4634	.
Adjusted # at risk	44.5	42.8	38.7	23.8	22.3					
Adenoma, any	0	0	1	0	3	.0049	.0337	.	.4634	.
SKIN										
# Evaluated	75	74	75	74	75					
Adjusted # at risk	50.8	51.2	41.4	28.7	27.4					
KERATOACANTHOMA	8	8	9	7	9	.0256	.0736	.2494	.3236	.6237
Adjusted # at risk	49.6	48.9	40.3	24.7	23.6					
SUBCUT TISS.-FIBROSARCOMA	0	1	0	0	2	.0357	.0990	.	.	.4948
Adjusted # at risk	51.2	52.1	42.1	30.9	29.7					
Sq.Cell Pap./Carc./Kerato.	11	11	10	10	12	.0136	.0532	1825	.4950	.6147

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Table 20 (cont.) Potentially Statistically Significant Neoplasms in Rats

gender organ tumor	Incidence Veh	Low	Med	MedHi	High	Significance Levels Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
Male rats										
STOMACH										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	49.2	50.1	60.0	61.3					
NONGLAND.- SQUAMOUS CELL CARCINOMA	0	5	18	51	58	<.0001	<.0001	<.0001	<.0001	.0281
Adjusted # at risk	49.6	53.5	51.4	55.7	58.4					
NONGLAND.- SQ. CELL PAP.	0	22	24	46	49	<.0001	<.0001	<.0001	<.0001	<.0001
Adjusted # at risk	49.6	53.5	55.3	70.9	71.1					
Nongland.Sq.Cell Pap./Carc.	0	22	34	68	70	<.0001	<.0001	<.0001	<.0001	<.0001
TESTES										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	50.3	49.0	41.4	30.2	32.8					
INTERSTITIAL CELL- ADENOMA	3	3	2	9	17	<.0001	<.0001	.0053	.7514	.6415
Adjusted # at risk	49.6	48.6	40.3	25.3	23.5					
INTERSTITIAL CELL- ADENOMA, BILATERAL	0	0	0	0	2	.0149	.0990	.	.	.
Adjusted # at risk	50.3	49.0	41.4	30.2	34.0					
Intersit. Adenoma, any	3	3	2	9	19	<.0001	<.0001	.0053	.7514	.6415
Female Rats										
CAVITY, ABDOMINAL										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.9					
HISTIOCYTIC SARCOMA	0	0	0	0	2	.0397	.2335	.	.	.
KIDNEYS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.9					
RENAL TUBULE-CARCINOMA	0	0	0	2	4	.0015	.0523	.2190	.	.
Adjusted # at risk	54.9	53.2	48.7	48.1	52.4					
Renam Tub. Adenoma/Carc.	1	0	0	2	5	.0033	.0942	.4555	1	1
MAMMARY GLAND										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	57.8	56.6	52.7	50.3	56.8					
CARCINOMA	10	13	13	8	19	.0688	.0372	.6800	.2364	.3036
STOMACH										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	49.6	56.6	65.8					
NONGLANDULAR-SQUAMOUS CELL CARCINOMA	0	1	4	30	48	<.0001	<.0001	<.0001	.0479	.4953
Adjusted # at risk	54.8	55.0	53.7	56.4	61.2					
NONGLANDULAR- SQUAMOUS CELL PAPILLOMA	0	11	21	31	24	<.0001	<.0001	<.0001	<.0001	.0003
Adjusted # at risk	54.8	55.0	54.3	61.1	69.3					
Nongland. Sq, Pap./Carc.	0	11	23	48	58	<.0001	<.0001	<.0001	<.0001	.0003
VAGINA										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	52.2					
Endo. Stromal polyp/sarcoma	0	0	0	1	2	.0314	.2383	.4706	.	.

In male rats, even adjusting for multiplicity, the tests of trend and all pairwise comparisons of the four treated groups to HPMC vehicle in nonglandular squamous cell papilloma and pooled papilloma and carcinoma were all highly statistical significant (all

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p<0.0001, with both trend < 0.025 and pairwise tests < 0.05). The same holds for nonglandular squamous cell carcinoma except that the comparison between the Low dose group and vehicle was just statistically significant (p=0.0281 < 0.05). The tests of trend and pairwise differences between the High dose and the HPMC vehicle in interstial cell adenoma of the testes were both highly statistically significant (p < 0.0001 < 0.005 and 0.1, respectively). Accepting the increase in probable error from including other tests, the pairwise comparison between the Medium dose group and vehicle would also be classified as statistically significant (p = 0.0053 < 0.01). Since adding the interstial cell carcinoma only affects incidence in the High dose group, the tests for pooled interstitial cell adenoma and carcinoma are, at least to the printed significance levels, identical to those for carcinoma are identical to those for interstial cell adenoma alone. . In this organ, the simple test of trend in interstial cell bilateral adenoma was also statistically significant (p = 0.0149 < 0.025), though not extremely. The test of trend in renal tubule adenoma of the kidneys was also statistically significant (p = 0.0006 < 0.025), as were the tests of granular cell tumor of the brain (p = 0.0149 < 0.025) and the test of pooled adenomas of the parathyroid (p = 0.0049 < 0.025). The test of trend in simple adenoma of the parathyroid was close to statistical significance (p= 0.0251 > 0.025). No other test achieved the multiplicity adjusted levels of statistical significance.

Results in female rats are rather similar. In female rats, the tests of trend and all pairwise comparisons between the high, medium high, and medium dose groups with vehicle in nonglandular squamous cell papilloma and pooled papilloma and carcinoma were all highly statistical significant (all p < 0.0001, with both trend < 0.025 and pairwise tests < 0.05) even adjusting for multiplicity. For both of these the comparison between the Low dose and vehicle was also statistically significant (for both tumors, p = 0.0003 < 0.05). These results also hold for the tests of trend and pairwise comparisons between the High and Medium High dose groups and vehicle in nonglandular squamous cell carcinoma (p < 0.0001, with both trend < 0.025 and pairwise tests < 0.05). Accepting the inflation of Type I error, the comparison between the Medium dose and vehicle was barely statistically significant (p = 0.0479 < 0.05). The test of trend in renal tubule carcinoma of the kidneys was also statistically significant (p = 0.0015 < 0.025), as was the test of pooled adenoma and carcinoma (p = 0.0033 < 0.005). Again, no other test achieved the multiplicity adjusted levels of statistical significance, although several were somewhat close.

A Bayesian analysis of carcinogenicity in rats, as originally presented in the review for IND 73061, is given in Appendix 3. This Bayesian analysis is also generally consistent with the analysis above. Although it is hardly surprising given the incidence, in both male and female rats the posterior probability that there is no effect of increasing dose on nonglandular squamous cell papilloma and carcinoma are both essentially zero to a number of decimal places. The posterior probabilities of no differences between the High dose group and vehicle in these tumors in females is similar, as well for nonglandular squamous cell carcinoma in males. In males the posterior probability that there is no difference between nonglandular squamous cell papilloma is actually 0.0002 (so the estimated probability that there is difference is about 1 - 0.0002 = 0.9998), i.e., almost certainly. In male rats the estimated posterior probability that there is no trend in interstitial cell adenoma in the testes is also 0.0 to a number of decimal places, while the

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corresponding probability that there is no difference between the high dose group and control is 0.091 (so the estimated probability of a difference is 1 - 0.091 = 0.909). In male rats the estimated posterior probability that there is no trend in renal tubule adenoma in the kidneys is essentially 0.086 (so the probability there is a difference in 1 - 0.086 = 0.914), while in female rats the estimated posterior probability that there is no trend in renal tubule carcinoma in the kidneys is essentially 0.0074 (with 1- 0.0074 = 0.9926). More details are included in this appendix.

Complete tumor incidence tables, including the adjusted number at risk, are provided in tables A.2.3 and A.2.4 of Appendix 2.

3.2.2. Study P00012-05-03 Two-Year Oral (Gavage) Carcinogenicity Study in Mice with BG00012.

STUDY DURATION: 104 Weeks
EXPERIMENTAL START DATE: 28 June 2005
EXPERIMENTAL TERMINATION: 11 June 2007
MOUSE STRAIN: [redacted] (b) (4) CD-1 [Crl:CD-1®(ICR)Br] Mice
ROUTE: Daily Oral Gavage

Table 21. Design of Mouse Study

Treatment Group	# animals (Toxicokinetic animals)		Vehicle or Test Article	BG00012 Dosage (mg/kg/day)	Dose Volume (mL/kg)	Dosing Concen-tration[a]
	Males	Females				
1. Vehicle[a]	75 (12)	75 (12)	HPMC	0	10	0
2. Low	75 (30)	75 (30)	BG00012	25	10	2.5
3. Medium	75 (30)	75 (30)	BG00012	75	10	7.5
4. Med-High	75 (30)	75 (30)	BG00012	200	10	20
5. High	75 (30)	75 (30)	BG00012	600/400[b]	10	60/40[b]

[a] Hydroxypropylmethylcellulose or Hypromellose (3,500-5,600 cps), 0.8% w/v in reverse osmosis deionized water.
[b] Due to mortality observed in the high-dose group, the dose level for Group 5 was decreased to 400 mg/kg/day (40 mg/mL) beginning on Day 9. For tests it is treated as dosage at 400 mg/kg/day.

The Sponsor described study conduct as follows; "The test and control articles were administered by once daily oral gavage 7 days per week to the appropriate mice in the carcinogenicity phase as follows: Group 1-4 males and females for 104 weeks, Group 5 males for 72 weeks, and Group 5 females for 82 weeks. The test and control articles were administered to the appropriate mice in the toxicokinetic phase by once daily oral gavage 7 days per week for 180 days. The dose volume for each animal was based on the most recent body weight measurement. The doses were given using a syringe with attached study-specific ball-tipped oral gavage needle. The first day of dosing was designated as Study Day 1." (pages 26 and 27 of mouse report)

Further the Sponsor notes that the study was modified as follows: "Test article-related mortality was observed in the 600 mg/kg/day dose group (Group 5) during the first week of

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treatment. Fifteen males and thirteen females in this dose group were found dead during Days 5-8. As a result, Group 5 animals were not dosed on Days 6-8. Dosing resumed on Day 9 in Group 5 animals (60 males and 62 females) at a dose of 400 mg/kg/day." (page 15 of mouse report) For all tests used in the FDA analysis dosage in the High dose group is treated as 400 mg/kg/day.

"Prior to randomization procedures, the animals were weighed and examined in detail. Animals determined to be suitable as test subjects were divided into two main populations, those for possible assignment to the carcinogenicity phase and those for possible assignment to the toxicokinetic phase. Animals in each population were then randomly assigned to groups by a stratified randomization scheme designed to achieve similar group mean body weights. The animals were approximately 8 weeks of age at the time of randomization with body weights ranging from 27.1 to 34.7 grams for the males and 22.1 to 29.1 grams for the females." (page 25 of mouse report) Note that several animals were replaced for death or injury.

In addition to the main study animals: "TK animals in Group 1 consisted of twelve animals/sex; sampling was conducted for two subgroups of three animals/sex, with an additional six animals/sex reserved as possible replacement animals. TK animals in Groups 2-5 consisted of thirty animals/sex/group; sampling was conducted for eight subgroups of three animals/sex, with an additional six animals/sex reserved as possible replacement animals. The six extra animals/sex/group were dosed in the same manner as the other animals in each group. Blood samples were collected on Days 1, 90,and 180 . . . In addition, on Day 1, blood was collected from six animals per sex prior to dosing in order to provide pre-dose samples. These animals were arbitrarily selected from alternates not placed on study; the samples from these animals were processed the same as the TK samples." (page 31 of mouse report)

"An additional 20 male and 20 female sentinel animals were arbitrarily selected from animals not utilized for this study and maintained in the study room. Blood was collected from five males and five females during Weeks 26, 52, 78, and 105. A minimal blood volume (~0.4 mL) was collected to allow sentinel animals that were bled to continue on study to assure that a sufficient number of animals would survive to Week 105. The same animals were used for each blood collection interval when possible." (page 24 of mouse report)

Dose levels were justified as follows: "The dose levels were selected by the Sponsor according to FDA-CDER recommendations as a June, 2005 Executive CAC response to Carcinogenicity Special Protocol Assessment Request.

"The dose selection for a 2-year carcinogenicity assay was proposed based primarily on the marked dose-dependent increase in stomach weights and gross and histological changes in the forestomach in treated animals compared to control animals in a 90-day dose range-finding study in CD-1 mice. The initial high dose of 200 mg/kg was based on the increase in stomach weights and histological findings after 90 days of DMF treatment and is estimated to be the approximate maximum tolerated dose (MTD). The inclusion of a higher dose of 600 mg/kg/day was based upon a recommendation of the FDA CDER CAC response to evaluate higher doses than 200 mg/kg in order to determine an MTD within the mouse study (June 2005). The low dose of 25

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mg/kg was predicted to elicit minimal or no toxicity over 2 years based on the mild effects seen at 50 mg/kg after 90 days. The mid dose of 75 mg/kg is a multiple between the low and high dose and was expected to elicit some toxicity in the animals after 2 years of treatment while yielding relevant and useful data to predict the human risk. The reference clinical dose was the maximum therapeutic dose of approximately 10 mg/kg/day of BG00012 or approximately 370 mg/m2 (720 mg/day assuming a 70 kg person)." (page 26 of mouse report)

After randomization, animals were housed individually with food and water available *ad libitum*.

3.2.1.1. Sponsor's Results and Conclusions

This section will present a summary of the Sponsor's analysis on survivability and tumorigenicity in mice.

Survival Analysis:

The following table is copied from the mouse report (page 6 of statistical report, page 4820 of mouse report)

Table 22. (Sponsor Table 5.1.1) Kaplan-Meier Estimates of Survivale

Table 5.1.1 Kaplan-Meier Estimates of Survival

		Deaths[a] / At Risk[b] (KM)				
Sex	Interval (Weeks)	Control	25 mg/kg/day	75 mg/kg/day	200 mg/kg/day	600/400 mg/kg/day
M	0 - 50	9/75 (88)	9/75 (88)	10/75 (87)	5/75 (93)	34/75 (55)
	51 - 80	15/66 (68)	13/66 (71)	10/65 (73)	21/70 (65)	24/41 (23)
	81 - EOS	27/51 (32)	18/53 (45)	29/55 (35)	30/49 (25)	7/17 (13)
	Term. Sac	24	35	26	19	10
	p-value	<.0001* (T)	0.0958	0.5788	0.4876	<.0001*
F	0 - 50	4/75 (95)	6/75 (92)	3/75 (96)	3/75 (96)	17/75 (77)
	51 - 80	10/70 (81)	10/69 (79)	16/72 (74)	14/72 (77)	34/58 (32)
	81 - EOS	27/60 (45)	32/59 (36)	26/54 (39)	33/57 (32)	14/24 (13)
	Term. Sac	33	27	28	24	10
	p-value	<.0001* (T)	0.2300	0.3635	0.1056	<.0001*

a - Deaths = Number of natural deaths or moribund sacrifices. Does not include accidental deaths
b - At Risk = Number of animals at risk (on study) at start of interval. Does not include accidental deaths that occurred in previous interval(s)
KM = Kaplan-Meier estimate of survival at end of interval (%).
EOS = end of study (up to terminal sacrifice)
Term. = Number of animals surviving until terminal sacrifice
p-values: (T) = Dose response trend test. Otherwise, listed p-values are for pairwise comparison with control.
* - statistically significant at the 0.05 significance level

(page 42 of mouse report)

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The Sponsor summarizes results in the statistical analysis report as follows: " A summary of Kaplan-Meier estimates together with the results of statistical analyses is shown in Table 5.1.1 [above]. Among both males and females there was a statistically significant decreasing dose response trend in the survival rates. In addition the pairwise comparison of control with the 600/400 mg/kg/day was significant. No other comparisons were statistically significant." (page 5 of statistical report, page 4819 of mouse report)

Tumorigenicity analysis:

The Sponsor's statistical analysis report presents results of a Peto analysis of tumorigenicty. These results are summarized as follows: "Table[s] 5.2.1 and 5.2.2[, copied below with slight editing,] summarize selected tumor types for which at least one comparison resulted in $p < 0.05$. . . . [T]he significance level for each tumor type was dependent on whether a trend test or pairwise comparison with the control was conducted and whether the tumor was classified as rare or common based on concurrent and historical control information.

"Males

"Kidney

"There was a statistically significant dose-related increasing trend in the onset of adenoma, carcinoma, and the combination adenoma/carcinoma. In pairwise comparisons with control, there was an increase in the onset of carcinoma and the combination adenoma/carcinoma in both the 200 and 600/400 mg/kg/day groups.

"Stomach

There was a statistically significant dose-related increasing trend in the onset of leiomyosarcoma, papilloma, squamous cell carcinoma, and the combination papilloma/squamous cell carcinoma. In pairwise comparisons with control, there was an increase in the onset of papilloma and the combination papilloma/squamous cell carcinoma in both the 200 and 600/400 mg/kg/day groups. There was also an increase in the onset of squamous cell carcinoma in the 600/400 mg/kg/day group.

"There were no other statistically significant tumor findings among males.

"Females

"Kidney

There was a statistically significant dose-related increasing trend in the onset of adenoma and the combination adenoma/carcinoma. In pairwise comparisons with control, there was an increase in the onset of adenoma and the combination adenoma/carcinoma in the 600/400 mg/kg/day groups.

"Lung with Bronchi

Although increases in tumor findings were noted for bronchiolo-alveolar adenoma and the combination bronchiolo-alveolar adenoma/adenocarcinoma, the findings were not statistically significant.

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"Spleen
Although increases in tumor findings were noted for hemangiosarcoma the findings were not statistically significant.

"Stomach
"There was a statistically significant dose-related increasing trend in the onset of fibrosarcoma, leiomyosarcoma, papilloma, squamous cell carcinoma, and the combination papilloma/squamous cell carcinoma. In pairwise comparisons with control, there was an increase in the onset of squamous cell carcinoma and the combination papilloma/squamous cell carcinoma in both the 200 and 600/400 mg/kg/day groups.

"There was also an increase in the onset of papilloma in the 600/400 mg/kg/day group.

"Uterus
"Although increases in tumor findings were noted for endometrial stromal polyp the findings were not statistically significant.

"There were no other statistically significant tumor findings among females." (pages 7-8 of statistical report, pages 4821-4822 of mouse report)

Table 23. Sponsor's Table 5.2.1 Summary of Statistical Analyses for Selected Tumor Types: Males

ORGAN	TUMOR	R/C		CONTROL	25 MG/KG	75 MG/KG	200 MG/KG	600/400 MG/KG	TREND
KIDNEY	TOTAL EXAMINED (N)			75	75	75	75	75	
	CARCINOMA	R	(a)	0	0	2	4	3	
			(p)		1.0000	0.2748	0.0455*	0.0250*	0.0004*
	ADENOMA/CARCINOMA	R	(a)	1	2	2	8	5	
			(p)		0.5919	0.5367	0.0057*	0.0144*	0.0002*
	ADENOMA R		(a)	1	2	0	5	3	
			(p)		0.5919	1.0000	0.1026	0.2129	0.0131*
STOMACH	TOTAL EXAMINED (N)			74	75	75	75	75	
	SQUAMOUS CELL CARCINOMA	R	(a)	0	1	0	2	6	
			(p)		0.5034	1.0000	0.2274	<.0001*	<.0001*
	PAPILLOMA/SQUAMOUS CELL CARCINOMA	R	(a)	0	2	3	12	19	
			(p)		0.2041	0.1385	0.0001*	<.0001*	<.0001*
	PAPILLOMA	R	(a)	0	1	3	12	14	
			(p)		0.4211	0.1385	0.0001*	0.0005*	<.0001*
	LEIOMYOSARCOMA	R	(a)	0	0	0	0	3	
			(p)		1.0000	1.0000	1.0000	0.1016	0.0059*

(N) NUMBER OF ANIMALS EXAMINED
(a) NUMBER OF ANIMALS WITH TUMOR
(p) P-VALUES FOR PETO ANALYSES INCLUDING CONTROL:
LISTED UNDER INDIVIDUAL TREATMENT GROUP: 1-SIDED PAIRWISE COMPARISON OF CONTROL WITH TREATMENT GROUP
LISTED UNDER 'TREND': 1-SIDED TREND TEST INCLUDING CONTROL AND ACTIVE TREATMENT GROUPS
SIGNIFICANCE: R = RARE TUMOR – P<0.025 (TREND), P<0.05 (PAIRWISE); C=COMMON TUMOR – P<0.005 (TREND), P<0.01 (PAIRWISE)
* STATISTICALLY SIGNIFICANT AT THE DEFINED SIGNIFICANCE LEVEL

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Table 24. Sponsor's Table 5.2.2 Summary of Statistical Analyses for Selected Tumor Types: Females

ORGAN	TUMOR	R/C		CONTROL	25 MG/KG	75 MG/KG	200 MG/KG	600/400 MG/KG	TREND
KIDNEY	TOTAL EXAMINED (N)			75	75	75	75	75	
	ADENOMA/CARCINOMA	R	(a)	0	0	0	2	4	
			(p)		1.0000	1.0000	0.1801	0.0246*	0.0003*
	ADENOMA	R	(a)	0	0	0	2	4	
			(p)		1.0000	1.0000	0.1801	0.0246*	0.0003*
LUNG WITH BRONCHI	TOTAL EXAMINED (N)			75	75	75	75	75	
	BRONCHIOLO-ALVEOLAR ADENOMA/ ADENOCARCINOMA	C	(a)	16	21	14	26	10	
			(p)		0.1273	0.6385	0.0197	0.6358	0.4124
	BRONCHIOLO-ALVEOLAR ADENOMA	C	(a)	12	14	9	20	10	
			(p)		0.2707	0.7696	0.0364	0.3640	0.1929
SPLEEN	TOTAL EXAMINED (N)			75	74	75	75	75	
	HEMANGIOSARCOMA	R	(a)	1	0	1	1	2	
			(p)		1.0000	0.7327	0.6894	0.1812	0.0406
STOMACH	TOTAL EXAMINED (N)			75	75	74	75	75	
	SQUAMOUS CELL CARCINOMA	R	(a)	0	1	1	5	12	
			(p)		0.4653	0.4624	0.0254*	<.0001*	<.0001*
	PAPILLOMA/SQUAMOUS CELL CARCINOMA	R	(a)	1	1	4	11	26	
			(p)		0.7030	0.1691	0.0013*	<.0001*	<.0001*
	PAPILLOMA	R	(a)	1	0	3	6	16	
			(p)		1.0000	0.3015	0.0696	<.0001*	<.0001*
	LEIOMYOSARCOMA	R	(a)	0	0	0	0	3	
			(p)		1.0000	1.0000	1.0000	0.1532	0.0109*
	FIBROSARCOMA R		(a)	0	0	0	0	2	
			(p)		1.0000	1.0000	1.0000	0.0843	0.0100*
UTERUS	TOTAL EXAMINED (N)			75	75	75	75	75	
	ENDOMETRIAL STROMAL POLYP	C	(a)	6	9	14	11	8	
			(p)		0.1975	0.0194	0.0747	0.0456	0.1633

(N) NUMBER OF ANIMALS EXAMINED
(a) NUMBER OF ANIMALS WITH TUMOR
(p) P-VALUES FOR PETO ANALYSES INCLUDING CONTROL LISTED UNDER INDIVIDUAL TREATMENT GROUP: 1-SIDED PAIRWISE COMPARISON OF CONTROL WITH TREATMENT GROUP
LISTED UNDER 'TREND': 1-SIDED TREND TEST INCLUDING CONTROL AND ACTIVE TREATMENT GROUPS
SIGNIFICANCE: R=RARE TUMOR – P<0.025 (TREND), P<0.05 (PAIRWISE); C=COMMON TUMOR – P<0.005 (TREND), P<0.01 (PAIRWISE)
* STATISTICALLY SIGNIFICANT AT THE DEFINED SIGNIFICANCE LEVEL

3.2.1.2. FDA Reviewer's Results

This section will present the Agency findings on survival and tumorigenicity in male and female rats.

Survival analysis:

The following tables (Table 23 for male mice, Table 24 for females) summarize the mortality results for the study groups. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent that survived at the end of the interval. In these tables the terminal period only includes those animals were sacrificed. Animals that died of other causes during the terminal period are included in the preceding, but overlapping time period. The Kaplan-Meier survival plots in Appendix 1 provide a more detailed picture of the profile of mortality losses.

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Table 25. Summary of Male Mice Survival (dose/weeks dosing)

Period (Weeks)	HPMC 0/ 1-105	Low 25/ 1- 105	Medium 75/ 1- 105	Med- High 200/ 1- 105	High 400[4]/ 1-105
1-52	9/75[1] 88.0%[2]	10/75 86.7%	10/75 90.7%	5/75 93.3%	36/75 52.0%
53-78	15/66 68.0%	9/65 74.7%	9/65 62.7%	17/70 70.7%	21/39 24.0%
79-91	11/51 53.3%	12/56 58.7%	13/56 57.3%	17/53 48.0%	4/18 18.7%
92-105	16/40 32.0%	9/44 46.7%	17/43 34.7%	17/36 25.3%	4/14 13.3%
Terminal [3] 105	24	35	26	19	10

[1] number of deaths / number at risk
[2] overall per cent survival to end of period.
[3] number of animals that survived to terminal sacrifice.
[4] on Day 9 the dose level for Group 5 was decreased from 600 to 400 mg/kg/day.

Table 26. Summary of Female Mice Survival (dose/weeks dosing)

Period (Weeks)	HPMC 0/ 1-105	Low 25/ 1- 105	Medium 75/ 1- 105	Med- High 200/ 1- 105	High 400[4]/ 1-105
1-52	5/75[1] 93.3%[2]	7/75 90.7%	5/75 93.3%	4/75 94.7%	19/75 74.7%
53-78	9/70 81.3%	9/68 78.7%	16/70 72.0%	12/71 78.7%	29/56 36.0%
79-91	7/61 72.0%	12/59 62.7%	10/54 58.7%	17/59 56.0%	10/27 22.7%
92-105	21/54 44.0%	20/47 36.0%	16/44 37.3%	18/42 32.0%	7/17 13.3%
Terminal [3] 105	33	27	28	24	10

[1] number of deaths / number at risk
[2] overall per cent survival to end of period.
[3] number of animals that survived to terminal sacrifice.
[4] on Day 9 the dose level for Group 5 was decreased from 600 to 400 mg/kg/day.

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The following table, Table 27 (a repeat of Table 4 and Table A.1.2 in Appendix 1), summarizes the results from tests comparing survival profiles across study groups in the tumorigenicity data sets:

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Table 27. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Mouse Study

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Mouse Homogeneity over Groups 1-5 [a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Homogeneity over Groups 1-4	0.1115	0.3129	0.4603	0.5208
No trend over Groups 1-5 [a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
No trend over Groups 1-4	0.1119	0.3181	0.1847	0.2348
No Difference Between Groups 1 vs 5[a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
No Difference Between Groups 1 vs 4	0.4876	0.7711	0.1099	0.1322

[a] Printed P-value bounds are identical whether one conditions on survival to day 9 or not.

Recall that in mice due to high mortality in the first week, beginning on Day 9 of the study, the dose level for the High dose, Group 5, was decreased to 400 mg/kg/day. The survival curves for the High dose groups for each mouse gender in Figures A.1.3 and A.1.4 show the effect of these early deaths. Because of this initial high mortality, two additional separate adjustments were performed. The first deleted the high dose from analysis and conducted the analysis with the remaining four dose groups. The second analysis deleted those animals that animals that died before day 9 from the High dose group. Note that this is essentially an analysis conditional upon the mouse surviving at least 9 days on study. Conditional survival curves reflecting these deletions are presented in Figures A.1.5 and A.1.6.

Results for statistical tests of differences in survival in mice are presented below:

Figures A.1.3 and A.1.4, below, display the gender specific survival curves over the five dose groups. Note that in each gender the High dose group is clearly separated from the remaining dose groups. This is sufficient to result in the highly statistically significant tests of homogeneity, lack of trend, and no difference between the High dose and the vehicle dose group (for each gender all six $p < 0.0001$). One might speculate that the separation of the High dose from the other dose groups may be due solely to the few early deaths in the High dose group. However, as shown in Figures A.1.5 and A.1.6, below, i.e., the survival curves over the five dose groups conditional on survival for the first week of the study, the High dose remains seperated from the remaining dose groups. The significance levels for the tests of homogeneity and trend over groups 1-5, and the pairwise comparison between the High dose and vehicle, although larger, will all still be highly statistically significant (i.e., still have all six $p < 0.0001$).

In both sets of plots, for both genders, the survival curves for the dose groups 1-4 are more or less closely intertwined, but with much higher survival than that in the High dose group. This is consistent with the tests of survival completely deleting the High dose group, i.e., none of the tests of homogeneity, lack of trend, and no difference between the High dose and the vehicle dose group were particularly statistically significant, at least at the usual 0.05 level (Males: all six $p \geq 0.1115$, Females all six $p \geq 0.1009$). This suggests that differences in survival are almost all due to differences in the High dose from the remaining dose groups.

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Tumorigenicity analysis:

Those organ tumor combinations with at leat one tests of trend and comparisons that are potentially statistically significant (have a significance level of 0.05 or les) are given below:

Table 28. Potentially Statistically Significant Neoplasms in Mice

gender organ tumor	Incidence Veh	Low	Med	MedHi	High	Significance Levels Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
Male Mice										
KIDNEY										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	48.7	22.1					
Adenoma	1	2	0	5	3	.0074	.0922	.1067	1	.5382
Adjusted # at risk	47.5	52.1	50.7	49.3	22.8					
Adenoma/Carcinoma	1	2	2	8	5	.0003	.0109	.0179	.5234	.5382
Adjusted # at risk	47.5	52.1	50.7	47.7	22.0					
Carcinoma	0	0	2	4	3	.0015	.0265	.0585	.2631	.
LUNG WITH BRONCHI										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	50.0	53.9	52.5	51.4	23.2					
Bronchiolo-Alveolar Adenocarcinoma	6	6	5	11	5	.0411	.2292	.1541	.7598	.6607
STOMACH										
# Evaluated	74	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	47.1	23.0					
Leiomyosarcoma	0	0	0	0	3	.0010	.0324	.	.	.
Adjusted # at risk	47.5	52.5	51.1	50.0	30.5					
Papilloma	0	1	3	12	14	<.0001	<.0001	.0002	.1369	.5253
Adjusted # at risk	47.5	52.4	50.6	47.7	22.3					
Squamous Cell Carcinoma	0	1	0	2	6	<.0001	.0006	.2473	.	.5253
Female Mice										
HEMOLYMPHORETICULAR										
# Evaluated	23	18	20	19	12					
Adjusted # at risk	15.7	12.4	14.6	10.3	6.0					
Leukemia	1	0	0	0	2	.0269	.1404	1	1	1
KIDNEY										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.1	51.8	29.1					
Adenoma	0	0	0	2	4	.0002	.0117	.2248	.	.
Adjusted # at risk	56.6	52.9	52.1	51.8	29.1					
Adenoma/Carcinoma	0	0	0	2	4	.0002	.0117	.2248	.	.
LUNG WITH BRONCHI										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	58.6	56.9	54.6	55.8	31.8					
Bronchiolo-Alv. Adenoma	12	14	9	20	10	.0372	.1714	.0503	.7839	.3725

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Table 28. (cont.) Potentially Statistically Significant Neoplasms in Mice

gender organ tumor	Incidence Veh	Low	Med	MedHi	High	Significance Levels Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
Female Mice (cont.)										
STOMACH										
# Evaluated	75	75	74	75	75					
Adjusted # at risk	56.6	52.9	52.0	51.8	28.2					
Fibrosarcoma	0	0	0	0	2	.0134	.1084	.	.	.
Adjusted # at risk	56.6	52.9	52.0	51.8	29.9					
Leiomyoma/Leiomysarcoma	0	0	0	0	3	.0016	.0370	.	.	.
Adjusted # at risk	56.6	52.9	52.0	51.8	29.9					
Leiomyosarcoma	0	0	0	0	3	.0016	.0370	.	.	.
Adjusted # at risk	56.6	52.9	52.6	53.4	37.0					
Papilloma	1	0	3	6	16	<.0001	<.0001	.0483	.2815	1
Adjusted # at risk	56.6	53.2	52.2	52.7	33.1					
Squamous Cell Carcinoma	0	1	1	5	12	<.0001	<.0001	.0233	.4815	.4862
UTERUS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	57.4	56.3	55.1	54.4	30.3					
Endometrial Stromal Polyp	6	9	14	11	8	.0597	.0529	.1197	.0340	.2776

As with rats, in male mice, the test of trend and pairwise comparisons between the high, dose group with vehicle in papilloma of the stomach was highly statistical significant (both $p < 0.0001$, with trend < 0.025 and pairwise test < 0.05) even adjusting for multiplicity. The pairwise test between the medium high dose and vehicle was also statistically significant ($p = 0.0002 < 0.05$). The tests of trend and pairwise comparison of the high dose to vehicle in terms of squamous cell carcinoma of the stomach were also statistically significant ($p < 0.0001 < 0.025$ and $p = 0.0006 < 0.05$, respectively), as were the tests of Leiomysarcoma ($p < 0.0010 < 0.025$ and $p = 0.0324 < 0.05$, respectively). In the kidneys the tests of trend in carcinoma and pooled carcinoma and adenoma were also statistically significant ($p = 0.0015 < 0.025$ and $0.0003 < 0.005$, respectively). Again, although a couple of p values were close, no other test achieved the multiplicity adjusted levels of statistical significance.

As with rats, results in female mice are similar to those in male mice. The tests of trend and pairwise comparison between the high dose group with vehicle in squamous cell carcinoma of the stomach was highly statistical significant (both $p < 0.0001$, with trend < 0.025 and pairwise test < 0.05) even adjusting for multiplicity. Results are similar for papilloma of the stomach with significant tests of trend ($p < 0.0001 < 0.005$) and comparison between the high dose and vehicle ($p < 0.0001 < 0.01$). The comparison to vehicle of the medium high dose was also barely statistically significant ($p = 0.0233 < 0.025$) in stomach squamous cell carcinoma. The tests of trend and pairwise comparison of the high dose to vehicle in terms of Leiomysarcoma were statistically significant ($p = 0.0016 < 0.025$ and $p = 0.0370 < 0.05$, respectively). In the kidneys the tests of trend in carcinoma and pooled carcinoma and adenoma were identical, and were also statistically significant (both $p = 0.0002 < 0.025$ and $0.0117 < 0.025$, respectively). Again, although several were close, no other test achieved the multiplicity adjusted levels of statistical significance.

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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

NA

5. SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

Please see Section 1.3 above.

5.2. Conclusions and Recommendations

Please see Section 1.1 above.

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APPENDICES

Appendix 1. FDA Survival Analysis

Simple summary life tables in mortality are presented in the report (Tables 14, 15, 19, and 20 above). Kaplan-Meier estimated survival curves across study groups for each gender are displayed below in Figures A.1.1 and A.1.2 for rats and Figures A.1.3 - A.1.6 for mice. Because of high mortlity in the first week in the high dose group (Group 5) in both genders in mice, dosage was decreased. Figures A.1.5 and A.1.6 show survival plots ignoring these early deaths. The plots include 95% confidence intervals around each survival curve (colored area around each curve). These plots are also supported by tests of homogeneity in survival over the five different treatment groups, tests of homogeneity and trend over all five treatment groups, and the results of pairwise comparisons of the high dose to the vehicle. The statistical significance levels (i.e., p-values) are provided in Tables A.1.1. and A.1.2., below. One might note that the log rank tests places greater weight on later events, while the Wilcoxon test tends to weight them more equally, and thus places more weight on differences in earlier events than does the log rank test.

Table A.1.1. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Rat Study

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Rat Homogeneity over Groups 1-5	< 0.0001	< 0.0001	0.4421	0.2737
Homogeneity over Groups 1-4	< 0.0001	< 0.0001	0.2904	0.1602
Homogeneity over Groups 1-3	0.0292	0.0153	0.2090	0.1594
No trend over Groups 1-5	< 0.0001	< 0.0001	0.3427	0.2033
No trend over Groups 1-4	< 0.0001	< 0.0001	0.1345	0.0389
No trend over Groups 1-3	0.0169	0.0119	0.1386	0.0734
No Difference Between Groups 1 vs 5	< 0.0001	< 0.0001	0.4943	0.3229
No Difference Between Groups 1 vs 4	< 0.0001	< 0.0001	0.2503	0.0931
No Difference Between Groups 1 vs 3	0.0180	0.0142	0.1205	0.0613

From Figure A.1.1, in male rats, the HPMC vehicle and Low dose group are largely intertwined, with the highest survival, while the Medium dose group has the next highest survival, and the Medium-High and High dose groups having the lowest but quite close survival over the study period. These groups were sacrificed early due to low survival. Although such This is sufficient to cause significant tests of lack of homogeneity, no trend, and no difference between the highest doses and vehicle in groups 1-4 and groups 1-5 (all 12 $p < 0.0001$, usually much less than the 0.0001 level). Even the seperation of the Medium dose group from the Vehicle and Low dose is sufficient to result in consistently statistically significant results (all six $p \leq 0.0292$). The situation in female rats is quite different. From Figure A.1.2, in female rats, although the HPMC vehicle seems to have slightly highest survival, the survival curves of the other dose groups are generally quite close and are largely intertwined. While this is not strong evidence of no differences it is evidence of no strong differences (all six $p \geq 0.2033$). Results of the tests using treatment subgroups 1-4 and 1-3 really only included to match those of for male

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rats. Note that the Wilcoxon test is more sensitive to early differences in survival and the corresponding test of lack of trend is barely statistically significant at the usual level (i.e., Wilcoxon p = 0.0389), but this conclusion is not supported by the Logrank test (p = 0.1386).

Figure A.1.1 Kaplan-Meier Survival Curves for Male Rats

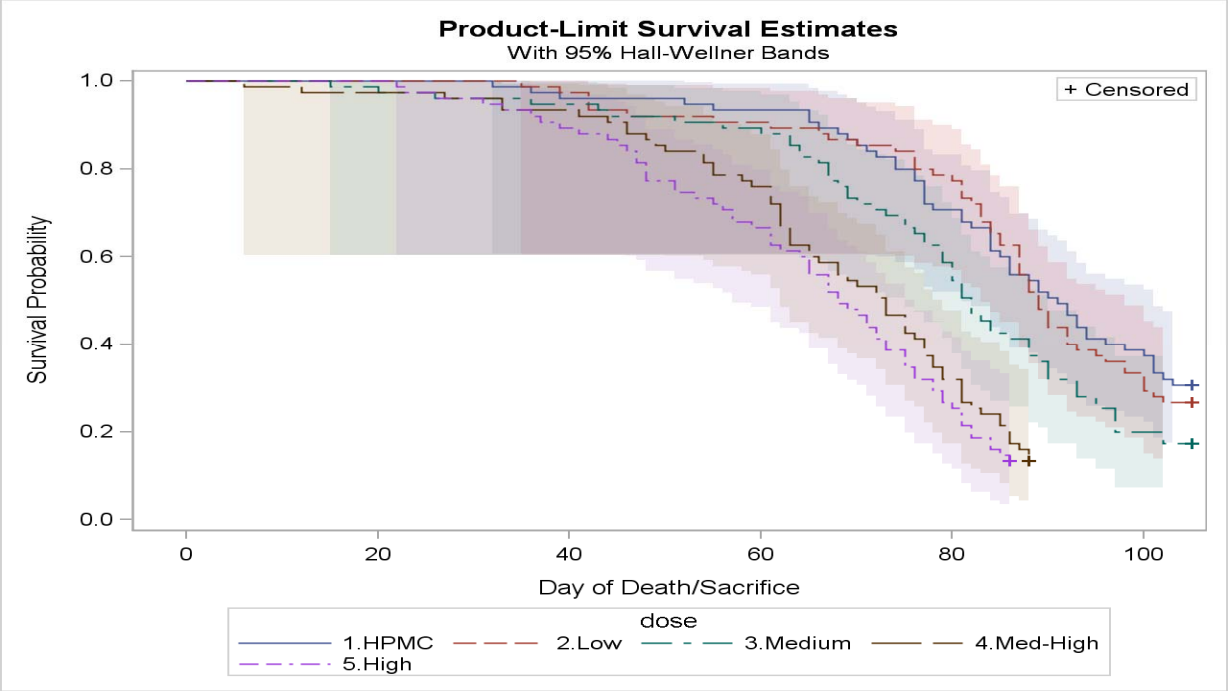
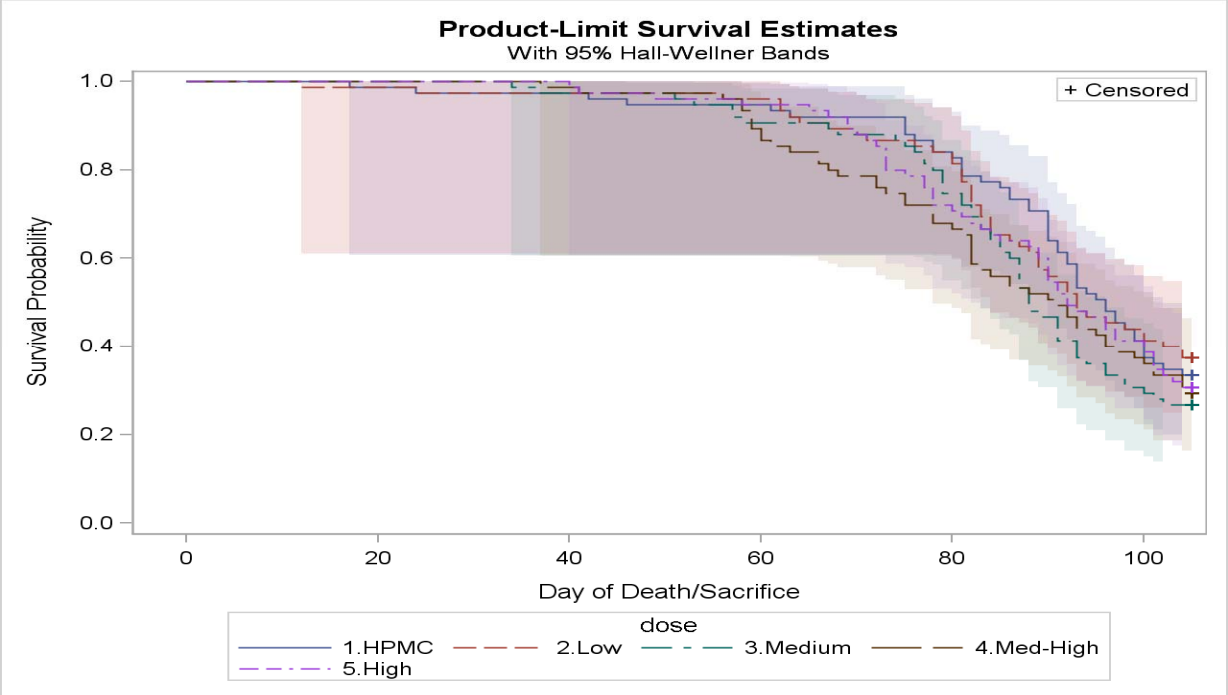


Figure A.1.2 Kaplan-Meier Survival Curves for Female Rats



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Recall that in mice due to high mortality in the first week, beginning on Day 9 of the study, the dose level for the High dose, Group 5, was decreased to 400 mg/kg/day. The survival curves for the High dose groups for each mouse gender in Figures A.1.3 and A.1.4 show the effect of these early deaths. Because of this initial high mortality, two additional separate adjustments were performed. The first deleted the high dose from analysis and conducted the analysis with the remaining four dose groups. The second analysis deleted those animals that animals that died before day 9 from the High dose group. Note this is essentially an analysis conditional upon the mouse surviving at least 9 days on study. Conditional survival curves reflecting these deletions are presented in Figures A.1.5 and A.1.6.

Results for statistical tests of differences in survival in mice are presented below:

Table 4. Statistical Significances of Tests of Homogeneity and Trend in Survival in the Mouse Study

Hypothesis Tested	Males		Females	
	Log rank	Wilcoxon	Log rank	Wilcoxon
Mouse Homogeneity over Groups 1-5 [a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Homogeneity over Groups 1-4	0.1115	0.3129	0.4603	0.5208
No trend over Groups 1-5 [a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
No trend over Groups 1-4	0.1119	0.3181	0.1847	0.2348
No Difference Between Groups 1 vs 5[a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001
No Difference Between Groups 1 vs 4	0.4876	0.7711	0.1099	0.1322

[a] Printed P-value bounds are identical whether one conditions on survival to day 9 or not.

Figures A.1.3 and A.1.4, below, display the gender specific survival curves over the five dose groups. Note that in each gender the High dose group is clearly separated from the remaining dose groups. This is sufficient to result in the highly statistically significant tests of homogeneity, lack of trend, and no difference between the High dose and the vehicle dose group (for each gender all six $p < 0.0001$). One might speculate that the separation of the High dose from the other dose groups may be due solely to the few early deaths in the High dose group. However, as shown in Figures A.1.5 and A.1.6, below, i.e., the survival curves over the five dose groups conditional on survival for the first week of the study, the High dose remains seperated from the remaining dose groups. The significance levels for the tests of homogeneity and trend over groups 1-5, and the pairwise comparison between the High dose and vehicle, although larger, will all still be highly statistically significant (i.e., still have all six $p < 0.0001$).

In both sets of plots, for both genders, the survival curves for the dose groups 1-4 are more or less closely intertwined, but with much higher survival than that in the High dose group. This is consistent with the tests of survival completely deleting the High dose group, i.e., none of the tests of homogeneity, lack of trend, and no difference between the High dose and the vehicle dose group were particularly statistically significant, at least at the usual 0.05 level (Males: all six $p \geq 0.1115$, Females all six $p \geq 0.1009$). This suggests that differences in survival are almost all due to differences in the High dose from the remaining dose groups.

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Figure A.1.3 Kaplan-Meier Survival Curves for Male Mice

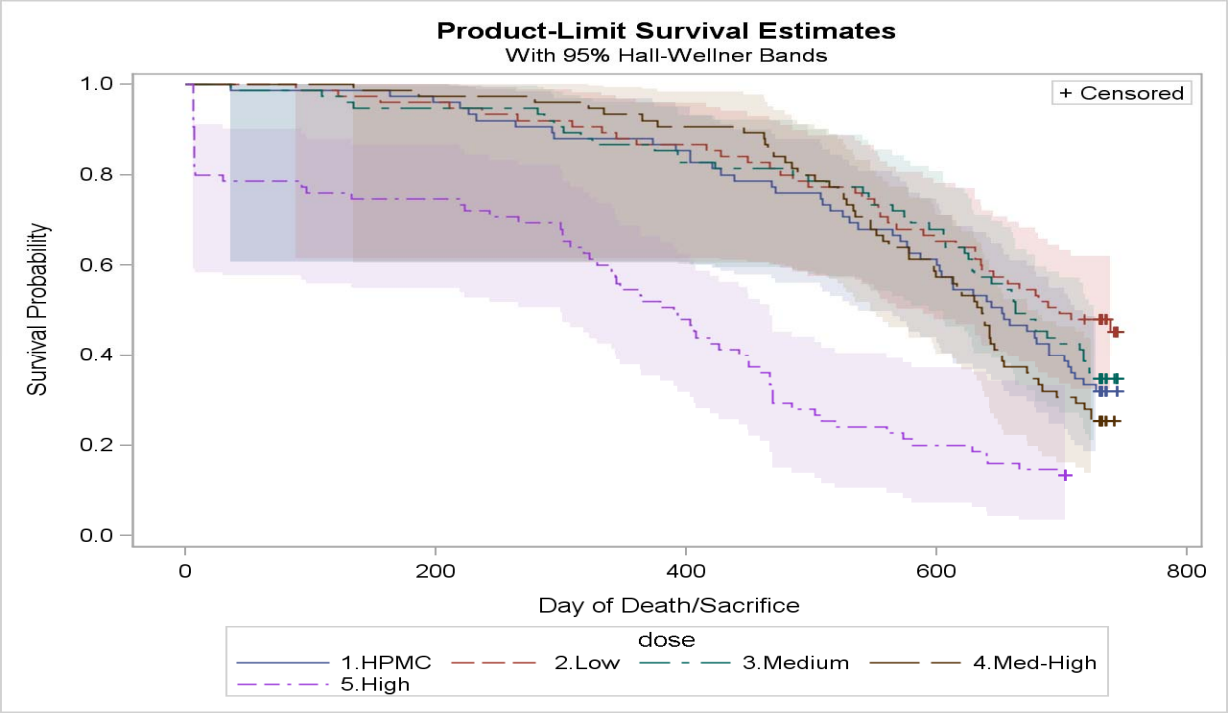


Figure A.1.4 Kaplan-Meier Survival Curves for Female Mice

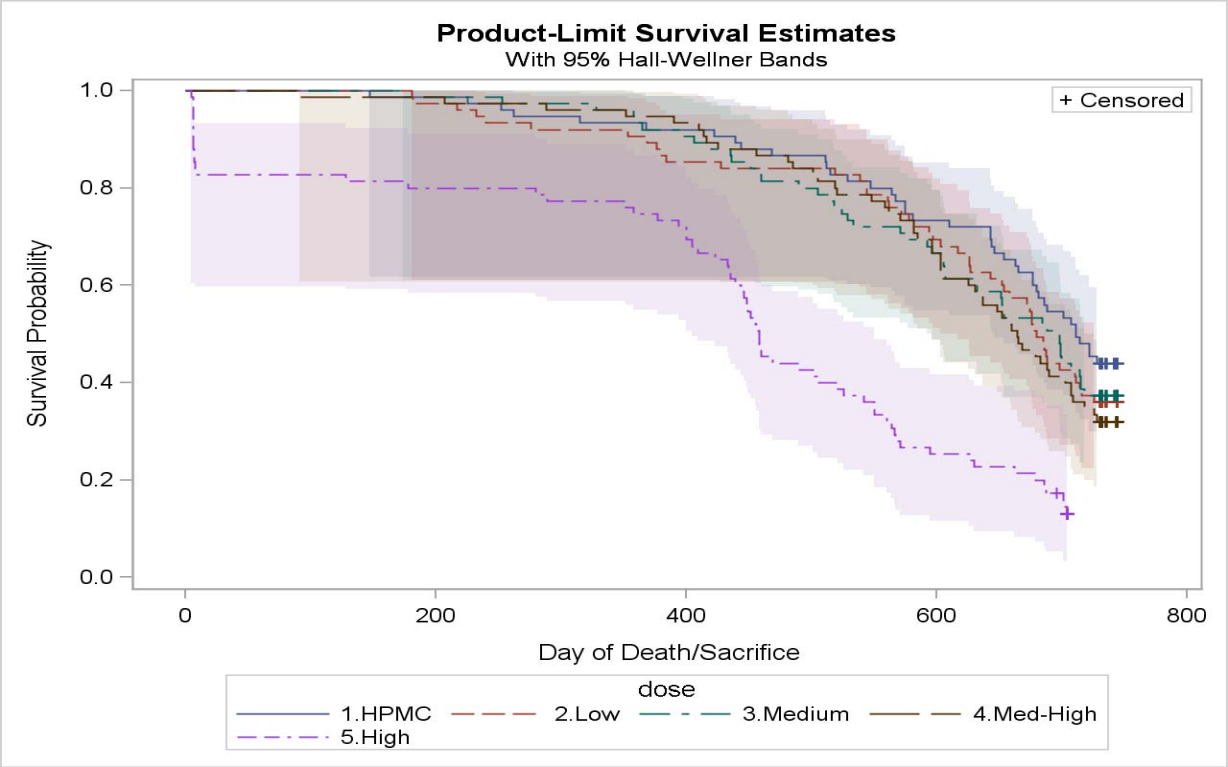


Figure A.1.5 Kaplan-Meier Survival Curves for Male Mice Deleting Early Deaths

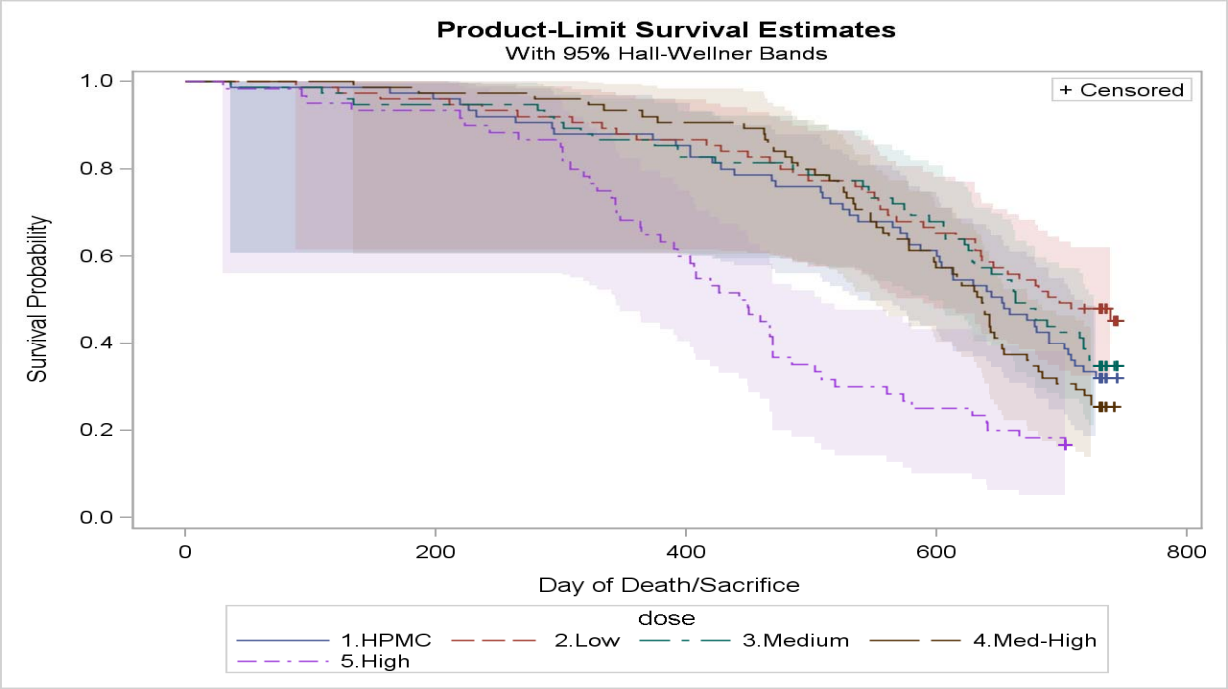
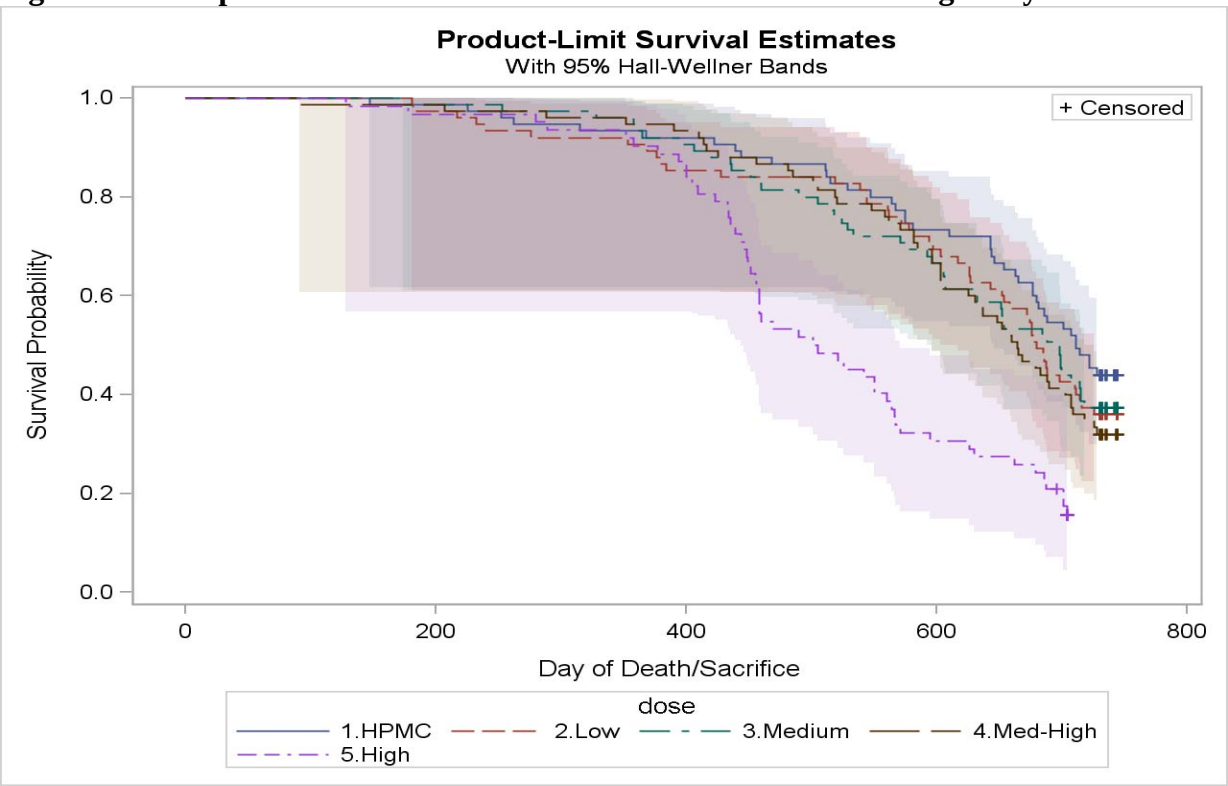


Figure A.1.6 Kaplan-Meier Survival Curves for Female Mice Deleting Early Deaths



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Appendix 2. FDA Poly-k Tumorigenicity Analysis

The poly-k test, here with k=3, modifies the original Cochran-Armitage test to adjust for differences in mortality (please see Bailer & Portier, 1988, Bieler & Williams, 1993). The tests used here are small sample exact permutation tests of tumor incidence. When there were no tumors of the specific type being analyzed in either column of the 2x2 table corresponding to a pairwise comparison an argument could be made that the p-value for this test should be 1.0. However, largely for readability, in the tables below these p-values are considered as missing (i.e., corresponding to a null test), denoted by a period ".". Note that the StatXact program used for these analyses adjusts for the variance, which would be 0. Then the significance levels of the test statistics are based on the result of a division by 0, i.e., undefined, and hence StatXact codes these p-values as missing.

For each species by gender by organ the number of animals analyzed and used in the statistical tests is presented first. Note that indicating an organ was not examined requires a specification in the data (please see section 2.2 above). The entry for each tumor is preceded by the adjusted number of animals at risk for that tumor. It seems clear that an animal that dies early without a tumor reduces the size of the risk set for that getting that particular umor. The poly-k test down weights such animals, and as discussed in Section 1.3.1.3, above, the sum of these poly-k weights seems to be a better estimate of the number of animals at risk of getting that tumor. This sum is given in the row labeled "Adjusted # at risk". Tumor incidence is presented next, with the significance levels of the tests of trend, and the results of pairwise tests between the high, medium-high, medium, and low dose groups versus HPMC vehicle. For this analysis, incidence in the vehicle group is used to assess background tumor incidence, and thus whether a tumor is considered to be rare (background incidence <1%) or common.

To adjust for the multiplicity of tests the so-called Haseman-Lin-Rahman (HLR) rules discussed in Section 1.3.1.4 are often applied. That is, when testing for trend over dose groups 1-4 and the difference between the highest dose group with a control group, to control the overall Type I error rate to roughly 10% for a standard two species, two sex study, one compares the unadjusted significance level of the trend test to 0.005 for common tumors and 0.025 for rare tumors, and the pairwise test to 0.01 for common tumors and 0.05 for rare tumors. Using these adjustments for other tests, like testing the comparisons between the low, medium, and medium-high dose groups versus vehicle can be expected to increase the overall type I error rate to some value above the nominal rough 10% level, possibly considerably higher than the nominal 10% rate.

Table A.2.1 in rats and Table A.2.2 in mice show the tumors that had at least one mortality adjusted test whose nominal statistical significance was at least no more than 0.05. Note that when one adjusts for multiplicity these nominally significant comparisons may not be statistically significant. Tables A.2.3 and A.2.4 display all incidences and statistical test results for male and female rats, respectively, while Tables A.2.5 and A.2.6 present similar results in male and female mice. The p-values of the poly-k test are based on exact tests from StatXact as

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discussed above. As also noted above, the period '.' denotes the p-values of tests of dose groups with no tumors in any group.

Table A.2.1 Potentially Statistically Significant Neoplasms in Rats

gender organ tumor	Incidence Veh	Low	Med	MedHi	High	Significance Levels Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
Male Rats										
BRAIN										
# Evaluated	73	75	75	75	74					
Adjusted # at risk	49.5	48.6	40.3	25.3	23.1					
CEREBRUM- GRANULAR CELL TUMOR	0	0	0	0	2	.0149	.0990	.	.	.
KIDNEYS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.7	25.9	25.2					
RENAL TUBULE- ADENOMA	0	0	1	1	4	.0006	.0110	.3378	.4494	.
LIVER										
# Evaluated	75	74	75	75	75					
Adjusted # at risk	50.1	49.9	42.2	25.3	22.2					
Hepato. Adenoma/Carcinoma	2	8	5	0	0	.9542	1	1	.1520	.0426
PARATHYROID										
# Evaluated	68	64	70	71	70					
Adjusted # at risk	44.5	42.8	38.7	23.8	21.5					
ADENOMA	0	0	1	0	2	.0251	.1010	.	.4634	.
Adjusted # at risk	44.5	42.8	38.7	23.8	22.3					
Adenoma, any	0	0	1	0	3	.0049	.0337	.	.4634	.
SKIN										
# Evaluated	75	74	75	74	75					
Adjusted # at risk	50.8	51.2	41.4	28.7	27.4					
KERATOACANTHOMA	8	8	9	7	9	.0256	.0736	.2494	.3236	.6237
Adjusted # at risk	49.6	48.9	40.3	24.7	23.6					
SUBCUT TISS.-FIBROSARCOMA	0	1	0	0	2	.0357	.0990	.	.	.4948
Adjusted # at risk	51.2	52.1	42.1	30.9	29.7					
Sq.Cell Pap./Carc./Kerato.	11	11	10	10	12	.0136	.0532	1825	.4950	.6147
STOMACH										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	49.2	50.1	60.0	61.3					
NONGLAND.- SQUAMOUS CELL CARCINOMA	0	5	18	51	58	<.0001	<.0001	<.0001	<.0001	.0281
Adjusted # at risk	49.6	53.5	51.4	55.7	58.4					
NONGLAND.- SQ. CELL PAP.	0	22	24	46	49	<.0001	<.0001	<.0001	<.0001	<.0001
Adjusted # at risk	49.6	53.5	55.3	70.9	71.1					
Nongland.Sq.Cell Pap./Carc.	0	22	34	68	70	<.0001	<.0001	<.0001	<.0001	<.0001
TESTES										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	50.3	49.0	41.4	30.2	32.8					
INTERSTITIAL CELL- ADENOMA	3	3	2	9	17	<.0001	<.0001	.0053	.7514	.6415
Adjusted # at risk	49.6	48.6	40.3	25.3	23.5					
INTERSTITIAL CELL- ADENOMA, BILATERAL	0	0	0	0	2	.0149	.0990	.	.	.
Adjusted # at risk	50.3	49.0	41.4	30.2	34.0					
Intersit. Adenoma, any	3	3	2	9	19	<.0001	<.0001	.0053	.7514	.6415

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Table A.2.1 (cont.) Potentially Statistically Significant Neoplasms in Rats

gender organ tumor	Incidence Veh	Low	Med	MedHi	High	Trend	Significance Levels Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
Female Rats										
CAVITY, ABDOMINAL										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.9					
HISTIOCYTIC SARCOMA	0	0	0	0	2	.0397	.2335	.	.	.
KIDNEYS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.9					
RENAL TUBULE-CARCINOMA	0	0	0	2	4	.0015	.0523	.2190	.	.
Adjusted # at risk	54.9	53.2	48.7	48.1	52.4					
Renam Tub. Adenoma/Carc.	1	0	0	2	5	.0033	.0942	.4555	1	1
MAMMARY GLAND										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	57.8	56.6	52.7	50.3	56.8					
CARCINOMA	10	13	13	8	19	.0688	.0372	.6800	.2364	.3036
STOMACH										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	49.6	56.6	65.8					
NONGLANDULAR-SQUAMOUS CELL CARCINOMA	0	1	4	30	48	<.0001	<.0001	<.0001	.0479	.4953
Adjusted # at risk	54.8	55.0	53.7	56.4	61.2					
NONGLANDULAR- SQUAMOUS CELL PAPILLOMA	0	11	21	31	24	<.0001	<.0001	<.0001	<.0001	.0003
Adjusted # at risk	54.8	55.0	54.3	61.1	69.3					
Nongland. Sq, Pap./Carc.	0	11	23	48	58	<.0001	<.0001	<.0001	<.0001	.0003
VAGINA										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	52.2					
Endo. Stromal polyp/sarcoma	0	0	0	1	2	.0314	.2383	.4706	.	.

In male rats, the tests of trend and all pairwise comparisons of the four treated groups to HPMC vehicle in nonglandular squamous cell papilloma and pooled papilloma and carcinoma were all highly statistical significant (all p<0.0001, with both trend < 0.025 and pairwise tests < 0.05) even adjusting for multiplicity. The same holds for nonglandular squamous cell carcinoma except that the comparison between the low dose group and vehickle was just statistically significant (p=0.0281 < 0.05). The tests of trend and pairwise differences between the high dose and vehicle in interstial cell adenoma of the testes were both highly statistically significant (p < 0.0001 < 0.005 and 0.1, respectively). Accepting the increase in probable error from including other tests, the pairwise comparison between the medium dose group and vehicle would also be classified as statistically significant (p = 0.0053 < 0.01). Since adding the interstial cell carcinoma only affects incidence in the high dose group, the tests for pooled interstitial cell adenoma and carcinoma are, at least to the printed significance levels, identical to those for carcinoma are identical to those for interstial cell adenoma alone. . In this organ, the simple test of trend in interstial cell bilateral adenoma was also statistically significant (p = 0.0149 < 0.025), though not extremely. The test of trend in renal tubule adenoma of the kidneys was also statistically significant (p = 0.0006 < 0.025), as were the tests of granular cell tumor of the brain (p = 0.0149 < 0.025) and the test of pooled adenomas of the parathyroid (p = 0.0049 < 0.025). The test of trend in simple adenoma of the parathyroid was close to statistical

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significance (p= 0.0251 > 0.025). No other test achieved the multiplicity adjusted levels of statistical significance.

Results in female rats are rather similar. In female rats, the tests of trend and all pairwise comparisons between the high, medium high, and medium dose groups with vehicle in nonglandular squamous cell papilloma and pooled papilloma and carcinoma were all highly statistical significant (all p < 0.0001, with both trend < 0.025 and pairwise tests < 0.05) even adjusting for multiplicity. For both of these the comparison between the low dose and vehicle was also statistically significant (for both tumors, p = 0.0003 < 0.05). These results also hold for the tests of trend and pairwise comparisons between the high and medium high dose groups in nonglandular squamous cell carcinoma (p < 0.0001, with both trend < 0.025 and pairwise tests < 0.05). The comparison between the medium dose and vehicle was barely statistically significant (p = 0.0479 < 0.05). The test of trend in renal tubule carcinoma of the kidneys was also statistically significant (p = 0.0015 < 0.025), as was the test of pooled adenoma and carcinoma (p = 0.0033 < 0.005). Again, no other test achieved the multiplicity adjusted levels of statistical significance, although several were somewhat close.

Those organ-tumor combinations with at least one nominally statistically significant result (p ≤ 0.05) in mice are summarized below:

Table A.2.2 Potentially Statistically Significant Neoplasms in Mice

gender	Incidence					Significance Levels				
organ tumor	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
Male Mice										
KIDNEY										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	48.7	22.1					
Adenoma	1	2	0	5	3	.0074	.0922	.1067	1	.5382
Adjusted # at risk	47.5	52.1	50.7	49.3	22.8					
Adenoma/Carcinoma	1	2	2	8	5	.0003	.0109	.0179	.5234	.5382
Adjusted # at risk	47.5	52.1	50.7	47.7	22.0					
Carcinoma	0	0	2	4	3	.0015	.0265	.0585	.2631	.
LUNG WITH BRONCHI										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	50.0	53.9	52.5	51.4	23.2					
Bronchiolo-Alveolar Adenocarcinoma	6	6	5	11	5	.0411	.2292	.1541	.7598	.6607
STOMACH										
# Evaluated	74	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	47.1	23.0					
Leiomyosarcoma	0	0	0	0	3	.0010	.0324	.	.	.
Adjusted # at risk	47.5	52.5	51.1	50.0	30.5					
Papilloma	0	1	3	12	14	<.0001	<.0001	.0002	.1369	.5253
Adjusted # at risk	47.5	52.4	50.6	47.7	22.3					
Squamous Cell Carcinoma	0	1	0	2	6	<.0001	.0006	.2473	.	.5253

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Table A.2.2 (cont.) Potentially Statistically Significant Neoplasms in Mice

gender organ tumor	Incidence Veh	Low	Med	MedHi	High	Significance Levels Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
Female Mice										
HEMOLYMPHORETICULAR										
# Evaluated	23	18	20	19	12					
Adjusted # at risk	15.7	12.4	14.6	10.3	6.0					
Leukemia	1	0	0	0	2	.0269	.1404	1	1	1
KIDNEY										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.1	51.8	29.1					
Adenoma	0	0	0	2	4	.0002	.0117	.2248	.	.
Adjusted # at risk	56.6	52.9	52.1	51.8	29.1					
Adenoma/Carcinoma	0	0	0	2	4	.0002	.0117	.2248	.	.
LUNG WITH BRONCHI										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	58.6	56.9	54.6	55.8	31.8					
Bronchiolo-Alv. Adenoma	12	14	9	20	10	.0372	.1714	.0503	.7839	.3725
STOMACH										
# Evaluated	75	75	74	75	75					
Adjusted # at risk	56.6	52.9	52.0	51.8	28.2					
Fibrosarcoma	0	0	0	0	2	.0134	.1084	.	.	.
Adjusted # at risk	56.6	52.9	52.0	51.8	29.9					
Leiomyoma/Leiomysarcoma	0	0	0	0	3	.0016	.0370	.	.	.
Adjusted # at risk	56.6	52.9	52.0	51.8	29.9					
Leiomyosarcoma	0	0	0	0	3	.0016	.0370	.	.	.
Adjusted # at risk	56.6	52.9	52.6	53.4	37.0					
Papilloma	1	0	3	6	16	<.0001	<.0001	.0483	.2815	1
Adjusted # at risk	56.6	53.2	52.2	52.7	33.1					
Squamous Cell Carcinoma	0	1	1	5	12	<.0001	<.0001	.0233	.4815	.4862
UTERUS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	57.4	56.3	55.1	54.4	30.3					
Endometrial Stromal Polyp	6	9	14	11	8	.0597	.0529	.1197	.0340	.2776

As with rats, in male mice, the test of trend and pairwise comparisons between the high, dose group with vehicle in papilloma of the stomach was highly statistical significant (both $p < 0.0001$, with trend < 0.025 and pairwise test < 0.05) even adjusting for multiplicity. The pairwise test between the medium high dose and vehicle was also statistically significant ($p = 0.0002 < 0.05$). The tests of trend and pairwise comparison of the high dose to vehicle in terms of squamous cell carcinoma of the stomach were also statistically significant ($p < 0.0001 < 0.025$ and $p = 0.0006 < 0.05$, respectively), as were the tests of Leiomysarcoma ($p < 0.0010 < 0.025$ and $p = 0.0324 < 0.05$, respectively). In the kidneys the tests of trend in carcinoma and pooled carcinoma and adenoma were also statistically significant ($p = 0.0015 < 0.025$ and $0.0003 < 0.005$, respectively). Again, although a couple were close, no other test achieved the multiplicity adjusted levels of statistical significance.

As with rats, results in female mice are similar to those in male mice. The tests of trend and pairwise comparison between the high dose group with vehicle in squamous cell carcinoma of the stomach was highly statistical significant (both $p < 0.0001$, with trend < 0.025 and pairwise test < 0.05) even adjusting for multiplicity. Results are similar for papilloma of the stomach with significant tests of trend ($p < 0.0001 < 0.005$) and comparison between the high

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dose and vehicle ($p < 0.0001 < 0.01$). The comparison to vehicle of the medium high dose was also barely statistically significant ($p = 0.0233 < 0.025$) in stomach squamous cell carcinoma. The tests of trend and pairwise comparison of the high dose to vehicle in terms of Leiomysarcoma were statistically significant ($p = 0.0016 < 0.025$ and $p = 0.0370 < 0.05$, respectively). In the kidneys the tests of trend in carcinoma and pooled carcinoma and adenoma were identical, and were also statistically significant (both $p = 0.0002 < 0.025$ and $0.0117 < 0.025$, respectively). Again, although several were close, no other test achieved the multiplicity adjusted levels of statistical significance.

No other tests or comparisons achieved the Haseman-Lin-Rahman multiplicity adjusted levels of significance. Complete incidence tables in each species by gender combination are presented below:

Table A.2.3 Incidence and Significance Levels of all Tests on Neoplasms in Male Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
ADRENALS										
# Evaluated	75	74	75	74	74					
Adjusted # at risk	49.6	47.9	40.3	24.7	21.8					
CORTEX- ADENOMA	2	1	0	0	0	.9810	1	1	1	.8711
Adjusted # at risk	52.5	49.8	43.4	26.1	25.2					
MEDULLA- PHEOCHROMOCYTOMA, BENI	15	6	14	3	6	.7020	.7617	.9813	.4326	.9902
Adjusted # at risk	50.0	49.0	40.3	24.7	22.2					
MEDULLA- PHEOCHROMOCYTOMA, MALI	2	2	0	0	1	.6695	.6714	1	1	.6758
Adjusted # at risk	52.9	50.9	43.4	26.1	25.6					
Medulla, Pheochromocytoma Any	17	8	14	3	7	.7448	.7490	.9919	.5914	.9864
Adjusted # at risk	52.5	49.8	43.4	26.1	25.2					
Medulla, Pheochromocytoma [B]	15	6	14	3	6	.7020	.7617	.9813	.4326	.9902
BRAIN										
# Evaluated	73	75	75	75	74					
Adjusted # at risk	50.2	49.3	41.4	25.7	22.2					
Astrocytoma [M] Both	1	1	2	1	0	.5825	1	.5586	.4252	.7475
Adjusted # at risk	50.2	49.3	41.4	25.7	23.1					
Astrocytoma [M]/Gran.Cell Tmr	1	1	2	1	2	.0997	.2319	.5586	.4252	.7475
Adjusted # at risk	49.5	48.6	40.3	25.7	22.2					
CEREBELLUM- ASTROCYTOMA, MALIGN	0	0	0	1	0	.2554	.	.3378	.	.
Adjusted # at risk	49.5	48.8	40.3	25.3	22.2					
CEREBELLUM- MENINGES- SARCOMA	0	1	0	0	0	.7337	.	.	.	.4948
Adjusted # at risk	50.2	49.3	41.4	25.3	22.2					
CEREBRUM- ASTROCYTOMA, MALIGNAN	1	1	2	0	0	.7784	1	1	.4252	.7475
Adjusted # at risk	49.5	48.6	40.3	25.3	23.1					
CEREBRUM- GRANULAR CELL TUMOR,	0	0	0	0	2	.0149	.0990	.	.	.
CAVITY, ABDOMINAL										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.9	40.3	25.3	22.2					
FIBROMA	0	1	0	0	0	.7337	.	.	.	.4948
Adjusted # at risk	49.6	49.1	40.3	25.3	22.2					
HEMANGIOMA	0	1	0	0	0	.7351	.	.	.	.5000
Adjusted # at risk	49.6	48.6	40.9	25.3	22.2					
HEMANGIOSARCOMA	0	0	1	0	0	.4728	.	.	.4494	.
Adjusted # at risk	49.7	48.6	40.3	25.3	22.2					
HISTIOCYTIC SARCOMA	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	50.5	48.6	40.3	25.3	22.2					
MESOTHELIOMA, MALIGNANT	1	0	0	0	0	1	1	1	1	1

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Table A.2.3 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
CAVITY, ORAL										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	41.1	25.9	22.2					
SQUAMOUS CELL CARCINOMA	0	0	1	1	0	.3021	.	.3378	.4556	.
Adjusted # at risk	49.6	48.9	40.3	25.3	22.2					
SQUAMOUS CELL PAPILLOMA	0	1	0	0	0	.7337	.	.	.	.4948
Adjusted # at risk	49.6	48.9	41.1	25.9	22.2					
Sq. Cell Papilloma/Carcinoma	0	1	1	1	0	.4018	.	.3378	.4556	.4948
CAVITY, THORACIC										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.9	25.3	22.2					
HEMANGIOSARCOMA	0	0	1	0	0	.4728	.	.	.4494	.
EAR										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.3	25.3	22.8					
EXTERNAL CANAL, SQUAMOUS CELL P	0	0	0	0	1	.1196	.3099	.	.	.
Adjusted # at risk	49.6	48.6	40.3	25.3	22.2					
SQUAMOUS CELL PAPILLOMA	0	1	0	0	0	.7337	.	.	.	.4948
Adjusted # at risk	49.6	48.6	40.3	25.3	22.8					
Sq. Cell Pap./Ext. Canal	0	1	0	0	1	.1792	.3099	.	.	.4948
EPIDIDYMIDES										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.9	48.6	40.3	25.3	22.2					
MESOTHELIOMA, MALIGNANT	1	0	0	0	0	1	1	1	1	1
HEAD										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.3	25.8	22.2					
NASOTURBINATE- ADENOCARCINOMA	0	0	0	1	0	.2554	.	.3378	.	.
JEJUNUM										
# Evaluated	65	65	64	58	61					
Adjusted # at risk	46.5	44.5	38.2	20.0	18.5					
LEIOMYOMA	0	0	1	0	0	.4545	.	.	.4524	.
KIDNEYS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.3	25.7	22.2					
HEMANGIOSARCOMA	0	0	0	1	0	.2554	.	.3378	.	.
Adjusted # at risk	50.0	48.6	40.3	25.3	22.2					
LIPOMA	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	49.6	48.6	40.3	25.3	22.7					
LIPOSARCOMA	0	0	0	0	1	.1196	.3099	.	.	.
Adjusted # at risk	50.0	48.6	40.3	25.9	22.7					
Lipoma/-sarcoma/Sarcoma	1	0	0	1	1	.1492	.5268	.5646	1	1
Adjusted # at risk	50.0	48.6	40.3	25.3	22.7					
Lipoma/Liposarcoma	1	0	0	0	1	.3026	.5268	1	1	1
Adjusted # at risk	49.6	48.6	40.7	25.9	25.2					
RENAL TUBULE- ADENOMA	0	0	1	1	4	.0006	.0110	.3378	.4494	.
Adjusted # at risk	49.6	48.6	40.3	25.9	22.2					
SARCOMA	0	0	0	1	0	.2554	.	.3378	.	.
LIVER										
# Evaluated	75	74	75	75	75					
Adjusted # at risk	49.6	48.4	40.3	25.3	22.2					
HEPATOCELLULAR ADENOMA	0	2	1	0	0	.7175	.	.	.4494	.2423
Adjusted # at risk	50.1	49.7	42.2	25.3	22.2					
HEPATOCELLULAR CARCINOMA	2	6	4	0	0	.9421	1	1	.2593	.1278
Adjusted # at risk	49.6	48.2	40.3	26.0	22.2					
HISTIOCYTIC SARCOMA	0	0	0	1	0	.2554	.	.3378	.	.
Adjusted # at risk	50.1	49.9	42.2	25.3	22.2					
Hepato. Adenoma/Carcinoma	2	8	5	0	0	.9542	1	1	.1520	.0426

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Table A.2.3 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
LUNG WITH BRONCHI										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.3	25.3	22.2					
ALVEOLAR BRONCHIAL ADENOMA	0	0	1	0	0	.4728	.	.	.4494	.
LYMPH NODE, RENAL										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.7	25.3	22.2					
LYMPHOMA, PLEOMORPHIC	0	0	1	0	0	.4728	.	.	.4494	.
MAMMARY GLAND										
# Evaluated	73	74	72	72	74					
Adjusted # at risk	48.6	48.1	39.8	24.0	21.9					
CARCINOMA	0	0	1	0	0	.4667	.	.	.4483	.
Adjusted # at risk	48.6	48.1	39.6	24.0	21.9					
FIBROADENOMA	0	0	1	0	0	.4667	.	.	.4483	.
PANCREAS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	49.1	40.3	25.3	22.2					
ACINUS- ADENOMA	0	1	1	0	0	.6056	.	.	.4494	.5000
Adjusted # at risk	50.5	49.9	41.4	25.9	23.6					
ISLETS- ADENOMA	4	7	4	1	2	.7209	.6204	.8772	.5264	.2505
Adjusted # at risk	49.6	49.2	41.2	25.7	22.2					
ISLETS- CARCINOMA	1	4	2	1	0	.7667	1	.5646	.4328	.1810
Adjusted # at risk	50.5	50.5	42.3	26.3	23.6					
Islets Adenoma/Carinoma	5	11	6	2	2	.8244	.7144	.7653	.3770	.0857
PARATHYROID										
# Evaluated	68	64	70	71	70					
Adjusted # at risk	44.5	42.8	38.7	23.8	21.5					
ADENOMA	0	0	1	0	2	.0251	.1010	.	.4634	.
Adjusted # at risk	44.5	42.8	38.2	23.8	21.1					
ADENOMA, BILATERAL	0	0	0	0	1	.1250	.3231	.	.	.
Adjusted # at risk	44.5	42.8	38.7	23.8	22.3					
Adenoma, any	0	0	1	0	3	.0049	.0337	.	.4634	.
PITUITARY										
# Evaluated	75	74	75	74	74					
Adjusted # at risk	60.5	54.6	46.5	32.3	26.0					
PARS DISTALIS- ADENOMA	34	24	14	13	7	.9944	.9976	.9543	.9982	.9322
PREPUTIAL GLAND										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	49.1	40.3	25.3	22.2					
ADENOMA	1	1	0	0	0	.9309	1	1	1	.7526
Adjusted # at risk	49.6	48.6	40.6	25.3	22.2					
CARCINOMA	0	2	1	0	0	.7175	.	.	.4494	.2423
Adjusted # at risk	49.6	48.6	41.3	25.3	22.2					
Carcinoma incl. Sq. Cell	1	2	2	0	0	.8320	1	1	.4328	.4922
Adjusted # at risk	49.6	49.1	41.3	25.3	22.2					
Carcinoma/Adenoma	2	3	2	0	0	.9312	1	1	.6215	.5000
Adjusted # at risk	49.6	48.6	41.1	25.3	22.2					
SQUAMOUS CELL CARCINOMA	1	0	1	0	0	.7927	1	1	.7064	1
PROSTATE										
# Evaluated	73	74	75	75	75					
Adjusted # at risk	49.2	47.6	41.3	25.3	22.2					
ADENOCARCINOMA	0	0	1	0	0	.4783	.	.	.4556	.
RECTUM										
# Evaluated	74	75	75	74	74					
Adjusted # at risk	49.6	48.6	40.6	24.8	22.0					
ADENOMA	0	0	1	0	0	.4670	.	.	.4494	.
Adjusted # at risk	49.6	49.1	40.3	24.8	22.0					
LEIOMYOSARCOMA	0	1	0	0	0	.7322	.	.	.	.5000

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Table A.2.3 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
SKIN										
# Evaluated	75	74	75	74	75					
Adjusted # at risk	49.6	48.5	40.3	24.7	22.2					
BASAL CELL- ADENOMA	0	1	0	0	0	.7322	.	.	.	.4948
Adjusted # at risk	49.6	48.1	40.3	24.7	22.2					
HEMANGIOMA	0	1	0	0	0	.7322	.	.	.	.4948
Adjusted # at risk	50.8	51.2	41.4	28.7	27.4					
KERATOACANTHOMA	8	8	9	7	9	.0256	.0736	.2494	.3236	.6237
Adjusted # at risk	49.6	48.1	40.3	24.7	22.2					
SEBACEOUS CELL- ADENOMA	1	0	1	0	0	.7881	1	1	.6997	1
Adjusted # at risk	49.6	48.8	41.1	26.5	23.0					
SQUAMOUS CELL CARCINOMA	0	1	1	2	1	.0703	.3099	.1171	.4556	.4948
Adjusted # at risk	50.0	48.3	40.3	25.3	23.7					
SQUAMOUS CELL PAPILLOMA	3	3	0	1	2	.4278	.5063	.8105	1	.6415
Adjusted # at risk	50.8	48.5	40.3	25.2	22.2					
SUBCUT TISSUE- FIBROMA	5	4	0	1	0	.9867	1	.9211	1	.7358
Adjusted # at risk	49.6	48.9	40.3	24.7	23.6					
SUBCUT TISSUE- FIBROSARCOMA	0	1	0	0	2	.0357	.0990	.	.	.4948
Adjusted # at risk	49.6	48.1	40.9	24.7	22.2					
SUBCUT TISSUE- HEMANGIOPERICYTO	0	0	1	0	0	.4699	.	.	.4494	.
Adjusted # at risk	50.0	48.1	40.3	25.7	22.2					
SUBCUT TISSUE- HISTIOCYTIC SARC	1	0	0	1	0	.4904	1	.5586	1	1
Adjusted # at risk	49.6	48.1	40.7	24.7	22.2					
SUBCUT TISSUE- LIPOMA	0	1	1	0	0	.6027	.	.	.4494	.4948
Adjusted # at risk	49.6	48.5	40.3	24.7	22.2					
SUBCUT TISSUE- SCHWANNOMA, BENI	0	1	0	0	0	.7322	.	.	.	.4948
Adjusted # at risk	49.6	48.2	41.0	24.7	22.2					
SUBCUT TISSUE- SCHWANNOMA, MALI	0	1	2	0	0	.6018	.	.	.2047	.4948
Adjusted # at risk	51.2	52.1	42.1	30.9	29.7					
Sq.Cell Pap./Carc./Kerato.	11	11	10	10	12	.0136	.0532	.1825	.4950	.6147
Adjusted # at risk	50.0	49.0	41.1	27.0	24.5					
Sq.Cell Pap./Carcinoma	3	4	1	3	3	.1459	.2966	.3330	.9138	.4886
Adjusted # at risk	49.6	48.9	40.9	24.7	23.6					
Subcut.Fibro/Hemangiopericyt	0	1	1	0	2	.0540	.0990	.	.4494	.4948
Adjusted # at risk	50.8	48.6	41.0	25.2	22.2					
Sucut Tis.Fibroma/-sarcoma	5	5	2	1	0	.9792	1	.9211	.9072	.6033
SPINAL CORD, CERVICAL										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.4	25.3	22.2					
ASTROCYTOMA	0	0	1	0	0	.4728	.	.	.4494	.
SPLEEN										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.3	26.5	22.2					
GRANULOCYTIC LEUKEMIA	0	0	0	2	0	.1180	.	.1171	.	.
Adjusted # at risk	50.2	48.6	40.3	25.3	22.2					
HISTIOCYTIC SARCOMA	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	50.4	49.6	41.1	26.2	22.2					
LYMPHOCYTIC LYMPHOMA	1	1	1	1	0	.6024	1	.5702	.7009	.7475

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Table A.2.3 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
STOMACH										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.9	25.3	22.2					
GLANDULAR- ADENOMA	0	0	1	0	0	.4728	.	.	.4494	.
Adjusted # at risk	49.6	49.2	40.3	25.3	22.2					
LEIOMYOMA	0	1	0	0	0	.7351	.	.	.	.5000
Adjusted # at risk	49.6	49.2	50.1	60.0	61.3					
NONGLANDULAR- SQUAMOUS CELL CAR	0	5	18	51	58	<0.0001	<0.0001	<0.0001	<0.0001	.0281
Adjusted # at risk	49.6	53.5	51.4	55.7	58.4					
NONGLANDULAR- SQUAMOUS CELL PAP	0	22	24	46	49	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Adjusted # at risk	49.6	53.5	55.3	70.9	71.1					
Nongland. Sq.Cell Pap./Carc.	0	22	34	68	70	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Adjusted # at risk	49.6	53.5	51.4	55.7	58.4					
Nongland. Sq.Cell Papilloma	0	22	24	46	49	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
SUBMAX SALIVARY GLANDS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.3	25.3	22.2					
ADENOCARCINOMA	0	0	1	0	0	.4728	.	.	.4494	.
Systemic										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	49.1	40.3	25.3	22.2					
HEMANGIOMA	0	2	0	0	0	.7898	.	.	.	.2474
Adjusted # at risk	49.6	48.6	41.4	25.7	22.2					
HEMANGIOSARCOMA	0	0	2	1	0	.3046	.	.3378	.2047	.
Adjusted # at risk	50.2	49.4	40.3	26.0	22.2					
HISTIOCYTIC SARCOMA	2	1	0	1	0	.7774	1	.7097	1	.8750
Adjusted # at risk	49.6	49.1	41.4	25.7	22.2					
Hemangioma/-sarcoma	0	2	2	1	0	.4952	.	.3378	.2047	.2474
Adjusted # at risk	50.4	49.6	41.1	26.2	22.2					
Lymphoma, Either	1	1	1	1	0	.6024	1	.5702	.7009	.7475
TESTES										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	50.3	49.0	41.4	30.2	32.8					
INTERSTITIAL CELL- ADENOMA	3	3	2	9	17	<0.0001	<0.0001	.0053	.7514	.6415
Adjusted # at risk	49.6	48.6	40.3	25.3	23.5					
INTERSTIT.CELL-ADENOMA,BILATERAL	0	0	0	0	2	.0149	.0990	.	.	.
Adjusted # at risk	50.3	49.0	41.4	30.2	34.0					
Intersit. Adenoma, any	3	3	2	9	19	<0.0001	<0.0001	.0053	.7514	.6415
Adjusted # at risk	49.9	48.6	40.3	25.3	22.2					
MESOTHELIOMA, MALIGNANT	1	0	0	0	0	1	1	1	1	1
THYMUS										
# Evaluated	75	75	74	73	75					
Adjusted # at risk	49.6	48.6	39.8	25.1	22.2					
THYMOMA, BENIGN	0	0	0	1	0	.2568	.	.3378	.	.
THYROID										
# Evaluated	75	75	75	74	75					
Adjusted # at risk	50.7	49.8	41.5	26.2	22.7					
C CELL- ADENOMA	8	12	10	3	1	.9538	.9706	.8047	.2307	.2116
Adjusted # at risk	49.6	48.6	40.7	24.8	22.2					
C CELL- CARCINOMA	0	0	1	0	0	.4699	.	.	.4494	.
Adjusted # at risk	50.7	49.8	41.9	26.2	22.7					
C-cell Adenoma/Carcinoma	8	12	11	3	1	.9512	.9706	.8047	.1574	.2116
Adjusted # at risk	50.2	49.4	41.1	27.1	23.9					
FOLLICULAR CELL- ADENOMA	3	4	2	5	3	.0686	.2781	.0946	.7514	.4886
TISSUE NONSPECIFIC										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	49.4	40.3	25.3	22.2					
HISTIOCYTIC SARCOMA	0	1	0	0	0	.7351	.	.	.	.5000

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Table A.2.3 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
TONGUE										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.6	48.6	40.3	25.9	22.2					
LIPOSARCOMA	0	0	0	1	0	.2554	.	.3378	.	.
URINARY BLADDER										
# Evaluated	74	75	75	75	74					
Adjusted # at risk	49.4	49.6	40.3	25.3	22.2					
TRANSITIONAL EPITHELIUM- CARCIN	0	1	0	0	0	.7351	.	.	.	.5000
ZYMBAL'S GLAND										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	50.0	48.6	41.1	25.3	22.2					
CARCINOMA	1	0	1	0	0	.7893	1	1	.7009	

Table A.2.4 Incidence and Significance Levels of all Tests on Neoplasms in Female Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
ADRENALS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.3	49.2	48.4	51.5					
CORTEX- ADENOMA	1	1	1	1	0	.7932	1	.7222	.7276	.7477
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
CORTEX- ADENOMA, BILATERAL	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	54.9	53.2	48.7	48.1	51.5					
CORTEX- CARCINOMA	1	1	0	0	0	.9555	1	1	1	.7477
Adjusted # at risk	54.8	53.3	49.2	48.4	51.5					
Cortex Adenoma, Any	2	1	1	1	0	.9029	1	.8555	.8597	.8750
Adjusted # at risk	54.9	53.3	49.2	48.4	51.5					
Cortex Adenoma/Carcinoma	3	2	1	1	0	.9718	1	.9256	.9285	.8126
Adjusted # at risk	55.0	53.6	49.4	48.4	51.5					
MEDULLA- PHEOCHROMOCYTOMA, BENI	2	3	2	1	2	.6599	.6692	.8555	.6536	.4911
Adjusted # at risk	54.8	53.2	49.3	48.1	51.5					
MEDULLA- PHEOCHROMOCYTOMA, MALI	0	0	1	0	0	.5804	.	.	.4757	.
Adjusted # at risk	55.0	53.6	50.0	48.4	51.5					
Medulla, Pheochromocytoma Any	2	3	3	1	2	.6806	.6692	.8555	.4633	.4911
Adjusted # at risk	55.0	53.6	49.4	48.4	51.5					
Medulla, Pheochromocytoma [B]	2	3	2	1	2	.6599	.6692	.8555	.6536	.4911
BRAIN										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	55.0	53.4	49.4	48.1	52.0					
CEREBRUM- ASTROCYTOMA, MALIGNAN	1	2	1	0	2	.4715	.4784	1	.7276	.4929
Adjusted # at risk	55.0	53.2	48.7	48.1	51.5					
CEREBRUM- OLIGODENDROGLIOMA, MA	1	0	0	0	0	1	1	1	1	1
CAVITY, ABDOMINAL										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.9					
HISTIOCYTIC SARCOMA	0	0	0	0	2	.0397	.2335	.	.	.
Adjusted # at risk	54.8	53.2	49.1	48.1	51.5					
LIPOMA	0	0	1	0	0	.5804	.	.	.4757	.
Adjusted # at risk	55.3	53.2	48.7	48.1	51.5					
SCHWANNOMA, MALIGNANT	1	0	0	0	0	1	1	1	1	1
CERVIX										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.9					
SQUAMOUS CELL CARCINOMA	0	0	0	0	1	.2008	.4857	.	.	.

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Table A.2.4 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
CLITORAL GLAND										
# Evaluated	75	75	74	75	75					
Adjusted # at risk	54.8	53.2	49.0	48.1	51.7					
CARCINOMA	0	1	1	0	2	.1592	.2335	.	.4706	.4953
Adjusted # at risk	55.1	53.2	48.5	48.1	51.9					
SQUAMOUS CELL CARCINOMA	1	0	0	0	1	.4666	.7332	1	1	1
Adjusted # at risk	54.8	53.2	48.5	48.1	51.5					
SQUAMOUS CELL PAPILLOMA	0	0	1	0	0	.5787	.	.	.4706	.
DUODENUM										
# Evaluated	71	72	72	74	75					
Adjusted # at risk	52.5	51.8	46.9	47.3	51.5					
LEIOMYOMA	1	1	0	0	0	.9564	1	1	1	.7476
EAR										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	49.6	48.1	51.9					
PINNA- NEUROFIBROMA	0	0	1	0	1	.2270	.4857	.	.4757	.
HEAD										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	52.3					
LIP- SQUAMOUS CELL PAPILLOMA	0	0	0	0	1	.2039	.4906	.	.	.
Adjusted # at risk	54.8	53.7	48.7	48.9	51.5					
NASOTURBINATE- SQUAMOUS CELL CA	0	1	0	1	0	.5479	.	.4706	.	.4953
Adjusted # at risk	54.8	53.2	49.2	48.3	52.1					
SQUAMOUS CELL CARCINOMA	0	0	1	1	1	.1776	.4906	.4706	.4757	.
Adjusted # at risk	54.8	53.2	49.0	48.1	51.5					
SQUAMOUS CELL PAPILLOMA	0	0	1	0	0	.5804	.	.	.4757	.
Adjusted # at risk	54.8	53.2	49.5	48.3	52.1					
Squamous Cell Pap./Carc.	0	0	2	1	1	.2321	.4906	.4706	.2239	.
ILEUM										
# Evaluated	70	72	73	70	73					
Adjusted # at risk	52.2	51.8	47.4	45.0	50.4					
LEIOMYOMOA	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	51.9	51.8	47.6	45.0	50.4					
LYMPHOCYTIC LYMPHOMA	0	0	1	0	0	.5802	.	.	.4796	.
JEJUNUM										
# Evaluated	64	67	68	70	69					
Adjusted # at risk	48.1	49.2	44.8	44.5	48.1					
PLEOMORPHIC LYMPHOMA	0	1	0	0	0	.7940	.	.	.	.5052
KIDNEYS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
LIPOMA	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	54.8	53.2	48.7	48.1	51.8					
LIPOSARCOMA	0	0	0	0	1	.2008	.4857	.	.	.
Adjusted # at risk	54.8	53.2	48.7	48.1	51.8					
Lipoma/Liposarcoma	1	0	0	0	1	.4687	.7379	1	1	1
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
PELVIS- TRANSITIONAL EPITHELIUM	0	0	0	0	1	.2008	.4857	.	.	.
Adjusted # at risk	54.9	53.2	48.7	48.1	52.0					
RENAL TUBULE- ADENOMA	1	0	0	0	2	.1783	.4857	1	1	1
Adjusted # at risk	54.8	53.2	48.7	48.1	51.9					
RENAL TUBULE- CARCINOMA	0	0	0	2	4	.0015	.0523	.2190	.	.
Adjusted # at risk	54.9	53.2	48.7	48.1	52.4					
Renam Tub. Adenoma/Carc.	1	0	0	2	5	.0033	.0942	.4555	1	1

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Table A.2.4 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
LIVER										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
CHOLANGIOMA	0	0	0	1	0	.3898	.	.4706	.	.
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
HEPATOCELLULAR ADENOMA	0	2	0	0	0	.8664	.	.	.	.2430
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
HEPATOCELLULAR CARCINOMA	0	0	0	0	1	.2008	.4857	.	.	.
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
Hepato. Adenoma/Cholangioma	0	2	0	1	0	.7045	.	.4706	.	.2430
LUNG WITH BRONCHI										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
ALVEOLAR BRONCHIAL ADENOMA	1	0	0	0	0	1	1	1	1	1
LYMPH NODE, MANDIBULAR										
# Evaluated	74	74	75	75	74					
Adjusted # at risk	54.1	52.2	48.7	48.7	51.2					
LYMPHOCYTIC LYMPHOMA	0	0	0	1	0	.3913	.	.4706	.	.
Adjusted # at risk	54.1	52.3	48.7	48.1	51.2					
PLEOMORPHIC LYMPHOMA	0	1	0	0	0	.7866	.	.	.	.4906
LYMPH NODE, MEDIASTINAL										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.9	48.1	51.5					
HISTIOCYTIC SARCOMA	0	0	1	0	0	.5787	.	.	.4706	.
MAMMARY GLAND										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
ADENOCARCINOMA	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	56.4	54.6	52.0	49.8	54.1					
ADENOMA	11	6	10	7	9	.5728	.7422	.8378	.6160	.9344
Adjusted # at risk	54.9	53.3	48.7	48.7	51.9					
ADENOMA, MULTIPLE	1	1	1	1	1	.5059	.7379	.7222	.7222	.7477
Adjusted # at risk	56.5	54.7	52.0	50.4	54.5					
Adenoma, all	12	7	11	8	10	.5715	.7318	.8317	.6056	.9239
Adjusted # at risk	64.8	61.2	61.9	58.6	63.5					
Adenoma/Fibro-/Carc.	49	39	48	38	43	.8216	.8938	.9392	.4724	.9595
Adjusted # at risk	57.8	56.6	52.7	50.3	56.8					
CARCINOMA	10	13	13	8	19	.0688	.0372	.6800	.2364	.3036
Adjusted # at risk	56.4	54.6	49.3	49.0	51.9					
CARCINOMA, MULTIPLE	7	9	4	4	4	.9027	.8670	.8432	.8516	.3636
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
CARCINOSARCOMA	0	0	0	1	0	.3898	.	.4706	.	.
Adjusted # at risk	59.3	57.9	53.4	51.2	57.2					
Carcinoma, all	17	22	17	12	23	.3075	.1331	.8004	.4324	.1792
Adjusted # at risk	59.7	55.8	53.1	53.1	56.2					
FIBROADENOMA	23	15	20	20	17	.6681	.8784	.6289	.6289	.9367
Adjusted # at risk	56.1	56.1	51.5	52.1	54.3					
FIBROADENOMA, MULTIPLE	12	17	14	13	9	.8560	.8097	.4159	.3084	.1942
Adjusted # at risk	60.9	58.8	55.9	57.2	58.9					
Fibroadenoma, all	35	32	34	33	26	.9204	.9509	.5931	.4247	.7027
OVARIES										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.5	48.7	48.1	51.5					
HEMANGIOMA	0	1	0	0	0	.7874	.	.	.	.4953
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
SERTOLI CELL- ADENOMA	0	1	0	0	0	.7874	.	.	.	.4953
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
Sertoli Cell Adenoma/Thecoma	0	1	0	0	1	.3113	.4857	.	.	.4953
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
THECOMA	0	0	0	0	1	.2008	.4857	.	.	.

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Table A.2.4 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
PANCREAS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.5	49.5	48.1	51.8					
ISLETS- ADENOMA	2	3	4	1	2	.7012	.6692	.8555	.2938	.4911
Adjusted # at risk	55.6	54.3	48.7	48.7	51.6					
ISLETS- CARCINOMA	3	5	0	2	1	.9084	.9313	.7733	1	.3477
Adjusted # at risk	55.6	54.5	49.5	48.7	51.9					
Islets Adenoma/Carc.	5	8	4	3	3	.8995	.8391	.8164	.6947	.2662
PITUITARY										
# Evaluated	75	75	74	73	75					
Adjusted # at risk	69.2	62.8	66.1	60.1	60.3					
PARS DISTALIS- ADENOMA	53	49	54	39	36	.9983	.9879	.9530	.3074	.4631
Adjusted # at risk	54.8	53.6	48.2	47.8	51.5					
PARS DISTALIS- CARCINOMA	0	1	0	0	0	.7866	.	.	.	.4953
Adjusted # at risk	54.8	53.7	48.2	47.8	51.5					
PARS INTERMEDIA- ADENOMA	0	1	0	0	0	.7866	.	.	.	.4953
Adjusted # at risk	69.2	63.2	66.1	60.1	60.3					
Pars Dist. Adenoma/Carc.	53	50	54	39	36	.9984	.9879	.9530	.3074	.4438
SKELETAL MUSCLE (THIGH)										
# Evaluated	75	75	74	74	75					
Adjusted # at risk	55.0	53.2	48.6	47.3	51.5					
HISTIOCYTIC SARCOMA	1	0	0	0	0	1	1	1	1	1
SKIN										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	49.4	48.1	51.5					
BASAL CELL- ADENOMA	0	0	1	0	0	.5804	.	.	.4757	.
Adjusted # at risk	54.8	53.2	48.7	48.1	51.9					
BASAL CELL- CARCINOMA	0	0	0	0	1	.2008	.4857	.	.	.
Adjusted # at risk	54.8	53.2	49.4	48.1	51.9					
Basal Cell Adenoma/Carc.	0	0	1	0	1	.2270	.4857	.	.4757	.
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
FIBROMA	0	1	0	0	0	.7874	.	.	.	.4953
Adjusted # at risk	54.8	53.2	48.7	48.9	51.5					
HEMANGIOSARCOMA	0	0	0	1	0	.3898	.	.4706	.	.
Adjusted # at risk	54.8	53.4	49.1	48.1	51.5					
KERATOACANTHOMA	0	1	1	1	0	.5999	.	.4706	.4757	.4953
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
SQUAMOUS CELL CARCINOMA	0	0	1	0	0	.5787	.	.	.4706	.
Adjusted # at risk	55.1	53.2	48.7	48.1	51.5					
SQUAMOUS CELL PAPILLOMA	1	2	2	0	1	.7491	.7332	1	.4486	.4860
Adjusted # at risk	54.8	53.2	48.7	48.5	51.5					
SUBCUT TISSUE- FIBROMA	1	0	0	1	0	.6637	1	.7222	1	1
Adjusted # at risk	55.4	53.2	48.7	48.6	51.5					
SUBCUT TISSUE- FIBROSARCOMA	1	0	1	1	0	.7018	1	.7173	.7173	1
Adjusted # at risk	55.3	54.5	48.7	48.3	52.3					
SUBCUT TISSUE- HISTIOCYTIC SARC	2	3	0	1	2	.6086	.6696	.8517	1	.4912
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
SUBCUT TISSUE- SCHWANNOMA, MALI	0	0	1	0	0	.5787	.	.	.4706	.
Adjusted # at risk	55.1	53.2	48.7	48.1	51.5					
Sq. Cell Pap./Carc.	1	2	3	0	1	.7646	.7332	1	.2592	.4860
Adjusted # at risk	55.1	53.4	49.1	48.1	51.5					
Sq.Cell Pap./Carc/Kerato.	1	3	4	1	1	.7572	.7332	.7173	.1475	.2951
Adjusted # at risk	55.4	53.2	48.7	49.0	51.5					
Subcut. Fibroma/-sarcoma	2	0	1	2	0	.7339	1	.6463	.8517	1

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Table A.2.4 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
SPLEEN										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
HEMANGIOMA	0	0	0	0	1	.2008	.4857	.	.	.
Adjusted # at risk	54.8	53.8	48.7	48.1	51.5					
LYMPHOCYTIC LYMPHOMA	0	1	0	0	0	.7874	.	.	.	.4953
STOMACH										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	55.2	53.2	48.7	48.1	51.5					
LEIOMYOMA	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	54.8	53.2	48.7	48.7	51.5					
NONGLANDULAR- CARCINOMA	0	0	0	1	0	.3898	.	.4706	.	.
Adjusted # at risk	54.8	53.2	49.6	56.6	65.8					
NONGLANDULAR- SQUAMOUS CELL CAR	0	1	4	30	48	<0.0001	<0.0001	<0.0001	.0479	.4953
Adjusted # at risk	54.8	55.0	53.7	56.4	61.2					
NONGLANDULAR- SQUAMOUS CELL PAP	0	11	21	31	24	<0.0001	<0.0001	<0.0001	<0.0001	.0003
Adjusted # at risk	54.8	55.0	54.3	61.1	69.3					
Nongland. Pap./Carc.	0	11	23	48	58	<0.0001	<0.0001	<0.0001	<0.0001	.0003
Systemic										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.5	48.7	48.1	51.5					
HEMANGIOMA	0	3	0	1	1	.5059	.4857	.4706	.	.1180
Adjusted # at risk	54.8	53.2	48.7	48.9	51.5					
HEMANGIOSARCOMA	0	0	0	1	0	.3898	.	.4706	.	.
Adjusted # at risk	55.0	53.2	48.9	48.1	51.9					
HISTIOCYTIC SARCOMA	1	0	1	0	2	.2287	.4784	1	.7222	1
Adjusted # at risk	54.8	53.5	48.7	48.9	51.5					
Hemangioma/-sarcoma	0	3	0	2	1	.3997	.4857	.2190	.	.1180
Adjusted # at risk	56.4	53.9	49.3	48.7	51.5					
Lymphoma, Either	2	3	2	1	0	.9499	1	.8478	.6390	.4737
TAIL										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
HEMANGIOMA	0	1	0	1	0	.5479	.	.4706	.	.4953
THYMUS										
# Evaluated	75	75	74	75	75					
Adjusted # at risk	56.4	53.2	49.0	48.1	51.5					
LYMPHOCYTIC LYMPHOMA	2	0	1	0	0	.9609	1	1	.8521	1
THYROID										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	55.2	54.4	49.3	49.1	51.5					
C CELL- ADENOMA	9	6	4	6	1	.9858	.9991	.8090	.9426	.8586
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
C CELL- ADENOMA, MULTIPLE	0	0	0	0	1	.2008	.4857	.	.	.
Adjusted # at risk	54.8	53.7	48.7	48.1	51.5					
C CELL- CARCINOMA	0	1	0	1	0	.5479	.	.4706	.	.4953
Adjusted # at risk	55.2	54.4	49.3	49.1	51.5					
C-Cell Adenoma	9	6	4	6	2	.9643	.9942	.8090	.9426	.8586
Adjusted # at risk	55.2	54.9	49.3	49.1	51.5					
C-Cell Adenoma/Carcinoma	9	7	4	6	2	.9728	.9942	.8090	.9426	.7795
Adjusted # at risk	54.8	53.2	48.7	48.7	51.5					
FOLLICLE- EPITHELIUM- ADENOMA	0	0	0	1	0	.3898	.	.4706	.	.
URINARY BLADDER										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
TRANSITIONAL EPITHELIUM- PAPILL	0	2	0	0	0	.8664	.	.	.	.2430

Reference ID: 3207500

Table A.2.4 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Rats

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
UTERUS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
ADENOMA	0	0	1	0	0	.5787	.	.	.4706	.
Adjusted # at risk	54.8	53.2	48.7	48.1	51.5					
HEMANGIOMA	0	1	0	0	0	.7874	.	.	.	.4953
Adjusted # at risk	55.0	53.7	49.1	48.5	51.6					
POLYP, ENDOMETRIAL-STROMAL	3	3	4	2	4	.4038	.4576	.7733	.4352	.6429
VAGINA										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.2	48.7	48.1	51.6					
ENDOMETRIAL-STROMAL POLYP	0	0	0	1	1	.1159	.4857	.4706	.	.
Adjusted # at risk	54.8	53.2	48.7	48.1	52.1					
ENDOMETRIAL-STROMAL SARCOMA	0	0	0	0	1	.2039	.4906	.	.	.
Adjusted # at risk	54.8	53.2	48.7	48.1	52.2					
Endo. Stromal polyp/sarcoma	0	0	0	1	2	.0314	.2383	.4706	.	.
Adjusted # at risk	54.8	53.2	48.7	48.3	51.5					
SCHWANNOMA, MALIGNANT	0	0	0	1	0	.3898	.	.4706	.	.
Adjusted # at risk	54.8	53.2	48.7	48.3	51.5					
SQUAMOUS CELL CARCINOMA	0	0	0	1	1	.1159	.4857	.4706	.	.
Adjusted # at risk	55.2	53.2	48.7	48.1	51.5					
STROMAL POLYP	1	1	0	0	1	.5971	.7332	1	1	.7430
Adjusted # at risk	55.2	53.2	48.7	48.1	52.2					
Stromal polyp/Sarcoma	1	1	0	1	3	.0918	.2880	.7173	1	.7430
ZYMBAL'S GLAND										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	54.8	53.6	48.7	48.1	51.5					
CARCINOMA	0	1	0	0	0	.7874	.	.	.	.4953
Adjusted # at risk	55.0	53.2	48.7	48.1	51.5					
SQUAMOUS CELL PAPILLOMA	1	0	0	0	0	1	1	1	1	1

Table A.2.5 Incidence and Significance Levels of all Tests on Neoplasms in Male Mice

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
ADRENAL GLAND										
# Evaluated	74	75	75	73	74					
Adjusted # at risk	46.6	52.1	50.6	45.1	19.6					
Adenoma	1	2	0	0	0	.9559	1	1	1	.5463
Adjusted # at risk	46.6	52.1	50.6	45.1	19.6					
Endo. Stromal Polyp/Sarcoma	1	2	0	0	0	.9559	1	1	1	.5463
BONE, FEMUR										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Chondroma	1	0	0	0	0	1	1	1	1	1
BONE, MISCELLANEOUS										
# Evaluated	0	1	0	1	0					
Adjusted # at risk	0.0	0.9	0.0	1.0	0.0					
Osteoma	0	0	0	1	0	1	.	.	.	.
CAVITY, ABDOMINAL										
# Evaluated	3	1	2	1	2					
Adjusted # at risk	1.3	0.7	0.9	1.0	1.0					
Hemangiosarcoma	0	0	0	0	1	.3333	.5000	.	.	.

Reference ID: 3207500

Table A.2.5 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Mice

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
COLON										
# Evaluated	75	75	75	74	75					
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Adenoma	0	0	0	1	0	.3102	.	.5000	.	.
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Endo. Stromal Polyp/Sarcoma	0	0	0	1	0	.3102	.	.5000	.	.
DUODENUM										
# Evaluated	67	67	69	72	70					
Adjusted # at risk	43.8	49.1	47.8	46.1	20.2					
Adenoma	1	0	0	0	1	.2355	.5376	1	1	1
Adjusted # at risk	43.8	49.1	47.8	46.1	20.2					
Endo. Stromal Polyp/Sarcoma	1	0	0	0	1	.2355	.5376	1	1	1
EPIDIDYMIS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Interstitial Cell Adenoma	0	1	1	0	0	.6899	.	.	.5155	.5253
Adjusted # at risk	47.5	52.1	50.6	47.5	20.5					
Schwannoma	0	0	0	1	0	.3102	.	.5000	.	.
HARDERIAN GLAND										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	49.9	53.0	51.4	49.4	20.7					
Adenoma	9	8	6	8	2	.7225	.8939	.7027	.8860	.7473
Adjusted # at risk	49.9	53.0	51.4	49.4	20.7					
Adenoma/Carcinoma	9	8	6	8	2	.7225	.8939	.7027	.8860	.7473
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Carcinoma	0	1	0	0	0	.7824	.	.	.	.5253
HEMOLYMPHORETICULAR										
# Evaluated	7	7	3	3	5					
Adjusted # at risk	5.6	5.2	1.0	2.2	2.0					
Histiocytic Sarcoma	4	2	0	1	1	.6943	.9524	.9524	1	.9762
Adjusted # at risk	4.4	4.1	1.0	2.1	2.4					
Leukemia	0	1	0	0	1	.1923	.3333	.	.	.5000
Adjusted # at risk	5.8	5.9	3.0	2.9	3.5					
Lymphoma	3	4	3	2	3	.0735	.3571	.4762	.3571	.5000
ILEUM										
# Evaluated	68	65	69	64	67					
Adjusted # at risk	44.6	48.8	47.1	41.9	20.0					
Adenocarcinoma	1	0	0	0	0	1	1	1	1	1
KIDNEY										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	48.7	22.1					
Adenoma	1	2	0	5	3	.0074	.0922	.1067	1	.5382
Adjusted # at risk	47.5	52.1	50.7	49.3	22.8					
Adenoma/Carcinoma	1	2	2	8	5	.0003	.0109	.0179	.5234	.5382
Adjusted # at risk	47.5	52.1	50.7	47.7	22.0					
Carcinoma	0	0	2	4	3	.0015	.0265	.0585	.2631	.
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Hemangioma	0	1	0	0	0	.7824	.	.	.	.5253
Adjusted # at risk	47.7	52.1	50.6	47.1	20.5					
Hemangiosarcoma	1	0	0	0	0	1	1	1	1	1
LIVER										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	50.4	52.4	50.7	47.7	20.5					
Hemangiosarcoma	6	2	3	1	0	.9854	1	.9922	.9202	.9739
Adjusted # at risk	49.8	52.7	51.5	48.2	21.6					
Hepato.Adenoma/Carcinoma	11	9	5	4	3	.8889	.8677	.9876	.9781	.8153
Adjusted # at risk	48.1	52.1	51.5	47.8	20.6					
Hepatocellular Adenoma	3	5	3	1	1	.8319	.7611	.9389	.6897	.4035
Adjusted # at risk	49.2	52.7	51.1	47.6	21.5					
Hepatocellular Carcinoma	9	6	3	3	2	.8792	.9068	.9834	.9885	.8936

Reference ID: 3207500

Table A.2.5 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Mice

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
LUNG WITH BRONCHI										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	50.0	53.9	52.5	51.4	23.2					
Bronchiolo-Alveolar Adenocarcin	6	6	5	11	5	.0411	.2292	.1541	.7598	.6607
Adjusted # at risk	52.4	53.6	51.4	49.3	25.8					
Bronchiolo-Alveolar Adenoma	14	15	8	11	8	.3570	.4187	.7734	.9494	.5241
Adjusted # at risk	47.5	52.1	50.6	47.7	20.5					
Hepato.Adenoma/Carcinoma	0	0	0	1	0	.3102	.	.5000	.	.
Adjusted # at risk	47.5	52.1	50.6	47.7	20.5					
Hepatocellular Carcinoma	0	0	0	1	0	.3102	.	.5000	.	.
LYMPH NODE, MESENTERIC										
# Evaluated	74	74	74	75	75					
Adjusted # at risk	47.4	52.0	50.5	47.1	20.5					
Hemangiosarcoma	0	0	1	0	0	.5417	.	.	.5155	.
PANCREAS										
# Evaluated	75	75	75	75	74					
Adjusted # at risk	47.5	52.1	50.8	47.1	20.5					
Adenoma	0	0	1	0	0	.5417	.	.	.5155	.
Adjusted # at risk	47.5	52.1	50.8	47.1	20.5					
Endo. Stromal Polyp/Sarcoma	0	0	1	0	0	.5417	.	.	.5155	.
SEMINAL VESICLE										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	47.1	21.4					
Adenocarcinoma	0	0	0	0	1	.0968	.3088	.	.	.
SKIN										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	47.1	20.6					
Basal Cell Tumor	0	0	0	0	1	.0926	.2985	.	.	.
Adjusted # at risk	47.5	52.2	50.6	47.1	20.5					
Fibrosarcoma	0	1	0	0	0	.7824	.	.	.	.5253
Adjusted # at risk	48.9	52.5	50.6	47.1	20.8					
Hemangiosarcoma	3	1	0	1	1	.4755	.7611	.9389	1	.9504
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Papilloma	0	0	1	0	0	.5417	.	.	.5155	.
Adjusted # at risk	48.4	52.1	50.8	47.1	20.5					
Schwannoma	1	0	1	0	0	.7888	1	1	.7627	1
SPLEEN										
# Evaluated	75	75	74	75	75					
Adjusted # at risk	47.8	52.6	50.4	47.1	20.6					
Hemangiosarcoma	2	2	1	0	1	.6173	.6615	1	.8900	.7286
STOMACH										
# Evaluated	74	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Adenocarcinoma	1	2	1	1	0	.7580	1	.7527	.7678	.5382
Adjusted # at risk	47.5	52.1	50.6	47.1	20.8					
Fibrosarcoma	0	0	0	0	1	.0926	.2985	.	.	.
Adjusted # at risk	47.5	52.1	50.6	47.1	23.0					
Leiomyoma/-sarcoma	0	0	0	0	3	.0010	.0324	.	.	.
Adjusted # at risk	47.5	52.1	50.6	47.1	23.0					
Leiomyosarcoma	0	0	0	0	3	.0010	.0324	.	.	.
Adjusted # at risk	47.5	52.1	50.6	47.8	20.5					
Mast Cell Tumor	0	0	0	1	0	.3102	.	.5000	.	.
Adjusted # at risk	47.5	52.5	51.1	50.0	30.5					
Papilloma	0	1	3	12	14	<0.0001	<0.0001	.0002	.1369	.5253
Adjusted # at risk	47.5	52.4	50.6	47.7	22.3					
Squamous Cell Carcinoma	0	1	0	2	6	<0.0001	.0006	.2473	.	.5253

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Table A.2.5 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Male Mice

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
Systemic										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	48.2	52.1	50.6	47.1	20.5					
Hemangioma	1	1	0	0	0	.9519	1	1	1	.7721
Adjusted # at risk	52.8	53.3	51.3	47.7	21.2					
Hemangioma/-sarcoma	13	6	5	2	3	.9280	.9097	.9996	.9900	.9818
Adjusted # at risk	52.1	53.3	51.3	47.7	21.2					
Hemangiosarcoma	12	5	5	2	3	.8790	.8797	.9992	.9824	.9857
Adjusted # at risk	49.8	53.9	52.6	47.9	22.5					
Lymphoma	4	4	4	2	3	.3251	.3729	.8882	.6754	.6856
Adjusted # at risk	48.4	52.1	50.8	47.5	20.5					
Schwannoma	1	0	1	1	0	.5332	1	.7474	.7627	1
TAIL										
# Evaluated	3	0	2	2	6					
Adjusted # at risk	2.1	0.0	1.3	1.0	1.1					
Fibrosarcoma	0	0	1	0	0	.5000	.	.	.3333	.
TESTIS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Adenoma	0	0	1	0	0	.5417	.	.	.5155	.
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Endo. Stromal Polyp/Sarcoma	0	0	1	0	0	.5417	.	.	.5155	.
Adjusted # at risk	48.2	52.1	50.6	47.1	20.5					
Hemangioma	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	47.5	52.3	51.3	47.1	20.5					
Interstitial Cell Adenoma	1	3	2	1	0	.8376	1	.7527	.5309	.3478
THYMUS										
# Evaluated	75	75	75	75	73					
Adjusted # at risk	47.5	52.1	51.2	47.1	20.4					
Histiocytic Sarcoma	0	0	1	0	0	.5438	.	.	.5204	.
Adjusted # at risk	48.4	52.1	50.6	47.1	20.4					
Lymphoma	1	0	1	0	0	.7888	1	1	.7627	1
URINARY BLADDER										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Leiomyoma/-sarcoma	0	0	1	0	0	.5417	.	.	.5155	.
Adjusted # at risk	47.5	52.1	50.6	47.1	20.5					
Leiomyosarcoma	0	0	1	0	0	.5417	.	.	.5155	.

Reference ID: 3207500

Table A.2.6 Incidence and Significance Levels of all Tests on Neoplasms in Female Mice

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
ADRENAL GLAND										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.5	51.8	27.4					
Adenoma	3	1	2	0	0	.9693	1	1	.7944	.9315
Adjusted # at risk	56.6	53.1	52.5	51.8	27.4					
Adenoma/Carcinoma	3	3	2	0	0	.9879	1	1	.7944	.6341
Adjusted # at risk	56.6	53.1	52.1	51.8	27.4					
Carcinoma	0	2	0	0	0	.8415	.	.	.	.2341
Adjusted # at risk	56.6	52.9	52.1	52.1	27.4					
Carcinosarcoma	0	0	0	1	0	.3305	.	.4815	.	.
BONE, FEMUR										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.1	51.8	27.5					
Osteoma	0	0	0	0	1	.1134	.3253	.	.	.
BONE, MISCELLANEOUS										
# Evaluated	0	2	1	2	5					
Adjusted # at risk	0.0	2.0	0.3	1.5	3.6					
Osteoma	0	0	0	1	1	.4000	.	.	.	.
BRAIN										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	53.7	52.1	51.8	27.4					
Meningeal Sarcoma	0	1	0	0	0	.7657	.	.	.	.4862
CAVITY, ABDOMINAL										
# Evaluated	1	4	4	4	3					
Adjusted # at risk	1.0	2.8	2.9	1.6	1.2					
Mesothelioma	1	1	0	0	0	1	1	1	1	1
Adjusted # at risk	1.0	2.8	3.6	1.6	1.2					
Schwannoma	0	0	1	0	0	.6250	.	.	.7500	.
CAVITY, THORACIC										
# Evaluated	0	1	4	1	0					
Adjusted # at risk	0.0	0.8	3.6	1.0	0.0					
Fibrosarcoma	0	0	1	0	0	1	.	.	.	.
CECUM										
# Evaluated	71	69	72	71	70					
Adjusted # at risk	53.7	49.1	51.1	49.0	26.3					
Leiomyoma	0	0	1	0	0	.5526	.	.	.4904	.
Adjusted # at risk	53.7	49.1	51.1	49.0	26.3					
Leiomyoma/-sarcoma	0	0	1	0	0	.5526	.	.	.4904	.
COLON										
# Evaluated	75	75	74	75	75					
Adjusted # at risk	56.7	52.9	52.0	51.8	27.4					
Adenocarcinoma	1	0	0	0	0	1	1	1	1	1
HARDERIAN GLAND										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.1	51.8	27.4					
Adenocarcinoma	0	0	1	0	0	.5462	.	.	.4815	.
Adjusted # at risk	56.6	52.9	52.5	53.1	27.4					
Adenoma	3	3	3	4	0	.7784	1	.4691	.6247	.6247
Adjusted # at risk	56.6	52.9	52.5	53.1	27.4					
Adenoma/Adenocarcinoma	3	3	4	4	0	.7949	1	.4691	.4584	.6247
HEMOLYMPHORETICULAR										
# Evaluated	23	18	20	19	12					
Adjusted # at risk	16.9	13.4	15.3	11.7	4.4					
Histiocytic Sarcoma	3	3	1	4	0	.5262	1	.2792	.9422	.5648
Adjusted # at risk	15.7	12.4	14.6	10.3	6.0					
Leukemia	1	0	0	0	2	.0269	.1404	1	1	1
Adjusted # at risk	21.7	17.0	19.2	17.5	12.0					
Leukemia/Lymphoma	20	15	19	15	12	.4786	.6364	.9194	.5250	.8198
Adjusted # at risk	21.7	17.0	19.2	17.5	10.4					
Lymphoma	19	15	19	15	10	.3666	.4516	.7743	.2692	.6036

Reference ID: 3207500

Table A.2.6 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Mice

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
KIDNEY										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.1	51.8	29.1					
Adenoma	0	0	0	2	4	.0002	.0117	.2248	.	.
Adjusted # at risk	56.6	52.9	52.1	51.8	29.1					
Adenoma/Carcinoma	0	0	0	2	4	.0002	.0117	.2248	.	.
Adjusted # at risk	56.6	52.9	52.1	51.8	27.6					
Carcinoma	0	0	0	0	1	.1134	.3253	.	.	.
Adjusted # at risk	56.6	52.9	52.6	51.8	27.4					
Mesenchymal Tumor	0	0	1	0	0	.5462	.	.	.4815	.
LIVER										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	53.0	51.8	27.4					
Cholangioma	0	0	1	0	0	.5462	.	.	.4815	.
Adjusted # at risk	56.6	53.1	52.2	51.8	27.4					
Hemangioma	0	1	2	0	0	.7373	.	.	.2295	.4862
Adjusted # at risk	57.9	52.9	52.1	52.9	27.9					
Hemangiosarcoma	2	0	1	2	1	.2498	.6929	.6555	.8606	1
Adjusted # at risk	56.7	53.3	52.1	51.8	27.5					
Hepato.Adenoma/Carcinoma	2	3	1	0	1	.7370	.6983	1	.8642	.4737
Adjusted # at risk	56.7	52.9	52.1	51.8	27.4					
Hepatocellular Adenoma	2	0	1	0	0	.9179	1	1	.8642	1
Adjusted # at risk	56.6	53.3	52.1	51.8	27.5					
Hepatocellular Carcinoma	0	3	0	0	1	.4394	.3253	.	.	.1116
LUNG WITH BRONCHI										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	58.5	54.9	52.7	53.5	28.3					
Bronchiolo-Alveolar Adenocarcin	6	8	6	6	1	.8857	.9440	.5541	.5401	.3339
Adjusted # at risk	58.6	56.9	54.6	55.8	31.8					
Bronchiolo-Alveolar Adenoma	12	14	9	20	10	.0372	.1714	.0503	.7839	.3725
Adjusted # at risk	56.6	52.9	52.1	51.8	27.4					
Mesothelioma	0	0	0	1	0	.3277	.	.4766	.	.
LYMPH NODE, MEDIASTINAL										
# Evaluated	75	73	73	75	75					
Adjusted # at risk	56.6	52.7	51.7	51.8	27.4					
Lymphoma	0	0	1	0	0	.5443	.	.	.4766	.
LYMPH NODE, MESENTERIC										
# Evaluated	75	75	73	73	74					
Adjusted # at risk	56.6	53.4	51.7	49.9	27.2					
Hemangioma	0	1	0	0	0	.7627	.	.	.	.4862
Adjusted # at risk	56.6	52.9	51.7	49.9	28.0					
Histiocytic Sarcoma	0	0	0	0	1	.1149	.3253	.	.	.
MAMMARY GLAND										
# Evaluated	75	74	75	75	74					
Adjusted # at risk	56.6	52.5	52.2	51.8	27.2					
Adenoacanthoma	2	2	2	0	0	.9579	1	1	.6625	.6625
Adjusted # at risk	56.6	52.2	52.1	51.8	27.2					
Adenocarcinoma	0	1	1	0	0	.6919	.	.	.4815	.4815
Adjusted # at risk	56.6	51.9	52.4	51.8	27.2					
Adenoma	1	0	1	0	0	.7972	1	1	.7335	1
Adjusted # at risk	56.9	51.9	52.1	51.8	27.2					
Fibroadenoma	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	56.6	51.9	52.4	51.8	27.2					
Fibroma/Fibrosarcoma	1	0	1	0	0	.7972	1	1	.7335	1

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Table A.2.6 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Mice

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
OVARY										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.1	52.3	27.4					
Adenocarcinoma	0	0	0	1	0	.3305	.	.4815	.	.
Adjusted # at risk	56.6	52.9	52.1	51.8	27.4					
Adenoma	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	56.6	52.9	52.1	52.3	27.4					
Adenoma/Adenocarcinoma	1	0	0	1	0	.5528	1	.7335	1	1
Adjusted # at risk	56.8	52.9	52.1	51.8	27.4					
Cystadenocarcinoma	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	56.9	52.9	52.1	51.8	28.2					
Cystadenoma	2	1	2	1	1	.4882	.7091	.8603	.6625	.8642
Adjusted # at risk	56.8	52.9	52.1	51.8	27.4					
Cystadenoma/-carcinoma	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	57.1	52.9	52.1	51.8	27.4					
Gran.Cell Tmr/Luteoma/Leiomsarc	4	1	0	0	0	.9993	1	1	1	.9642
Adjusted # at risk	56.8	53.2	52.1	52.3	27.4					
Granulosa Cell Tumor	2	1	1	1	0	.8171	1	.8642	.8642	.8680
Adjusted # at risk	57.2	52.9	52.9	51.8	27.4					
Hemangioma	1	1	1	1	0	.6859	1	.7238	.7288	.7288
Adjusted # at risk	56.6	52.9	52.1	51.8	27.4					
Hemangiosarcoma	1	0	0	0	0	1	1	1	1	1
Adjusted # at risk	56.6	52.9	52.1	52.2	27.4					
Leiomyoma/-sarcoma	0	0	0	1	0	.3305	.	.4815	.	.
Adjusted # at risk	56.6	52.9	52.1	52.2	27.4					
Leiomyosarcoma	0	0	0	1	0	.3305	.	.4815	.	.
Adjusted # at risk	56.9	52.9	52.1	51.8	27.4					
Luteoma	1	1	0	0	0	.9454	1	1	1	.7335
Adjusted # at risk	56.8	52.9	52.1	51.8	27.4					
Sertoli Cell Adenoma	3	0	0	0	0	1	1	1	1	1
PANCREAS										
# Evaluated	75	75	74	75	75					
Adjusted # at risk	56.6	52.9	52.0	51.8	27.8					
Acinar Cell Carcinoma	0	0	0	0	1	.1139	.3253	.	.	.
PITUITARY GLAND										
# Evaluated	74	75	75	75	75					
Adjusted # at risk	55.6	53.2	52.2	53.0	27.4					
Adenoma	4	5	3	5	0	.8598	1	.4642	.7575	.4763
Adjusted # at risk	55.6	53.2	52.2	53.0	27.4					
Fibroma/Fibrosarcoma	4	5	3	5	0	.8598	1	.4642	.7575	.4763
SKIN										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.7	51.8	27.4					
Fibroma	0	0	1	0	0	.5462	.	.	.4815	.
Adjusted # at risk	56.6	53.1	52.1	51.8	27.4					
Fibrosarcoma	0	1	1	0	0	.6907	.	.	.4815	.4862
Adjusted # at risk	56.6	52.9	52.4	51.8	27.4					
Keratoacanthoma	0	0	1	0	0	.5462	.	.	.4815	.
Adjusted # at risk	56.6	52.9	52.1	51.8	27.4					
Papilloma	0	0	1	0	0	.5462	.	.	.4815	.
Adjusted # at risk	56.6	53.9	52.1	51.8	27.4					
Schwannoma	0	1	0	0	0	.7657	.	.	.	.4862
Adjusted # at risk	56.6	52.9	52.2	51.8	27.4					
Trichoepithelioma	0	0	2	0	0	.5960	.	.	.2295	.
SPINAL CORD, LUMBAR										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.1	51.8	27.4					
Meningeal Sarcoma	0	0	1	0	0	.5462	.	.	.4815	.

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Table A.2.6 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Mice

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
SPLEEN										
# Evaluated	75	74	75	75	75					
Adjusted # at risk	56.6	52.4	52.4	52.1	28.3					
Hemangiosarcoma	1	0	1	1	2	.0538	.2565	.7335	.7335	1
STOMACH										
# Evaluated	75	75	74	75	75					
Adjusted # at risk	56.6	52.9	52.0	52.1	27.4					
Adenocarcinoma	0	0	0	2	0	.2615	.	.2295	.	.
Adjusted # at risk	56.6	52.9	52.0	51.8	27.4					
Adenoma	0	1	0	0	0	.7637	.	.	.	.4815
Adjusted # at risk	56.6	52.9	52.0	52.1	27.4					
Adenoma/Adenocarcinoma	0	1	0	2	0	.3571	.	.2295	.	.4815
Adjusted # at risk	56.6	52.9	52.0	51.8	28.2					
Fibrosarcoma	0	0	0	0	2	.0134	.1084	.	.	.
Adjusted # at risk	56.6	52.9	52.0	51.8	29.9					
Leiomyoma/-sarcoma	0	0	0	0	3	.0016	.0370	.	.	.
Adjusted # at risk	56.6	52.9	52.0	51.8	29.9					
Leiomyosarcoma	0	0	0	0	3	.0016	.0370	.	.	.
Adjusted # at risk	56.6	52.9	52.6	53.4	37.0					
Papilloma	1	0	3	6	16	<0.0001	<0.0001	.0483	.2815	1
Adjusted # at risk	56.6	53.2	52.2	52.7	33.1					
Squamous Cell Carcinoma	0	1	1	5	12	<0.0001	<0.0001	.0233	.4815	.4862
Systemic										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	57.4	53.5	53.0	52.5	27.4					
Hemangioma	3	5	3	2	0	.9500	1	.7883	.6253	.3180
Adjusted # at risk	58.7	53.5	53.7	53.9	28.8					
Hemangioma/-sarcoma	7	5	6	5	3	.5602	.6964	.7729	.6602	.7729
Adjusted # at risk	57.9	52.9	52.8	53.2	28.8					
Hemangiosarcoma	4	0	3	3	3	.1100	.4199	.7499	.7415	1
Adjusted # at risk	62.6	57.5	56.7	59.1	33.4					
Lymphoma	19	15	20	15	10	.5772	.6022	.7997	.3486	.7655
Adjusted # at risk	56.6	52.9	52.1	51.8	27.4					
Mesothelioma	1	1	0	1	0	.6726	1	.7284	1	.7335
Adjusted # at risk	56.6	53.9	52.7	51.8	27.4					
Schwannoma	0	1	1	0	0	.6907	.	.	.4815	.4862
TAIL										
# Evaluated	3	0	1	2	4					
Adjusted # at risk	2.9	0.0	1.0	1.5	1.3					
Osteoma	1	0	0	0	0	1	1	1	.	.
TONGUE										
# Evaluated	75	74	75	75	75					
Adjusted # at risk	56.6	51.9	52.4	51.8	27.4					
Papilloma	0	0	1	0	0	.5485	.	.	.4815	.

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Table A.2.6 (cont.) Incidence and Significance Levels of all Tests on Neoplasms in Female Mice

Organ/Tumor	Incidence					Significance Levels				
	Veh	Low	Med	MedHi	High	Trend	Hi vs Veh	MedHi vs Veh	Med vs Veh	Low vs Veh
UTERUS										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.2	51.8	27.4					
Adenocarcinoma	1	0	2	0	0	.7726	1	1	.4720	1
Adjusted # at risk	57.4	56.3	55.1	54.4	30.3					
Endometrial Stromal Polyp	6	9	14	11	8	.0597	.0529	.1197	.0340	.2776
Adjusted # at risk	57.5	53.5	52.2	52.2	27.5					
Endometrial Stromal Sarcoma	6	3	2	1	1	.9247	.9416	.9911	.9595	.9007
Adjusted # at risk	56.6	53.0	52.1	51.8	27.4					
Fibroma	0	1	0	0	0	.7647	.	.	.	.4815
Adjusted # at risk	56.8	52.9	52.1	52.5	27.4					
Hemangioma	2	2	0	1	0	.8734	1	.8642	1	.6625
Adjusted # at risk	56.6	52.9	52.5	51.8	27.4					
Hemangiosarcoma	0	0	1	0	0	.5462	.	.	.4815	.
Adjusted # at risk	56.6	52.9	52.1	51.8	27.4					
Histiocytic Sarcoma	0	1	0	0	0	.7647	.	.	.	.4815
Adjusted # at risk	56.6	52.9	52.1	51.8	27.4					
Leiomyoma	0	0	1	0	0	.5462	.	.	.4815	.
Adjusted # at risk	56.6	52.9	52.4	51.8	27.4					
Leiomyoma/-sarcoma	1	1	3	0	0	.8710	1	1	.2815	.7335
Adjusted # at risk	56.6	52.9	52.4	51.8	27.4					
Leiomyosarcoma	1	1	2	0	0	.8618	1	1	.4720	.7335
VAGINA										
# Evaluated	75	75	75	75	75					
Adjusted # at risk	56.6	52.9	52.1	52.3	27.4					
Endometrial Stromal Polyp	0	0	0	1	0	.3305	.	.4815	.	.
Adjusted # at risk	56.6	52.9	52.1	52.1	27.4					
Endometrial Stromal Sarcoma	0	0	0	1	0	.3305	.	.4815	.	.
Adjusted # at risk	56.6	52.9	52.1	51.8	27.4					
Leiomyoma	1	1	0	1	0	.6726	1	.7284	1	.7335
Adjusted # at risk	56.6	52.9	52.1	51.8	27.4					
Leiomyoma/-sarcoma	1	1	0	1	0	.6726	1	.7284	1	.7335
Adjusted # at risk	57.3	52.9	52.1	51.8	27.4					
Papilloma	1	0	0	0	0	1	1	1	1	1

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Appendix 3. Bayesian Tumorigenicity Analysis in Rats

Note that this analysis is copied directly from the original report of the rat study included in the statistical carcinogenicity analysis of IND 70361. This study is the same as that analyzed in this report. The Bayesian analysis from that report here is included here becaue it may be of some interest. Time constaints precluded a similar analysis of the mouse study.

The frequentist approach to testing in the presence of multiplicities is to adjust the type I error rate (i.e., the probability of rejecting a true hypothesis of no differences). For example, the Haseman-Lin-Rahman rules described in Section 1.3.1.4. and also noted in Appendix 2 above, are designed to control the type I error for tests of trend and for pairwise tests each at about a 10% error rate. The Bayesian approach is less tied to Type I error, and assesses the probability of each of the multiple events on the basis of all information in the trial, including other events. The fact that these are conditional on observed data allows one to specify analyses conditional on data based criteria. The criterion used here was that there should be at least three tumors in the high dose group.

For this analysis we define a two stage mixture model on the treatment parameters in a simple logit model for tests of trend and and pairwise comparisons. For testing trend, we define p_{ijk} as the probability of tumor i in subject j in treatment group k. That is, with i = 1 to n_t tumors and j = 1 to n_s tumors, and dose d_k, leaving the experiment at time t_i and subject effect δ_i:

(b) (4)

[redacted]

These models were implemented in WinBUGS 1.4. There were a number of problems parameterizing these models so that the Markov chains were sufficiently well behaved to depend upon the ergodic results. Note that the priors used for the intercept and time effect parameters

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are actually mildly informative (they were chosen to be close to the maximum likelihood estimates for each tumor), with prior variances that, while much larger than those implied by the data, are still not as large as one would often prefer to enforce a strongly noninformative prior.

As noted before, the choice of tumors chosen for analysis is conditioned on there being at least three tumors in the high dose group. Tables A.3.1 for males and A.3.3 for females, below, indicate the observed frequency of tumors for the tumors chosen to be used in the Bayesian analysis. Complete incidence tables are include in Appendix 2 and are not replicated here. The first column in Tables A.3.1 and A.3.3 refers to the beta parameters for the effect of dose on the incidence of each tumor for both the model with linear trend and the model comparing the high dose group to the control. The second column of Tables A.3.2 and A.3.4 shows the estimated probability that the beta parameter is zero, i.e., there is no effect of dose. The remaining columns provide summary information about the beta parameters.

Although it is hardly surprising given the incidence, in both male and female rats the posterior probability that there is no effect of increasing dose on nonglandular squamous cell papilloma and carcinoma are both essentially zero to a number of decimal places. The posterior probability of no difference between the high dose group and controls in these tumors in females is similar, as well for nonglandular squamous cell carcinoma in males. In males the posterior probability that there is no difference between nonglandular squamous cell papilloma is 0.0002 (so the estimated probability that there is difference is about 1 - 0.0002 = 0.9998). In male rats the posterior probability is of a trend in pooled follicular cell adenoma and carcinoma in the thyroid is estimated as 0.6996 (= 1 - 0.3004). In male rats the estimated posterior probability that there is no trend in interstitial cell adenoma in the testes is essentially 0.0, while the probability that there is no difference between the high dose group and control is 0.09115. In male rats the estimated posterior probability that there is no trend in renal tubule adenoma in the kidneys is essentially 0.086, but the simple probability that there is no difference between the high dose group and control is 0.4587. This is because the assessment of trend is more powerful (using frequentist terminology). The evidence of no trend in medulla pheochromocytoma is weak evidence (i.e., probability of about 0.5). In female rats the estimated posterior probability that there is no trend in renal tubule carcinoma in the kidneys is essentially 0.0074, and the simple probability that there is no difference between the high dose group and control is 0.0747. In male rats the probability of a decreasing trend over dose in pars distalis adenoma of the pituitary is nearly certain (i.e., close to 1), while in female rats the probability of a decreasing trend is 0.8358 (= 1 - .1642).

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Table A.3.1 Incidence of Tumors in Males Used in Bayesian Analysis

para-meter	organ	tumor	Incidence: ctrl	low	med	med-high	high
beta[1]	PITUITARY	PARS DISTALIS- ADENOMA	34	24	14	13	7
beta[2]	ADRENALS	MEDULLA- PHEOCHROMOCYTOMA, BENIGN	12	6	12	3	6
beta[3]	THYROID	FOLLICULAR CELL- ADENOMA	3	4	2	5	3
beta[4]	SKIN	KERATOACANTHOMA	8	8	9	7	9
beta[5]	SKIN	Sq.Cell Pap./Carcinomas	3	4	1	3	3
beta[6]	SKIN	Sq.Cell Neoplasms/Keratocan.	11	11	10	10	12
beta[7]	TESTES	INTERSTITIAL CELL- ADENOMA	3	3	2	9	17
beta[8]	KIDNEYS	RENAL TUBULE- ADENOMA	0	0	1	1	4
beta[9]	STOMACH	NONGLANDULAR- SQUAMOUS CELL PAPILLOMA	0	22	23	46	49
beta[10]	STOMACH	NONGLANDULAR- SQUAMOUS CELL CARCINOMA	0	5	18	51	58

Table A.3.2 Numeric Summaries of Dose Parameter Estimates in Males for Each Selected Tumor.

_ Node	Pr = 0	mean	sd	MC error	2.5%	median	97.5%
Trend							
beta[1]	0.0158	-0.4339	0.1332	0.00821	-0.6874	-0.4368	-0.1501
beta[2]	0.8133	0.0250	0.0831	0.00456	-0.0342	0.0	0.3025
beta[3]	0.5261	0.1462	0.1999	0.01337	0.0	0.0	0.6134
beta[4]	0.8662	-0.0078	0.0559	0.00247	-0.1872	0.0	0.06714
beta[5]	0.7429	-0.0560	0.1343	0.00622	-0.4691	0.0	0.01922
beta[6]	0.8748	-0.0107	0.0540	0.00234	-0.1998	0.0	0.02846
beta[7]	0.0	0.8053	0.1582	0.01055	0.5032	0.8064	1.115
beta[8]	0.086	0.7086	0.3624	0.02363	0.0	0.7318	1.381
beta[9]	0.0	0.8025	0.1152	0.00609	0.5828	0.8025	1.032
beta[10]	0.0	1.359	0.411	0.00778	1.094	1.355	1.648
Hi vs Low							
beta[1]	0.0	-3.18	0.6164	0.02118	-4.374	-3.183	-1.959
beta[2]	0.5168	-0.2945	0.5676	0.02002	-1.768	0.0	0.5019
beta[3]	0.5436	-0.0065	0.542	0.01171	-1.308	0.0	1.282
beta[4]	0.4048	-0.5101	0.6722	0.02721	-2.044	-0.1862	0.2988
beta[5]	0.412	-0.5084	0.739	0.01831	-2.208	-0.0559	0.5063
beta[6]	0.3271	-0.6502	0.6968	0.02703	-2.111	-0.5497	0.2043
beta[7]	0.09115	1.439	0.795	0.03523	0.0	1.486	2.911
beta[8]	0.4537	0.3679	0.732	0.01467	-0.8236	0.0	2.152
beta[9]	0.0002	2.595	0.706	0.02199	1.22	2.587	4.022
beta[10]	0.0	3.959	0.6784	0.02388	2.639	3.945	5.301

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Table A.3.3 Incidence of Tumors in Females Used in Bayesian Analysis

para-meter	organ	tumor	Incidence: ctrl	low	med	med-hi	hi
beta[1]	PITUITARY	PARS DISTALIS- ADENOMA	53	49	54	39	36
beta[2]	MAMMARY GLAND	FIBROADENOMA	23	15	20	20	17
beta[3]	MAMMARY GLAND	CARCINOMA, MULTIPLE	7	9	4	4	4
beta[4]	MAMMARY GLAND	ADENOMA	11	6	10	7	9
beta[5]	MAMMARY GLAND	CARCINOMA	10	13	13	8	19
beta[6]	MAMMARY GLAND	FIBROADENOMA, MULTIPLE	12	17	14	13	9
beta[7]	MAMMARY GLAND	Adenomas/Fibroadenomas	42	33	41	35	32
beta[8]	MAMMARY GLAND	Various Carcinomas	17	22	17	12	23
beta[9]	UTERUS	POLYP, ENDOMETRIAL-STROMAL	3	3	4	2	4
beta[10]	PANCREAS	Islets Adenomas/Carcinomas	5	8	4	3	3
beta[11]	KIDNEYS	RENAL TUBULE- CARCINOMA	0	0	0	2	4
beta[12]	STOMACH	NONGLANDULAR- SQUAMOUS CELL PAPILLOMA	0	11	21	31	24
beta[13]	STOMACH	NONGLANDULAR- SQUAMOUS CELL CARCINOMA	0	1	4	30	48

Table A.3.4 Numeric Summaries of Dose Parameter Estimates in Females for Each Selected Tumor.

Females

Node	Pr = 0	mean	sd	MC error	2.5%	median	97.5%
Trend							
beta[1]	0.1642	-0.2286	0.1296	0.007752	-0.4282	-0.2516	0.0
beta[2]	0,9468	0.00123	0.01655	3.691E-4	0.0	0.0	0.0
beta[3]	0.9419	-0.005505	0.04131	7.691E-4	-0.1194	0.0	0.0
beta[4]	0.9615	0.002352	0.0264	6.812E-4	0.0	0.0	0.0245
beta[5]	0.9259	0.009572	0.04385	0.001612	0.0	0.0	0.1694
beta[6]	0.9014	-0.01681	0.06351	0.002512	-0.2519	0.0	0.0
beta[7]	0.9712	-0.001665	0.02211	4.702E-4	0.0	0.0	0.0
beta[8]	0.959	0.002863	0.02212	5.557E-4	0.0	0.0	0.04855
beta[9]	0.8947	0.01909	0.07343	0.001963	0.0	0.0	0.2781
beta[10]	0.9587	-0.003165	0.0325	5.622E-4	-0.0353	0.0	0.0
beta[11]	0.0074	1.15	0.4097	0.02134	0.4896	1.106	2.082
beta[12]	0.0	0.5688	0.08388	0.002895	0.4087	0.568	0.7364
beta[13]	0.0	1.52	0.1364	0.004969	1.261	1.519	1.792
High vs Low							
beta[1]	0.2266	-1.143	0.8267	0.0443	-2.666	-1.23	0.0
beta[2]	0.7837	-0.1184	0.3675	0.01441	-1.304	0.0	0.1835
beta[3]	0.7454	-0.1474	0.5436	0.01308	-1.862	0.0	0.6172
beta[4]	0.8101	-0.01602	0.3129	0.007477	-0.896	0.0	0.699
beta[5]	0.5251	0.5105	0.6953	0.02769	0.0	0.0	2.136
beta[6]	0.74	-0.1793	0.4987	0.01541	-1.711	0.0	0.285
beta[7]	0.6781	-0.2636	0.5152	0.02303	-1.679	0.0	0.04334
beta[8]	0.6358	0.3311	0.5864	0.02605	-0.07609	0.0	1.842
beta[9]	0.6526	0.3408	0.7307	0.01993	-0.4054	0.0	2.381
beta[10]	0.7866	-0.04253	0.4385	0.007109	-1.285	0.0	0.8586
beta[11]	0.0747	3.72	2.098	0.08632	0.0	3.652	8.204
beta[12]	0.0	6.12	1.6	0.1019	3.592	5.907	9.908
beta[13]	0.0	8.317	1.393	0.07935	5.928	8.191	11.55

Reference ID: 3207500

Appendix 4. References

Bailer, A. and Portier, C. (1988), "Effects of Treatment-Induced Mortality on Tests for Carcinogenicity in Small Samples", *Biometrics*, **44**, 4, 417-431.

Bieler, G.S., and Williams, R.L. (1993), "Ratio Estimates, the Delta Method, and Quantal Response Tests for Increased Carcinogenicity", *Biometrics*, **49**, 4, 793-801.

Chu, K.C., Ceuto, C., and Ward, J.M. (1981), "Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays", *Journal of Toxicology and Environmental Health,* 8, 251-280.

De Iorio, M., Muller, P., Rosner, R.L., and MacEachern, S. (2004), "An ANOVA Model for Dependent Random Measures", Bayesian Nonparametric Nonproportional Hazards Survival Modeling", *Journal of the American Statistical Association*. **99**, 465, 205-215.

De Iorio, M., Johnson, W.O., Mueller, P., and Rosner, R.L. (2009), "Bayesian Nonparametric Nonproportional Hazards Survival Modeling", *Biometrics*, 65, 3, 762-771.

Haseman, J. K. (1983), "A Reexamination of False-positive Rates for Carcinogenicity Studies", *Fundamental and Applied Toxicology,* 3, 334-339.

Jara, A. (2007), "Applied Bayesian Non- and Semi-parametric Inference using DPpackage", *Rnews***, 7**, 3, 17-26.

Lin, K. K. and Ali, M.W. (2006), "Statistical Review and Evaluation of Animal Tumorigenicity Studies", *Statistics in the Pharmaceutical Industry, Third Edition,* edited by C.R. Buncher and J.Y. Tsay, Marcel Dekker, Inc. New York.

Lin, K. K. and Rahman, M.A. (1998), "Overall False Positive Rates in Tests for Linear Trend in Tumor Incidence in Animal Carcinogenicity Studies of New Drugs", Journal of Biopharmaceutical Statistics. 8, 1, 1-15.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986), "Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies", *Journal of the National Cancer Institute*. **76**, 283-289.

Peto, R., Pike, M.C., Day, N.E., Gray, R.G., Lee, P.N., Parrish, S., Peto, J., Richards, S., and Wahrendorf, J. (1980). "Guidelines for sample sensitive significance tests for carcinogenic effects in long-term animal experiments", *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, supplement 2: Long term and Short term Screening Assays for Carcinogens: A Critical Appraisal*, International Agency for Research Against Cancer, 311-426.

Reference ID: 3207500

R Development Core Team (2009). *R: A language and environment for statistical computing. R Foundation for Statistical Computing*, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org.

Rahman, M.A. and Lin, K.K. (2008), "A Comparison of False Positive Rates of Peto and Poly-3 Methods for Long Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics*. 18, 949-958.

STP Peto Working Group (2002), "Statistical Methods for Carcinogenicity Studies", *Toxicologic Pathology*. 30 (3), 403-414.

U.S. Department of Health and Human Services (2001), Guidance for Industry Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (DRAFT GUIDANCE), Center for Drug Evaluation and Research, Food and Drug Administration

Reference ID: 3207500

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/s/

STEVEN F THOMSON
10/23/2012
Statistical Carcinogenicity Review

KARL K LIN
10/24/2012
Concur with review

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 204063
Drug Name:	BG00012 (Dimethyl Fumarate) delayed release capsules
Indication(s):	Relapsing multiple sclerosis
Applicant:	Biogen Idec Inc.
Date(s):	Submission date: 02/27/2012
	PDUFA Date: 12/27/12
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiang Ling, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader
	James Hung, Ph.D., Director
Medical Division:	Division of Neuropharmacological Drug Products, HFD-120
Clinical Team:	Heather Fitter, M.D., Clinical reviewer
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Project Manager:	Nicole Bradley

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1 EXECUTIVE SUMMARY

The data overall provided adequate evidence to support for the efficacy of BG00012 as treatment of patients with relapsing multiple sclerosis.

In both pivotal studies, treatment with BG00012 BID and TID resulted in a statistically significant effect on relapses and MRI lesion accumulation. Study 301 also yielded a statistically significant effect of BG00012 on disability progression, and in Study 302 BG00012 groups had numerically fewer subjects with disability progression compared to the placebo group. The effect of BG00012 was generally consistent across a variety of subgroups defined by demographic and baseline disease characteristics.

Since flushing is a known side effect of BG00012 and occurred to high percentage of subjects, the agency was concerned about perceived unblinding of subjects' treatment assignments by observing flushing related events. To assess the robustness of the primary analysis result against potentially biased relapse assessment in case of perceived unblinding, this reviewer conducted worst case scenario analyses, in which all relapses prior to and after alternative MS medications were included for subjects in BG00012 groups but only relapses that met objective criteria as assessed by sites, confirmed by a blinded Independent Neurology Evaluation Committee (INEC), and occurred prior to alternative MS medications, were included for placebo subjects. The results of the worst case analysis still reached statistical significance.

The treatment discontinuation rate was high in both studies, partly because the studies allowed subjects to cross over to alternative MS treatments. However, as shown in a series of sensitivity analyses including analyses of the worst case scenario, treatment discontinuation or the switch to alternative MS medications did not appear to have a significant effect on the efficacy results or conclusions.

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2 INTRODUCTION

2.1 Overview

BG00012 is an oral formulation containing the single active ingredient dimethyl fumarate (DMF) for the intended treatment of subjects with relapsing multiple sclerosis (MS). BG00012 was developed under IND 73061. SPA was submitted for pivotal Studies 109MS301 and 109MS302 (hereafter referred to as "Study 301" and "Study 302," respectively) without reaching Agency agreement. However, advices from the Agency were incorporated into the study protocols before the studies were initiated, such as inclusion of the 240 mg BID dose group, changing the primary endpoint in one study from proportion relapsed to annualized relapse rate, and requiring subjects to remain on study treatment for 1 year before being eligible for rescue treatment with an approved therapy due to relapse. Statistical analysis plan (SAP) was submitted for Agency review (SN143) and revised according to the agency's comments.

Studies 301 and 302 were Phase 3, randomized, placebo-controlled studies that evaluated the efficacy and safety of 2 dosing regimens of BG00012 (240 mg BID and 240 mg TID) versus placebo. Study 302 also included an active reference comparator (GA). A total of 1237 RRMS subjects were enrolled into Study 301 and 1430 subjects into Study 302. Subjects were required to have an EDSS between 0 and 5 at randomization and must have experienced a least 1 relapse within the year prior to randomization or have had a Gd-enhancing lesion on MRI scan obtained within 6 weeks prior to randomization. The only difference between the eligibility criteria of the 2 studies was in exposure to GA. In Study 302, no prior exposure to GA was allowed, whereas in Study 301, subjects could have received prior treatment with GA but had to have discontinued for at least 3 months prior to randomization.

2.2 Data Sources

Materials reviewed for this application include the clinical study reports, raw and derived datasets, SAS codes used to generate the derived datasets and tables, protocols, statistical analysis plans, and documents of regulatory communications, which are located in the following directory: \\cdsesub5\EVSPROD\NDA204063\0000.

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

From raw tabulation, key efficacy endpoints were reproduced by this reviewer. Documentation of statistical analysis methods was included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Enrollment into Study 301 began under Version 1, dated 21 September 2006. The protocol was subsequently amended 5 times with most of the amendments occurred early in the study and the last amendment dated 26 May 2010. The first subject was treated on 14 March 2007, and the last subject completed the study on 23 February 2011. Statistical Analysis Plan (SAP) was finalized on 10 March 2011, prior to database lock.

Enrollment into Study 302 began under Version 1, dated 16 October 2006. The protocol was subsequently amended 3 times with the final version dated 09 January 2008. The first subject was treated on 28 July 2007, and the last subject completed the study on 24 August 2011. SAP was finalized on 3 October 2011, prior to database lock.

Study design
Studies 301 and 302 were Phase 3, randomized, placebo-controlled studies that evaluated the efficacy and safety of 2 dose regimens of BG00012 (240 mg BID and 240 mg TID) versus placebo. Study 302 also included an active reference comparator (GA 20 mg SC injection QD). Oral treatments (placebo or BG00012) were double-blind and GA treatment was single-blind. Both studies were also rater-blinded.

The sample size was planned to be approximately 1010 subjects for Study 301 and 1230 for Study 302. A total of 1237 RRMS subjects were enrolled into Study 301 and 1430 subjects into Study 302. Subjects were randomized equally to the study arms. All subjects who were randomized at sites where MRI was deemed feasible had the option of participating in the MRI portion of the study (MRI cohort). In both studies, approximately 90% to 95% of subjects at qualified sites chose to participate in the MRI scanning, and about 40% to 45% of the randomized subjects were part of the MRI cohort. Randomization in both Studies 301 and 302 was stratified by investigational site to ensure that the number of subjects in the MRI cohort would be approximately balanced across treatment groups.

The duration of blinded study treatment in both studies was 96 weeks and clinic visits occurred every 4 weeks. Subjects who discontinued the study treatment prematurely for any reason were to remain in the study and continue with an abbreviated visit schedule.

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If subjects experienced confirmed disability progression or if they had completed 48 weeks of blinded treatment and experienced INEC- confirmed relapses (1 relapse on or after Week 24 in Study 301 or 2 relapses at any time in Study 302), they were offered the option of remaining on blinded treatment, discontinuing treatment and continuing in the study, or switching to alternative MS medications and continuing in the study. Data after such medications were administered were excluded from analyses unless stated otherwise.

Efficacy Endpoints in Studies 301 and 302

In Study 302, the primary efficacy endpoint was annualized relapse rate at 2 years, which is the most common measure of relapse used in confirmatory MS trials. In Study 301, the primary efficacy endpoint was the proportion of subjects relapsed at 2 years.

Table 1. Study Efficacy Endpoints

Efficacy Endpoints ***(measured at or over 2 years comparing BG00012 to placebo)***	**Study 301**	**Study 302**
Primary endpoint	Proportion of subjects relapsed	Annualized relapse rate
Secondary endpoints (listed in descending rank order)	Number of new or newly enlarging T2 hyperintense lesions	Number of new or newly enlarging T2 hyperintense lesions
	Number of Gd-enhancing lesions	Number of new T1 hypointense lesions
	Annualized relapse rate	Proportion of subjects relapsed
	Disability progression measured by EDSS	Disability progression measured by EDSS

Clinical Relapses

Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. New or recurrent neurologic symptoms that evolved gradually over months were considered disease progression, not an acute relapse. New or recurrent neurologic symptoms that occurred fewer than 30 days following the onset of a relapse as defined above were to be considered part of the same relapse.

Subjects who experienced new neurologic symptoms were to contact the site to determine the necessity of an Unscheduled Relapse Assessment Visit. If required, the subject was then evaluated by the treating neurologist, subsequently assessed by the examining neurologist, and then, based on the examining neurologist's findings, the treating neurologist determined whether

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new objective findings (i.e., an objective relapse) had occurred. The protocol-defined objective relapses assessed by the sites then had to be reviewed and confirmed by a blinded Independent Neurology Evaluation Committee (INEC). The same INEC was used in both studies.

The annualized relapse rate (ARR) for an individual subject was calculated as the number of relapses for that patient divided by the number of patient-years followed. The proportion of subjects who experienced a relapse was estimated as the probability of relapse at 2 years from the Kaplan-Meier curve.

Confirmed disability progression

Over the time course of MS, recovery from clinical relapses tends to be incomplete, leading to the accumulation of functional disability. In the Phase 3 studies, confirmed disability progression was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 that was sustained for 12 weeks or a 1.5 point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks. The EDSS score is based on scores determined for ambulation and 7 functional systems and ranges from 0.0 (normal exam) to 10.0 (death due to MS). EDSS scores were obtained at regular clinic visits (i.e., every 12 weeks) as well as at any unscheduled relapse assessment visits.

The date of the initial visit at which the minimum increase in the EDSS score was met was the date of onset of the progression (tentative progression). Death due to MS was counted as progression. If the subject was in the midst of a tentative progression at the time of death, the progression date was the date of the start of the progression. Otherwise, the progression date was the date of death.

Progression was defined as confirmed when this minimum EDSS change is present on the next study visit occurring after 74 days or longer from the initial observation. The 74 day interval was based on the visit windows allowed in the protocol around the target visit day. A progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse. If a subject met the above criteria for confirmed progression and was also experiencing a relapse, the subject had to meet the defined minimum criteria at the next visit in order for the progression to be confirmed. Progression could be confirmed at the Premature Study Withdrawal Visit or after the start of alternative MS medications, or the Week 12 data from the safety extension study 109MS303.

Subjects who did not have a sustained progression based on the above rules were censored. The censoring date was the last EDSS evaluation that is not a tentative progression prior to end of study or alternative MS medications.

MRI endpoints

In each study, brain MRI scans with and without Gd were performed at baseline, 6 months, 1 year, and 2 years. MRI scans were forwarded to a central MRI reading center for evaluation by staff who were blinded to individual subjects' treatment assignments. MRI endpoints included the number of new or newly enlarging T2 hyperintense lesions, the number of T1 hypointense Lesions and the number of Gd-enhancing lesions.

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Reviewer's comment:
Flushing is a known side effect of BG00012. The study had taken measures to protect against perceived unblinding of subjects' treatment assignments, such as using separate study personnel to conduct efficacy assessments and treat subjects, requiring confirmation of relapses by INEC, instructing subjects not to take their dose of study treatment within 4 hours before a clinic visit to prevent site personnel from observing any drug-induced symptoms. Still, as flushing is a common event that has been observed for high percentage of subjects on BG00012, the agency is concerned about the possible blind breaking. Sensitivity analyses were conducted by this reviewer to check the robustness of the study result against potential unblinding, as discussed in the following sections.

3.2.2 Statistical Methodologies

Analysis Population
Statistical analyses of clinical endpoints were based on the intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least one dose of study treatment. Subjects were analyzed according to their randomized treatment assignment.

MRI endpoints were analyzed using the MRI Cohort, consisting of ITT subjects participating at sites that had adequate MRI equipment, who had at least one MRI scan available for analysis.

Statistical Testing Procedures
The endpoints were tested in the fixed order as shown in Table 1. If statistical significance was not achieved for an endpoint for a particular dose level, all endpoint(s) of a lower rank for that dose level were not considered statistically significant. For each endpoint, the TID group was compared with placebo and if statistically significant ($p \leq 0.050$), the BID group was compared with placebo.

Missing Data
In the primary analyses of all efficacy endpoints, except for that of confirmed disability progression based on EDSS scores, observed data after the initiation of alternative MS medications were excluded, or subjects were censored at the time the alternative MS medications were started if the subject had not experienced the event. In the analysis of disability progression based on EDSS, EDSS evaluations performed after the initiation of alternative MS medications were used to confirm tentative progression that started prior to the switch to alternative MS medications.

For the analysis of MRI secondary endpoints, post-baseline data that were missing for any reason (e.g., early withdrawal, skipped visits, or the exclusion of data after alternative MS medications were started) were imputed.

Details on missing data handling were discussed below in the analysis methods for each endpoint.

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Analysis Methods

Proportion of subjects who experienced a relapse
The analysis method for the proportion of subjects relapsed was a Cox proportional hazards model for time to first relapse, adjusted for baseline number of relapses in the year prior to study entry, baseline age (<40 versus ≥40 years), EDSS score (≤2.0 versus >2.0), and region. The proportion of subjects who experienced a relapse was estimated as the probability of relapse at 2 years from the Kaplan-Meier curve.

Note that in the final protocol for both studies, the baseline EDSS score used in primary analysis of the proportion of subjects relapsed at 2 years was categorized as ≤3.5 vs. >3.5. However, the SAPs used EDSS score ≤2.0 versus >2.0. Since the SAPs were dated after the protocols, this reviewer accepted the use of EDSS score ≤2.0 versus >2.0 in the primary analysis and conducted additional analyses using EDSS score ≤3.5 versus >3.5 to check the robustness of the primary analysis result.

Only INEC-confirmed relapses were included in the primary analyses. Data after subjects switched to alternative MS medications were excluded, and the subject's time on study were censored at the time the alternative MS medication was started. The following pre-specified sensitivity analyses were performed:
1) A logistic regression with the outcome of relapse (Yes/No) over the course of 2 years in the ITT population. Each subject with unknown relapse status (subject did not experience an INEC-confirmed relapse prior to withdrawal from study or switch to alternative MS medications) were classified as having experienced a relapse in the analysis if the reasons on either CRF page were indicative of relapse, death due to MS, disease worsening, disease progression, or lack of efficacy, or switch to alternative MS medication;
2) Logistic regression on INEC confirmed relapses in which subjects with unknown relapse status were considered as relapsed;
3) Cox proportional hazards model on INEC-confirmed relapses in the per-protocol population;
4) Cox proportional hazards model on all relapses recorded on CRF, regardless of whether they met objective criteria or were INEC-confirmed;
5) Cox proportional hazards model on objective relapses; and
6) Cox proportional hazards model on INEC-confirmed relapses including those prior to and after alternative MS medications.
All sensitivity analyses adjusted for the same covariates used in the primary analysis.

Annualized relapse rate (ARR)
ARR was analyzed using a negative binomial regression model adjusted for baseline EDSS score (≤2.0 versus>2.0), baseline age (<40 versus ≥40 years), region, and the number of relapses in the year prior to study entry. The logarithmic transformation of the time on study was included in the model as the offset parameter. Dispersion was evaluated from the Pearson Chi-Square statistic. It was planned that if the data were underdispersed, or if the negative binomial regression model did not converge, a Poisson regression model would be used instead.

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The primary analysis of ARR was based on INEC-confirmed relapses. Relapses that occurred after subjects received alternative MS medications were excluded from the analyses of relapse rate, and the subject's time on study was censored at the time the alternative MS medication was started. The following four sensitivity analyses were pre-specified for ARR using the same negative binomial regression model as the primary analysis, on different population or with additional relapses:
(1) INEC-confirmed relapses in the per-protocol population;
(2) objective relapses (INEC confirmed or not);
(3) all relapses recorded on the Unscheduled Relapse (regardless of whether they met objective criteria or were INEC-confirmed)
(4) INEC-confirmed relapses both before and after initiation of alternative MS medications.

Disability progression
Disability progression measured by EDSS over 2 years was analyzed using a Cox proportional hazards model, adjusted by baseline EDSS value as a continuous variable, region, and age (<40 versus ≥40 years). Two pre-specified sensitivity analyses were performed by the sponsor, which differed from the primary analysis only in that they used the per-protocol population or required that disability progression be confirmed after 24 weeks.

MRI endpoints
Negative binomial regression was used to analyze the number of new or newly-enlarging T2 hyperintense lesions and the number of new T1 hypointense lesions over 2 years. The model included treatment group and adjusted for region and baseline volume of T2/T1 lesions. Missing post-baseline data were imputed based on the assumption that new lesions develop at a constant rate (constant rate assumption). For example, if a subject had 1 new lesion that developed between Week 24 and 48, then had a missing value for Week 96, the number of new lesions developed at Week 96 was assumed to be 2, since the time interval between Week 48 to Week 96 is twice that between Week 24 to Week 48. Missing data were not imputed for subjects with no post-baseline data. To reduce the influence of outliers, any imputed values greater than the biggest observed value were truncated at the biggest observed value in the analysis. Two sensitivity analyses will be performed using 1) the observed data prior to start of alternative MS treatments; and 2) all observed data, prior to and after alternative MS medications.

Since the majority of subjects have no Gd-enhancing lesions, ordinal logistic regression was used for the analysis of the number of Gd-enhancing lesions at 2 years. The categories for the number of lesions are 0, 1, 2, 3-4 and ≥5. The model included treatment group, and adjusted for region and the baseline number of Gd-enhancing lesion. If there were a few subjects with an extremely large number of Gd-enhancing lesions at baseline, extreme values above 30 were considered as 30 in the model. Missing data for Gdenhancing lesions were imputed using the method of last observation carried forward. Baseline data were not carried forward. A sensitivity analysis using only observed data prior to start of alternative MS treatment was performed.

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3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In Study 301, a total of 1237 subjects were randomized at 198 sites in 28 countries worldwide. The highest enrolling countries were the US (203 subjects), Germany (172 subjects), Poland (132 subjects), and India (114 subjects). Of the randomized subjects, 3 subjects were not dosed hence excluded from the ITT population; 540 dosed subjects at 76 sites in 14 countries participated in the MRI cohort (180, 176, and 184 subjects in the placebo, BG00012 BID and BG00012 TID groups, respectively).

Table 2. Subject Disposition (Study 301)

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Total
Number of subjects randomized	410	411	416	1237
Number of subjects dosed	408 (100)	410 (100)	416 (100)	1234 (100)
Number of subjects who completed study drug	265 (65)	284 (69)	289 (69)	838 (68)
Number of subjects who discontinued study drug	143 (35)	126 (31)	127 (31)	396 (32)
MS relapse	31 (8)	4 (<1)	10 (2)	45 (4)
MS progression	14 (3)	7 (2)	7 (2)	28 (2)
Adverse event	22 (5)	61 (15)	56 (13)	139 (11)
Lost to follow-up	7 (2)	9 (2)	11 (3)	27 (2)
Consent withdrawn	34 (8)	18 (4)	18 (4)	70 (6)
Investigator decision	4 (<1)	4 (<1)	2 (<1)	10 (<1)
Subject non-compliance	3 (<1)	3 (<1)	9 (2)	15 (1)
Death	0	0	1 (<1)	1 (<1)
Other	28 (7)	20 (5)	13 (3)	61 (5)
Number of subjects who completed study	317 (78)	315 (77)	320 (77)	952 (77)
Number of subjects who withdrew from study	91 (22)	95 (23)	96 (23)	282 (23)
Adverse event	22 (5)	40 (10)	36 (9)	98 (8)
Lost to follow-up	9 (2)	11 (3)	11 (3)	31 (3)
Consent withdrawn	31 (8)	22 (5)	19 (5)	72 (6)
Investigator decision	4 (<1)	4 (<1)	3 (<1)	11 (<1)
Subject non-compliance	4 (<1)	4 (<1)	8 (2)	16 (1)
Death	0	0	1 (<1)	1 (<1)
Other	21 (5)	14 (3)	18 (4)	53 (4)

Source: Study 301 CSR Table 10-1.

In Study 302, a total of 1430 subjects were randomized at 200 sites in 28 countries worldwide. The highest enrolling countries were Poland (282 subjects), US (267 subjects), India (107 subjects), and Ukraine (104 subjects). Thirteen subjects (3 randomized to BG00012 BID and 10 randomized to GA) were randomized but not dosed. Among the 10 subjects randomized to GA, 8 withdrew consent upon learning that they had been randomized to open-label GA treatment. One subject randomized to BG00012 240 mg TID actually received GA. The MRI cohort comprised 48% of the ITT population and included 681 subjects (167, 169, 170, and 175 subjects in the placebo, BG00012 BID, BG00012 TID, and GA groups, respectively) who were enrolled at 111 sites in 17 countries.

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Table 3. Subject Disposition (Study 302)

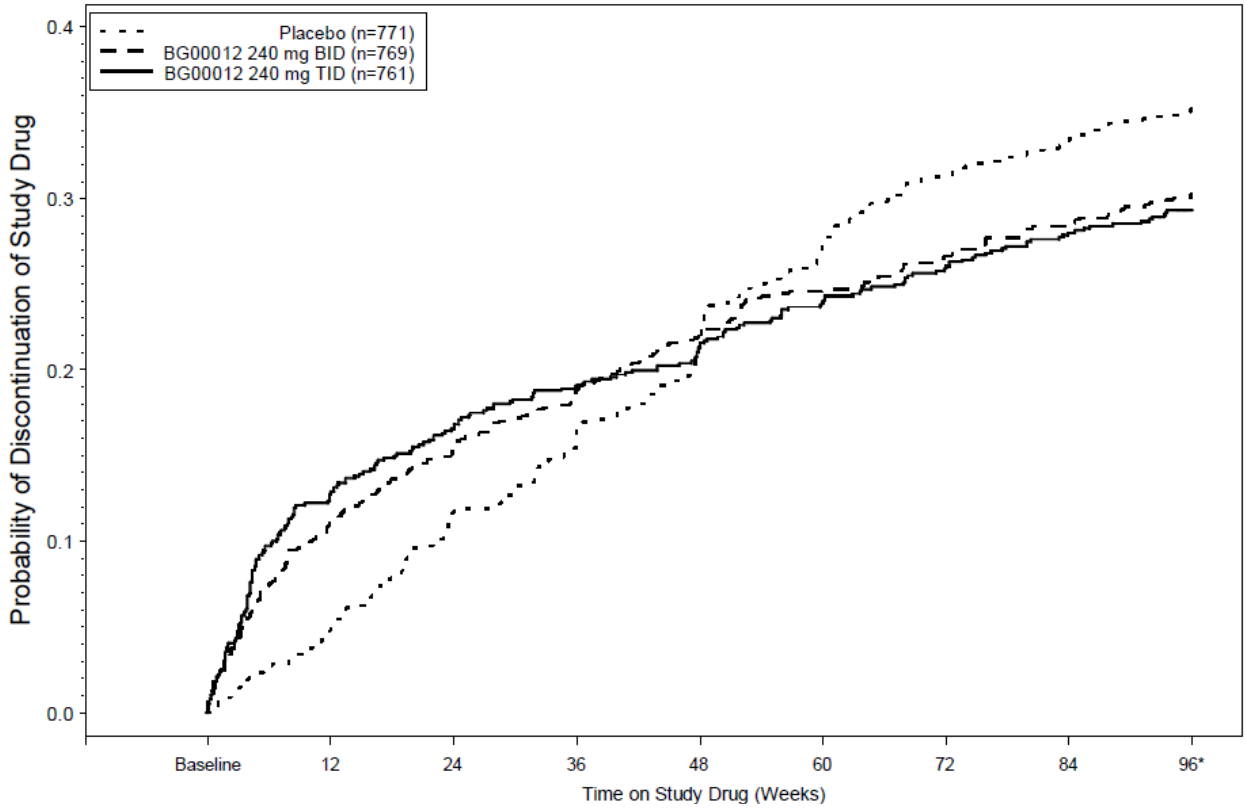
	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	GA	Total
Number of subjects randomized	363	362	345	360	1430
Number of subjects dosed	363 (100)	359 (100)	345 (100)	350 (100)	1417 (100)
Number of subjects who completed study drug	234 (64)	253 (70)	249 (72)	264 (75)	1000 (71)
Number of subjects who discontinued study drug	129 (36)	106 (30)	96 (28)	86 (25)	417 (29)
MS relapse	28 (8)	8 (2)	6 (2)	9 (3)	51 (4)
MS progression	10 (3)	8 (2)	7 (2)	9 (3)	34 (2)
Adverse event	22 (6)	38 (11)	42 (12)	27 (8)	129 (9)
Lost to follow-up	7 (2)	8 (2)	4 (1)	8 (2)	27 (2)
Consent withdrawn	12 (3)	8 (2)	10 (3)	9 (3)	39 (3)
Investigator decision	3 (<1)	2 (<1)	1 (<1)	2 (<1)	8 (<1)
Subject non-compliance	9 (2)	4 (1)	3 (<1)	3 (<1)	19 (1)
Death	0	0	0	1 (<1)	1 (<1)
Other	38 (10)	30 (8)	23 (7)	18 (5)	109 (8)
Number of subjects who completed study	278 (77)	284 (79)	273 (79)	292 (83)	1127 (80)
Number of subjects who withdrew from study	85 (23)	75 (21)	72 (21)	58 (17)	290 (20)
MS Relapse	2 (<1)	0	1 (<1)	3 (<1)	6 (<1)
MS Progression	1 (<1)	0	0	0	1 (<1)
Adverse event	12 (3)	22 (6)	28 (8)	13 (4)	75 (5)
Lost to follow-up	11 (3)	9 (3)	8 (2)	11 (3)	39 (3)
Consent withdrawn	12 (3)	8 (2)	14 (4)	11 (3)	45 (3)
Investigator decision	6 (2)	2 (<1)	1 (<1)	2 (<1)	11 (<1)
Subject non-compliance	8 (2)	4 (1)	3 (<1)	3 (<1)	18 (1)
Death	1 (<1)	0	0	1 (<1)	2 (<1)
Other	32 (9)	30 (8)	17 (5)	14 (4)	93 (7)

Note: The consent withdrawn descriptions recorded on the study case report forms were reviewed by the team and the reason of consent withdrawn and other were reclassified for 31 subjects.
Source: Study 302 CSR Table 69.

In Study 301, a total of 952 subjects (77%) completed the study and 838 subjects (68%) completed study treatment. The treatment discontinuation rate was similar across treatment groups. In Study 302, a total of 1127 subjects (80%) completed the study and 1000 subjects (71%) completed study treatment. The percentage of subjects who discontinued study treatment was 30% in the BG00012 BID group, 28% in the BG00012 TID group, 25% in the GA group, and 36% in the placebo group. For both studies, the most common reasons for discontinuing the study treatment were MS relapse or “other” in the placebo group, and experiencing an AE in the BG00012 groups. Treatment discontinuations were more common with BG00012 than with placebo in the first 3 months, due to AEs and/or tolerability issues associated with initiation of BG00012 treatment. After Week 48 more placebo subjects discontinued treatment (Figure 1).

Reference ID: 3203073

Figure 1. Time to discontinuation of study drug - Studies 301 and 302 Pooled



Source: NDA module 2.7.3 Figure 3.

The treatment discontinuation rate in both studies is high, partly because the studies allowed subjects to cross over to alternative MS treatments. In Study 301, the proportion of subjects who switched to alternative MS medications was higher in the placebo group (13%) than in the BG00012 BID (6%) and BG00012 TID (5%) groups. Similarly, in Study 302, the proportions of subjects who switched to alternative MS medications were 11%, 7%, 8% and 6% in the placebo, BG00012 BID & TID, and GA groups respectively. Subjects who prematurely discontinued study treatment, including those who switched to an alternative MS medication, were given the option of remaining in the study and continuing a modified schedule of follow-up evaluations.

Reference ID: 3203073

For both studies, the treatment groups were generally well balanced with respect to baseline demographic characteristics in the ITT population (Table 4). Subjects were enrolled from 34 countries, which were grouped into 3 pre-defined regions based on geography, type of health care system, and access to health care: Region 1 (US), Region 2 (Canada, Western Europe, Israel, New Zealand, Australia (Study 301 only), South Africa (Study 301 only) and Costa Rica (Study 302 only)]), and Region 3 (Eastern Europe, India, Mexico, and Guatemala (Study 301 only)). In Study 301, 16% of subjects were enrolled from Region 1, and the remaining subjects were enrolled in equal percentages from Regions 2 and 3 (approximately 42 % each). In Study 302, 19% of subjects were from Region 1, 15% of subjects from Region 2, and 66% of subjects from Region 3. The demographic profile of the MRI cohort was similar to that of the non-MRI cohort.

Table 4. Demography for Studies 301 and 302, ITT population

	Study 301			Study 302		
	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
No. (%) of subjects	408 (100)	410 (100)	416 (100)	363 (100)	359 (100)	345 (100)
Age (years)						
18-19	6 (1)	3 (<1)	5 (1)	5 (1)	5 (1)	3 (<1)
20-29	71 (17)	83 (20)	63 (15)	83 (23)	73 (20)	71 (21)
30-39	129 (32)	138 (34)	146 (35)	125 (34)	130 (36)	119 (34)
40-49	156 (38)	136 (33)	158 (38)	111 (31)	104 (29)	112 (32)
50-55	44 (11)	50 (12)	42 (10)	38 (10)	47 (13)	40 (12)
>55	2 (<1)	0	2 (<1)	1 (<1)	0	0
Median	39	38	39	37	38	38
Min, max	18, 56	18, 55	18, 56	18, 56	18, 55	18, 55
Sex						
Female	306 (75)	296 (72)	306 (74)	251 (69)	245 (68)	250 (72)
Male	102 (25)	114 (28)	110 (26)	112 (31)	114 (32)	95 (28)
Race						
White	318 (78)	321 (78)	330 (79)	305 (84)	304 (85)	292 (85)
Asian	42 (10)	38 (9)	36 (9)	28 (8)	28 (8)	26 (8)
Unknown	22 (5)	21 (5)	20 (5)	11 (3)	11 (3)	10 (3)
Other	18 (4)	22 (5)	20 (5)	10 (3)	14 (4)	12 (3)
Black	8 (2)	8 (2)	10 (2)	9 (2)	2 (<1)	5 (1)
Geographic location						
Region 1[1]	64 (16)	65 (16)	72 (17)	73 (20)	65 (18)	64 (19)
Region 2[2]	172 (42)	174 (42)	173 (42)	55 (15)	55 (15)	52 (15)
Region 3[3]	172 (42)	171 (42)	171 (41)	235 (65)	239 (67)	229 (66)

Source: NDA module 2.7.3 Table 7.

Reference ID: 3203073

For both studies, the treatment groups were well balanced with respect to baseline disease characteristics (Table 5).

Table 5. Baseline MS Disease Characteristics in Studies 301 and 302, ITT population

	Study 301			Study 302		
	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
No. (%) of subjects	408 (100)	410 (100)	416 (100)	363 (100)	359 (100)	345 (100)
EDSS score[1]						
≤2	202 (50)	212 (52)	224 (54)	160 (44)	161 (45)	159 (46)
>2	206 (50)	197 (48)	192 (46)	203 (56)	198 (55)	186 (54)
≤3.5	335 (82)	337 (82)	359 (86)	300 (83)	299 (83)	292 (85)
>3.5	73 (18)	73 (18)	57 (14)	63 (17)	60 (17)	53 (15)
n	408	409	416	363	359	345
Mean	2.48	2.40	2.36	2.59	2.56	2.52
SD	1.241	1.290	1.188	1.170	1.202	1.185
Median	2.5	2	2	2.5	2.5	2.5
Min, max	0, 6	0, 6.5	0, 6	0, 5	0, 5.5	0, 5
No. of relapses within the previous 12 months						
0	18 (4)	13 (3)	9 (2)	9 (2)	13 (4)	13 (4)
1	274 (67)	276 (67)	294 (71)	245 (67)	239 (67)	211 (61)
2	98 (24)	100 (24)	94 (23)	92 (25)	91 (25)	99 (29)
3	12 (3)	19 (5)	17 (4)	11 (3)	14 (4)	16 (5)
4 or more	6 (1)	2 (<1)	2 (<1)	5 (1)	2 (<1)	5 (1)
Unknown	0	0	0	1 (<1)	0	1 (<1)
n	408	410	416	362	359	344
Median	1	1	1	1	1	1
Min, max	0, 4	0, 6	0, 4	0, 8	0, 4	0, 5

Source: NDA module 2.7.3 Table 8.

In the MRI cohort for each study, the treatment groups were generally well balanced with respect to baseline MRI parameters.

Reference ID: 3203073

3.2.4 Results and Conclusions

3.2.4.1 Study 301

Proportion of Subjects Relapsed at 2 Years
The Kaplan-Meier estimate of the proportion of subjects relapsed at 2 years was 46% in the placebo group compared with 27% in the BG00012 BID group and 26% in the TID group. The hazard ratios were 0.51 for BG00012 BID versus placebo and 0.50 for BG00012 TID versus placebo. This indicated the risk of relapse at 2 years was reduced by 49% (p<0.0001) and 50% (p<0.0001) following treatment with BG00012 BID and TID, respectively, compared with placebo (Table 6). The proportional hazards assumption was checked and the assumption held. The results of all pre-specified sensitivity analyses were consistent with the result of the primary analysis. Additionally, similar result was obtained using EDSS score ≤3.5 versus >3.5 as a covariate instead of EDSS score ≤2.0 versus >2.0 in the analysis. This reviewer also conducted a sensitivity analysis using logrank test, and the result was consistent with the primary analysis (p<0.0001 for both comparisons).

The primary analysis was based on relapses that were protocol-defined and confirmed by INEC. Most (94%) of the relapse cases reported by the subjects were assessed as protocol-defined objective relapses by the site and 88% of the protocol-defined objective relapses were confirmed by the INEC. This reviewer conducted two worst case scenario analyses, in which all relapses prior to and after alternative MS medications were included for subjects in BG00012 groups but only INEC-confirmed relapses prior to alternative MS medications were included for placebo subjects. This analysis was to assess the robustness of the analysis result against potential biased relapse assessment in case of perceived unblinding and the impact of treatment discontinuation. The worst case scenario analyses used the Cox model and the logistic regression with unknown status classified according to the pre-specified rule based on the reasons for end of treatment/study or AE. The analysis results for the worst case scenario also supported the primary analysis (p≤0.0001 for all comparisons, Table 6).

Table 6. Summary of Proportion of Subjects Relapsed at 2 Years (Study 301)

	Placebo	BG00012 BID	BG00012 TID
N	408	409	416
Primary Analysis			
Number of subjects relapsed			
Yes	171 (42)	98 (24)	95 (23)
No (Censored)	237 (58)	312 (76)	321 (77)
Estimated proportion of subjects relapsed at 2 years	0.46	0.27	0.26
Hazard ratio (95% CI)		0.51 (0.40, 0.66)	0.50 (0.39, 0.65)
Percentage reduction (95% CI)		48.5 (33.9, 59.9)	49.5 (35.0, 60.7)
p-value		<0.0001	<0.0001
Worst Case Scenario Analysis Using Cox Model			
Number of subjects relapsed			
Yes	171 (42)	111 (27)	114 (27)
No (Censored)	237 (58)	299 (73)	302 (73)

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	Placebo	BG00012 BID	BG00012 TID
Estimated proportion of subjects relapsed at 2 years	0.46	0.30	0.30
Hazard ratio (95% CI)		0.60 (0.47, 0.76)	0.63 (0.50, 0.80)
Percentage reduction (95% CI)		40.5 (24.3, 53.2)	37.0 (20.1, 50.3)
p-value		<0.0001	0.0001
Worst Case Scenario Analysis Using Logistic Regression			
Relapse status at 2 years (unknown status assigned)			
Yes	182 (45)	118 (29)	122 (29)
No	226 (55)	292 (71)	294 (71)
Odds ratio (95% CI)		0.49 (0.36, 0.65)	0.52 (0.38, 0.69)
Percentage reduction (95% CI)		51.3 (34.5, 63.8)	48.4 (30.8, 61.5)
p-value		<0.0001	<0.0001

Source: FDA reviewer.

This reviewer further examined the treatment effect for patients with or without flushing. As shown in Table 7 below, the treatment effect was preserved in both subgroups, although the result should be interpreted with caution as the subgroups were not defined based on baseline characteristics.

Table 7. Estimated Proportion of Relapsing Patients based on the presence of the adverse event of flushing (Study 301)

	BG00012 BID	BG00012 TID
With flushing	0.22	0.23
Without flushing	0.31	0.28

Source: FDA reviewer.

Total Number of New or Newly Enlarging T2 Hyperintense Lesions at 2 Years

BG00012 BID and TID reduced the number of new or newly enlarging T2 hyperintense lesions that developed over 2 years by 85% and 74%, respectively, compared with placebo (p <0.0001 for both comparisons). The primary analysis imputed missing data based on constant rate assumption. The pre-specified sensitivity analyses using observed data confirmed the primary analysis result. However, those sensitivity analyses only used observed data on week 96 (primary time point) but not data on week 24 or week 48 when week 96 data was missing. Therefore, this reviewer performed two sensitivity analyses using the last observed data. One analysis used only observed data prior to the switch to alternative MS medications and the other analysis used observed data including those after switching to alternative MS medications. To account for different length of time on study, the logarithmic transformation of the time of the last MRI scan relative to week 96 was included in the model as the offset parameter. The results were consistent with the primary result and indicated that neither the data imputation method used in the primary analysis nor the exclusion of data after subjects switched to alternative MS medications affected the results (Table 8).

Reference ID: 3203073

Table 8. Number of New or Newly Enlarging T2 Lesions at 2 Years (Study 301)

	Placebo	BG00012 BID	BG00012 TID
Primary Analysis (with imputation)			
N	165	152	152
Adjusted mean	17.0	2.6	4.4
Percent reduction (95% CI)		-85 (-90, -77)	-74 (-83, -62)
p-value		<0.0001	<0.0001
Sensitivity Analysis using last observed data prior to alternative MS medications			
N	165	152	152
Adjusted mean	18.5	2.5	4.4
Lesion mean ratio (95% CI)		-87 (-91, -80)	-76 (-84, -65)
p-value		<0.0001	<0.0001
Sensitivity Analysis using last observed data including those after alternative MS medications			
N	166	153	156
Adjusted mean	16.8	2.5	4.2
Percent reduction (95% CI)		-85 (-90, -78)	-75 (-83, -64)
p-value		<0.0001	<0.0001

Source: FDA reviewer.

Number of Gd-Enhancing Lesions at 2 Years

BG00012 BID and TID reduced the odds of having greater Gd-enhancing lesion activity at 2 years by 90% and 73%, respectively, compared with placebo (p<0.0001 for both comparisons,Table 9). The pre-specified sensitivity analysis yielded similar result.

Table 9. Number of Gd-Enhancing Lesions at 2 Years (Study 301)

	Placebo	BG00012 BID	BG00012 TID
N	165	152	152
mean	1.8	0.1	0.5
Odds ratio (95% CI)		0.10 (0.05, 0.22)	0.27 (0.15, 0.46)
p-value		<0.0001	<0.0001

Source: FDA reviewer.

Annualized Relapse Rate at 2 years

BG00012 BID and TID reduced the annualized relapse rate over 2 years by 53% and 48%, respectively, compared with placebo (p<0.0001 for both comparisons). Results of all pre-specified sensitivity were consistent with the primary results. This reviewer conducted worst case scenario analysis using the same model but with all relapses prior to and after alternative MS medications included for subjects in BG00012 groups but only INEC-confirmed relapses prior to alternative MS medications for placebo subjects. The result also supported the primary analysis (Table 10).

Reference ID: 3203073

Table 10. Summary of Annualized Relapse Rate at 2 Years (Study 301)

	Placebo	BG00012 BID	BG00012 TID
N	408	409	416
Primary Analysis			
Adjusted ARR	0.364	0.172	0.189
(95% CI)	(0.303,0.436)	(0.138,0.214)	(0.153,0.234)
Rate ratio		0.473	0.521
(95% CI)		(0.365,0.613)	(0.404,0.670)
Percentage reduction		52.7	47.9
(95% CI)		(38.7, 63.5)	(33.0, 59.6)
p-value		<0.0001	<0.0001
Worst Case Scenario Analysis			
Adjusted ARR	0.378	0.223	0.241
(95% CI)	(0.316,0.452)	(0.183,0.272)	(0.198,0.292)
Rate ratio		0.590	0.636
(95% CI)		(0.462,0.755)	(0.499,0.812)
Percentage reduction		41.0	36.4
(95% CI)		(24.5, 53.8)	(18.8, 50.1)
p-value		<0.0001	0.0003

Source: FDA reviewer.

Disability Progression by EDSS at 2 Years

Treatment with BG00012 BID and TID reduced the risk of confirmed (12-week) disability progression at 2 years by 38% (p = 0.0050) and 34% (p = 0.0128), respectively, compared with placebo. Sensitivity analysis of 24-week confirmed disability progression did not achieve statistical significance (p=0.1893 and 0.0760 for BG00012 BID and TID versus placebo, respectively).

This reviewer conducted a sensitivity analysis to examine disability progression that was sustained through the end of study, with a minimum of 12 weeks. This analysis was to assess more rigorous measurement of sustained progression, i.e, the increase in EDSS was not recovered for a longer period, similar to the concept of 24-week confirmed disability progression. However, this analysis included those disability progressions that might not have the chance to be confirmed after 12 weeks due to the end of the study (whereas the 24-week confirmed disability progression did not include those cases). The result supported primary analysis (p=0.0491 and 0.0274 for BG00012 BID and TID versus placebo, respectively) (Table 11).

The reviewer conducted the following additional sensitivity analyses: 1) Cox proportional hazards model in which disability progression after switching to alternative medications were counted; and 2) logrank test. The results were consistent with the primary analysis.

Reference ID: 3203073

Table 11. Summary of Disability Progression by EDSS at 2 Years (Study 301)

	Placebo	BG00012 BID	BG00012 TID
N	408	410	416
Primary Analysis – 12-week confirmed disability progression			
Number of subjects progressed	89 (22)	57 (14)	62 (15)
Estimated proportion of subjects with progression	0.271	0.164	0.177
Hazard ratio (95% CI)		0.62(0.44, 0.87)	0.66(0.48, 0.92)
Percentage reduction (95% CI)		38.0(13.4, 55.6)	33.8(8.4, 52.2)
p-value		0.0050	0.0128
Sensitivity Analysis – 24-week confirmed disability progression			
Number of subjects progressed	57 (14)	44 (11)	41 (10)
Estimated proportion of subjects with progression	0.169	0.128	0.119
Hazard ratio (95% CI)		0.77(0.52, 1.14)	0.69(0.46, 1.04)
Percentage reduction (95% CI)		23.2(-13.9, 48.3)	30.5(-3.9, 53.5)
p-value		0.1893	0.0760
Sensitivity Analysis –disability progression sustained through the end of study with a minimum of 12 weeks			
Sensitivity Analysis of sustained disability progression			
Number of subjects progressed	54 (13)	36 (9)	35 (8)
Estimated proportion of subjects with progression	0.179	0.100	0.097
Hazard ratio (95% CI)		0.66(0.43, 1.00)	0.62(0.40, 0.95)
Percentage reduction (95% CI)		34.6(0.2, 57.2)	38.1(5.2, 59.6)
p-value		0.0491	0.0274

Source: FDA reviewer.

Summary

The efficacy results of the studies demonstrated that BG00012, whether administered as 240 mg BID or TID, had a clinically meaningful and statistically significant effect on the primary efficacy endpoint and all secondary endpoints.

3.2.4.2 Study 302

Annualized Relapse Rate

The adjusted ARR at 2 years was 0.401 (95% CI, 0.329, 0.488) in the placebo group, compared with 0.224 (95% CI, 0.179, 0.282) in the BG00012 BID group and 0.198 (95% CI, 0.156, 0.252) in the BG00012 TID group. Treatment with BG00012 240 mg administered BID and TID reduced the ARR at 2 years by 44.0% and 50.5%, respectively, over placebo ($p<0.0001$ for both comparisons, Table 12). Results of the 4 pre-specified sensitivity analyses were consistent with that of the primary analysis.

The primary analysis was based on relapses that were protocol-defined and confirmed by INEC. Most (95%) of the relapse cases reported by the subjects were assessed by the sites as protocol-defined objective relapses and 92% of the protocol-defined objective relapses were confirmed by the INEC. The result of the worst case scenario analysis conducted by the reviewer also supported the primary analysis. In this analysis, all relapses, regardless of whether they met

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objective criteria or were INEC-confirmed, both before and after subjects switched to alternative MS medications were included for the BG00012 groups; while only INEC-confirmed relapses that occurred before subjects received alternative MS medications were included for placebo or GA subjects. This confirmed that the potential unblinding by observing the frequent flushing event of subjects on BG00012 or the exclusion of data after subjects switched to alternative MS medications did not have a significant effect on the results.

Table 12. Summary of Annualized Relapse Rate at 2 Years (Study 302)

	Placebo	BG00012 BID	BG00012 TID	GA
N	362	359	344	350
Primary Analysis				
Adjusted ARR	0.401	0.224	0.198	0.286
(95% CI)	(0.329,0.488)	(0.179,0.282)	(0.156,0.252)	(0.232,0.353)
Rate ratio		0.560	0.495	0.714
(95% CI)		(0.423,0.740)	(0.369,0.662)	(0.548,0.931)
Percentage reduction		44.0	50.5	28.6
(95% CI)		(26.0, 57.7)	(33.8, 63.1)	(6.9, 45.2)
p-value		<0.0001	<0.0001	0.0128
Worst Case Scenario Analysis				
Adjusted ARR	0.410	0.272	0.241	0.293
(95% CI)	(0.338,0.497)	(0.221,0.335)	(0.194,0.299)	(0.239,0.359)
Rate ratio		0.664	0.588	0.714
(95% CI)		(0.510,0.864)	(0.447,0.773)	(0.550,0.927)
Percentage reduction		33.6	41.2	28.6
(95% CI)		(13.6, 49.0)	(22.7, 55.3)	(7.3, 45.0)
p-value		0.0023	0.0001	0.0115

Source: FDA reviewer.

This reviewer further examined the treatment effect for patients with or without flushing. As shown in Table 13 below, the treatment effect was preserved in both subgroups, although the result should be interpreted with caution as the subgroups were not defined based on baseline characteristics.

Table 13. Estimated ARR based on the presence of the adverse event of flushing (Study 302)

	BG00012 BID	BG00012 TID
With flushing	0.22	0.23
Without flushing	0.31	0.28

Source: FDA reviewer.

Total Number of New or Newly Enlarging T2 Hyperintense Lesions at 2 Years

BG00012 BID and TID reduced the number of new or newly enlarging T2 hyperintense lesions that developed over 2 years by 71% and 73%, respectively, compared with placebo (p <0.0001 for both comparisons). All sensitivity analyses conducted by the sponsor and this reviewer confirmed the primary analysis (Table 14).

Reference ID: 3203073

Table 14. Number of New or Newly Enlarging T2 Lesions at 2 Years (Study 302)

	Placebo	BG00012 BID	BG00012 TID	GA
Primary Analysis (with imputation)				
N	139	140	140	153
Adjusted mean (95% CI)	17.4(13.5,22.4)	5.1 (3.9, 6.6)	4.7 (3.6, 6.2)	8.0 (6.3,10.2)
Percent reduction (95% CI)		71(59, 79)	73(62, 80)	54(37, 67)
p-value		<0.0001	<0.0001	<0.0001
Sensitivity Analysis using last observed data prior to alternative MS medication				
N	139	140	140	153
Adjusted mean	17.5(13.6,22.5)	5.0 (3.9, 6.5)	4.7 (3.6, 6.2)	7.9 (6.3,10.1)
Percent reduction (95% CI)		71(60, 79)	73(62, 80)	55(38, 67)
p-value		<0.0001	<0.0001	<0.0001
Sensitivity Analysis using last observed data including those after alternative MS medications				
N	145	145	144	157
Adjusted mean	16.7(13.1,21.2)	5.0 (3.9, 6.4)	5.0 (3.8, 6.4)	7.9 (6.2, 9.9)
Percent reduction (95% CI)		70(59, 78)	70(59, 78)	53(36, 65)
p-value		<0.0001	<0.0001	<0.0001

Source: FDA reviewer.

Total Number of New or Newly Enlarging T1 Hypointense Lesions at 2 Years

BG00012 BID and TID reduced the number of new or newly enlarging T1 hypointense lesions that developed over 2 years by 57% and 65%, respectively, compared with placebo (p<0.0001 for both comparisons, Table 15). All sensitivity analyses confirmed the primary analysis.

Table 15. Number of New or Newly Enlarging T1 Lesions at 2 Years (Study 302)

	Placebo	BG00012 BID	BG00012 TID	GA
T1				
N	139	140	140	154
Adjusted mean (95% CI)	7.0(5.3, 9.2)	3.0 (2.3, 4.0)	2.4 (1.8, 3.2)	4.1 (3.2, 5.3)
Percent reduction (95% CI)		57(39, 70)	65(51, 76)	41(18, 58)
p-value		<0.0001	<0.0001	0.0021

Source: FDA reviewer.

Proportion of Subjects Relapsed at 2 Years

The Kaplan-Meier estimate of the proportion of subjects relapsed at 2 years was 41% in the placebo group compared with 29% in the BG00012 BID group and 24% in the BG00012 TID group. The hazard ratios (95% CI) were 0.66 (0.51, 0.86) for BG00012 BID and 0.55 (0.42, 0.73) for BG00012 TID, corresponding to reductions of 34% (p=0.0020) and 45% (p <0.0001), respectively, in the risk of relapse following treatment with BG00012 BID and TID compared with placebo (Table 16). The results of all pre-specified sensitivity analyses were consistent with that of the primary analysis.

Reference ID: 3203073

Table 16. Summary of Proportion of Subjects Relapsed at 2 Years (Study 302)

	Placebo	BG00012 BID	BG00012 TID	GA
N	362	359	344	350
Number of subjects relapsed				
Yes	140 (39)	93 (26)	76 (22)	104 (30)
No (Censored)	223 (61)	266 (74)	269 (78)	246 (70)
Estimated proportion of subjects relapsed at 2 years	0.41	0.29	0.24	0.32
Hazard ratio (95% CI)		0.66 (0.51, 0.86)	0.55 (0.42, 0.73)	0.71 (0.55, 0.92)
Percentage reduction (95% CI)		34.0 (14.1, 49.3)	44.6 (26.6, 58.1)	28.6 (7.8, 44.6)
p-value		0.0020	<0.0001	0.0097

Source: FDA reviewer.

Disability Progression by EDSS at 2 Years

Treatment with BG00012 BID and TID reduced the risk of confirmed (12-week) disability progression at 2 years by 21% (p = 0.25) and 24% (p = 0.20), respectively, compared with placebo. The differences between the BG00012 and placebo groups were not statistically significant. Pre-specified sensitivity analysis of 24-week confirmed disability progression approached statistical significance for the BID group (p=0.0630 for BID, and p=0.1172 for TID). This reviewer conducted a sensitivity analysis on sustained disability progression, defined as increase in EDSS sustained through the end of study, with a minimal 12 weeks. This analysis yielded larger estimate treatment effect for BG00012 BID group (Table 17).

Table 17. Summary of Disability Progression by EDSS at 2 Years (Study 302)

	Placebo	BG00012 BID	BG00012 TID	GA
N	363	359	345	350
Primary Analysis – 12-week confirmed disability progression				
Number of subjects progressed	52 (14)	40 (11)	38 (11)	48 (14)
Estimated proportion of subjects with progression	0.169	0.128	0.130	0.156
Hazard ratio (95% CI)		0.79(0.52, 1.19)	0.76(0.50, 1.16)	0.93(0.63, 1.37)
p-value (compared to placebo)		0.2536	0.2041	0.7036
Sensitivity Analysis – 24-week confirmed disability progression				
Number of subjects progressed	52 (14)	40 (11)	38 (11)	48 (14)
Estimated proportion of subjects with progression	0.125	0.078	0.086	0.108
Hazard ratio (95% CI)		0.62(0.37, 1.03)	0.67(0.40, 1.11)	0.87(0.55, 1.38)
p-value (compared to placebo)		0.0630	0.1172	0.5528
Sensitivity Analysis –disability progression sustained through the end of study with a minimum of 12 weeks				
Number of subjects progressed	37 (10)	20 (6)	26 (8)	32 (9)
Estimated proportion of subjects with progression	0.125	0.064	0.091	0.109
Hazard ratio (95% CI)		0.52(0.30, 0.90)	0.73(0.44, 1.20)	0.83(0.52, 1.34)
p-value (compared to placebo)		0.0200	0.2123	0.4491

Source: FDA reviewer.

Reference ID: 3203073

Summary
The efficacy results of the studies demonstrated that BG00012, whether administered as 240 mg BID or TID, had a clinically meaningful and statistically significant effect on the primary efficacy endpoint and all secondary endpoints, except for disability progression.

3.3 Evaluation of Safety

Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The subgroup analysis results for the primary endpoint of proportion relapsing for Study 301 were in Table 18. The treatment effect was generally consistent across the subgroups, although it appeared to be greater among subjects younger than 40 year of age.

Table 18. Summary of proportion of subjects relapsed by demographics subgroups (Study 301)

	Placebo	BG00012 BID	BG00012 TID
Number of subjects in ITT population	408 (100)	410 (100)	416 (100)
Gender			
Male			
n	102	114	110
Estimated % of subjects relapsed	0.416	0.218	0.232
Hazard ratio (p-value)		0.47 (0.0045)	0.55 (0.0240)
Female			
n	306	296	306
Estimated % of subjects relapsed	0.476	0.291	0.272
Hazard ratio (p-value)		0.53 (<0.0001)	0.49 (<0.0001)
Baseline age			
< 40 yrs			
n	206	224	214
Estimated % of subjects relapsed	0.533	0.265	0.270
Hazard ratio (p-value)		0.41 (<0.0001)	0.44 (<0.0001)
>= 40 yrs			
n	202	186	202
Estimated % of subjects relapsed	0.388	0.276	0.251
Hazard ratio (p-value)		0.74 (0.1256)	0.63 (0.0182)
Race			
White			
n	318	321	330
Estimated % of subjects relapsed	0.482	0.279	0.252

Reference ID: 3203073

	Placebo	BG00012 BID	BG00012 TID
Hazard ratio (p-value)		0.53 (<0.0001)	0.47 (<0.0001)
Asian			
n	42	38	36
Estimated % of subjects relapsed	0.450	0.270	0.293
Hazard ratio (p-value)		0.54 (0.1535)	0.59 (0.1975)
Other			
n	48	51	50
Estimated % of subjects relapsed	0.336	0.216	0.294
Hazard ratio (p-value)		0.54 (0.1555)	0.64 (0.2957)
Regions			
Region 1			
n	64	65	72
Estimated % of subjects relapsed	0.319	0.142	0.198
Hazard ratio (p-value)		0.35 (0.0197)	0.62 (0.2169)
Region 2			
n	172	174	173
Estimated % of subjects relapsed	0.503	0.291	0.276
Hazard ratio (p-value)		0.51 (0.0003)	0.47 (<0.0001)
Region 3			
n	172	171	171
Estimated % of subjects relapsed	0.468	0.293	0.266
Hazard ratio (p-value)		0.57 (0.0026)	0.52 (0.0007)

Source: FDA reviewer.

The subgroup analysis results for the primary endpoint of annualized relapse rate relapsing for Study 302 were in Table 19. In general, the treatment effect was consistent across the subgroups, while treatment with BG00012 BID and TID appeared to have a larger effect among subjects aged ≥40 years.

Table 19. Summary of annualized relapse rate by demographics subgroups (Study 302)

	Placebo	BG00012 BID	BG00012 TID	GA
Number of subjects in ITT	363 (100)	359 (100)	345 (100)	350 (100)
Gender				
Male				
n	112	114	95	103
Adjusted relapse rate	0.358	0.204	0.208	0.213
Rate ratio (p-value)		0.570 (0.0303)	0.580 (0.0436)	0.596 (0.0444)
Female				
n	251	245	250	247
Adjusted relapse rate	0.404	0.227	0.194	0.315
Rate ratio (p-value)		0.561 (0.0007)	0.480 (<0.0001)	0.780 (0.1174)
Baseline age				
< 40 yrs				
n	213	208	193	215
Adjusted relapse rate	0.528	0.278	0.176	0.308
Rate ratio (p-value)		0.527 (0.0002)	0.334 (<0.0001)	0.583 (0.0013)
>= 40 yrs				
n	150	151	152	135
Adjusted relapse rate	0.265	0.169	0.230	0.273

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	Placebo	BG00012 BID	BG00012 TID	GA
Rate ratio (p-value)		0.637 (0.0703)	0.870 (0.5505)	1.032 (0.8893)
Race				
White				
n	305	304	292	290
Adjusted relapse rate	0.392	0.218	0.202	0.272
Rate ratio (p-value)		0.556 (0.0002)	0.516 (<0.0001)	0.695 (0.0149)
Asian				
n	28	28	26	25
Adjusted relapse rate	0.190	0.142	0.073	0.258
Rate ratio (p-value)		0.744 (0.6130)	0.386 (0.1410)	1.357 (0.5846)
Other				
n	30	27	27	35
Adjusted relapse rate	0.460	0.235	0.182	0.275
Rate ratio (p-value)		0.512 (0.0969)	0.396 (0.0309)	0.598 (0.1654)
Regions				
Region 1				
n	73	65	64	66
Adjusted relapse rate	0.302	0.202	0.183	0.409
Rate ratio (p-value)		0.669 (0.2820)	0.604 (0.1745)	1.353 (0.3501)
Region 2				
n	55	55	52	50
Adjusted relapse rate	0.468	0.318	0.226	0.213
Rate ratio (p-value)		0.680 (0.1903)	0.483 (0.0257)	0.455 (0.0127)
Region 3				
n	235	239	229	234
Adjusted relapse rate	0.375	0.192	0.181	0.252
Rate ratio (p-value)		0.512 (0.0002)	0.483 (<0.0001)	0.671 (0.0176)

Source: FDA reviewer.

4.2 Other Special/Subgroup Populations

In both studies, Treatment effect appeared to be similar between the MRI cohort and non-MRI cohort. The study population was approximately evenly divided between subjects with a baseline EDSS score of ≤2.0 and those with a baseline EDSS score of >2.0. Treatment effect appeared to be greater among subjects with a baseline EDSS score of ≤2.0 (Table 20 and Table 21).

Table 20. Summary of proportion of subjects relapsed by other subgroups (Study 301)

	Placebo	BG00012 BID	BG00012 TID
Number of subjects in ITT population	408 (100)	410 (100)	416 (100)
MRI Cohort			
Yes			
n	180	176	184
Estimated % of subjects relapsed	0.539	0.252	0.328
Hazard ratio (p-value)		0.41 (<0.0001)	0.56 (0.0010)
No			
n	228	234	232
Estimated % of subjects relapsed	0.393	0.284	0.208

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	Placebo	BG00012 BID	BG00012 TID
Hazard ratio (p-value)		0.63 (0.0089)	0.45 (<0.0001)
Baseline EDSS			
> 2.0			
n	206	197	192
Estimated % of subjects relapsed	0.465	0.362	0.338
Hazard ratio (p-value)		0.71 (0.0465)	0.68 (0.0243)
<= 2.0			
n	202	212	224
Estimated % of subjects relapsed	0.457	0.188	0.188
Hazard ratio (p-value)		0.35 (<0.0001)	0.34 (<0.0001)

Source: FDA reviewer.

Table 21. Summary of annualized relapse rate by other subgroups (Study 302)

	Placebo	BG00012 BID	BG00012 TID	GA
MRI Cohort				
Yes				
n	167	169	170	175
Adjusted relapse rate	0.478	0.238	0.270	0.348
Rate ratio (p-value)		0.497 (0.0007)	0.564 (0.0051)	0.727 (0.0932)
No				
n	196	190	175	175
Adjusted relapse rate	0.345	0.215	0.139	0.233
Rate ratio (p-value)		0.623 (0.0140)	0.402 (<0.0001)	0.673 (0.0383)
Baseline EDSS				
> 2.0				
n	203	198	186	194
Adjusted relapse rate	0.444	0.281	0.278	0.348
Rate ratio (p-value)		0.634 (0.0085)	0.626 (0.0084)	0.785 (0.1410)
<= 2.0				
n	160	161	159	156
Adjusted relapse rate	0.380	0.183	0.128	0.235
Rate ratio (p-value)		0.482 (0.0027)	0.338 (<0.0001)	0.619 (0.0375)

Source: FDA reviewer.

Reference ID: 3203073

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Since flushing is a known side effect of BG00012 and occurred to high percentage of subjects, the agency was concerned about perceived unblinding of subjects' treatment assignments by observing flushing related events. To assess the robustness of the primary analysis result against potential biased relapse assessment in case of perceived unblinding, this reviewer conducted worst case scenario analyses, in which all relapses prior to and after alternative MS medications were included for subjects in BG00012 groups but only INEC-confirmed relapses prior to alternative MS medications were included for placebo subjects. The results of the worst case analyses still reached statistical significance.

The treatment discontinuation rate was high in both studies, partly because the studies allowed subjects to cross over to alternative MS treatment. However, as shown in a series of sensitivity analyses including analyses of worst case scenario, treatment discontinuation or the switch to alternative MS medications did not appear to have a significant effect on the efficacy results or conclusions.

5.2 Collective Evidence

In both pivotal studies, treatment with BG00012, administered as BID and TID orally, significantly reduced clinical relapses (as assessed by annualized relapse rate and the proportion of subjects relapsed) over the 2-year treatment period, and improved MRI measures of disease activity (the number of new or newly enlarging T2 hyperintense lesions, Gd-enhancing lesions, and new T1 hypointense lesions), compared with placebo. Study 301 also yielded statistically significant effect of BG00012 on disability progression, and in Study 302 numerical reduction in disability progression was observed in BG00012 groups. Study 302 had smaller sample size per group and may not have sufficient power to detect a minimal yet clinically meaningful effect of BG00012 on disability progression. The effect of BG00012 was generally consistent across a variety of subgroups defined by demographic and baseline disease characteristics.

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Table 22. Summary of Primary and Secondary Endpoints for Study 301 and 302

	Study 301				Study 302		
Endpoint	**Placebo**	**240 mg BID**	**240 mg TID**	**Endpoint**	**Placebo**	**240 mg BID**	**240 mg TID**
Primary							
Proportion relapsing[1]	0.461	0.270 $p<0.0001^a$	0.260 $p<0.0001^a$	**Annualized relapse rate**	0.401	0.224 $p<0.0001^b$	0.198 $p<0.0001^b$
Secondary (listed in descending rank order)							
New or newly enlarging T2 hyperintense lesions (adjusted mean number)	17.0	2.6 $p<0.0001^b$	4.4 $p<0.0001^b$	**New or newly enlarging T2 hyperintense lesions** (adjusted mean number)	17.4	5.1 $p<0.0001^b$	4.7 $p<0.0001^b$
GdE lesions (mean number)	1.8 [c]	0.1 $p<0.0001^c$	0.5 $p<0.0001^c$	**New T1 hypointense lesions** (adjusted mean number)	7.0	3.0 $p<0.0001^b$	2.4 $p<0.0001^b$
Annualized relapse rate	0.364	0.172 $p<0.0001^b$	0.189 $p<0.0001^b$	**Proportion relapsing**[1]	0.410	0.291 $p=0.0020^a$	0.241 $p<0.0001^a$
Disability progression (proportion progressing[2])	0.271	0.164 $p=0.0050^a$	0.177 $p=0.0128^a$	**Disability progression** (proportion progressing[2])	0.169	0.128 $p=0.2536^a$	0.130 $p=0.2041^a$

Source: NDA module 2.7.3 Table 6.

5.3 Conclusions and Recommendations

The data overall provided adequate evidence to support the efficacy of BG00012 240 mg BID and TID as treatment of subjects with relapsing MS.

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/s/

XIANG LING
10/12/2012

KUN JIN
10/14/2012
I concur with the review.

HSIEN MING J HUNG
10/15/2012