CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

Statistical Review and Evaluation
CARCINOGENICITY STUDIES

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Statistical Reviewer:	Matthew Jackson, PhD
Concurring Reviewer:	Karl Lin, PhD
Medical Division:	Division of Neorology Products
Reviewing Pharmacologist:	Richard Houghtling, PhD
Project Manager:	

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Background

In this submission the sponsor included reports of two animal carcinogenicity studies, in mice and rats, to assess the carcinogenic potential of CAR0093 when administered by gavage, once daily at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist, Richard Houghtling, PhD.

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

Chapter 1

Mouse Study

1.1 Experimental design

This study consisted of two experiments, one each in female and male Crl:CD1(ICR) mice. Each experiment consisted of six groups of sixty animals. Three groups were control groups; two received the control article (a potato starch solution), and the third received deionized water. These substances were administered by gavage. The three remaing groups received daily doses of HMR1726 in an aqueous solution of potato starch, for doses of 1, 4, and 12 mg per kilogram of body weight. Again, these treatments were administered by gavage. All surviving animals were sacrificed after 104 weeks, except for the high dose males, who were sacrificed after 95 weeks.

Animals were checked twice daily (except weekends and holidays) for mortality. Animals were checked for clinical signs, and underwent palpation exams, once every four weeks during the first year of the study, and once every two weeks subsequently.

After death, all animals underwent a full necroscopy.

1.2 Sponsor's analysis

1.2.1 Survival analysis

A series of log-rank tests were performed, comparing each treated group with each of the vehicle control groups, and the combined vehicle control group.

Among female mice, there was evidence of a dose-related increasing trend in mortality. When the combined vehicle control group was used, the test of trend yielded a p-value of 0.0483, and the comparison between the high dose group and the control yielded a p-value of 0.0079. Since the first vehicle control group had better survival outcomes than the second, comparisons with the first vehicle control group also yielded significant results for these two tests ($p = 0.0069$ for the test of trend, and $p - 0.0048$ for the pairwise comparison with the high dose group). Conversely, comparisons with the second vehicle control group yielded no significant results.

The situation was similar among male mice, although the effects were generally more pronounced. When the combined vehicle control group was used, the test of trend yielded a p-value of 0.0043, and the comparison between the high dose group and the control yielded a p-value of 0.0002. Since the first vehicle control group had better survival outcomes than the second, comparisons with the first vehicle control group also yielded significant results for these two tests ($p = 0.0004$ for the test of trend, and $p < 0.0001$ for the pairwise comparison with the high dose group). As with the female mice, comparisons with the second vehicle control group yielded no significant results.

1.2.2 Tumor analysis

A modified Peto test [6] was used with time intervals separated at 50 weeks, 80 weeks, and sacrifice.

No notable findings were reported for the female mice.

Among the male mice, the only notable finding reported is for the combination endpoint of adenomas and adenomas and carcinomas in the duodenum and jejunum. When the combined vehicle control is used, the p-value of the test of trend is 0.0056, and the p-value of the comparison between the high dose group and the control is 0.0075. Since no vehicle control animals were found to develop such tumors, the results are similar when just one control group is used, although the p-values are larger, reflecting the greater noise inherent in using a smaller sample.

The sponsor concludes:

> There were no statistically significant increases at the 2.5% level (trend test using pooled controls or either of the two controls) for the mortality-adjusted incidence of neoplastic lesions (individual or combined) in females.
>
> There were no statistically significant increases at the 2.5% level (trend test using pooled controls or either of the two controls) in the onset rates of observable tumors (individual or combined) in males or females.

1.3 Data analysis

1.3.1 Survival analysis

The Kaplan-Meier survival plots are shown as figures 1.1 and 1.2. The numbers and proportions of animals surviving to various times are presented in table 1.1. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table 1.2, and the results of log-rank survival tests comparing the treated groups with the combined vehicle control group are presented in table 1.3.

Figures 1.1 and 1.2 clearly chow that the high dose groups in both sexes experienced significantly elevated mortality. This apparent effect is also evident in table 1.1, and is borne out in the results of statistical tests: the test of trend indicated strongly significant dose related increases in mortality in both female ($p = 0.0014$) and male ($p < 0.0001$) mice. As revealed in table1.3, these trends are almost entirely driven by the increased mortality in the high dose groups; comparisons of the low and mid dose groups with the combined control group do not yield significant results.

Figure 1.1: Survival curves for female mice

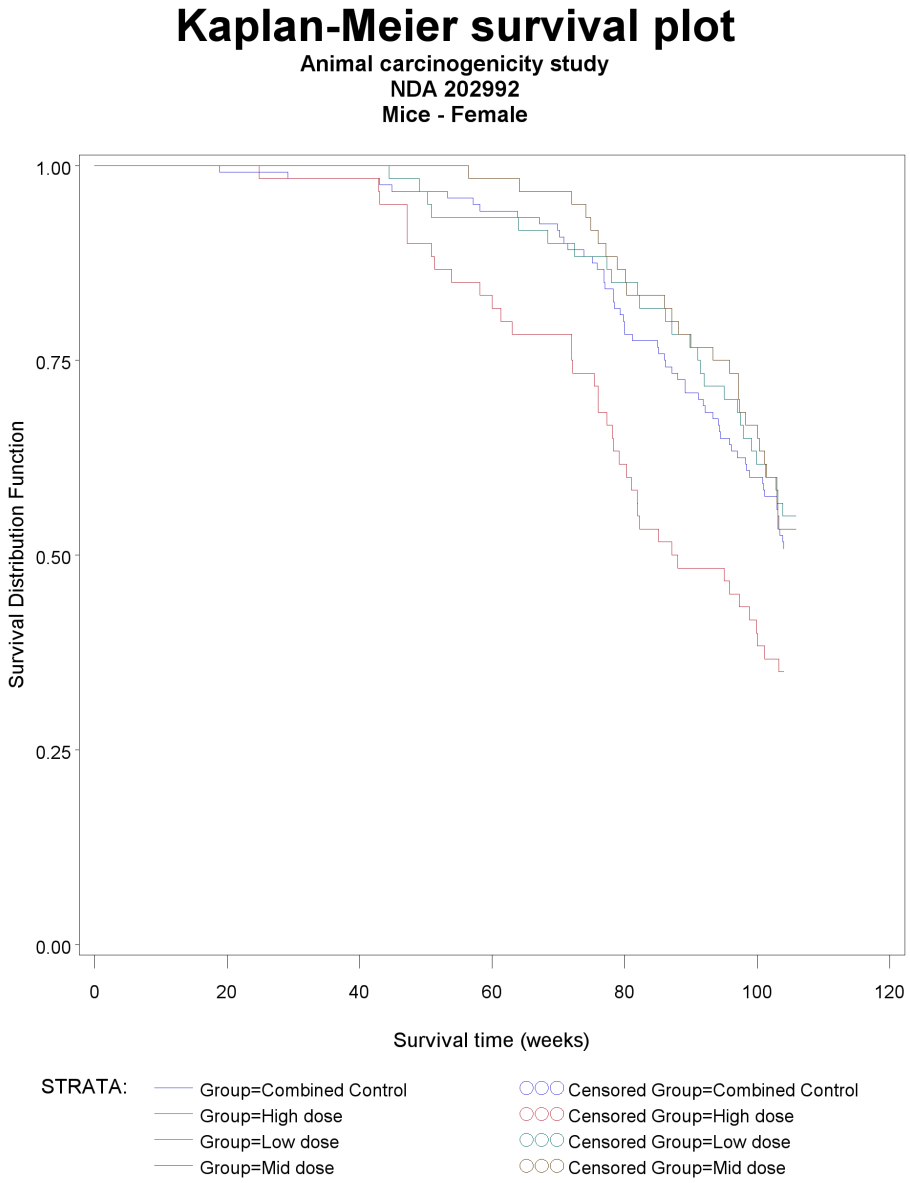

Figure 1.2: Survival curves for male mice

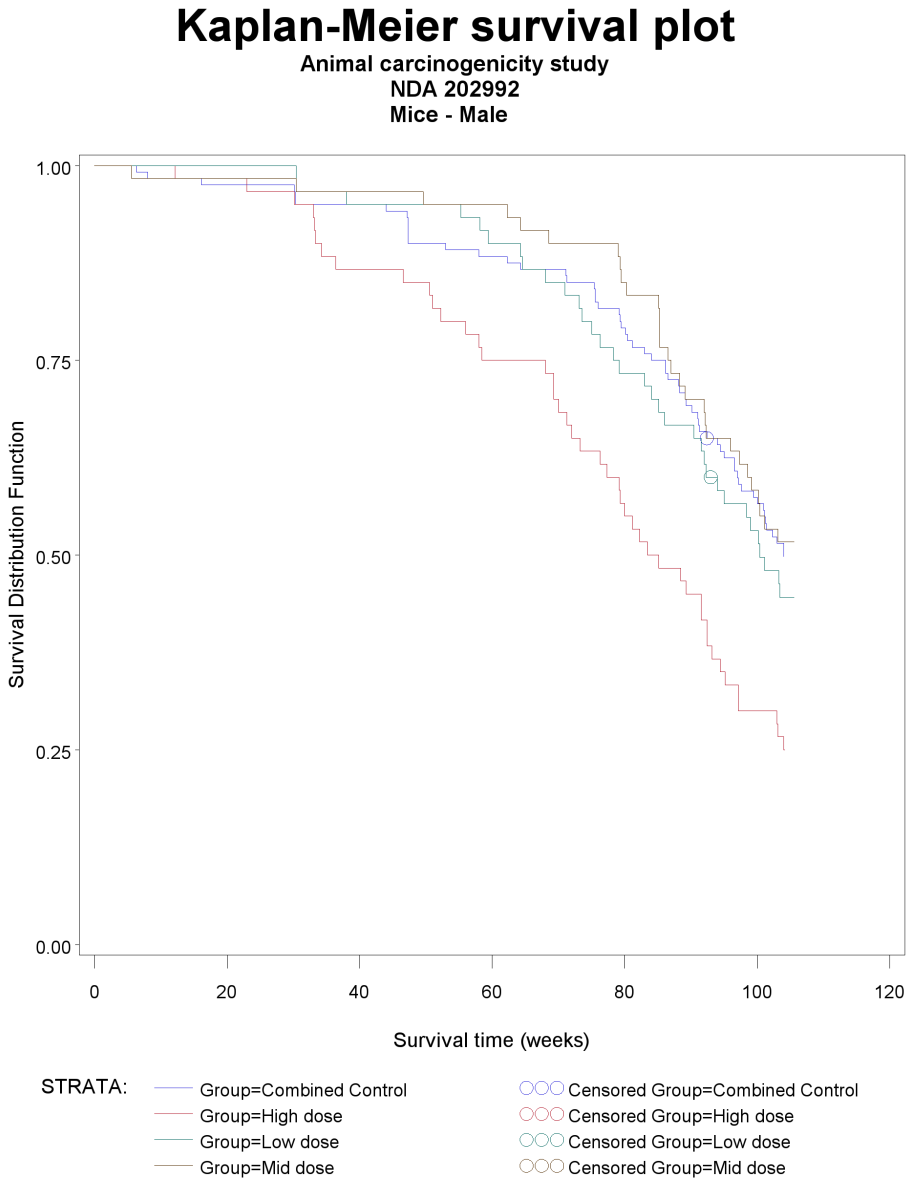

Table 1.1

Survival rates at key times
NDA 202992
Animal carcinogenicity study
Mice

Species and Sex	*Dose Group*	*Dose (mg per kg)*	*Number at start*	*Number alive after 52 weeks*	*Proportion alive after 52 weeks*	*Number alive after 78 weeks*	*Proportion alive after 78 weeks*	*Number alive after 90 weeks*	*Proportion alive after 90 weeks*	*Number alive at termination*	*Proportion alive at termination*
Mice - Female	Combined Control	0	120	116	97%	101	84%	85	71%	62	52%
	Low dose	1	60	56	93%	52	87%	47	78%	33	55%
	Mid dose	4	60	60	100%	53	88%	46	77%	32	53%
	High dose	12	60	52	87%	40	67%	29	48%	21	35%
Mice - Male	Combined Control	0	120	108	90%	98	82%	83	69%	61	51%
	Low dose	1	60	57	95%	46	77%	40	67%	26	43%
	Mid dose	4	60	57	95%	54	90%	42	70%	31	52%
	High dose	12	60	49	82%	36	60%	27	45%	16	27%

Comparison of control groups Kaplan-Meier plots of the control groups are shown as figures 1.3 and 1.4. The results of log-rank tests of survival between the control groups are presented in table 1.4.

Although the Kaplan-Meier plots appear to show disparities in mortality rates between the two control groups, in both the female and male mouse experiments, the log-rank tests do not indicate a statistically significant difference in either case.

Table 1.2: Results of log-rank tests of survival across all groups (mouse study)

Log-rank tests of survival
NDA 202992
Animal carcinogenicity study
Mice

Sex	*Test of homogeneity: chi squared statistic*	*Test of homogeneity: degrees of freedom*	*Number of groups*	*Test of homogeneity: p-value*	*Test of trend (two tailed): p-value*	*Test of trend (one tailed): p-value*
Female	12.9102	3	4	0.0048	0.0027	0.0014
Male	18.5791	3	4	0.0003	0.0002	<.0001

Table 1.3

Pairwise comparisons (log-rank) of survival between treated groups and controls
NDA 202992
Animal carcinogenicity study
Mice

Species and Sex	*Quantity*	*Low dose*	*Mid dose*	*High dose*
Mice - Female	Chi squared test statistic	0.1860	0.1747	4.2561
	p-value of comparison with control	0.6663	0.6760	0.0391
Mice - Male	Chi squared test statistic	0.9099	0.0416	10.6902
	p-value of comparison with control	0.3401	0.8384	0.0011

Figure 1.3: Survival curves for control groups (female mouse experiment)

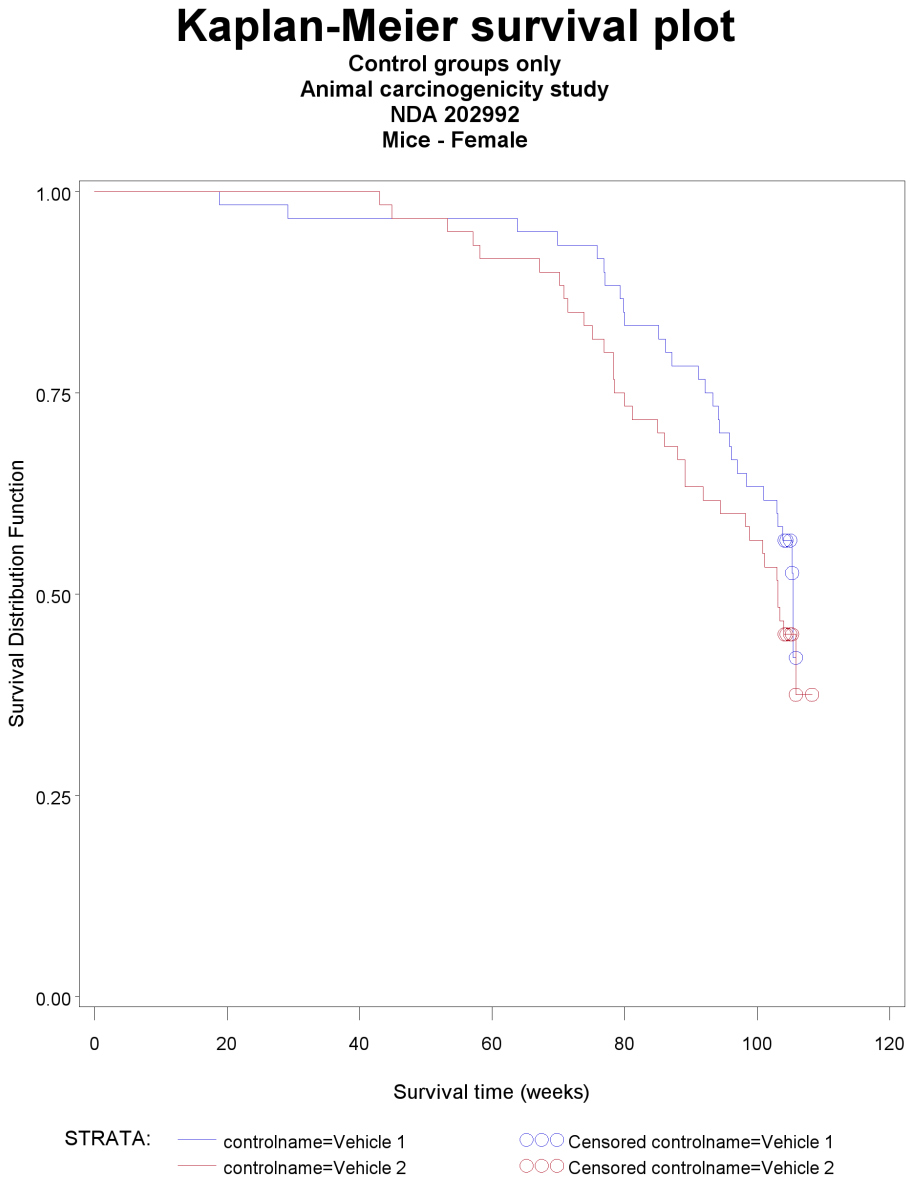

Figure 1.4: Survival curves for control groups (male mouse experiment)

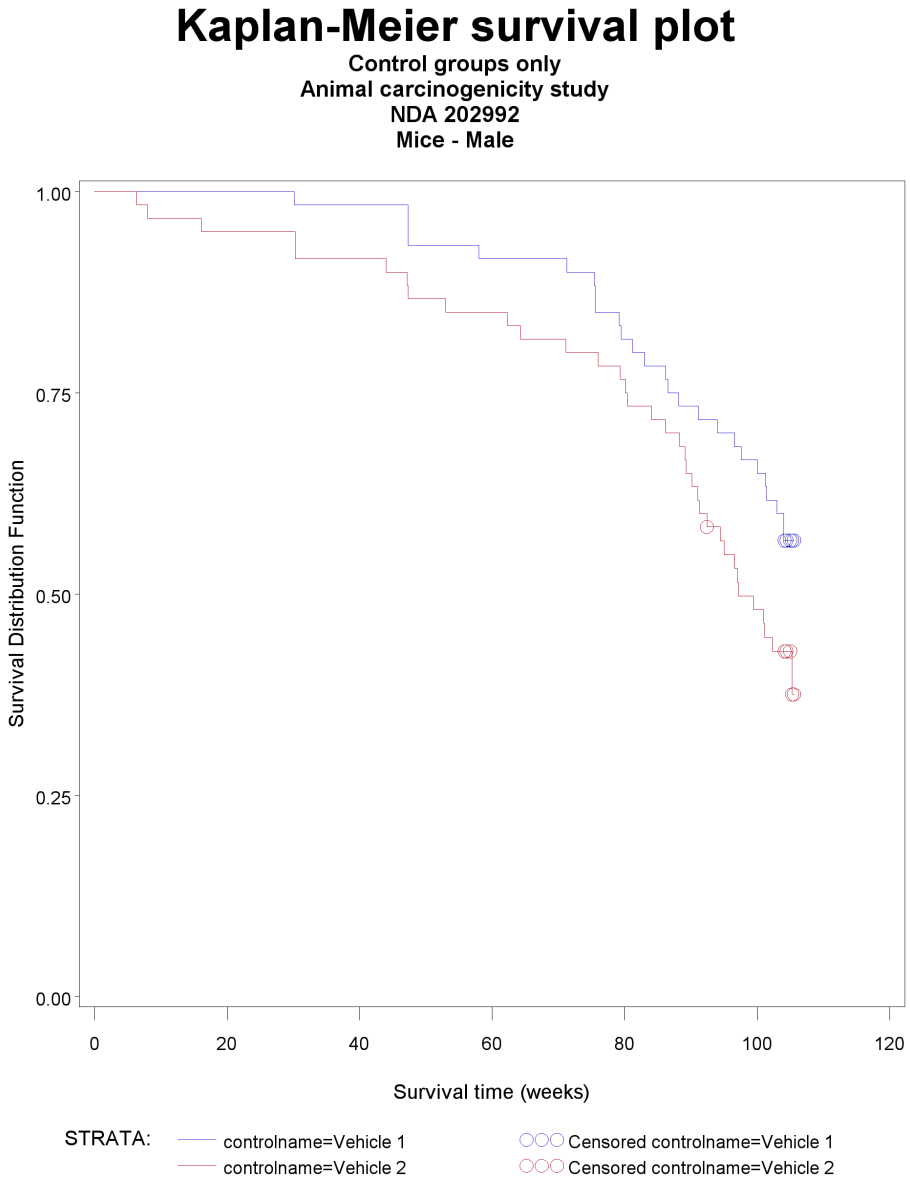

Table 1.4

Log-rank tests of heterogeneity of survival between control groups
NDA 202992
Animal carcinogenicity study

Species and Sex	*Chi^2*	*DF*	*P-value*
Mice - Female	1.3885	1	0.2387
Mice - Male	3.2534	1	0.0713
Rats - Female	3.6706	1	0.0554
Rats - Male	0.0344	1	0.8528

1.3.2 Tumor analysis

Endpoints

Analyses have been conducted using the sponsor's submitted dataset, and the sponsor's chosen nomenclature. In this dataset, organs or tissue types are described as being either tumorous, examined but found unusable due to autolysis, or unexamined. An organ that has been examined but was not found to be tumorous is not mentioned in the dataset.

From these data, we can infer the numbers of animals for which each organ or tissue type was examined, but only in those cases where at least one anomalous finding (i.e., a tumor was found, or a sample that was planned to be analyzed could not be, either because no sample was taken or becasue the sample was unusable due to autolosys) was reported. Organs which can thus be deduced to have been successfully analyzed in the majority of animals are, for the purposes of this review, considered *primary*. The lists of primary organs in the experiments on female and male mice respectively are presented in tables 1.5 and 1.6.

Organ or tissue types which were examined in only a few animals are considered *secondary*. It is worth noting that mammay glands in male mice have been characterized as secondary. In fact, not one male mouse had its mammary glands undergo histopathological examination.

Secondary organs in the male and female mouse experiments are presented in tables 1.7 and 1.8 respectively.

Each tumor type found in a primary organ of at least one animal is considered a primary endpoint. In addition, in consultation with Richard Houghtling, PhD, a list of combination endpoints has been drawn up. This list is presented in table 1.9.

Table 1.5

Primary organs in study of female mice
NDA 202992
Animal carcinogenicity study

Organ or tissue name
ADRENAL GLD: CORTE
ADRENAL GLD: MEDUL
AORTA
BONE MARROW: FEMUR
BONE MARROW: STERN
BONE: FEMUR
BONE: STERNUM
BRA N
CLITORAL GLAND
ESOPHAGUS
EYE
GALL BLADDER
HARDERIAN GLAND
HEART
INTEST NE: CECUM
INTEST NE: COLON
INTEST NE: DUODENU
INTEST NE: GALT
INTEST NE: ILEUM
INTEST NE: JEJUNUM
INTEST NE: RECTUM
JOINT
KIDNEY
LACRIMAL GLAND
LIVER
LN: MANDIBULAR
LN: MESENTERIC
LUNG
M: DIAPHRAGM
MAMMARY GLAND
NASAL TISSUE
NERVE: OPTIC
NERVE: SCIATIC
OVARY
OVIDUCT
PANCREAS
PARATHYROID GLAND
PITUITARY GLAND

Primary organs in study of female mice
NDA 202992
Animal carcinogenicity study

Organ or tissue name
SALIV.GLD: MANDIB.
SALIV.GLD: PAROTID
SALIV.GLD: SUBL N.
SKIN/SUBCUTIS
SPINAL CORD: CERVI
SPINAL CORD: LUMBA
SPINAL CORD: THORA
SPLEEN
STOMACH: NONGLANDU
SYSTEMIC NEOPLASM
THYMUS
THYROID GLAND
TONGUE
TRACHEA
URETER
URINARY BLADDER
UTERUS
UTERUS: CERVIX
VAGINA

Reference ID: 3158913

Table 1.6

Primary organs in study of male mice
NDA 202992
Animal carcinogenicity study

Organ or tissue name
ADRENAL GLD: CORTE
ADRENAL GLD: MEDUL
AORTA
BONE MARROW: FEMUR
BONE MARROW: STERN
BONE: FEMUR
BONE: STERNUM
EPIDIDYMIS
ESOPHAGUS
EYE
GALL BLADDER
HARDERIAN GLAND
HEART
INTEST NE: CECUM
INTEST NE: COLON
INTEST NE: DUODENU
INTEST NE: GALT
INTEST NE: ILEUM
INTEST NE: JEJUNUM
INTEST NE: RECTUM
JOINT
KIDNEY
LACRIMAL GLAND
LIVER
LN: MANDIBULAR
LN: MESENTERIC
LUNG
M: DIAPHRAGM
NASAL TISSUE
NERVE: OPTIC
PANCREAS
PARATHYROID GLAND
PITUITARY GLAND
PREPUTIAL GLAND
PROSTATE GLAND
SALIV.GLD: MAND B.
SALIV.GLD: PAROTID
SALIV.GLD: SUBLIN.

Primary organs in study of male mice
NDA 202992
Animal carcinogenicity study

Organ or tissue name
SEMINAL VESICLE
SKELETAL MUSCLE
SKIN/SUBCUTIS
SPINAL CORD: CERVI
SPINAL CORD: LUMBA
SPINAL CORD: THORA
SPLEEN
STOMACH: GLANDULAR
STOMACH: NONGLANDU
SYSTEMIC NEOPLASM
TESTIS
THYMUS
THYROID GLAND
TONGUE
TRACHEA
URETER
URINARY BLADDER

Reference ID: 3158913

Table 1.7

Secondary organs in study of female mice
NDA 202992
Animal carcinogenicity study

Organ or tissue name
BODY CAV: ABDOMINA
BODY CAVITY
BONE
MESENTERY

Reference ID: 3158913

Table 1.8

Secondary organs in study of male mice
NDA 202992
Animal carcinogenicity study

Organ or tissue name
BODY CAV: ABDOMINA
BODY CAVITY
BONE
MAMMARY GLAND
MESENTERY

Reference ID: 3158913

Table 1.9

Customized and combination endpoints analyzed
NDA 202992
Animal carcinogenicity study

Composite endpoint
Adenomas and adenocarcinomas of the small intestine
Adenomas and carcinomas of the adrenal cortex
All lipomas
All pheochromocytomas
Astrocytomas
Bronchioloalveolar tumors
C-cell tumors
Fibrosarcomas and Sarcomas (NOS) of the skin
Hemangiomas and hemangiosarcomas
Hepatocellular tumors
Lipomas and hibernomas
Lipomas and liposarcomas
Lipomas, lipomasarcomas and hibernomas
Luteomas and ovarian granulosa cell tumors
Mammary adenocarcinomas and adenocanthomas
Mammary adenomas and fibroadenomas
Mammary tumors
Ovarian tubulostromal adenocarcinomas and cystadenomas
Pancreatic acinar and acinar-islet cell tumors
Pancreatic acinar cell tumors
Pancreatic islet and acinar-islet cell tumors
Pancreatic islet cell tumors
Pituitary pars distalis tumors
Pituitary pars intermedia tumors
Renal tubule tumors
Schwannomas
Squamous cell papillomas and carcinomas of the skin
Uterine adenocarcinomas and glandular polyps
Uterine leiomyomas, leiomyosarcomas, and endometrial stromal polyps and sarcomas
Vaginal squamous cell tumors and polyps

Reference ID: 3158913

Statistical procedure

The tumor data were analyzed for dose response relationships and pairwise comparisons of tumor incidence in each of the treated groups versus the combined vehicle control group. Both the dose response relationship tests and pairwise comparisons were performed using the poly-k method described in the paper of Bailer and Portier[1] and developed in the paper of Bieler and Williams[2]. In this method, given a tumor type T, an animal h that lives the full study period (w_m) or dies before the terminal sacrifice with at least one tumor of type T gets a score of $s_h = 1$. An animal that dies at week w_h before the end of the study without such a tumor gets a score of

$$s_h = \left(\frac{w_h}{w_m}\right)^k < 1.$$

The adjusted group size is defined as $\sum_h s_h$. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops at least one tumor of type T, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. The test is repeated for each tumor type T.

One critical point to consider in the application of the poly-k test is the choice of the appropriate value of k, which depends on the relationship between tumor onset time and increased dose. For long term 104 week standard rat and mouse studies, a value of $k = 3$ is suggested in the literature, and so has been used in this review. For the calculation of p-values, the exact permutation method was used.

For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of significance levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for a submission with two species, and a significance level $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for a submission with one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control, the FDA guidance suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors, for both submissions with one or two species, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman [5]. In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin [7] showed that this rule for multiple testing for dose response relationship is also suitable for poly-k tests.

Since this is a study involving two species, it follows that for the comparisons of CAR0093 with combined vehicle control, we use the thresholds for significance presented in table 1.10.

Noteworthy results

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables 1.11 (female mice) and 1.12 (male mice). The results of analyses of customized endpoints (see table 1.9) are presented in tables 1.13 and 1.14.

Individual tumor types in female mice for which tests yielding p-values below 0.05 were conducted are presented in table 1.15, which is excerpted from table 1.11. Combination tumor types for which tests yielding p-values below 0.05 were conducted are presented in table 1.17, which is excerpted from table 1.13. Individual tumor types in male mice for which tests yielding p-values below 0.05 were conducted are presented in table 1.16, which is excerpted from table 1.12. Combination tumor types for which tests yielding p-values below 0.05 were conducted are presented in table 1.18, which is excerpted from table 1.14.

Incidence rates for tumors found in secondary organs have not been analyzed statistically. Count data for such tumors are presented in table 1.19.

Table 1.10: Critical p-values used to determine statistical significance

Type of test	Rare tumor	Common tumor
Trend	0.025	0.005
Pairwise test between placebo and high dose	0.05	0.01

Adenomas and adenocarcinomas of the small intestine in male mice When considering incidence rates for adenomasa and adenocarcinomas of the small intestine, both the test of trend ($p = 0.0088$) and the comparison between the high dose group and the combined vehicle control group ($p = 0.0185$) yielded striking results. These results were driven by the fact that while no animals in the combined vehicle control group developed such tumors, one low dose animal, two mid dose animals, and three high dose animals did. If these are considered rare tumors, then both of these results are significant. However, if adenomas and adenocarcinomas of the small intestine are considered common, then both of these results narrowly miss significance.

The answer to the question of whether these are indeed common tumors (i.e., with an underlying incidence rate below 1%) in male mice is unclear. There were no reported cases of adenomas or adenocarcinomas of the small intestine in the combined vehicle control group. This fact lends support for the position that these are rare tumors. However, it must also be noted that four such tumors were observed in the water control group. If the results for all male control groups are combined, there are four cases from one hundred and eighty animals, with an overall incidence rate of 2.2%. It should be pointed out, however, that the 95% (Clopper-Pearson) confidence interval is $(0.61\%, 5.6\%)$, suggesting that the observed data are both consistent with the tumor combionation being being rare, and with it being common.

Taking all of these results together, one's decision of whether to consider these rare ultimately comes down to how much risk one is prepared to take. If one wishes to adopt a conservative position, then one should probably consider these rare tumors, and thus consider this a positive finding. However, if one has a higher appetite for risk, then it is reasonable to consider these to be common tumors, and to dismiss the observed results as a negative finding.

Other findings A number of tests have been conducted that have yielded p-values below 0.05. However, in all except one case, the significant results have been for the comparison between the low dose group and the combined vehicle control group, and have not been supported by results in the other tests. In that one case (bronchioloalveolar tumors in female mice, the situation is similar, but with the significant result coming from the comparison between the *mid dose* group and the combined vehicle control.

None of these tests generate p-values below 0.01, so only after making an adjustment for testing multiple endpoints, there are no grounds whatsoever for further consideration of any of these results associated with common tumor types. Based on the incidence in the combined vehicle control and in the distilled water control, the rare tumors under consideration are:

- Uterine leimyomas in female mice
- Cortical cell adenomas in male mice
- Splenetic hemangiosarcomas in male mice

However, even in these cases, with the absense of significant results for the test of trend, or the comparison between the higher (or even mid) dose group with the control, it is reasonable to consider these to be false positives. The mouse

The mouse study should therefore be considered a negative study.

1.3.3 Analysis of unexamined and autolytic organs

Unexamined animals

Two vehicle control animals, animal number 163 (a male mouse) and animal number 273 (a female mouse) were reported as having experienced accidental death,

Organs reported autolytic

The numbers of organs found in female mice to be autolytic to the extent that analysis of collected tiussue was not possible are presented in table 1.20. The numbers of such organs found in male mice are presented in table 1.21.

Very few organs in any animals were reported as having been autolyzed to the extent that no usable sample was attainable. There is no reason to suspect that autolytic organs had any impact on the validity of the study.

Organs reported as unexamined

The numbers of animals with organs reported as being unexamined are presented in tables 1.22 and 1.23.

Although many organs were reported as being unexamined in a few animals, apart from the secndary organs, the only noteworthy observation is that INTESTINE: GALT is reported as being unexamined in 30% of female mice (ranging from 23% in the high dose group to 35% in the mid dose group. These rates are large enough that in the absence of positive tumor findings for this organ group, the study should be considered inconclusive rather than negative.

It should also be noted that the mammary glands of male animals did not undergo routine histopathologic analysis.

1.3.4 Tables of results

Table 1.11

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLD: CORTE	Adenoma: subcapsular	P-value of test of trend or comparison	.8214	.4245	.7312	1
		Number of animals reported with tumor	2	2	1	0
		Poly-3 adjusted incidence rate	2.2%	4.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.26,7.6)	(0.5,14.3)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	92.2	48.8	50.3	37.5
ADRENAL GLD: MEDUL	Pheochromocytoma·benign	P-value of test of trend or comparison	.1636			.2869
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,7.9)	(0,7.5)	(0.07,14.9)
		Poly-3 adjusted number of animals at risk	88.0	46.0	47.5	35.4
	Pheochromocytoma·malignant	P-value of test of trend or comparison	.3860		.3556	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,7.9)	(0.05,11.1)	(0,10.0)
		Poly-3 adjusted number of animals at risk	88.0	46.0	48.0	35.3
BONE MARROW: FEMUR	Hemangioma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.26,7.6)	(0,7.5)	(0,7.1)	(0,9.7)
		Poly-3 adjusted number of animals at risk	93.5	47.7	50.3	36.7
	Hemangiosarcoma	P-value of test of trend or comparison	.6152	1	.5755	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(0,7.5)	(0.05,10.6)	(0,9.7)
		Poly-3 adjusted number of animals at risk	94.3	47.7	50.5	36.7
BONE: FEMUR	Chondroma	P-value of test of trend or comparison	.3805		.3497	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	0.0%

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Table 1.11

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,3.9)	(0,7.5)	(0.05,10.6)	(0,9.7)
		Poly-3 adjusted number of animals at risk	93.5	47.7	50.3	36.7
BRAIN	Meningeoma-malignant	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(0,7.4)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	94.4	48.8	50.3	37.5
GALL BLADDER	Adenoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,7.5)	(0,7.5)	(0,9.7)
		Poly-3 adjusted number of animals at risk	87.5	47.1	47.1	36.8
HARDERIAN GLAND	Adenoma	P-value of test of trend or comparison	.6836	.4607	.9547	.7215
		Number of animals reported with tumor	6	4	1	2
		Poly-3 adjusted incidence rate	6.4%	8.2%	2.0%	5.3%
		95% CI for poly-3 adjusted incidence rate (%)	(2.38,13.5)	(2.27,20.0)	(0.05,10.6)	(0.64,18.2)
		Poly-3 adjusted number of animals at risk	93.8	48.8	50.2	38.0
HEART	Hemangiosarcoma	P-value of test of trend or comparison	.6186	1	.5755	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(0,7.5)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	94.3	47.8	50.5	37.5
INTESTINE: COLON	Adenoma	P-value of test of trend or comparison	.5893	.3429		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,3.9)	(0.05,11.1)	(0,7.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	93.0	49.0	48.4	37.0
INTESTINE: DUODENU	Adenoma	P-value of test of trend or comparison	.8320	.5573	1	1

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Table 1.11

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	1.1%	2.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0.06,12.0)	(0,7.4)	(0,10.3)
		Poly-3 adjusted number of animals at risk	88.4	44.0	48.5	34.8
KIDNEY	Carcinoma: renal tubule	P-value of test of trend or comparison	.5921	.3404		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,3.9)	(0.05,11.1)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.5	48.8	50.3	37.5
LIVER	Carcinoma: hepatocyte	P-value of test of trend or comparison	.6186	1	.5786	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(0,7.4)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.5	48.8	50.3	37.5
	Cholangioma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(0,7.4)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.5	48.8	50.3	37.5
	Hemangioma	P-value of test of trend or comparison	.0789	.4242	1	.1364
		Number of animals reported with tumor	2	2	0	3
		Poly-3 adjusted incidence rate	2.1%	4.1%	0.0%	8.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.26,7.5)	(0.49,14.0)	(0,7.1)	(1.66,21.9)
		Poly-3 adjusted number of animals at risk	94.1	49.1	50.3	37.5
	Hemangiosarcoma	P-value of test of trend or comparison	.6926	.4513	.6806	.8156
		Number of animals reported with tumor	4	3	2	1
		Poly-3 adjusted incidence rate	4.2%	6.0%	3.9%	2.7%

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Table 1.11

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(1.16,10.5)	(1.25,16.9)	(0.48,13.7)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	94.8	49.7	50.9	37.6
LN: MESENTERIC	Hemangioma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,9.5)	(0,9.3)	(0,10.9)
		Poly-3 adjusted number of animals at risk	78.8	37.3	38.9	32.1
	Hemangiosarcoma	P-value of test of trend or comparison	.3817		.3333	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.5%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.6)	(0,9.5)	(0.06,13.5)	(0,10.9)
		Poly-3 adjusted number of animals at risk	78.8	37.3	39.5	32.1
LUNG	Adenoma: bronchioloalveolar	P-value of test of trend or comparison	.6010	.5698	.1253	1
		Number of animals reported with tumor	1	1	3	0
		Poly-3 adjusted incidence rate	1.1%	2.1%	6.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.9)	(0.05,11.1)	(1.23,16.5)	(0,9.5)
		Poly-3 adjusted number of animals at risk	92.5	48.8	50.3	37.5
	Carcinoma: bronchioloalveolar	P-value of test of trend or comparison	.7580	.4868	.1171	.9044
		Number of animals reported with tumor	10	6	10	2
		Poly-3 adjusted incidence rate	11%	12%	19%	5.3%
		95% CI for poly-3 adjusted incidence rate (%)	(5.16,18.7)	(4.53,24.8)	(9.44,32.5)	(0.64,18.2)
		Poly-3 adjusted number of animals at risk	94.1	49.6	52.2	37.5
	Mesothelioma·malignant	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.9)	(0,7.4)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	92.5	48.8	50.3	37.5

Table 1.11

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
MAMMARY GLAND	Adenoacanthoma: maligmamt	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.9)	(0,7.4)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	92.1	48.4	50.3	37.5
	Adenocarcinoma	P-value of test of trend or comparison	.8845	.8177	.8279	1
		Number of animals reported with tumor	3	1	1	0
		Poly-3 adjusted incidence rate	3.2%	2.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.67,9.2)	(0.05,11.1)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	92.5	48.4	50.3	37.5
	Adenoma	P-value of test of trend or comparison	.1688	.3453		.2891
		Number of animals reported with tumor	0	1	0	1
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.0)	(0.05,11.1)	(0,7.1)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	92.0	48.5	50.3	37.5
OVARY	Adenocarcinoma: tubulostromal	P-value of test of trend or comparison	.5982	.3481		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0.05,11.3)	(0,7.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	88.2	47.0	48.7	36.1
	Cystadenoma	P-value of test of trend or comparison	.8018	1	1	.9157
		Number of animals reported with tumor	6	0	0	1
		Poly-3 adjusted incidence rate	6.8%	0.0%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(2.51,14.3)	(0,7.7)	(0,7.4)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	88.2	46.8	48.7	36.6
	Hemangioma	P-value of test of trend or comparison	.1362	.5614	.5802	.2338
		Number of animals reported with tumor	3	2	2	3

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Table 1.11

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	3.4%	4.3%	4.1%	8.1%
		95% CI for poly-3 adjusted incidence rate (%)	(0.7,9.6)	(0.52,14.8)	(0.5,14.3)	(1.7,22.5)
		Poly-3 adjusted number of animals at risk	88.5	46.8	48.9	36.9
	Hemangiosarcoma	P-value of test of trend or comparison	.8382	.5704	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	1.1%	2.1%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0.05,11.5)	(0,7.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	88.5	47.0	48.7	36.1
	Luteoma·benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
		Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.27,8.0)	(0,7.7)	(0,7.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	88.2	46.8	48.7	36.1
	Tumor·malignat: granulosa cell	P-value of test of trend or comparison	.1651			.2903
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0,7.7)	(0,7.4)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	88.2	46.8	48.7	36.1
PANCREAS	Adenoma: islet cell	P-value of test of trend or comparison	.8053	.4242	.7191	1
		Number of animals reported with tumor	2	2	1	0
		Poly-3 adjusted incidence rate	2.1%	4.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.26,7.5)	(0.49,14.0)	(0.05,10.9)	(0,10.0)
		Poly-3 adjusted number of animals at risk	94.1	49.1	49.4	35.2
PITUITARY GLAND	Adenoma: pars·distalis	P-value of test of trend or comparison	.8824	.5462	.8095	1
		Number of animals reported with tumor	3	2	1	0
		Poly-3 adjusted incidence rate	3.2%	4.2%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.66,9.1)	(0.51,14.5)	(0.05,11.3)	(0,10.0)
		Poly-3 adjusted number of animals at risk	93.5	47.8	47.5	35.0

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Table 1.11

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Adenoma: pars-intermedia	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.26,7.6)	(0,7.5)	(0,7.5)	(0,10.0)
		Poly-3 adjusted number of animals at risk	93.3	47.8	47.5	35.0
	Carcinoma: pars- intermedia	P-value of test of trend or comparison	.5830	.3404		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,3.9)	(0.05,11.1)	(0,7.5)	(0,10.0)
		Poly-3 adjusted number of animals at risk	93.3	48.2	47.5	35.0
	Carcinoma: pars-distalis	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(0,7.5)	(0,7.5)	(0,10.0)
		Poly-3 adjusted number of animals at risk	93.3	47.8	47.5	35.0
SKIN/SUBCUTIS	Carcinoma: squamous cell	P-value of test of trend or comparison	.6186	1	.5786	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(0,7.4)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.5	48.8	51.0	37.5
	Fibrosarcoma	P-value of test of trend or comparison	.9478	.8202	.8202	.9831
		Number of animals reported with tumor	11	4	4	1
		Poly-3 adjusted incidence rate	11%	8.0%	7.9%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(5.74,19.4)	(2.18,19.2)	(2.18,19.2)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	97.1	50.0	50.8	37.5
SPLEEN	Hemangioma	P-value of test of trend or comparison	.5921	.3404		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%

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Table 1.11

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,3.9)	(0.05,11.1)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.5	48.8	50.3	37.5
	Hemangiosarcoma	P-value of test of trend or comparison	.6165	1	.5755	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(0,7.4)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	94.3	48.8	50.5	37.5
SYSTEMIC NEOPLASM	Lymphoma·malignant	P-value of test of trend or comparison	.9938	.1552	.9994	.9720
		Number of animals reported with tumor	34	23	6	8
		Poly-3 adjusted incidence rate	34%	44%	12%	20%
		95% CI for poly-3 adjusted incidence rate (%)	(24.8,44.6)	(29.8,58.7)	(4.44,24.3)	(8.82,35.6)
		Poly-3 adjusted number of animals at risk	99.2	52.0	50.7	40.9
	Sarcoma: histiocytic	P-value of test of trend or comparison	.7103	.8737	.8832	.8143
		Number of animals reported with tumor	17	6	6	5
		Poly-3 adjusted incidence rate	18%	12%	12%	13%
		95% CI for poly-3 adjusted incidence rate (%)	(10.6,26.8)	(4.44,24.3)	(4.35,23.9)	(4.3,28.1)
		Poly-3 adjusted number of animals at risk	96.7	50.4	51.8	38.7
THYMUS	Thymoma·malignant	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.1)	(0,8.0)	(0,8.6)	(0,15.4)
		Poly-3 adjusted number of animals at risk	89.8	44.7	41.1	22.9
THYROID GLAND	Adenoma: follicular cell	P-value of test of trend or comparison	.6562	.5698	.5759	1
		Number of animals reported with tumor	1	1	1	0
		Poly-3 adjusted incidence rate	1.1%	2.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.9)	(0.05,11.1)	(0.05,10.9)	(0,9.5)
		Poly-3 adjusted number of animals at risk	92.3	48.8	49.3	37.1
UTERUS	Adenocarcinoma: endometrium	P-value of test of trend or comparison	.9334	.7162	1	1

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Table 1.11

Table of reported tumors in Mouse Study
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Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	2	1	0	0
		Poly-3 adjusted incidence rate	2.1%	2.1%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.26,7.6)	(0.05,11.1)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.9	48.8	50.3	37.5
	Hemangioma	P-value of test of trend or comparison	.6557	.5666	.5786	1
		Number of animals reported with tumor	1	1	1	0
		Poly-3 adjusted incidence rate	1.1%	2.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(0.05,11.1)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.1	48.4	50.3	37.5
	Hemangiosarcoma	P-value of test of trend or comparison	.5354	1	1	.7397
		Number of animals reported with tumor	3	0	0	1
		Poly-3 adjusted incidence rate	3.2%	0.0%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.66,9.0)	(0,7.4)	(0,7.1)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	94.2	48.4	50.3	37.6
	Leiomyoma	P-value of test of trend or comparison	.8334	.0458	.5786	1
		Number of animals reported with tumor	1	4	1	0
		Poly-3 adjusted incidence rate	1.1%	8.2%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(2.27,20.0)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.1	48.8	50.7	37.5
	Leiomyosarcoma	P-value of test of trend or comparison	.6557	.5666	.5786	1
		Number of animals reported with tumor	1	1	1	0
		Poly-3 adjusted incidence rate	1.1%	2.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(0.05,11.1)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.7	48.4	50.3	37.5
	Polyp: endometrial stroma	P-value of test of trend or comparison	.9746	.8749	.8864	1
		Number of animals reported with tumor	7	2	2	0
		Poly-3 adjusted incidence rate	7.5%	4.1%	4.0%	0.0%

Reference ID: 3158913

Table 1.11

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(3.05,14.9)	(0.5,14.3)	(0.48,13.7)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.7	48.4	50.5	37.5
	Polyp: glandular	P-value of test of trend or comparison	.9684	.1742	.8593	.9697
		Number of animals reported with tumor	9	8	3	1
		Poly-3 adjusted incidence rate	9.6%	16%	6.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(4.47,17.6)	(7.32,30.2)	(1.23,16.5)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	93.6	48.6	50.3	37.5
	Sarcoma: endometrial	P-value of test of trend or comparison	.7033	.2672	.5786	1
		Number of animals reported with tumor	1	2	1	0
		Poly-3 adjusted incidence rate	1.1%	4.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(0.5,14.3)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.5	48.5	51.0	37.5
	Tumor·benign: granular cell	P-value of test of trend or comparison	.0925		.1207	.2846
		Number of animals reported with tumor	0	0	2	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	4.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,3.9)	(0,7.4)	(0.48,13.7)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	93.1	48.4	50.4	37.5
UTERUS: CERVIX	Hemangioma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.2)	(0,7.1)	(0,10.6)
		Poly-3 adjusted number of animals at risk	88.5	43.4	50.3	33.7
	Leiomyosarcoma	P-value of test of trend or comparison	.0664	1	1	.1903
		Number of animals reported with tumor	1	0	0	2
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	5.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.2)	(0,7.1)	(0.7,19.7)
		Poly-3 adjusted number of animals at risk	87.8	43.4	50.3	34.3

Reference ID: 3158913

Table 1.11

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
VAGINA	Carcinoma: squamous cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.3)	(0,7.7)	(0,7.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	86.6	46.3	50.0	33.2
	Papilloma: squamous cell	P-value of test of trend or comparison	.8321	.2781	1	1
		Number of animals reported with tumor	1	2	0	0
		Poly-3 adjusted incidence rate	1.2%	4.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.3)	(0.52,14.8)	(0,7.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	86.7	46.3	50.0	33.2

Reference ID: 3158913

Table 1.12

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLD: CORTE	Adenoma: cortex	P-value of test of trend or comparison	.7464	.0109	.3459	
		Number of animals reported with tumor	0	4	1	0
		Poly-3 adjusted incidence rate	0.0%	9.3%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(2.53,22.1)	(0.05,11.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	87.3	43.1	46.8	33.0
	Adenoma: subcapsular	P-value of test of trend or comparison	.5914	.5469	.2745	1
		Number of animals reported with tumor	1	1	2	0
		Poly-3 adjusted incidence rate	1.1%	2.4%	4.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0.06,12.6)	(0.52,14.8)	(0,10.6)
		Poly-3 adjusted number of animals at risk	87.5	42.5	46.8	33.0
ADRENAL GLD: MEDUL	Pheochromocytoma·benign	P-value of test of trend or comparison	.5918	.3333		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.5%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.5)	(0.06,13.2)	(0,8.0)	(0,10.9)
		Poly-3 adjusted number of animals at risk	80.0	40.5	45.0	32.3
BONE MARROW: FEMUR	Hemangiosarcoma	P-value of test of trend or comparison	.9108	.4029	1	1
		Number of animals reported with tumor	2	2	0	0
		Poly-3 adjusted incidence rate	2.2%	4.5%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.27,7.9)	(0.54,15.5)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	89.7	44.2	47.4	33.2
BONE MARROW: STERN	Hemangioma	P-value of test of trend or comparison	.5810	.3231		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0.06,12.6)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	88.6	42.5	47.3	33.4
	Hemangiosarcoma	P-value of test of trend or comparison	.1571			.2727
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.0%

Table 1.12

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0,8.4)	(0,7.5)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	88.6	42.5	47.3	33.4
GALL BLADDER	Adenoma	P-value of test of trend or comparison	.5787	.3360		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.3)	(0.06,12.6)	(0,8.6)	(0,11.2)
		Poly-3 adjusted number of animals at risk	83.1	42.5	41.4	31.3
HARDERIAN GLAND	Adenoma	P-value of test of trend or comparison	.6147	.0374	.4160	.5403
		Number of animals reported with tumor	7	9	5	3
		Poly-3 adjusted incidence rate	7.8%	20%	10%	8.9%
		95% CI for poly-3 adjusted incidence rate (%)	(3.18,15.5)	(9.58,35.3)	(3.4,22.7)	(1.86,24.3)
		Poly-3 adjusted number of animals at risk	89.6	44.0	48.3	33.7
HEART	Hemangiosarcoma	P-value of test of trend or comparison	.3774		.3456	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	89.2	43.5	47.8	33.4
INTESTINE: CECUM	Adenocarcinoma	P-value of test of trend or comparison	.3824		.3588	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.3)	(0,8.4)	(0.05,11.3)	(0,11.2)
		Poly-3 adjusted number of animals at risk	84.7	42.8	47.1	31.5
	Adenoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.4)	(0,8.4)	(0,7.5)	(0,11.2)
		Poly-3 adjusted number of animals at risk	85.1	42.8	47.1	31.5
INTESTINE: DUODENU	Adenoma	P-value of test of trend or comparison	.0925		.1282	.2844

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Table 1.12

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	0	0	2	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	4.5%	3.1%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.6)	(0,8.8)	(0.54,15.5)	(0.08,16.7)
		Poly-3 adjusted number of animals at risk	78.1	40.4	44.2	31.8
INTESTINE: JEJUNUM	Adenocarcinoma	P-value of test of trend or comparison	.1587			.2773
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.4)	(0,7.5)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	87.0	43.0	47.4	33.4
	Adenoma	P-value of test of trend or comparison	.1610	.3281		.2773
		Number of animals reported with tumor	0	1	0	1
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	3.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0.06,12.6)	(0,7.5)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	87.0	43.0	47.4	33.4
KIDNEY	Adenoma: renal tubule	P-value of test of trend or comparison	.1564	.3258		.2705
		Number of animals reported with tumor	0	1	0	1
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	2.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0.06,12.3)	(0,7.5)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	89.6	43.5	47.4	33.9
	Carcinoma: renal tubule	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.27,7.9)	(0,8.2)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	89.6	43.5	47.4	33.4
LIVER	Adenoma: hepatocyte	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.1)	(0,8.2)	(0,7.5)	(0,10.6)

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Table 1.12

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	89.8	43.5	47.4	33.4
	Carcinoma: hepatocyte	P-value of test of trend or comparison	.7933	.6854	.5227	.8919
		Number of animals reported with tumor	14	6	8	3
		Poly-3 adjusted incidence rate	16%	14%	17%	8.8%
		95% CI for poly-3 adjusted incidence rate (%)	(8.67,24.7)	(5.17,27.9)	(7.32,30.2)	(1.86,24.3)
		Poly-3 adjusted number of animals at risk	90.1	43.9	48.1	34.0
	Cholangioma	P-value of test of trend or comparison	.3774		.3456	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	89.6	43.5	47.7	33.4
	Hemangioma	P-value of test of trend or comparison	.0900	.5471	1	.1776
		Number of animals reported with tumor	1	1	0	2
		Poly-3 adjusted incidence rate	1.1%	2.3%	0.0%	6.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.1)	(0.06,12.3)	(0,7.5)	(0.72,20.2)
		Poly-3 adjusted number of animals at risk	90.0	43.8	47.4	33.6
	Hemangiosarcoma	P-value of test of trend or comparison	.9050	.4057	.6729	1
		Number of animals reported with tumor	4	3	2	0
		Poly-3 adjusted incidence rate	4.4%	6.9%	4.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.21,11.0)	(1.43,19.1)	(0.51,14.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	90.8	43.8	47.8	33.4
LN: MESENTERIC	Hemangioma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.5%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.9)	(0,9.7)	(0,10.6)	(0,12.3)
		Poly-3 adjusted number of animals at risk	68.3	36.1	33.9	28.7
	Hemangiosarcoma	P-value of test of trend or comparison	.5879	.3462		

Reference ID: 3158913

Table 1.12

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.3)	(0.07,14.5)	(0,10.6)	(0,12.3)
		Poly-3 adjusted number of animals at risk	68.3	36.3	33.9	28.7
LUNG	Adenoma: bronchioloalveolar	P-value of test of trend or comparison	.6917	.1635	.8209	.7220
		Number of animals reported with tumor	3	4	1	1
		Poly-3 adjusted incidence rate	3.3%	8.9%	2.1%	3.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.69,9.5)	(2.48,21.7)	(0.05,11.3)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	89.6	44.7	47.4	33.4
	Carcinoma: bronchioloalveolar	P-value of test of trend or comparison	.8052	.5542	1	.7368
		Number of animals reported with tumor	16	8	0	5
		Poly-3 adjusted incidence rate	18%	18%	0.0%	15%
		95% CI for poly-3 adjusted incidence rate (%)	(10.3,27.0)	(8,32.7)	(0,7.5)	(4.81,31.1)
		Poly-3 adjusted number of animals at risk	91.4	44.4	47.4	34.1
	Hemangiosarcoma	P-value of test of trend or comparison	.3774		.3456	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	89.6	43.5	47.8	33.4
PANCREAS	Adenocarcinoma: acinar cell	P-value of test of trend or comparison	.3810		.3481	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0,8.4)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	88.8	42.8	47.4	33.4
PITUITARY GLAND	Adenoma: pars-distalis	P-value of test of trend or comparison	.4264	.3254	.3359	
		Number of animals reported with tumor	0	1	1	0
		Poly-3 adjusted incidence rate	0.0%	2.4%	2.3%	0.0%

Reference ID: 3158913

Table 1.12

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0.06,12.9)	(0.06,12.3)	(0,10.9)
		Poly-3 adjusted number of animals at risk	85.5	41.7	43.1	32.9
PROSTATE GLAND	Hemangiosarcoma	P-value of test of trend or comparison	.5777	.3308		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0.06,12.3)	(0,7.9)	(0,11.2)
		Poly-3 adjusted number of animals at risk	87.8	43.5	45.7	31.7
SEMINAL VESICLE	Tumor: granular cell benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.1)	(0,8.2)	(0,7.7)	(0,10.6)
		Poly-3 adjusted number of animals at risk	89.3	43.5	46.8	33.4
SKELETAL MUSCLE	Hemangiosarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.1)	(0,8.2)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	90.0	43.5	47.4	33.4
SKIN/SUBCUTIS	Carcinoma: basal cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.2)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	87.4	43.5	47.4	33.4
	Fibrosarcoma	P-value of test of trend or comparison	.7947	.5350	.9279	.8590
		Number of animals reported with tumor	5	3	1	1
		Poly-3 adjusted incidence rate	5.6%	6.7%	2.1%	3.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.85,12.8)	(1.4,18.7)	(0.05,11.3)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	88.9	44.8	47.6	33.4
	Hemangiosarcoma	P-value of test of trend or comparison	1	1	1	1

Reference ID: 3158913

Table 1.12

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	3	0	0	0
		Poly-3 adjusted incidence rate	3.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.7,9.6)	(0,8.2)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	88.9	43.5	47.4	33.4
	Mast cell tumor·malignant	P-value of test of trend or comparison	.3810		.3507	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	87.2	43.5	47.4	33.4
	Sarcoma: not other specified	P-value of test of trend or comparison	.3810		.3507	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	87.2	43.5	47.5	33.4
SPLEEN	Hemangiosarcoma	P-value of test of trend or comparison	.9129	.0421	1	1
		Number of animals reported with tumor	1	4	0	0
		Poly-3 adjusted incidence rate	1.1%	9.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(2.48,21.7)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	89.0	44.4	47.4	33.4
STOMACH: GLANDULAR	Adenoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.0)	(0,8.2)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	90.1	43.5	47.4	33.4
	Tumor·malignant: neuroendocrine	P-value of test of trend or comparison	.5802	.3258		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0.06,12.3)	(0,7.5)	(0,10.6)

Reference ID: 3158913

Table 1.12

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	89.6	43.5	47.4	33.4
STOMACH: NONGLANDU	Papilloma: squamous cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.0)	(0,8.2)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	90.2	43.5	47.4	33.4
SYSTEMIC NEOPLASM	Lymphoma·malignant	P-value of test of trend or comparison	.1493	.0321	1	.0642
		Number of animals reported with tumor	9	11	0	8
		Poly-3 adjusted incidence rate	9.9%	23%	0.0%	22%
		95% CI for poly-3 adjusted incidence rate (%)	(4.57,17.9)	(12,38.0)	(0,7.5)	(9.83,39.2)
		Poly-3 adjusted number of animals at risk	91.1	47.6	47.4	36.5
	Sarcoma: histiocytic	P-value of test of trend or comparison	.0970	.7979	.8209	.2088
		Number of animals reported with tumor	3	1	1	3
		Poly-3 adjusted incidence rate	3.3%	2.3%	2.1%	8.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.69,9.5)	(0.06,12.3)	(0.05,11.3)	(1.8,23.7)
		Poly-3 adjusted number of animals at risk	89.7	43.5	47.5	34.2
TESTIS	Adenoma: Leydig cell	P-value of test of trend or comparison	.6296	.6489	.6778	.7998
		Number of animals reported with tumor	4	2	2	1
		Poly-3 adjusted incidence rate	4.4%	4.5%	4.2%	3.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.22,11.1)	(0.54,15.5)	(0.51,14.5)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	89.9	44.5	47.4	33.4
	Adenoma: rete testis	P-value of test of trend or comparison	.3774		.3456	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	89.6	43.5	47.4	33.4
THYMUS	Sarcoma: not otherwise specified	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0

Reference ID: 3158913

Table 1.12

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	1.5%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,8.0)	(0,10.9)	(0,9.5)	(0,14.2)
		Poly-3 adjusted number of animals at risk	67.6	32.2	37.1	24.7
THYROID GLAND	Adenoma: follicular cell	P-value of test of trend or comparison	.6083	1	.5671	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.1)	(0,8.4)	(0.05,11.5)	(0,10.9)
		Poly-3 adjusted number of animals at risk	89.6	42.5	46.1	33.0

Reference ID: 3158913

Table 1.13

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 120*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 60*
Adenomas and adenocarcinomas of the small intestine	P-value of test of trend or comparison	.8347	.5666	1	1
	Number of animals reported with tumor	1	1	0	0
All pheochromocytomas	P-value of test of trend or comparison	.0989		.3556	.2869
	Number of animals reported with tumor	0	0	1	1
Bronchioloalveolar tumors	P-value of test of trend or comparison	.7735	.4221	.0344	.9288
	Number of animals reported with tumor	11	7	13	2
Fibrosarcomas and Sarcomas (NOS) of the skin	P-value of test of trend or comparison	.9478	.8202	.8202	.9831
	Number of animals reported with tumor	11	4	4	1
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.3950	.2701	.7631	.3780
	Number of animals reported with tumor	14	10	6	7
Hepatocellular tumors	P-value of test of trend or comparison	.6186	1	.5786	1
	Number of animals reported with tumor	1	0	1	0
Lipomas and liposarcomas	P-value of test of trend or comparison	.3816		.3497	
	Number of animals reported with tumor	0	0	1	0
Lipomas, lipomasarcomas and hibernomas	P-value of test of trend or comparison	.3816		.3497	
	Number of animals reported with tumor	0	0	1	0
Luteomas and ovarian granulosa cell tumors	P-value of test of trend or comparison	.1651			.2903
	Number of animals reported with tumor	0	0	0	1
Mammary adenocarcinomas and adenocanthomas	P-value of test of trend or comparison	.9344	.8821	.8902	1
	Number of animals reported with tumor	4	1	1	0
Mammary adenomas and fibroadenomas	P-value of test of trend or comparison	.1688	.3453		.2891
	Number of animals reported with tumor	0	1	0	1
Mammary tumors	P-value of test of trend or comparison	.7023	.6724	.8902	.8213
	Number of animals reported with tumor	4	2	1	1
Ovarian tubulostromal adenocarcinomas and cystadenomas	P-value of test of trend or comparison	.8432	.9541	1	.9157
	Number of animals reported with tumor	6	1	0	1

Reference ID: 3158913

Table 1.13

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 120*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 60*
Pancreatic islet and acinar-islet cell tumors	P-value of test of trend or comparison	.8053	.4242	.7191	1
	Number of animals reported with tumor	2	2	1	0
Pancreatic islet cell tumors	P-value of test of trend or comparison	.8053	.4242	.7191	1
	Number of animals reported with tumor	2	2	1	0
Pituitary pars distalis tumors	P-value of test of trend or comparison	.9313	.6584	.8754	1
	Number of animals reported with tumor	4	2	1	0
Pituitary pars intermedia tumors	P-value of test of trend or comparison	.9288	.7162	1	1
	Number of animals reported with tumor	2	1	0	0
Renal tubule tumors	P-value of test of trend or comparison	.5921	.3404		
	Number of animals reported with tumor	0	1	0	0
Uterine adenocarcinomas and glandular polyps	P-value of test of trend or comparison	.9684	.1742	.8593	.9697
	Number of animals reported with tumor	9	8	3	1
Uterine leiomyomas, leiomyosarcomas, and endometrial stromal polyps and sarcomas	P-value of test of trend or comparison	.9925	.2227	.6635	1
	Number of animals reported with tumor	10	8	5	0
Vaginal squamous cell tumors and polyps	P-value of test of trend or comparison	.9196	.4346	1	1
	Number of animals reported with tumor	2	2	0	0

Reference ID: 3158913

Table 1.14

Table of reported tumors in Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Control Size = 120*	*Low dose Size = 60*	*Mid dose Size = 60*	*High dose Size = 60*
Adenomas and adenocarcinomas of the small intestine	P-value of test of trend or comparison	.0088	.3258	.1178	.0185
	Number of animals reported with tumor	0	1	2	3
All pheochromocytomas	P-value of test of trend or comparison	.5918	.3333		
	Number of animals reported with tumor	0	1	0	0
Bronchioloalveolar tumors	P-value of test of trend or comparison	.8537	.2916	.9999	.7383
	Number of animals reported with tumor	19	12	1	6
Fibrosarcomas and Sarcomas (NOS) of the skin	P-value of test of trend or comparison	.7551	.5350	.7701	.8590
	Number of animals reported with tumor	5	3	2	1
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.6514	.1670	.9098	.5953
	Number of animals reported with tumor	8	7	2	3
Hepatocellular tumors	P-value of test of trend or comparison	.8291	.7395	.5884	.9157
	Number of animals reported with tumor	15	6	8	3
Pancreatic acinar and acinar-islet cell tumors	P-value of test of trend or comparison	.3810		.3481	
	Number of animals reported with tumor	0	0	1	0
Pancreatic acinar cell tumors	P-value of test of trend or comparison	.3810		.3481	
	Number of animals reported with tumor	0	0	1	0
Pituitary pars distalis tumors	P-value of test of trend or comparison	.4264	.3254	.3359	
	Number of animals reported with tumor	0	1	1	0
Renal tubule tumors	P-value of test of trend or comparison	.4593	.6969	1	.6154
	Number of animals reported with tumor	2	1	0	1

Reference ID: 3158913

Table 1.15

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
UTERUS	Leiomyoma	P-value of test of trend or comparison	.8334	.0458	.5786	1
		Number of animals reported with tumor	1	4	1	0
		Poly-3 adjusted incidence rate	1.1%	8.2%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,5.8)	(2.27,20.0)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	93.1	48.8	50.7	37.5

Reference ID: 3158913

Table 1.16

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLD: CORTE	Adenoma: cortex	P-value of test of trend or comparison	.7464	.0109	.3459	
		Number of animals reported with tumor	0	4	1	0
		Poly-3 adjusted incidence rate	0.0%	9.3%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(2.53,22.1)	(0.05,11.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	87.3	43.1	46.8	33.0
HARDERIAN GLAND	Adenoma	P-value of test of trend or comparison	.6147	.0374	.4160	.5403
		Number of animals reported with tumor	7	9	5	3
		Poly-3 adjusted incidence rate	7.8%	20%	10%	8.9%
		95% CI for poly-3 adjusted incidence rate (%)	(3.18,15.5)	(9.58,35.3)	(3.4,22.7)	(1.86,24.3)
		Poly-3 adjusted number of animals at risk	89.6	44.0	48.3	33.7
SPLEEN	Hemangiosarcoma	P-value of test of trend or comparison	.9129	.0421	1	1
		Number of animals reported with tumor	1	4	0	0
		Poly-3 adjusted incidence rate	1.1%	9.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(2.48,21.7)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	89.0	44.4	47.4	33.4
SYSTEMIC NEOPLASM	Lymphoma-malignant	P-value of test of trend or comparison	.1493	.0321	1	.0642
		Number of animals reported with tumor	9	11	0	8
		Poly-3 adjusted incidence rate	9.9%	23%	0.0%	22%
		95% CI for poly-3 adjusted incidence rate (%)	(4.57,17.9)	(12,38.0)	(0,7.5)	(9.83,39.2)
		Poly-3 adjusted number of animals at risk	91.1	47.6	47.4	36.5

Reference ID: 3158913

Table 1.17

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202992
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Bronchioloalveolar tumors	P-value of test of trend or comparison	.7735	.4221	.0344	.9288
	Number of animals reported with tumor	11	7	13	2
	Poly-3 adjusted incidence rate	12%	14%	25%	5.3%
	95% CI for poly-3 adjusted incidence rate (%)	(5.92,20.0)	(5.82,27.2)	(13.8,38.9)	(0.64,18.2)
	Poly-3 adjusted number of animals at risk	94.1	49.6	52.2	37.5

Reference ID: 3158913

Table 1.18

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202992
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Adenomas and adenocarcinomas of the small intestine	P-value of test of trend or comparison	.0088	.3258	.1178	.0185
	Number of animals reported with tumor	0	1	2	3
	Poly-3 adjusted incidence rate	0.0%	2.3%	4.2%	8.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0,4.1)	(0.06,12.3)	(0.51,14.5)	(1.86,24.3)
	Poly-3 adjusted number of animals at risk	89.6	43.5	47.7	33.6

Table 1.19 ***Tumor counts for organs reported widely unanalyzed***
NDA 202992
Animal carcinogenicity study
Mice

Species and Sex	*Organ or tissue name*	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Mice - Female	BODY CAVITY	Liposarcoma	Number of tumors found	0	0	1	0
			Number of animals examined	3	0	2	0
	BONE	Osteoma	Number of tumors found	1	0	0	0
			Number of animals examined	1	0	0	0

Table 1.20

Organs reported as autolytic
NDA 202992
Animal carcinogenicity study
Female Mice

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
INTESTINE: CECUM	1	0.8%	.	.	.	.	.	.	1	0.3%
INTESTINE: ILEUM	2	1.7%	1	1.7%	1	1.7%	.	.	4	1.3%
INTESTINE: JEJUNUM	2	1.7%	.	.	.	.	1	1.7%	3	1.0%

Reference ID: 3158913

Table 1.21

Organs reported as autolytic
NDA 202992
Animal carcinogenicity study
Male Mice

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
GALL BLADDER	1	0.8%	.	.	1	1.7%	.	.	2	0.7%
INTESTINE: CECUM	.	.	.	.	.	.	2	3.3%	2	0.7%
INTESTINE: COLON	.	.	.	.	1	1.7%	.	.	1	0.3%
INTESTINE: DUODENU	1	0.8%	.	.	.	.	.	.	1	0.3%
INTESTINE: ILEUM	1	0.8%	.	.	.	.	.	.	1	0.3%
INTESTINE: JEJUNUM	1	0.8%	1	1.7%	.	.	.	.	2	0.7%

Table 1.22

Organs reported as unexamined
NDA 202992
Animal carcinogenicity study
Female Mice

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
ADRENAL GLD: CORTE	2	1.7%	.	.	.	.	.	.	2	0.7%
ADRENAL GLD: MEDUL	8	6.7%	3	5.0%	3	5.0%	3	5.0%	17	5.7%
AORTA	13	11%	4	6.7%	4	6.7%	4	6.7%	25	8.4%
BODY CAV: ABDOMINA	119	100%	60	100%	60	100%	60	100%	299	100%
BODY CAVITY	116	97%	60	100%	58	97%	60	100%	294	99%
BONE	118	99%	60	100%	60	100%	60	100%	298	100%
BONE MARROW: FEMUR	.	.	2	3.3%	.	.	2	3.3%	4	1.3%
BONE MARROW: STERN	1	0.8%	.	.	1	1.7%	1	1.7%	3	1.0%
BONE: FEMUR	.	.	2	3.3%	.	.	2	3.3%	4	1.3%
BONE: STERNUM	1	0.8%	.	.	1	1.7%	1	1.7%	3	1.0%
CLITORAL GLAND	16	13%	6	10%	7	12%	13	22%	42	14%
ESOPHAGUS	6	5.0%	4	6.7%	4	6.7%	.	.	14	4.7%
EYE	.	.	1	1.7%	.	.	.	.	1	0.3%
GALL BLADDER	8	6.7%	3	5.0%	4	6.7%	2	3.3%	17	5.7%
HARDERIAN GLAND	.	.	.	.	1	1.7%	.	.	1	0.3%
HEART	.	.	1	1.7%	.	.	.	.	1	0.3%
INTESTINE: CECUM	3	2.5%	1	1.7%	3	5.0%	5	8.3%	12	4.0%
INTESTINE: COLON	1	0.8%	.	.	3	5.0%	1	1.7%	5	1.7%
INTESTINE: DUODENU	8	6.7%	6	10%	2	3.3%	5	8.3%	21	7.0%
INTESTINE: GALT	35	29%	18	30%	21	35%	14	23%	88	30%
INTESTINE: ILEUM	7	5.9%	2	3.3%	1	1.7%	3	5.0%	13	4.4%
INTESTINE: JEJUNUM	2	1.7%	1	1.7%	1	1.7%	3	5.0%	7	2.3%
INTESTINE: RECTUM	5	4.2%	4	6.7%	2	3.3%	.	.	11	3.7%
JOINT	1	0.8%	3	5.0%	.	.	3	5.0%	7	2.3%
LACRIMAL GLAND	21	18%	8	13%	8	13%	14	23%	51	17%
LN: MANDIBULAR	4	3.4%	1	1.7%	1	1.7%	3	5.0%	9	3.0%
LN: MESENTERIC	18	15%	14	23%	13	22%	9	15%	54	18%

Table 1.22

Organs reported as unexamined
NDA 202992
Animal carcinogenicity study
Female Mice

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
LUNG	1	0.8%	.	.	.	.	.	.	1	0.3%
M: DIAPHRAGM	.	.	.	.	.	.	1	1.7%	1	0.3%
MAMMARY GLAND	3	2.5%	1	1.7%	.	.	.	.	4	1.3%
MESENTERY	118	99%	55	92%	58	97%	56	93%	287	96%
NASAL TISSUE	.	.	.	.	.	.	1	1.7%	1	0.3%
NERVE: OPTIC	15	13%	8	13%	9	15%	1	1.7%	33	11%
NERVE: SCIATIC	3	2.5%	.	.	.	.	1	1.7%	4	1.3%
OVARY	6	5.0%	2	3.3%	3	5.0%	2	3.3%	13	4.4%
OVIDUCT	10	8.4%	5	8.3%	4	6.7%	4	6.7%	23	7.7%
PANCREAS	.	.	.	.	1	1.7%	3	5.0%	4	1.3%
PARATHYROID GLAND	4	3.4%	.	.	2	3.3%	4	6.7%	10	3.4%
PITUITARY GLAND	2	1.7%	1	1.7%	3	5.0%	3	5.0%	9	3.0%
SALIV.GLD: MANDIB.	.	.	.	.	1	1.7%	.	.	1	0.3%
SALIV.GLD: PAROTID	2	1.7%	.	.	1	1.7%	.	.	3	1.0%
SALIV.GLD: SUBLIN.	5	4.2%	3	5.0%	1	1.7%	1	1.7%	10	3.4%
SPINAL CORD: CERVI	4	3.4%	1	1.7%	2	3.3%	2	3.3%	9	3.0%
SPINAL CORD: LUMBA	.	.	.	.	2	3.3%	1	1.7%	3	1.0%
SPINAL CORD: THORA	1	0.8%	.	.	1	1.7%	2	3.3%	4	1.3%
STOMACH: NONGLANDU	.	.	.	.	.	.	1	1.7%	1	0.3%
THYMUS	9	7.6%	6	10%	13	22%	20	33%	48	16%
THYROID GLAND	2	1.7%	.	.	1	1.7%	1	1.7%	4	1.3%
TONGUE	2	1.7%	.	.	.	.	1	1.7%	3	1.0%
TRACHEA	2	1.7%	.	.	.	.	1	1.7%	3	1.0%
URETER	8	6.7%	3	5.0%	2	3.3%	7	12%	20	6.7%
URINARY BLADDER	7	5.9%	4	6.7%	.	.	5	8.3%	16	5.4%
UTERUS	1	0.8%	1	1.7%	.	.	.	.	2	0.7%

Reference ID: 3158913

Table 1.22

Organs reported as unexamined
NDA 202992
Animal carcinogenicity study
Female Mice

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
UTERUS: CERVIX	8	6.7%	7	12%	.	.	6	10%	21	7.0%
VAGINA	9	7.6%	4	6.7%	1	1.7%	6	10%	20	6.7%

Reference ID: 3158913

Table 1.23

Organs reported as unexamined
NDA 202992
Animal carcinogenicity study
Male Mice

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
ADRENAL GLD: CORTE	3	2.5%	1	1.7%	1	1.7%	1	1.7%	6	2.0%
ADRENAL GLD: MEDUL	13	11%	3	5.0%	4	6.7%	3	5.0%	23	7.7%
AORTA	9	7.6%	2	3.3%	2	3.3%	1	1.7%	14	4.7%
BODY CAV: ABDOMINA	119	100%	60	100%	60	100%	60	100%	299	100%
BODY CAVITY	119	100%	60	100%	60	100%	60	100%	299	100%
BONE	119	100%	60	100%	60	100%	60	100%	299	100%
BONE MARROW: FEMUR	2	1.7%	.	.	.	.	1	1.7%	3	1.0%
BONE MARROW: STERN	1	0.8%	1	1.7%	1	1.7%	.	.	3	1.0%
BONE: FEMUR	2	1.7%	.	.	.	.	1	1.7%	3	1.0%
BONE: STERNUM	1	0.8%	1	1.7%	1	1.7%	.	.	3	1.0%
ESOPHAGUS	5	4.2%	2	3.3%	4	6.7%	3	5.0%	14	4.7%
EYE	.	.	.	.	.	.	1	1.7%	1	0.3%
GALL BLADDER	12	10%	1	1.7%	7	12%	6	10%	26	8.7%
HARDERIAN GLAND	1	0.8%	.	.	.	.	1	1.7%	2	0.7%
HEART	1	0.8%	.	.	.	.	.	.	1	0.3%
INTESTINE: CECUM	7	5.9%	1	1.7%	1	1.7%	2	3.3%	11	3.7%
INTESTINE: COLON	1	0.8%	2	3.3%	4	6.7%	1	1.7%	8	2.7%
INTESTINE: DUODENU	17	14%	6	10%	4	6.7%	4	6.7%	31	10%
INTESTINE: GALT	49	41%	23	38%	17	28%	21	35%	110	37%
INTESTINE: ILEUM	7	5.9%	3	5.0%	4	6.7%	3	5.0%	17	5.7%
INTESTINE: JEJUNUM	3	2.5%	.	.	.	.	.	.	3	1.0%
INTESTINE: RECTUM	6	5.0%	2	3.3%	5	8.3%	4	6.7%	17	5.7%
JOINT	2	1.7%	.	.	.	.	1	1.7%	3	1.0%
LACRIMAL GLAND	5	4.2%	.	.	3	5.0%	2	3.3%	10	3.4%
LN: MANDIBULAR	7	5.9%	.	.	2	3.3%	1	1.7%	10	3.4%
LN: MESENTERIC	28	24%	9	15%	18	30%	7	12%	62	21%
M: DIAPHRAGM	1	0.8%	.	.	1	1.7%	1	1.7%	3	1.0%

Table 1.23

Organs reported as unexamined
NDA 202992
Animal carcinogenicity study
Male Mice

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
MAMMARY GLAND	119	100%	60	100%	60	100%	60	100%	299	100%
MESENTERY	116	97%	59	98%	60	100%	60	100%	295	99%
NASAL TISSUE	1	0.8%	.	.	.	.	.	.	1	0.3%
NERVE: OPTIC	10	8.4%	6	10%	3	5.0%	5	8.3%	24	8.1%
PANCREAS	1	0.8%	1	1.7%	.	.	.	.	2	0.7%
PARATHYROID GLAND	9	7.6%	2	3.3%	3	5.0%	2	3.3%	16	5.4%
PITUITARY GLAND	6	5.0%	4	6.7%	5	8.3%	2	3.3%	17	5.7%
PREPUTIAL GLAND	5	4.2%	.	.	.	.	3	5.0%	8	2.7%
PROSTATE GLAND	3	2.5%	1	1.7%	2	3.3%	3	5.0%	9	3.0%
SALIV.GLD: PAROTID	.	.	.	.	1	1.7%	1	1.7%	2	0.7%
SALIV.GLD: SUBLIN.	4	3.4%	.	.	.	.	1	1.7%	5	1.7%
SEMINAL VESICLE	1	0.8%	.	.	1	1.7%	.	.	2	0.7%
SKIN/SUBCUTIS	3	2.5%	.	.	.	.	.	.	3	1.0%
SPINAL CORD: CERVI	2	1.7%	3	5.0%	1	1.7%	.	.	6	2.0%
SPINAL CORD: LUMBA	6	5.0%	1	1.7%	.	.	1	1.7%	8	2.7%
SPINAL CORD: THORA	4	3.4%	1	1.7%	.	.	.	.	5	1.7%
SPLEEN	1	0.8%	.	.	.	.	.	.	1	0.3%
THYMUS	31	26%	14	23%	13	22%	17	28%	75	25%
THYROID GLAND	.	.	1	1.7%	2	3.3%	2	3.3%	5	1.7%
TONGUE	2	1.7%	.	.	.	.	.	.	2	0.7%
TRACHEA	1	0.8%	1	1.7%	2	3.3%	2	3.3%	6	2.0%
URETER	11	9.2%	2	3.3%	2	3.3%	4	6.7%	19	6.4%
URINARY BLADDER	3	2.5%	2	3.3%	.	.	1	1.7%	6	2.0%

Reference ID: 3158913

Chapter 2

Rat Study

2.1 Experimental design

This study consisted of two experiments, one each in female and male Crl:CD(SD) rats. Each experiment consisted of six groups of sixty animals. Three groups were control groups; two received the control article (a potato starch solution), and the third received deionized water. These substances were administered by gavage. The three remaing groups received daily doses of HMR1726 in an aqueous solution of potato starch, for doses of 0.5, 1.5, and 4 mg per kilogram of body weight. Again, these treatments were administered by gavage. All surviving female animals were sacrificed after 104 weeks. All surviving male animals were sacrificed after 97 weeks, except for the high dose males, who were sacrificed after 92 weeks.

Animals were checked twice daily (except weekends and holidays) for mortality. Animals were checked for clinical signs, and underwent palpation exams, once every month during the first year of the study, and twice a month subsequently.

After death, all animals underwent a full necroscopy.

2.2 Sponsor's analysis

2.2.1 Survival analysis

A series of log-rank tests were performed, comparing each treated group with each of the vehicle control groups, and the combined vehicle control group.

No significant dose-related survival effects were noted in the female rat experiment. However, among the males rate, a trend of increasing mortality was noted ($p = 0.005$ using the combined control, $p = 0.014$ using the first vehicle control group and $p = 0.033$ using the second vehicle control group), and both the mid and high dose groups were found to have significantly higher mortality than both the combined vehicle control group ($p = 0.032$ and $p = 0.011$ respectively), and than the first vehicle control group ($p = 0.050$ and $p = 0.016$ respectively).

2.2.2 Tumor analysis

A modified Peto test [6] was used with time intervals separated at 50 weeks, 80 weeks, and sacrifice.

Among males, the only worrisome finding was for adenomas of the pars distalis. Using the combined vehicle control, both the test of trend ($p = 0.0017$) and the pairwise comparisons between all three treated groups (low, mid, and high) were significant ($p = 0.0026$, $p = 0.0330$, and $p = 0.0004$ respectively). When only the first vehicle control group was used, the results were even more striking: $p = 0.0014$ for the test of trend, and $p = 0.0023$, $p = 0.0421$ and $p = 0.0002$ for the pair wise tests (low, mid, and high respectively). The comparisons with the second vehicle control were not significant. except for the pairwise test with the high dose group ($p = 0.0195$).

Reference ID: 3158913

Among female rats, a significant treatment-related trend was noted for C-cell adenomas. When the combined vehicle control was used, the test of trend yielded a p-value of 0.0058 and the comparisons with control of the mid and high groups yielded p-values of 0.0299 and 0.0087 respectively. The tests did not yield significant results when conducted using the first vehicle control group, but did yidle similar results when the second vehicle control group was used ($p = 0.0038$ for the test of trend, $p = 0.0282$ for the mid-control comparison, and $p = 0.0056$ for the high to control comparison.

Somewahat surprisingly, after reporting these findings, the sponsor concludes:

> There were no statistically significant increases at the 2.5% level (trend test using pooled vehicle controls or both the individual vehicle control groups) in the onset rates of observable tumors in males or females.

2.3 Data analysis

2.3.1 Survival analysis

The Kaplan-Meier survival plots are shown as figures 2.1 and 2.2. The numbers and proportions of animals surviving to various times are presented in table 2.1. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table 2.2, and the results of log-rank survival tests comparing the treated groups with the combined vehicle control group are presented in table 2.3.

Figure 2.1

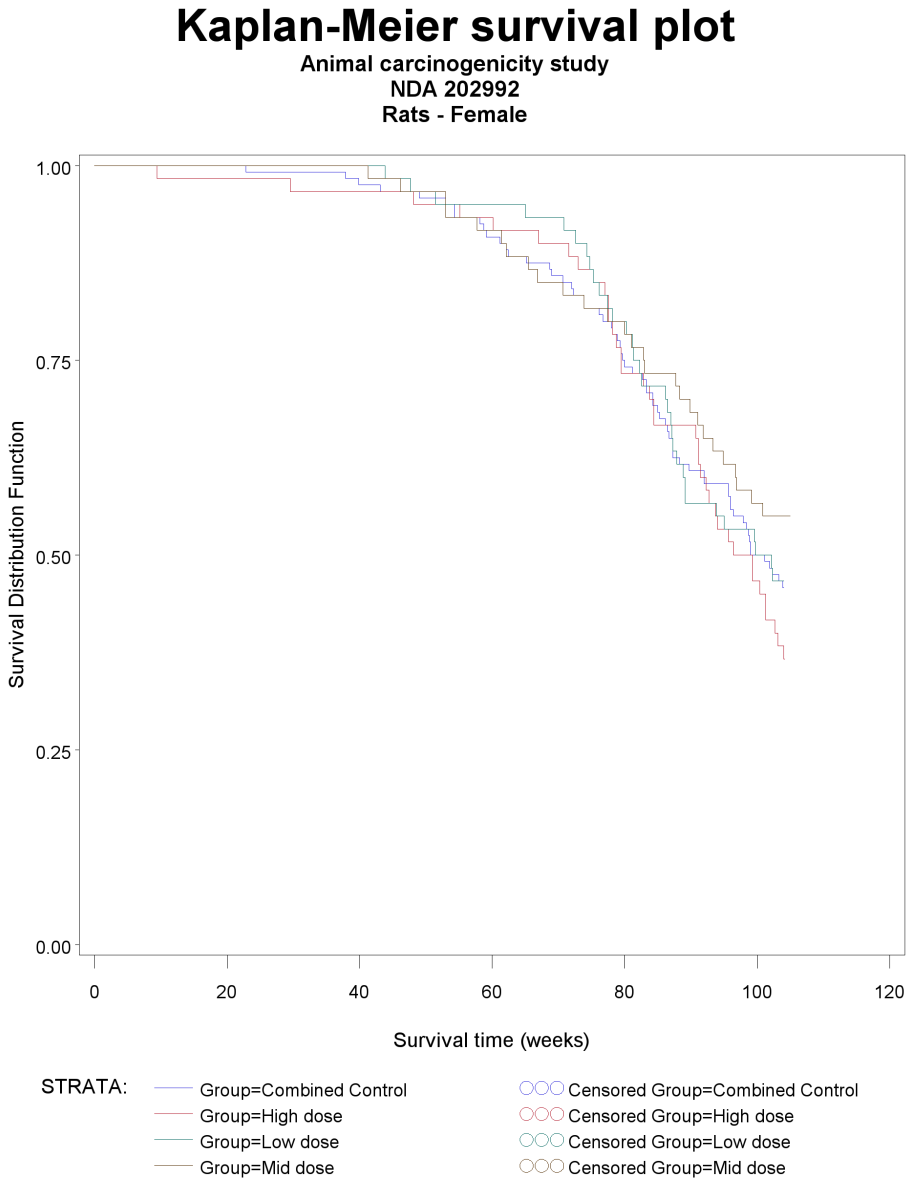
Kaplan-Meier survival plot
Animal carcinogenicity study
NDA 202992
Rats - Female
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
120
Survival time (weeks)
STRATA:
Group=Combined Control
Group=High dose
Group=Low dose
Group=Mid dose
Censored Group=Combined Control
Censored Group=High dose
Censored Group=Low dose
Censored Group=Mid dose

Figure 2.2

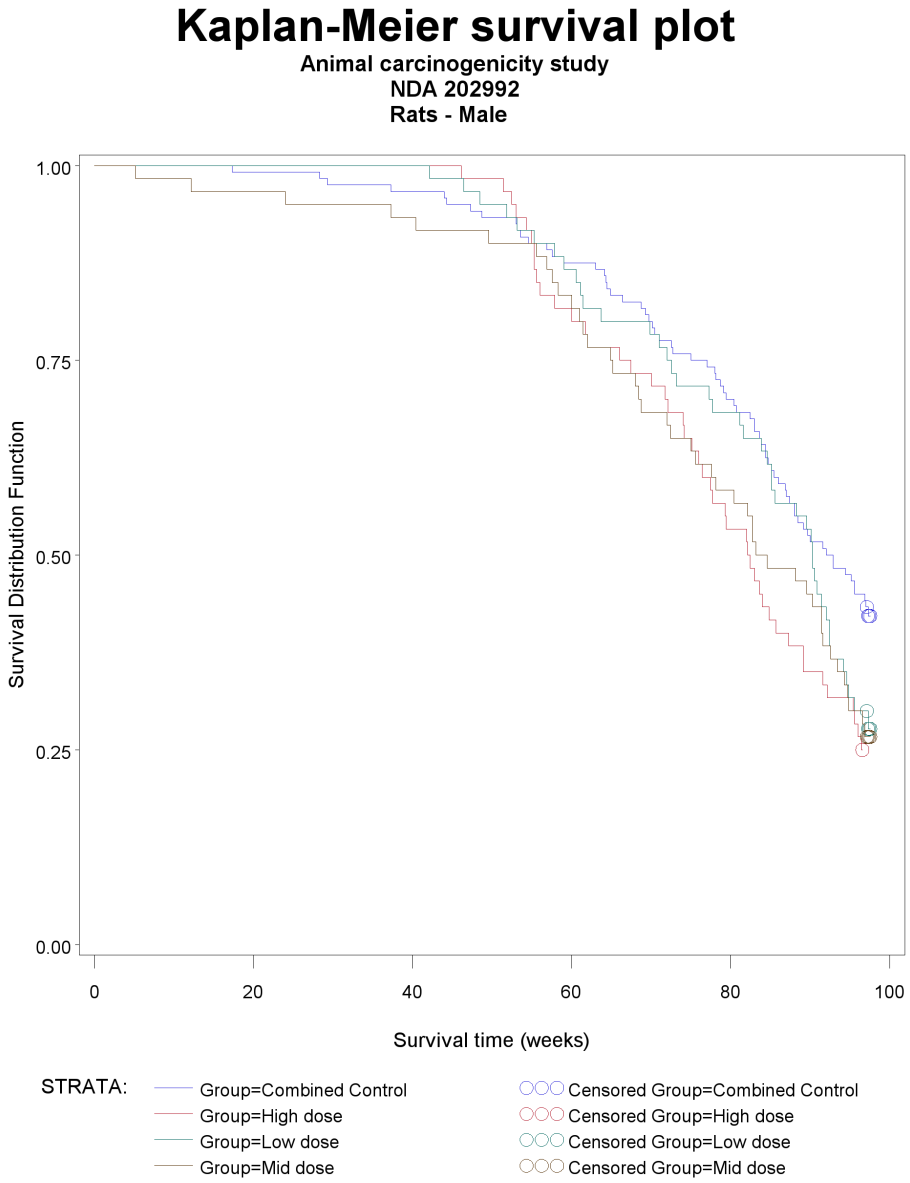
Kaplan-Meier survival plot
Animal carcinogenicity study
NDA 202992
Rats - Male
Survival Distribution Function
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
100
Survival time (weeks)
STRATA:
Group=Combined Control
Group=High dose
Group=Low dose
Group=Mid dose
Censored Group=Combined Control
Censored Group=High dose
Censored Group=Low dose
Censored Group=Mid dose

Table 2.1

Survival rates at key times
NDA 202992
Animal carcinogenicity study
Rats

Species and Sex	*Dose Group*	*Dose (mg per kg)*	*Number at start*	*Number alive after 52 weeks*	*Proportion alive after 52 weeks*	*Number alive after 78 weeks*	*Proportion alive after 78 weeks*	*Number alive after 90 weeks*	*Proportion alive after 90 weeks*	*Number alive at termination*	*Proportion alive at termination*
Rats - Female	Combined Control	0	120	115	96%	96	80%	73	61%	55	46%
	Low dose	0.5	60	57	95%	49	82%	34	57%	28	47%
	Mid dose	1.5	60	58	97%	48	80%	41	68%	33	55%
	High dose	4	60	57	95%	48	80%	40	67%	23	38%
Rats - Male	Combined Control	0	120	112	93%	89	74%	63	53%	0	0.0%
	Low dose	0.5	60	56	93%	41	68%	32	53%	0	0.0%
	Mid dose	1.5	60	54	90%	36	60%	27	45%	0	0.0%
	High dose	4	60	58	97%	34	57%	21	35%	0	0.0%

Commentry Inspection of the Kaplan-Meier plots reveals no sign of a dose related effect on mortality in the female rat experiment. Among the male rats, ther edoes appear to be some slight separation of the curves, with the mid and high dose groups experiencing a slightly higher mortality rate than the low dose and combined control groups. The log rank tests of survival confirm these observations; there is no significant result among the female rats, but among the male rats there is clear evidence of a dose related trend ($p = 0.0042$).

After these results, it is no surprise that hen individual treated groups are compared with the combined vehicle control, there are no significant results to report from the female rat experiment, but that among male rats, both the mid and high dose groups exhibited significantly higher mortality than the combined vehicle control group ($p = 0.0128$ and $p = 0.0039$) respectively. Additionally, the low dose male group also experienced a near-significant ($p = 0.0507$) increase in mortality compared to the control groups.

In conclusion, there is clear evidence of a dose related mortality effect in the male rats, even at the mid dose level, but not in the female rats.

Comparison of control groups Kaplan-Meier plots of the control groups are shown as figures 2.3 and 2.4. The results of log-rank tests of survival between the control groups are presented in table 1.4.

The Kaplan-Meier plot for female rats appears to show a higher mortality rate in the second control group than in the first, but this effect is not quite statistically significant ($p = 0.0554$). There is no such disparity among the male vehicle control groups ($p = 0.8528$).

2.3.2 Tumor analysis

Endpoints

As in the mouse study, organs have been classed as either primary or secondary (see Section 1.3.2). The lists of organs adduced to be primary are presented in tables 2.4 and 2.5. Secondary organs in the male and female rat experiments are presented in tables 2.6 and 2.7 respectively.

The same customized endpoints have been analyzed as were considered in the mouse study (see table 1.9).

It is noteworthy that "systemic neoplasm" is considered a secondary organ type in this study. This means that animals did not undergo routine histopathologic analysis testing for lymphomas, histioctytic sarcomas, or other systemic tumors, and that the reported cases of such tumors were detected only incidentally.

Table 2.2

Log-rank tests of survival
NDA 202992
Animal carcinogenicity study
Rats

Sex	*Test of homogeneity: chi squared statistic*	*Test of homogeneity: degrees of freedom*	*Number of groups*	*Test of homogeneity: p-value*	*Test of trend (two tailed): p-value*	*Test of trend (one tailed): p-value*
Female	2.9460	3	4	0.4000	0.5211	0.2605
Male	8.9479	3	4	0.0300	0.0084	0.0042

Table 2.3

Pairwise comparisons (log-rank) of survival between treated groups and controls
NDA 202992
Animal carcinogenicity study
Rats

Species and Sex	*Quantity*	*Low dose*	*Mid dose*	*High dose*
Rats - Female	Chi squared test statistic	0.0045	0.8962	0.2373
	p-value of comparison with control	0.9463	0.3438	0.6262
Rats - Male	Chi squared test statistic	3.8179	6.1997	8.3413
	p-value of comparison with control	0.0507	0.0128	0.0039

Figure 2.3: Survival curves for control groups (female rat experiment)

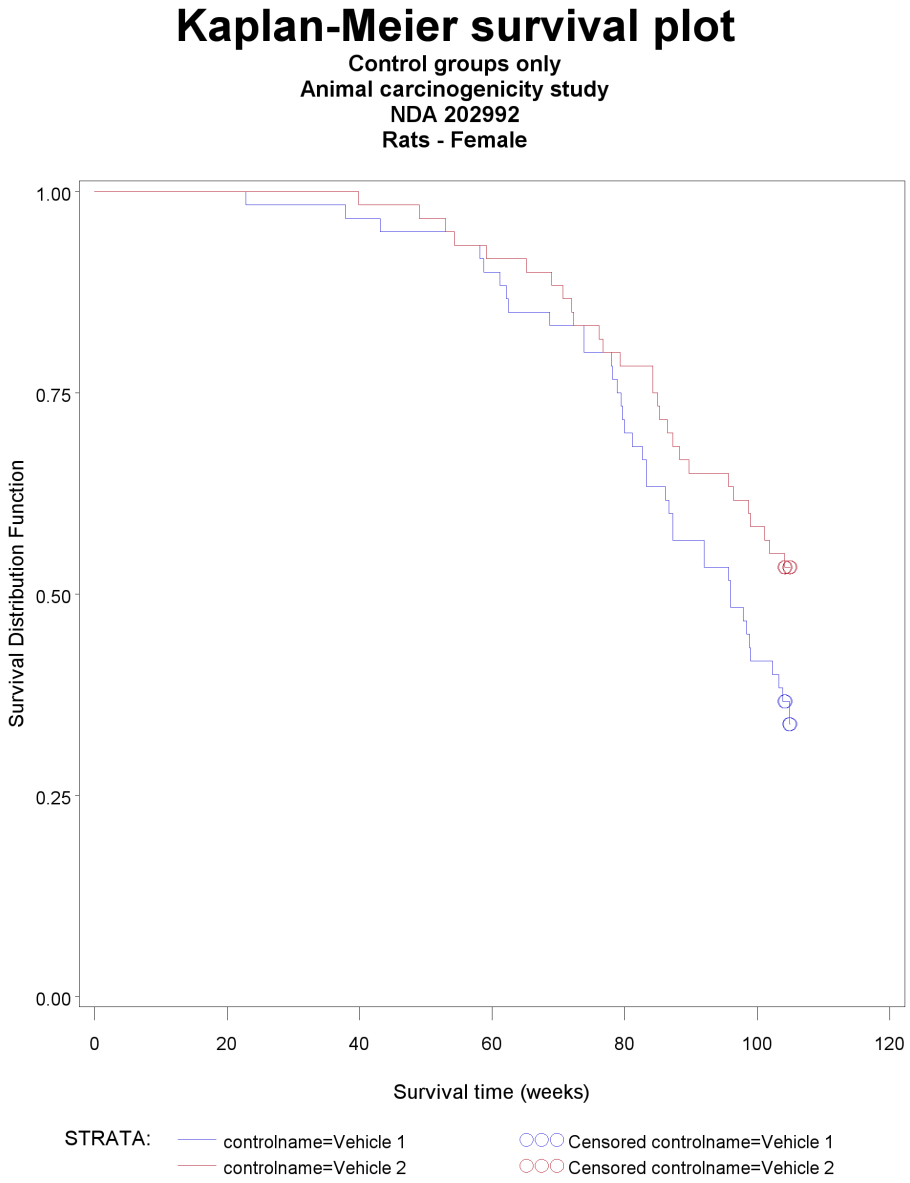

Figure 2.4: Survival curves for control groups (male rat experiment)

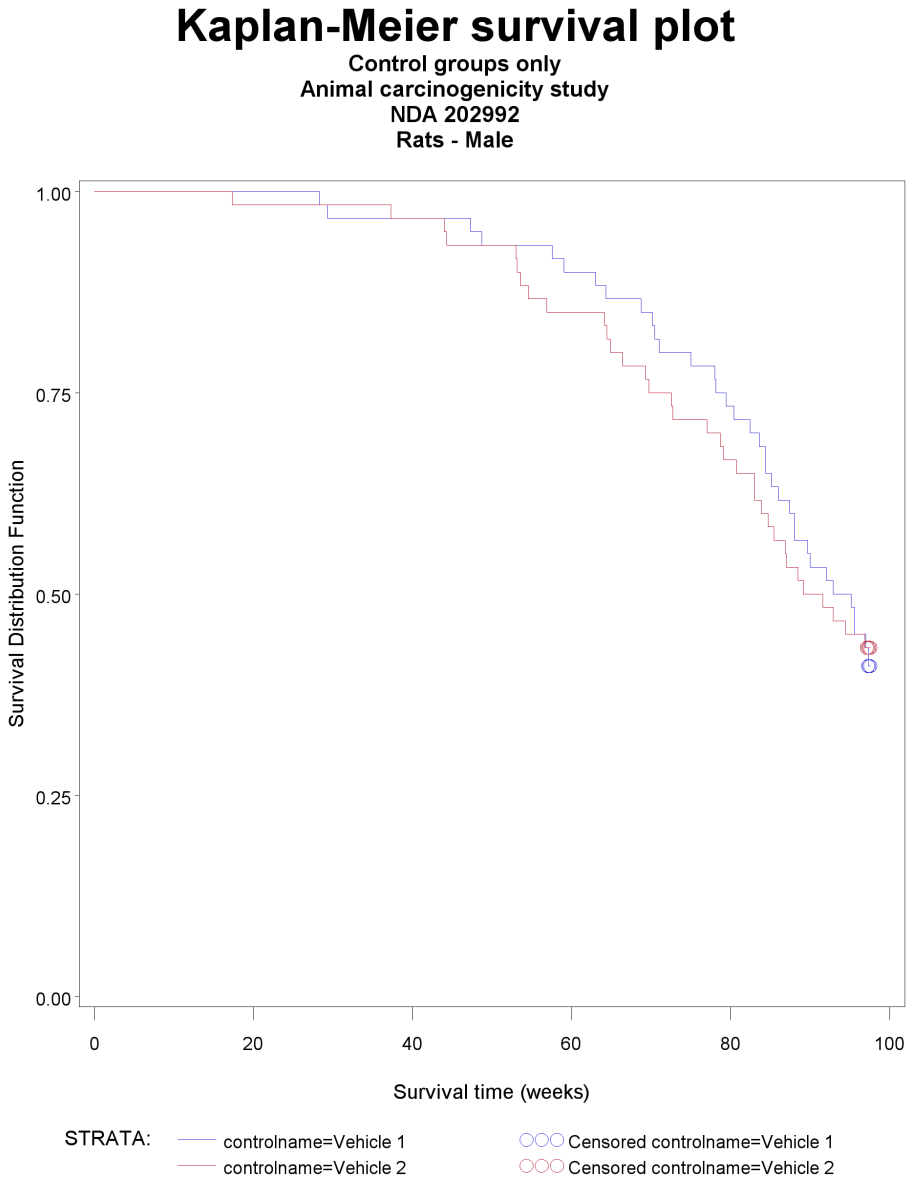

Table 2.4

Primary organs in study of female rats
NDA 202992
Animal carcinogenicity study

Organ or tissue name
ADRENAL GLAND
AORTA
BONE MARROW: FEMUR
BONE MARROW: STERN
BONE: FEMUR
BONE: STERNUM
BRA N
CLITORAL GLAND
EYE
HARDERIAN GLAND
HEART
INTEST NE: COLON
INTEST NE: DUODENU
INTEST NE: JEJUNUM
JOINT: FEMOROT BIA
KIDNEY
LACRIMAL GLAND
LIVER
LN: MESENTERIC
LN: SUBMANDIBULAR
LYMPH NODE
M: QUADRICEPS
MAMMARY GLAND
NASAL TISSUE
NERVE: OPTIC
NERVE: SCIATIC
OVARY
OVIDUCT
PANCREAS
PARATHYROID GLAND
PITUITARY GLAND
SALIV.GLD: MAND B.
SALIV.GLD: PAROTID
SALIV.GLD: SUBLIN.
SKIN
SPINAL CORD: CERVI
SPINAL CORD: LUMBA
SPINAL CORD: THORA

Primary organs in study of female rats
NDA 202992
Animal carcinogenicity study

Organ or tissue name
SPLEEN
THYMUS
THYROID GLAND
TONGUE
URETER
URINARY BLADDER
UTERUS: BODY/HORNS
UTERUS: CERVIX
VAGINA

Reference ID: 3158913

Table 2.5

Primary organs in study of male rats
NDA 202992
Animal carcinogenicity study

Organ or tissue name
ADRENAL GLAND
BONE MARROW: FEMUR
BONE: FEMUR
BRA N
ESOPHAGUS
EYE
HARDERIAN GLAND
HEART
INTEST NE: COLON
INTEST NE: GALT
INTEST NE: ILEUM
INTEST NE: JEJUNUM
JOINT: FEMOROT BIA
KIDNEY
LACRIMAL GLAND
LIVER
LN: MEDIAST NAL
LN: MESENTERIC
LN: SUBMANDIBULAR
LUNG/BRONCHI
M: QUADRICEPS
MAMMARY GLAND
NASAL TISSUE
NERVE: OPTIC
NERVE: SCIATIC
PANCREAS
PARATHYROID GLAND
PITUITARY GLAND
PREPUTIAL GLAND
PROSTATE GLAND
SALIV.GLD: MAND B.
SALIV.GLD: PAROTID
SALIV.GLD: SUBLIN.
SKIN
SPINAL CORD: CERVI
SPINAL CORD: LUMBA
SPINAL CORD: THORA
STOMACH

Primary organs in study of male rats
NDA 202992
Animal carcinogenicity study

Organ or tissue name
TESTIS
THYMUS
THYROID GLAND
TONGUE
TRACHEA
URETER
URINARY BLADDER

Reference ID: 3158913

Table 2.6

Secondary organs in study of female rats
NDA 202992
Animal carcinogenicity study

Organ or tissue name
BODY CAV: ABDOMINA
BONE: JAW
BONE: SKULL
LN: ILIAC
MESENTERIC TISSUE
NOSE
SKELETAL MUSCLE
SYSTEMIC NEOPLASM
TAIL

Reference ID: 3158913

Table 2.7

Secondary organs in study of male rats
NDA 202992
Animal carcinogenicity study

Organ or tissue name
BODY CAV: ABDOMINA
BONE: JAW
BONE: SKULL
LN: ILIAC
MESENTERIC TISSUE
NOSE
SKELETAL MUSCLE
SYSTEMIC NEOPLASM
TAIL

Reference ID: 3158913

Statistical procedure

The same statistical procedures are used to assess tumor incidence in rats are were used in mice (see Section 1.3.2). Note that the critical p-values used to determine significance are presented in table 1.10.

Noteworthy results

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables 2.8 (female rats) and 2.9 (male rats). The results of analyses of customized endpoints (see table 1.9) are presented in tables 2.10 and 2.11.

Individual tumor types in female rats for which tests yielding p-values below 0.05 were conducted are presented in table 2.12, which is excerpted from table 2.8. Combination tumor types for which tests yielding p-values below 0.05 were conducted are presented in table 2.14, which is excerpted from table 2.10. Individual tumor types in male rats for which tests yielding p-values below 0.05 were conducted are presented in table 2.13, which is excerpted from table 2.9. Combination tumor types for which tests yielding p-values below 0.05 were conducted are presented in table 2.15, which is excerpted from table 2.11.

Incidence rates for tumors found in secondary organs have not been analyzed statistically. Count data for such tumors are presented in table 2.16.

Thyroid tumors The data from the female rat experiment show an indication of an increasing trend incidence of C-cell adenomas; the survival adjusted incidence rate is 15% in the combined vehicle control group, 20% in the low dose group, 28% in the mid dose group, and 31% in the high dose group. Although the test of trend, the comparison between the mid dose group and the control group, and the comparison between the high dose group and the control all yield p-values below 0.05, none remain significant after making adjustments for multiple testing.

When all C-cell tumors are combined, the results are much the same, since the numbers of additional tumors (C-cell carcinomas) added to the analysis of C-cell adenomas is relatively small; two control animals and one high dose animal developed C-cell carcinomas but not C-cell adenomas[1].

When tested, the data from the male rat experiment also yielded a p-value below 0.05 for a thyroidal tumor type: the comparison of incidence of follicular cell adenomas between the low dose group yields a p-value of 0.0110. However, there is no indication of a dose related trend in the incidence, and neither the comparisons of the mid dose group or the high dose group with the control group yield any indication of a positive effect, so it is reasonable to conclude that this is a negative finding.

Hemangiomas and hemangiosarcomas in male rats Four male animals developed hemangiomas or hemangiosarcomas; two in the mid dose group and two in the high dose group (along with one in the water control group). The only reason for concern is the fact that p-value of the test of trend is 0.0266. This value narrowly misses significance for a rare tumor type, so it is appropriate to consider these data more carefully before concluding definitively that the finding is negative.

Pituitary tumors in male rats There is some indication of a possible dose related effect on the incidence of pars distalis adenomas in male rats. The survival adjusted incidence rates in the combined vehicle control group, the low dose group, the mid dose group and the high dose group are respectively 58%, 73%, 61%, and 75%. These are clearly common tumors, and none of the tests generate results that retain their significance after making an adjustment for multiple testing. This should be considered a nagative finding.

When all pars distalis tumors are combined, the results are the similar, as the numbers of pars distalis carcinomas are swamped by the adenomas.

[1] One additional female rat (a mid dose animal — number 684) also developed a C-cell carcinoma, but since this animal was also diagnosed as having a C-cell adenoma, it was already included in the analysis.

Sarcomas (NOS) and fibrosarcomas of the skin in female rats Five female rats developed fibrosarcomas or sarcomas (NOS) of the skin (collectively this endpoint includes all sarcomas of the skin except hemangiosarcomas); one in the combined vehicle control group, one in the low dose group, and the remaining three in the high dose group. The test of trend yields a p-value of 0.0447, but this does not remain significant after making an adjustment for multiple testing. The comparison between the high dose group and the combined vehicle control group yields a p-value of 0.1053. There is no reason to consider this a positive finding.

Astrocytomas in male rats Five male rats developed astrocytomas; two in the combined vehicle control group (for a survial adjusted incidence rate of 2.8%), and three in the high dose group (for a survival asjusted incidence rate of 9.7%). (In addition, one animal in the water control group developed an astrocytoma). The test of trend yields a value of $p = 0.0449$, which does not remain significant after making an adjustment for multiple testing. Additionally, the pairwise comparison between the high dose group and the control group yields a value of $p = 0.1537$. Taken together, there is no reason to consider this a positive finding.

2.3.3 Analysis of unexamined and autolytic organs

Unexamined animals

No animals have been reported as completely unexamined.

Organs reported autolytic

The numbers of organs found in female rats to be autolytic to the extent that analysis of collected tiussue was not possible are presented in table 2.17. The numbers of such organs found in male rats are presented in table 2.18.

The levels of autolysis are very low, and should not be viewed as having a negative impact on the study.

Organs reported as unexamined

The numbers of animals with organs reported as being unexamined are presented in tables 2.19 and 2.20. While a number of different organs are mentioned in these tables, most have been reported as unexamined in only a few animals. The exceptions are the secondary organs, notably including "systemic neoplasm", and, in the case of the male rats, the thymus. While only 7.3% of the male animals had their thymus reported as unexamined, these animals are disproportionaly concentrated in the high dose group, where 13% (8 animals) did not have their thymus examined. This level is sufficiently high that some skepticism concerning the negative findings for tumors of the thymus is warrented.

2.3.4 Tables of results

Table 2.8

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLAND	Adenoma: cortex	P-value of test of trend or comparison	.2356	.2585	.6689	.2585
		Number of animals reported with tumor	4	4	2	4
		Poly-3 adjusted incidence rate	4.6%	8.9%	4.4%	9.1%
		95% CI for poly-3 adjusted incidence rate (%)	(1.25,11.4)	(2.48,21.7)	(0.53,15.1)	(2.48,21.7)
		Poly-3 adjusted number of animals at risk	87.5	44.9	45.6	44.0
	Carcinoma: cortex	P-value of test of trend or comparison	.0992	1	1	.2541
		Number of animals reported with tumor	1	0	0	2
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	4.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0,7.9)	(0.56,15.8)
		Poly-3 adjusted number of animals at risk	88.0	44.5	45.6	43.8
	Pheochromocytoma·benign	P-value of test of trend or comparison	.9261	.4120	1	1
		Number of animals reported with tumor	2	2	0	0
		Poly-3 adjusted incidence rate	2.3%	4.5%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.28,8.1)	(0.54,15.5)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	88.0	44.6	45.6	43.4
	Pheochromocytoma·malignant	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	3	0	0	0
		Poly-3 adjusted incidence rate	3.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.71,9.7)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	87.6	44.5	45.6	43.4
BONE: STERNUM	Osteoma	P-value of test of trend or comparison	.1963			.3308
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.0)	(0,7.9)	(0.06,12.3)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
BRAIN	Astrocytoma·benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	4	0	0	0
		Poly-3 adjusted incidence rate	4.6%	0.0%	0.0%	0.0%

Reference ID: 3158913

Table 2.8

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(1.25,11.4)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	87.5	44.5	45.6	43.0
CLITORAL GLAND	Tumor-benign: basal cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.6)	(0,8.4)	(0,8.8)
		Poly-3 adjusted number of animals at risk	78.0	41.0	42.1	40.6
HEART	Schwannoma-benign: endocardial	P-value of test of trend or comparison	.1215		.3409	.3359
		Number of animals reported with tumor	0	0	1	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.0)	(0.06,11.8)	(0.06,12.0)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	44.4
INTESTINE: COLON	Lipoma	P-value of test of trend or comparison	.3991		.3409	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.0)	(0.06,11.8)	(0,8.4)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	42.4
INTESTINE: DUODENU	Adenoma	P-value of test of trend or comparison	.1963			.3308
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.0)	(0,7.9)	(0.06,12.3)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.9
	Fibroma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
INTESTINE: JEJUNUM	Leiomyoma	P-value of test of trend or comparison	1	1	1	1

Reference ID: 3158913

Table 2.8

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
KIDNEY	Lipoma: renal	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	88.0	44.5	45.6	43.4
LIVER	Adenoma: hepatocyte	P-value of test of trend or comparison	.2707	1	.5673	.5538
		Number of animals reported with tumor	1	0	1	1
		Poly-3 adjusted incidence rate	1.1%	0.0%	2.2%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0.06,11.8)	(0.06,12.3)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
	Cholangioma	P-value of test of trend or comparison	.4018		.3409	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
LN: MESENTERIC	Histiocytoma: fibrous-malignant	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
MAMMARY GLAND	Adenocarcinoma	P-value of test of trend or comparison	.4198	.8403	.4119	.5963
		Number of animals reported with tumor	18	7	11	9
		Poly-3 adjusted incidence rate	20%	15%	23%	20%

Reference ID: 3158913

Table 2.8

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(12.3,30.1)	(6.07,28.3)	(12,38.0)	(9.36,34.6)
		Poly-3 adjusted number of animals at risk	89.5	47.4	47.1	45.2
	Adenoma	P-value of test of trend or comparison	.9424	.3945	.2975	.9856
		Number of animals reported with tumor	9	6	7	1
		Poly-3 adjusted incidence rate	10%	13%	15%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(4.84,18.9)	(5.05,27.4)	(6.2,28.9)	(0.06,12.3)
		Poly-3 adjusted number of animals at risk	86.9	44.9	46.7	43.4
	Fibroadenoma	P-value of test of trend or comparison	.9660	.8313	.6434	.9837
		Number of animals reported with tumor	57	26	28	19
		Poly-3 adjusted incidence rate	58%	52%	56%	41%
		95% CI for poly-3 adjusted incidence rate (%)	(47.8,68.7)	(36.6,66.3)	(41.3,71.2)	(26.4,56.8)
		Poly-3 adjusted number of animals at risk	97.5	50.4	49.8	46.1
NASAL TISSUE	Invasion: squamous cell carcinom	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0,8.0)	(0,8.2)
		Poly-3 adjusted number of animals at risk	88.0	44.5	44.6	43.0
OVARY	Tumor·benign: granulosa cell	P-value of test of trend or comparison	.4018		.3409	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
PANCREAS	Adenoma: acinar-islet cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	87.5	44.5	45.6	43.4
	Adenoma: islet cell	P-value of test of trend or comparison	.8771	.1026	.4210	1

Reference ID: 3158913

Table 2.8

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	2	4	2	0
		Poly-3 adjusted incidence rate	2.3%	8.9%	4.4%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.28,8.1)	(2.42,21.2)	(0.53,15.1)	(0,8.2)
		Poly-3 adjusted number of animals at risk	87.4	45.1	45.6	43.4
	Lipoma	P-value of test of trend or comparison	.4018		.3409	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
	Sarcoma: not otherwise specified	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
PARATHYROID GLAND	Adenoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0,8.6)	(0,8.4)	(0,8.6)
		Poly-3 adjusted number of animals at risk	83.1	41.8	42.4	41.0
PITUITARY GLAND	Adenoma: pars·distalis	P-value of test of trend or comparison	.9832	.9879	.7013	.9970
		Number of animals reported with tumor	83	33	41	27
		Poly-3 adjusted incidence rate	77%	61%	74%	56%
		95% CI for poly-3 adjusted incidence rate (%)	(67,84.4)	(45.9,74.1)	(59.7,85.3)	(40.2,70.5)
		Poly-3 adjusted number of animals at risk	108	54.3	55.1	48.6
	Adenoma: pars·intermedia	P-value of test of trend or comparison	.3587	.2610	.0511	.5469
		Number of animals reported with tumor	1	2	4	1
		Poly-3 adjusted incidence rate	1.1%	4.5%	8.5%	2.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0.54,15.5)	(2.32,20.4)	(0.06,12.6)

Reference ID: 3158913

Table 2.8

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	87.4	44.9	47.0	42.3
	Carcinoma: pars-distalis	P-value of test of trend or comparison	.5818	.7099	.8724	.6856
		Number of animals reported with tumor	7	3	2	3
		Poly-3 adjusted incidence rate	7.7%	6.6%	4.3%	6.8%
		95% CI for poly-3 adjusted incidence rate (%)	(3.15,15.4)	(1.37,18.3)	(0.52,14.8)	(1.43,19.1)
		Poly-3 adjusted number of animals at risk	91.0	45.4	46.1	43.9
SALIV.GLD: MANDIB.	Adenoma	P-value of test of trend or comparison	.4037		.3435	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	86.2	44.4	45.6	43.0
SALIV.GLD: SUBLIN.	Lipoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.3)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	86.2	44.4	45.6	43.0
SKIN	Carcinoma: squamous cell	P-value of test of trend or comparison	.6905	.5608	.5676	1
		Number of animals reported with tumor	1	1	1	0
		Poly-3 adjusted incidence rate	1.2%	2.3%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.4)	(0.06,12.3)	(0.06,12.0)	(0,8.4)
		Poly-3 adjusted number of animals at risk	85.9	43.8	44.9	42.4
	Fibroma	P-value of test of trend or comparison	.7668	.7139	.4257	1
		Number of animals reported with tumor	2	1	2	0
		Poly-3 adjusted incidence rate	2.3%	2.3%	4.4%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.28,8.1)	(0.06,12.0)	(0.53,15.1)	(0,8.4)
		Poly-3 adjusted number of animals at risk	86.3	44.1	45.0	42.4
	Hemangioma	P-value of test of trend or comparison	.6434	1	.5676	1
		Number of animals reported with tumor	1	0	1	0

Reference ID: 3158913

Table 2.8

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	1.2%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.4)	(0,8.2)	(0.06,12.0)	(0,8.4)
		Poly-3 adjusted number of animals at risk	85.4	43.5	44.6	42.4
	Lipoma	P-value of test of trend or comparison	.4019		.3411	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.2)	(0.06,12.0)	(0,8.4)
		Poly-3 adjusted number of animals at risk	85.4	43.5	44.6	42.4
	Papilloma: squamous cell	P-value of test of trend or comparison	.4047		.3462	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.2)	(0.06,11.8)	(0,8.4)
		Poly-3 adjusted number of animals at risk	85.4	43.5	45.4	42.4
	Rhabdomyosarcoma	P-value of test of trend or comparison	.6028	.3359		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0.06,12.3)	(0,8.0)	(0,8.4)
		Poly-3 adjusted number of animals at risk	85.4	43.5	44.6	42.4
	Sarcoma: fibrosarcoma	P-value of test of trend or comparison	.1440	.5608	1	.2540
		Number of animals reported with tumor	1	1	0	2
		Poly-3 adjusted incidence rate	1.2%	2.3%	0.0%	4.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.4)	(0.06,12.3)	(0,8.0)	(0.57,16.2)
		Poly-3 adjusted number of animals at risk	85.4	43.7	44.6	42.6
	Sarcoma: hemangiosarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.3)	(0,8.2)	(0,8.0)	(0,8.4)
		Poly-3 adjusted number of animals at risk	86.2	43.5	44.6	42.4

Table 2.8

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Sarcoma: not otherwise specified	P-value of test of trend or comparison	.1963			.3307
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.2)	(0,8.0)	(0.06,12.6)
		Poly-3 adjusted number of animals at risk	85.4	43.5	44.6	42.5
THYMUS	Hibernoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0,8.4)	(0,8.4)	(0,8.8)
		Poly-3 adjusted number of animals at risk	83.8	42.4	42.9	40.1
	Thymoma·benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0,8.4)	(0,8.4)	(0,8.8)
		Poly-3 adjusted number of animals at risk	83.3	42.4	42.9	40.1
THYROID GLAND	Adenoma: C-cell	P-value of test of trend or comparison	.0154	.2874	.0487	.0233
		Number of animals reported with tumor	13	9	13	14
		Poly-3 adjusted incidence rate	15%	20%	28%	31%
		95% CI for poly-3 adjusted incidence rate (%)	(7.92,23.7)	(9.36,34.6)	(15.6,43.5)	(17.7,46.6)
		Poly-3 adjusted number of animals at risk	89.0	45.5	46.3	45.6
	Carcinoma: C-cell	P-value of test of trend or comparison	.4230	1	.7201	.7003
		Number of animals reported with tumor	2	0	1	1
		Poly-3 adjusted incidence rate	2.3%	0.0%	2.2%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.27,8.0)	(0,8.0)	(0.05,11.5)	(0.06,12.3)
		Poly-3 adjusted number of animals at risk	88.2	44.4	46.1	43.0
UTERUS: BODY/HORNS	Carcinoma: adenosquamous	P-value of test of trend or comparison	.4055		.3462	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%

Reference ID: 3158913

Table 2.8

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	85.6	44.5	45.7	43.4
	Polyp: endometrial stroma	P-value of test of trend or comparison	.3521	.6622	.5473	.4673
		Number of animals reported with tumor	12	6	7	7
		Poly-3 adjusted incidence rate	14%	13%	15%	16%
		95% CI for poly-3 adjusted incidence rate (%)	(7.42,23.4)	(4.83,26.3)	(6.07,28.3)	(6.64,30.7)
		Poly-3 adjusted number of animals at risk	85.8	46.2	47.6	43.6
UTERUS: CERVIX	Carcinoma: squamous cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.4)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	85.8	44.5	45.6	43.4
VAGINA	Carcinoma: squamous cell	P-value of test of trend or comparison	.6083	.3411		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.2%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0.06,12.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	85.6	45.0	45.6	43.4
	Polyp: vagina	P-value of test of trend or comparison	.3563	1	1	.5573
		Number of animals reported with tumor	1	0	0	1
		Poly-3 adjusted incidence rate	1.2%	0.0%	0.0%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.3)	(0,8.0)	(0,7.9)	(0.06,12.3)
		Poly-3 adjusted number of animals at risk	86.4	44.5	45.6	43.9
	Tumor-benign: granular cell	P-value of test of trend or comparison	.8915	1	.8217	1
		Number of animals reported with tumor	3	0	1	0
		Poly-3 adjusted incidence rate	3.5%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.73,10.0)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	85.9	44.5	45.8	43.4

Table 2.9

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLAND	Adenoma: cortex	P-value of test of trend or comparison	.8540	1	.7673	1
		Number of animals reported with tumor	3	0	1	0
		Poly-3 adjusted incidence rate	4.2%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.86,11.7)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	72.1	33.8	31.0	29.8
	Carcinoma: cortex	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.2	33.8	30.7	29.8
	Pheochromocytoma·benign	P-value of test of trend or comparison	.8710	.8801	.9642	.9086
		Number of animals reported with tumor	16	5	3	4
		Poly-3 adjusted incidence rate	21%	14%	9.6%	13%
		95% CI for poly-3 adjusted incidence rate (%)	(12.7,32.7)	(4.67,30.3)	(1.98,25.8)	(3.51,29.8)
		Poly-3 adjusted number of animals at risk	75.0	35.7	31.2	31.9
	Pheochromocytoma·malignant	P-value of test of trend or comparison	.3992	.6951	.3544	.6570
		Number of animals reported with tumor	2	1	2	1
		Poly-3 adjusted incidence rate	2.8%	2.9%	6.4%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.8)	(0.07,15.3)	(0.77,21.4)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	71.3	34.1	31.1	30.3
BRAIN	Astrocytoma·benign	P-value of test of trend or comparison	.0449	1	1	.1537
		Number of animals reported with tumor	2	0	0	3
		Poly-3 adjusted incidence rate	2.8%	0.0%	0.0%	9.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.8)	(0,10.6)	(0,11.6)	(2.04,26.5)
		Poly-3 adjusted number of animals at risk	71.1	33.8	30.7	30.9
	Carcinoma: Pineal Gland	P-value of test of trend or comparison	.5706	.3269		
		Number of animals reported with tumor	0	1	0	0

Reference ID: 3158913

Table 2.9

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	0.0%	2.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.3)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.2	34.1	30.7	29.8
	Ependymoma·benign	P-value of test of trend or comparison	.1790			.2929
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	70.2	33.8	30.7	30.0
	Granular cell tumor	P-value of test of trend or comparison	.1590	1	1	.3474
		Number of animals reported with tumor	2	0	0	2
		Poly-3 adjusted incidence rate	2.8%	0.0%	0.0%	6.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.9)	(0,10.6)	(0,11.6)	(0.79,22.1)
		Poly-3 adjusted number of animals at risk	70.8	33.8	30.7	30.2
	Meningioma·malignant	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.0	33.8	30.7	29.8
	Reticulosis·malignant	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.7)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.4	33.8	30.7	29.8
EYE	Invasion: squamous cell carcinom	P-value of test of trend or comparison	.3681		.3069	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.08,16.7)	(0,11.9)

Reference ID: 3158913

Table 2.9

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	70.8	33.8	31.5	29.2
	Schwannoma· benign	P-value of test of trend or comparison	.1790			.2929
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	70.8	33.8	30.7	29.4
HEART	Hemangioma	P-value of test of trend or comparison	.3681		.3069	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.8	33.8	31.2	29.8
	Schwannoma·malignant: endocardia	P-value of test of trend or comparison	.3681		.3069	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.8	33.8	31.1	29.8
INTESTINE: ILEUM	Adenocarcinoma	P-value of test of trend or comparison	.1790			.2929
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	70.8	33.8	30.7	30.0
KIDNEY	Adenoma: renal tubule	P-value of test of trend or comparison	.1840			.3000
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	70.8	33.8	30.7	30.2
	Liposarcoma: renal	P-value of test of trend or comparison	.6368	.1047		

Reference ID: 3158913

Table 2.9

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	0	2	0	0
		Poly-3 adjusted incidence rate	0.0%	5.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.7,19.7)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.8	34.2	30.7	29.8
LIVER	Adenoma: hepatocyte	P-value of test of trend or comparison	.3625	.5403	1	.5121
		Number of animals reported with tumor	1	1	0	1
		Poly-3 adjusted incidence rate	1.4%	2.9%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.7)	(0.07,15.8)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	71.0	34.0	30.7	30.6
	Carcinoma: hepatocyte	P-value of test of trend or comparison	.5132	.6951	1	.6570
		Number of animals reported with tumor	2	1	0	1
		Poly-3 adjusted incidence rate	2.8%	2.9%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.8)	(0.07,15.3)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	71.4	34.1	30.7	30.5
	Cholangioma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.7)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.0	33.8	30.7	29.8
	Hemangioma	P-value of test of trend or comparison	.3642		.3000	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.08,17.2)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.8	33.8	30.9	29.8
	Histiocytoma: fibrous·malignant	P-value of test of trend or comparison	.1790			.2929
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%

Reference ID: 3158913

Table 2.9

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	70.8	33.8	30.7	30.0
LUNG/BRONCHI	Metastasis: sarcoma·not otherwis	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.7)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.0	33.8	30.7	29.8
M: QUADRICEPS	Sarcoma: fibrosarcoma	P-value of test of trend or comparison	.3665		.3000	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.9)	(0.08,17.2)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.8	33.0	30.9	29.8
MAMMARY GLAND	Adenocarcinoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
		Poly-3 adjusted incidence rate	4.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.49,14.0)	(0,13.7)	(0,16.1)	(0,16.8)
		Poly-3 adjusted number of animals at risk	49.2	25.6	21.6	20.5
	Adenoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.3)	(0,13.7)	(0,16.1)	(0,16.8)
		Poly-3 adjusted number of animals at risk	48.0	25.6	21.6	20.5
	Fibroadenoma	P-value of test of trend or comparison	.9299	.7332	1	1
		Number of animals reported with tumor	2	1	0	0
		Poly-3 adjusted incidence rate	4.2%	3.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.5,14.3)	(0.09,19.6)	(0,16.1)	(0,16.8)
		Poly-3 adjusted number of animals at risk	48.2	26.1	21.6	20.5
NASAL TISSUE	Invasion: squamous cell carcinom	P-value of test of trend or comparison	.1790			.2929

Reference ID: 3158913

Table 2.9

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	70.8	33.8	30.7	30.0
PANCREAS	Adenocarcinoma: acinar cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.8	30.7	29.8
	Adenoma: acinar cell	P-value of test of trend or comparison	.5943	1	.5079	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0.08,17.2)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.7	33.8	30.8	29.8
	Adenoma: acinar-islet cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.7)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.0	33.8	30.7	29.8
	Adenoma: ductal cell	P-value of test of trend or comparison	.1840			.3000
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	70.8	33.8	30.7	30.2
	Adenoma: islet cell	P-value of test of trend or comparison	.7933	.8502	.4333	.9408
		Number of animals reported with tumor	7	2	4	1
		Poly-3 adjusted incidence rate	9.7%	5.8%	13%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(3.94,19.0)	(0.7,19.7)	(3.51,29.8)	(0.08,17.8)

Reference ID: 3158913

Table 2.9

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	72.3	34.5	31.7	30.0
	Carcinoma: islet cell	P-value of test of trend or comparison	.5132	.6951	1	.6570
		Number of animals reported with tumor	2	1	0	1
		Poly-3 adjusted incidence rate	2.8%	2.9%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.8)	(0.07,15.3)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	71.1	34.3	30.7	30.3
PARATHYROID GLAND	Adenoma	P-value of test of trend or comparison	.4243	1	.2565	.7607
		Number of animals reported with tumor	3	0	3	1
		Poly-3 adjusted incidence rate	4.3%	0.0%	10%	3.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0.89,12.2)	(0,10.9)	(2.04,26.5)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	69.2	32.3	30.0	29.6
PITUITARY GLAND	Adenoma: pars-distalis	P-value of test of trend or comparison	.0513	.0500	.3872	.0338
		Number of animals reported with tumor	51	34	25	34
		Poly-3 adjusted incidence rate	58%	73%	61%	75%
		95% CI for poly-3 adjusted incidence rate (%)	(46.4,68.4)	(57.4,85.7)	(44.5,77.3)	(58.9,87.1)
		Poly-3 adjusted number of animals at risk	88.4	46.8	40.8	45.6
	Adenoma: pars-intermedia	P-value of test of trend or comparison	.1423	.3204	.3000	.2929
		Number of animals reported with tumor	0	1	1	1
		Poly-3 adjusted incidence rate	0.0%	2.9%	3.2%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0.08,17.2)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	70.6	34.0	31.0	29.9
	Carcinoma: pars-distalis	P-value of test of trend or comparison	.7507	1	.6570	1
		Number of animals reported with tumor	2	0	1	0
		Poly-3 adjusted incidence rate	2.8%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.8)	(0,10.6)	(0.08,17.2)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.4	33.8	30.9	29.5
	Oligodendroglioma-benign	P-value of test of trend or comparison	.3681		.3069	
		Number of animals reported with tumor	0	0	1	0

Reference ID: 3158913

Table 2.9

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.6	33.8	31.0	29.5
PROSTATE GLAND	Adenocarcinoma	P-value of test of trend or comparison	.3681		.3069	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.8	33.8	31.3	29.8
SALIV.GLD: SUBLIN.	Adenoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.7)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.0	33.7	30.1	29.8
SKIN	Carcinoma: sebaceous cell	P-value of test of trend or comparison	.8171	.5491	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	1.4%	2.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.7)	(0.07,15.3)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.0	34.1	30.7	29.8
	Fibroma	P-value of test of trend or comparison	.9636	.8032	.4306	1
		Number of animals reported with tumor	9	3	5	0
		Poly-3 adjusted incidence rate	12%	8.7%	16%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(5.71,22.1)	(1.8,23.7)	(5.11,32.8)	(0,11.9)
		Poly-3 adjusted number of animals at risk	73.5	34.5	32.0	29.8
	Hemangioma	P-value of test of trend or comparison	.1840			.3000
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	70.8	33.8	30.7	30.2

Reference ID: 3158913

Table 2.9

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Histiocytoma: fibrous·malignant	P-value of test of trend or comparison	.6402	.5449	.5176	1
		Number of animals reported with tumor	1	1	1	0
		Poly-3 adjusted incidence rate	1.4%	2.9%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0.07,15.3)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.0	34.2	31.0	29.8
	Keratoacanthoma	P-value of test of trend or comparison	.8980	.5985	1	.9144
		Number of animals reported with tumor	6	3	0	1
		Poly-3 adjusted incidence rate	8.3%	8.7%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(3.08,17.3)	(1.8,23.7)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	72.3	34.4	30.7	30.0
	Lipoma	P-value of test of trend or comparison	.7275	.8584	1	.8271
		Number of animals reported with tumor	4	1	0	1
		Poly-3 adjusted incidence rate	5.6%	2.9%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(1.53,13.8)	(0.07,15.8)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	71.8	34.0	30.7	30.0
	Papilloma: squamous cell	P-value of test of trend or comparison	.9666	.7967	1	1
		Number of animals reported with tumor	3	1	0	0
		Poly-3 adjusted incidence rate	4.2%	2.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.87,11.9)	(0.07,15.3)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.9	34.5	30.7	29.8
	Sarcoma: fibrosarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	3	0	0	0
		Poly-3 adjusted incidence rate	4.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.86,11.7)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	72.1	33.8	30.7	29.8
	Sarcoma: hemangiosarcoma	P-value of test of trend or comparison	.3681		.3069	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%

Reference ID: 3158913

Table 2.9

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.8	33.8	31.6	29.8
	Tumor·benign: basal cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.2	33.8	30.7	29.8
SPINAL CORD: CERVI	Astrocytoma·benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.7	33.8	30.7	29.8
STOMACH	Leiomyoma:	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.8	30.7	29.8
TESTIS	Adenoma: Leydig cell	P-value of test of trend or comparison	.8769	.6815	.8182	.9408
		Number of animals reported with tumor	7	3	2	1
		Poly-3 adjusted incidence rate	9.7%	8.7%	6.4%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(3.94,19.0)	(1.8,23.7)	(0.77,21.4)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	72.4	34.5	31.0	30.0
	Seminoma·benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.8	33.8	30.7	29.8
THYMUS	Thymoma·benign	P-value of test of trend or comparison	.3510		.2842	

Reference ID: 3158913

Table 2.9

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.6%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.3)	(0,11.6)	(0.09,19.0)	(0,13.2)
		Poly-3 adjusted number of animals at risk	68.7	30.2	27.7	26.3
THYROID GLAND	Adenoma: C-cell	P-value of test of trend or comparison	.2136	.2744	.1657	.2649
		Number of animals reported with tumor	13	9	9	8
		Poly-3 adjusted incidence rate	17%	24%	27%	24%
		95% CI for poly-3 adjusted incidence rate (%)	(9.57,28.2)	(11.4,41.2)	(13.3,46.7)	(11.1,43.4)
		Poly-3 adjusted number of animals at risk	74.6	37.0	33.0	33.0
	Adenoma: follicular cell	P-value of test of trend or comparison	.7179	.0110	.3000	
		Number of animals reported with tumor	0	4	1	0
		Poly-3 adjusted incidence rate	0.0%	11%	3.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(3.11,26.7)	(0.08,17.2)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.3	35.7	30.7	29.8
	Carcinoma: C-cell	P-value of test of trend or comparison	.2409	.3902	.6570	.3421
		Number of animals reported with tumor	2	2	1	2
		Poly-3 adjusted incidence rate	2.8%	5.8%	3.3%	6.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.8)	(0.7,19.7)	(0.08,17.2)	(0.79,22.1)
		Poly-3 adjusted number of animals at risk	71.8	34.3	30.6	30.6
	Ganglioneuroma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
		Poly-3 adjusted incidence rate	2.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.9)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.7	33.8	30.4	29.8

Reference ID: 3158913

Table 2.10

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Adenomas and adenocarcinomas of the small intestine	P-value of test of trend or comparison	.1963			.3308
	Number of animals reported with tumor	0	0	0	1
	Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.0)	(0,7.9)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.9
Adenomas and carcinomas of the adrenal cortex	P-value of test of trend or comparison	.4363	.4530	.9571	.4530
	Number of animals reported with tumor	10	6	2	6
	Poly-3 adjusted incidence rate	11%	13%	4.4%	14%
	95% CI for poly-3 adjusted incidence rate (%)	(5.52,19.9)	(5.05,27.4)	(0.53,15.1)	(5.05,27.4)
	Poly-3 adjusted number of animals at risk	88.8	45.0	45.6	44.3
All lipomas	P-value of test of trend or comparison	.7401	.9192	.5540	.9153
	Number of animals reported with tumor	5	1	3	1
	Poly-3 adjusted incidence rate	5.7%	2.2%	6.6%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(1.87,12.9)	(0.06,12.0)	(1.37,18.3)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.6
All pheochromocytomas	P-value of test of trend or comparison	.9933	.7438	1	1
	Number of animals reported with tumor	5	2	0	0
	Poly-3 adjusted incidence rate	5.7%	4.5%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(1.85,12.8)	(0.54,15.5)	(0,7.9)	(0,8.2)
	Poly-3 adjusted number of animals at risk	88.1	44.6	45.6	43.4
Astrocytomas	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	4	0	0	0
	Poly-3 adjusted incidence rate	4.6%	0.0%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(1.25,11.4)	(0,8.0)	(0,7.9)	(0,8.2)
	Poly-3 adjusted number of animals at risk	87.5	44.5	45.6	43.4
Fibrosarcomas and Sarcomas (NOS) of the skin	P-value of test of trend or comparison	.0054	.4121	1	.0158
	Number of animals reported with tumor	2	2	0	6

Reference ID: 3158913

Table 2.10

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted incidence rate	2.3%	4.5%	0.0%	14%
	95% CI for poly-3 adjusted incidence rate (%)	(0.28,8.2)	(0.56,15.8)	(0,8.0)	(5.3,28.5)
	Poly-3 adjusted number of animals at risk	85.4	44.0	44.6	42.9
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.6433	1	.5673	1
	Number of animals reported with tumor	1	0	1	0
	Poly-3 adjusted incidence rate	1.1%	0.0%	2.2%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0.06,11.8)	(0,8.2)
	Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
Hepatocellular tumors	P-value of test of trend or comparison	.2707	1	.5673	.5538
	Number of animals reported with tumor	1	0	1	1
	Poly-3 adjusted incidence rate	1.1%	0.0%	2.2%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0.06,11.8)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
Lipomas and hibernomas	P-value of test of trend or comparison	.8103	.9476	.6481	.9447
	Number of animals reported with tumor	6	1	3	1
	Poly-3 adjusted incidence rate	6.8%	2.2%	6.6%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(2.54,14.4)	(0.06,12.0)	(1.37,18.3)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	87.8	44.5	45.6	43.6
Lipomas and liposarcomas	P-value of test of trend or comparison	.7401	.9192	.5540	.9153
	Number of animals reported with tumor	5	1	3	1
	Poly-3 adjusted incidence rate	5.7%	2.2%	6.6%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(1.87,12.9)	(0.06,12.0)	(1.37,18.3)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.6
Lipomas, lipomasarcomas and hibernomas	P-value of test of trend or comparison	.8103	.9476	.6481	.9447
	Number of animals reported with tumor	6	1	3	1
	Poly-3 adjusted incidence rate	6.8%	2.2%	6.6%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(2.54,14.4)	(0.06,12.0)	(1.37,18.3)	(0.06,12.3)

Reference ID: 3158913

Table 2.10

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted number of animals at risk	87.8	44.5	45.6	43.6
Luteomas and ovarian granulosa cell tumors	P-value of test of trend or comparison	.4018		.3409	
	Number of animals reported with tumor	0	0	1	0
	Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,4.2)	(0,8.0)	(0.06,11.8)	(0,8.2)
	Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	43.4
Mammary adenocarcinomas and adenocanthomas	P-value of test of trend or comparison	.4198	.8403	.4119	.5963
	Number of animals reported with tumor	18	7	11	9
	Poly-3 adjusted incidence rate	20%	15%	23%	20%
	95% CI for poly-3 adjusted incidence rate (%)	(12.3,30.1)	(6.07,28.3)	(12,38.0)	(9.36,34.6)
	Poly-3 adjusted number of animals at risk	89.5	47.4	47.1	45.2
Mammary adenomas and fibroadenomas	P-value of test of trend or comparison	.9947	.8425	.7045	.9978
	Number of animals reported with tumor	63	29	31	19
	Poly-3 adjusted incidence rate	64%	57%	62%	41%
	95% CI for poly-3 adjusted incidence rate (%)	(54,74.4)	(42.2,71.8)	(46.1,75.3)	(26.4,56.8)
	Poly-3 adjusted number of animals at risk	97.9	50.8	50.0	46.1
Mammary tumors	P-value of test of trend or comparison	.9928	.9033	.7699	.9974
	Number of animals reported with tumor	73	33	34	23
	Poly-3 adjusted incidence rate	72%	63%	67%	49%
	95% CI for poly-3 adjusted incidence rate (%)	(61.8,80.7)	(47.9,76.4)	(52.1,80.5)	(34.1,65.1)
	Poly-3 adjusted number of animals at risk	101	52.1	51.0	46.7
Pancreatic acinar and acinar-islet cell tumors	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	1	0	0	0
	Poly-3 adjusted incidence rate	1.1%	0.0%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0,7.9)	(0,8.2)
	Poly-3 adjusted number of animals at risk	87.5	44.5	45.6	43.4
Pancreatic islet and acinar-islet cell tumors	P-value of test of trend or comparison	.9202	.1792	.5567	1

Reference ID: 3158913

Table 2.10

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Number of animals reported with tumor	3	4	2	0
	Poly-3 adjusted incidence rate	3.4%	8.9%	4.4%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.71,9.7)	(2.42,21.2)	(0.53,15.1)	(0,8.2)
	Poly-3 adjusted number of animals at risk	87.5	45.1	45.6	43.4
Pancreatic islet cell tumors	P-value of test of trend or comparison	.8771	.1026	.4210	1
	Number of animals reported with tumor	2	4	2	0
	Poly-3 adjusted incidence rate	2.3%	8.9%	4.4%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.28,8.1)	(2.42,21.2)	(0.53,15.1)	(0,8.2)
	Poly-3 adjusted number of animals at risk	87.4	45.1	45.6	43.4
Pituitary pars distalis tumors	P-value of test of trend or comparison	.9901	.9912	.7437	.9985
	Number of animals reported with tumor	90	36	43	30
	Poly-3 adjusted incidence rate	80%	65%	77%	60%
	95% CI for poly-3 adjusted incidence rate (%)	(71.8,87.9)	(50.4,77.8)	(63.6,88.2)	(44.2,73.6)
	Poly-3 adjusted number of animals at risk	112	55.2	55.6	50.3
Pituitary pars intermedia tumors	P-value of test of trend or comparison	.3587	.2610	.0511	.5469
	Number of animals reported with tumor	1	2	4	1
	Poly-3 adjusted incidence rate	1.1%	4.5%	8.5%	2.4%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0.54,15.5)	(2.32,20.4)	(0.06,12.6)
	Poly-3 adjusted number of animals at risk	87.4	44.9	47.0	42.3
Schwannomas	P-value of test of trend or comparison	.2757	1	.5673	.5607
	Number of animals reported with tumor	1	0	1	1
	Poly-3 adjusted incidence rate	1.1%	0.0%	2.2%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0,8.0)	(0.06,11.8)	(0.06,12.0)
	Poly-3 adjusted number of animals at risk	87.4	44.5	45.6	44.4
Squamous cell papillomas and carcinomas of the skin	P-value of test of trend or comparison	.6585	.5607	.2745	1
	Number of animals reported with tumor	1	1	2	0
	Poly-3 adjusted incidence rate	1.1%	2.2%	4.3%	0.0%

Reference ID: 3158913

Table 2.10

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Vaginal squamous cell tumors and polyps	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.2)	(0.06,12.0)	(0.52,14.8)	(0,8.2)
	Poly-3 adjusted number of animals at risk	87.9	44.8	46.7	43.4
	P-value of test of trend or comparison	.4005	.5641	1	.5573
	Number of animals reported with tumor	1	1	0	1
	Poly-3 adjusted incidence rate	1.2%	2.2%	0.0%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.3)	(0.06,12.0)	(0,7.9)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	86.4	45.0	45.6	43.9

Reference ID: 3158913

Table 2.11

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Adenomas and adenocarcinomas of the small intestine	P-value of test of trend or comparison	.1790			.2929
	Number of animals reported with tumor	0	0	0	1
	Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0,11.6)	(0.08,17.8)
	Poly-3 adjusted number of animals at risk	70.8	33.8	30.7	30.0
Adenomas and carcinomas of the adrenal cortex	P-value of test of trend or comparison	.9008	.9273	.8900	.9468
	Number of animals reported with tumor	21	6	6	5
	Poly-3 adjusted incidence rate	27%	17%	19%	15%
	95% CI for poly-3 adjusted incidence rate (%)	(17.7,39.1)	(6.37,33.6)	(6.98,36.4)	(5.11,32.8)
	Poly-3 adjusted number of animals at risk	76.7	36.0	32.1	32.4
All lipomas	P-value of test of trend or comparison	.4481	.6359	.8356	.5788
	Number of animals reported with tumor	4	2	1	2
	Poly-3 adjusted incidence rate	5.6%	5.8%	3.2%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(1.53,13.8)	(0.7,19.7)	(0.08,17.2)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	71.8	34.2	30.9	30.2
All pheochromocytomas	P-value of test of trend or comparison	.8315	.8557	.8773	.8916
	Number of animals reported with tumor	18	6	5	5
	Poly-3 adjusted incidence rate	24%	17%	16%	15%
	95% CI for poly-3 adjusted incidence rate (%)	(14.7,35.3)	(6.37,33.6)	(5.28,33.7)	(5.11,32.8)
	Poly-3 adjusted number of animals at risk	75.4	36.0	31.7	32.4
Astrocytomas	P-value of test of trend or comparison	.0858	1	1	.2399
	Number of animals reported with tumor	3	0	0	3
	Poly-3 adjusted incidence rate	4.1%	0.0%	0.0%	9.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.86,11.7)	(0,10.6)	(0,11.6)	(2.04,26.5)
	Poly-3 adjusted number of animals at risk	72.6	33.8	30.7	30.9
Fibrosarcomas and Sarcomas (NOS) of the skin	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	6	0	0	0

Reference ID: 3158913

Table 2.11

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted incidence rate	8.2%	0.0%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(3.03,17.0)	(0,10.6)	(0,11.6)	(0,11.9)
	Poly-3 adjusted number of animals at risk	73.5	33.8	30.7	29.8
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.0266		.0921	.0879
	Number of animals reported with tumor	0	0	2	2
	Poly-3 adjusted incidence rate	0.0%	0.0%	6.4%	6.5%
	95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.77,21.4)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	70.8	33.8	31.3	30.7
Hepatocellular tumors	P-value of test of trend or comparison	.3889	.5230	1	.4821
	Number of animals reported with tumor	3	2	0	2
	Poly-3 adjusted incidence rate	4.2%	5.8%	0.0%	6.4%
	95% CI for poly-3 adjusted incidence rate (%)	(0.87,11.9)	(0.7,19.7)	(0,11.6)	(0.77,21.4)
	Poly-3 adjusted number of animals at risk	71.5	34.3	30.7	31.3
Lipomas and hibernomas	P-value of test of trend or comparison	.4481	.6359	.8356	.5788
	Number of animals reported with tumor	4	2	1	2
	Poly-3 adjusted incidence rate	5.6%	5.8%	3.2%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(1.53,13.8)	(0.7,19.7)	(0.08,17.2)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	71.8	34.2	30.9	30.2
Lipomas and liposarcomas	P-value of test of trend or comparison	.4481	.6359	.8356	.5788
	Number of animals reported with tumor	4	2	1	2
	Poly-3 adjusted incidence rate	5.6%	5.8%	3.2%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(1.53,13.8)	(0.7,19.7)	(0.08,17.2)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	71.8	34.2	30.9	30.2
Lipomas, lipomasarcomas and hibernomas	P-value of test of trend or comparison	.4481	.6359	.8356	.5788
	Number of animals reported with tumor	4	2	1	2
	Poly-3 adjusted incidence rate	5.6%	5.8%	3.2%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(1.53,13.8)	(0.7,19.7)	(0.08,17.2)	(0.79,22.1)

Table 2.11

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted number of animals at risk	71.8	34.2	30.9	30.2
Mammary adenocarcinomas and adenocanthomas	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	2	0	0	0
	Poly-3 adjusted incidence rate	4.1%	0.0%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.49,14.0)	(0,13.7)	(0,16.1)	(0,16.8)
	Poly-3 adjusted number of animals at risk	49.2	25.6	21.6	20.5
Mammary adenomas and fibroadenomas	P-value of test of trend or comparison	.9719	.8309	1	1
	Number of animals reported with tumor	3	1	0	0
	Poly-3 adjusted incidence rate	6.2%	3.8%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(1.28,17.2)	(0.09,19.6)	(0,16.1)	(0,16.8)
	Poly-3 adjusted number of animals at risk	48.4	26.1	21.6	20.5
Mammary tumors	P-value of test of trend or comparison	.9953	.9306	1	1
	Number of animals reported with tumor	5	1	0	0
	Poly-3 adjusted incidence rate	10%	3.8%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(3.33,22.2)	(0.09,19.6)	(0,16.1)	(0,16.8)
	Poly-3 adjusted number of animals at risk	49.7	26.1	21.6	20.5
Pancreatic acinar and acinar-islet cell tumors	P-value of test of trend or comparison	.8504	1	.7579	1
	Number of animals reported with tumor	3	0	1	0
	Poly-3 adjusted incidence rate	4.1%	0.0%	3.2%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.86,11.7)	(0,10.6)	(0.08,17.2)	(0,11.9)
	Poly-3 adjusted number of animals at risk	72.5	33.8	30.8	29.8
Pancreatic acinar cell tumors	P-value of test of trend or comparison	.7478	1	.6526	1
	Number of animals reported with tumor	2	0	1	0
	Poly-3 adjusted incidence rate	2.8%	0.0%	3.2%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.33,9.7)	(0,10.6)	(0.08,17.2)	(0,11.9)
	Poly-3 adjusted number of animals at risk	72.3	33.8	30.8	29.8
Pancreatic islet and acinar-islet cell tumors	P-value of test of trend or comparison	.7719	.8096	.5924	.8927

Reference ID: 3158913

Table 2.11

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Number of animals reported with tumor	9	3	4	2
	Poly-3 adjusted incidence rate	12%	8.6%	13%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(5.8,22.4)	(1.8,23.7)	(3.51,29.8)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	72.7	35.0	31.7	30.5
Pancreatic islet cell tumors	P-value of test of trend or comparison	.7719	.8096	.5924	.8927
	Number of animals reported with tumor	9	3	4	2
	Poly-3 adjusted incidence rate	12%	8.6%	13%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(5.8,22.4)	(1.8,23.7)	(3.51,29.8)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	72.7	35.0	31.7	30.5
Pituitary pars distalis tumors	P-value of test of trend or comparison	.0646	.0706	.3494	.0488
	Number of animals reported with tumor	53	34	26	34
	Poly-3 adjusted incidence rate	59%	73%	63%	75%
	95% CI for poly-3 adjusted incidence rate (%)	(48,69.8)	(57.4,85.7)	(46.9,79.4)	(58.9,87.1)
	Poly-3 adjusted number of animals at risk	89.2	46.8	41.0	45.6
Pituitary pars intermedia tumors	P-value of test of trend or comparison	.1423	.3204	.3000	.2929
	Number of animals reported with tumor	0	1	1	1
	Poly-3 adjusted incidence rate	0.0%	2.9%	3.2%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0.08,17.2)	(0.08,17.8)
	Poly-3 adjusted number of animals at risk	70.6	34.0	31.0	29.9
Renal tubule tumors	P-value of test of trend or comparison	.1840			.3000
	Number of animals reported with tumor	0	0	0	1
	Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0,11.6)	(0.08,17.2)
	Poly-3 adjusted number of animals at risk	70.8	33.8	30.7	30.2
Schwannomas	P-value of test of trend or comparison	.0988		.3069	.2929
	Number of animals reported with tumor	0	0	1	1
	Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	3.3%

Reference ID: 3158913

Table 2.11

Table of reported tumors in Rat Study
NDA 202992
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Squamous cell papillomas and carcinomas of the skin	95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.08,16.7)	(0.08,17.8)
	Poly-3 adjusted number of animals at risk	70.8	33.8	31.1	30.0
	P-value of test of trend or comparison	.9854	.8619	1	1
	Number of animals reported with tumor	4	1	0	0
	Poly-3 adjusted incidence rate	5.5%	2.9%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(1.51,13.6)	(0.07,15.3)	(0,11.6)	(0,11.9)
	Poly-3 adjusted number of animals at risk	72.2	34.5	30.7	29.8

Reference ID: 3158913

Table 2.12

Table of tumors reported significant in at least one arm - Rat Study
NDA 202992
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
SYSTEMIC NEOPLASM	Sarcoma: histiocytic	P-value of test of trend or comparison	.0238	1	.3333	.0714
		Number of animals reported with tumor	1	0	1	3
		Poly-3 adjusted incidence rate	20%	0.0%	100%	100%
		95% CI for poly-3 adjusted incidence rate (%)	(0.42,71.6)	(0,97.5)	(2.5,100)	(29.2,100)
		Poly-3 adjusted number of animals at risk	5.0	1.0	1.0	3.0
THYROID GLAND	Adenoma: C-cell	P-value of test of trend or comparison	.0154	.2874	.0487	.0233
		Number of animals reported with tumor	13	9	13	14
		Poly-3 adjusted incidence rate	15%	20%	28%	31%
		95% CI for poly-3 adjusted incidence rate (%)	(7.92,23.7)	(9.36,34.6)	(15.6,43.5)	(17.7,46.6)
		Poly-3 adjusted number of animals at risk	89.0	45.5	46.3	45.6

Reference ID: 3158913

Table 2.13

Table of tumors reported significant in at least one arm - Rat Study
NDA 202992
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
BRAIN	Astrocytoma·benign	P-value of test of trend or comparison	.0449	1	1	.1537
		Number of animals reported with tumor	2	0	0	3
		Poly-3 adjusted incidence rate	2.8%	0.0%	0.0%	9.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.8)	(0,10.6)	(0,11.6)	(2.04,26.5)
		Poly-3 adjusted number of animals at risk	71.1	33.8	30.7	30.9
PITUITARY GLAND	Adenoma: pars·distalis	P-value of test of trend or comparison	.0513	.0500	.3872	.0338
		Number of animals reported with tumor	51	34	25	34
		Poly-3 adjusted incidence rate	58%	73%	61%	75%
		95% CI for poly-3 adjusted incidence rate (%)	(46.4,68.4)	(57.4,85.7)	(44.5,77.3)	(58.9,87.1)
		Poly-3 adjusted number of animals at risk	88.4	46.8	40.8	45.6
THYROID GLAND	Adenoma: follicular cell	P-value of test of trend or comparison	.7179	.0110	.3000	
		Number of animals reported with tumor	0	4	1	0
		Poly-3 adjusted incidence rate	0.0%	11%	3.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(3.11,26.7)	(0.08,17.2)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.3	35.7	30.7	29.8

Reference ID: 3158913

Table 2.14

Table of tumors reported significant in at least one arm - Rat Study
NDA 202992
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Fibrosarcomas and Sarcomas (NOS) of the skin	P-value of test of trend or comparison	.0054	.4121	1	.0158
	Number of animals reported with tumor	2	2	0	6
	Poly-3 adjusted incidence rate	2.3%	4.5%	0.0%	14%
	95% CI for poly-3 adjusted incidence rate (%)	(0.28,8.2)	(0.56,15.8)	(0,8.0)	(5.3,28.5)
	Poly-3 adjusted number of animals at risk	85.4	44.0	44.6	42.9

Reference ID: 3158913

Table 2.15

Table of tumors reported significant in at least one arm - Rat Study
NDA 202992
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.0266		.0921	.0879
	Number of animals reported with tumor	0	0	2	2
	Poly-3 adjusted incidence rate	0.0%	0.0%	6.4%	6.5%
	95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.77,21.4)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	70.8	33.8	31.3	30.7
Pituitary pars distalis tumors	P-value of test of trend or comparison	.0646	.0706	.3494	.0488
	Number of animals reported with tumor	53	34	26	34
	Poly-3 adjusted incidence rate	59%	73%	63%	75%
	95% CI for poly-3 adjusted incidence rate (%)	(48,69.8)	(57.4,85.7)	(46.9,79.4)	(58.9,87.1)
	Poly-3 adjusted number of animals at risk	89.2	46.8	41.0	45.6

Table 2.16 ***Tumor counts for organs reported widely unanalyzed***
NDA 202992
Animal carcinogenicity study
Rats

Species and Sex	*Organ or tissue name*	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Rats - Female	BODY CAV: ABDOMINA	Lipoma	Number of tumors found	0	0	0	1
			Number of animals examined	0	1	0	2
		Sarcoma: fibrosarcoma	Number of tumors found	0	1	0	0
			Number of animals examined	0	1	0	2
	BONE: JAW	Carcinoma: squamous cell	Number of tumors found	0	0	0	1
			Number of animals examined	0	0	0	1
	MESENTERIC TISSUE	Lipoma	Number of tumors found	4	1	0	0
			Number of animals examined	7	1	2	0
	SYSTEMIC NEOPLASM	Leukemia: granulocytic	Number of tumors found	4	0	0	0
			Number of animals examined	8	1	1	3
		Lymphoma·malignant	Number of tumors found	3	1	0	0
			Number of animals examined	8	1	1	3
		Sarcoma: histiocytic	Number of tumors found	1	0	1	3
			Number of animals examined	8	1	1	3
	TAIL	Schwannoma·benign	Number of tumors found	1	0	0	0
			Number of animals examined	2	0	0	0
Rats - Male	BODY CAV: ABDOMINA	Fibroma	Number of tumors found	0	0	0	1
			Number of animals examined	0	0	0	1
	BONE: SKULL	Sarcoma: fibrosarcoma	Number of tumors found	0	0	0	1
			Number of animals examined	0	0	0	1
	MESENTERIC TISSUE	Lipoma	Number of tumors found	0	1	1	1
			Number of animals examined	0	1	1	1
	NOSE	Papilloma: squamous cell	Number of tumors found	1	0	0	0
			Number of animals examined	1	0	0	0
	SKELETAL MUSCLE	Hemangiosarcoma	Number of tumors found	0	0	0	1
			Number of animals examined	0	0	1	1
		Sarcoma: fibrosarcoma	Number of tumors found	0	0	1	0
			Number of animals examined	0	0	1	1
	SYSTEMIC NEOPLASM	Leukemia: granulocytic	Number of tumors found	1	2	2	0
			Number of animals examined	4	4	3	0
		Lymphoma·malignant	Number of tumors found	2	2	1	0
			Number of animals examined	4	4	3	0
		Sarcoma: histiocytic	Number of tumors found	1	0	0	0
			Number of animals examined	4	4	3	0

Table 2.17

Organs reported as autolytic
NDA 202992
Animal carcinogenicity study
Female Rats

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
THYMUS	.	.	1	1.7%	.	.	.	.	1	0.3%

Reference ID: 3158913

Table 2.18

Organs reported as autolytic
NDA 202992
Animal carcinogenicity study
Male Rats

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
INTESTINE: COLON	.	.	.	.	.	.	1	1.7%	1	0.3%
INTESTINE: GALT	3	2.5%	.	.	.	.	3	5.0%	6	2.0%
INTESTINE: JEJUNUM	1	0.8%	.	.	.	.	1	1.7%	2	0.7%

Table 2.19

Organs reported as unexamined
NDA 202992
Animal carcinogenicity study
Female Rats

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
AORTA	2	1.7%	.	.	.	.	.	.	2	0.7%
BODY CAV: ABDOMINA	120	100%	59	98%	60	100%	58	97%	297	99%
BONE MARROW: STERN	.	.	.	.	1	1.7%	.	.	1	0.3%
BONE: JAW	120	100%	60	100%	60	100%	59	98%	299	100%
BONE: SKULL	120	100%	60	100%	60	100%	60	100%	300	100%
BONE: STERNUM	.	.	.	.	1	1.7%	.	.	1	0.3%
BRAIN	.	.	.	.	.	.	1	1.7%	1	0.3%
CLITORAL GLAND	11	9.2%	6	10%	4	6.7%	4	6.7%	25	8.3%
EYE	1	0.8%	.	.	.	.	1	1.7%	2	0.7%
HARDERIAN GLAND	1	0.8%	.	.	.	.	1	1.7%	2	0.7%
HEART	.	.	.	.	1	1.7%	.	.	1	0.3%
INTESTINE: COLON	.	.	.	.	.	.	1	1.7%	1	0.3%
LACRIMAL GLAND	1	0.8%	.	.	.	.	1	1.7%	2	0.7%
LIVER	.	.	.	.	1	1.7%	.	.	1	0.3%
LN: ILIAC	119	99%	60	100%	60	100%	60	100%	299	100%
LN: SUBMANDIBULAR	2	1.7%	1	1.7%	.	.	1	1.7%	4	1.3%
LYMPH NODE	.	.	1	1.7%	.	.	.	.	1	0.3%
M: QUADRICEPS	1	0.8%	1	1.7%	.	.	1	1.7%	3	1.0%
MAMMARY GLAND	2	1.7%	.	.	.	.	.	.	2	0.7%
MESENTERIC TISSUE	113	94%	59	98%	58	97%	60	100%	290	97%
NASAL TISSUE	.	.	.	.	1	1.7%	1	1.7%	2	0.7%
NERVE: OPTIC	3	2.5%	3	5.0%	1	1.7%	3	5.0%	10	3.3%
NOSE	120	100%	60	100%	60	100%	60	100%	300	100%
PANCREAS	.	.	.	.	1	1.7%	.	.	1	0.3%
PARATHYROID GLAND	5	4.2%	4	6.7%	4	6.7%	3	5.0%	16	5.3%
PITUITARY GLAND	.	.	.	.	.	.	2	3.3%	2	0.7%
SALIV.GLD: MANDIB.	2	1.7%	1	1.7%	.	.	1	1.7%	4	1.3%

Reference ID: 3158913

Table 2.19

Organs reported as unexamined
NDA 202992
Animal carcinogenicity study
Female Rats

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
SALIV.GLD: PAROTID	2	1.7%	1	1.7%	.	.	1	1.7%	4	1.3%
SALIV.GLD: SUBLIN.	2	1.7%	1	1.7%	.	.	1	1.7%	4	1.3%
SKELETAL MUSCLE	120	100%	60	100%	60	100%	60	100%	300	100%
SKIN	2	1.7%	1	1.7%	1	1.7%	1	1.7%	5	1.7%
SPINAL CORD: CERVI	1	0.8%	.	.	.	.	.	.	1	0.3%
SPINAL CORD: LUMBA	1	0.8%	.	.	.	.	2	3.3%	3	1.0%
SPINAL CORD: THORA	1	0.8%	.	.	.	.	.	.	1	0.3%
SPLEEN	.	.	.	.	1	1.7%	.	.	1	0.3%
SYSTEMIC NEOPLASM	112	93%	59	98%	59	98%	57	95%	287	96%
TAIL	118	98%	60	100%	60	100%	60	100%	298	99%
THYMUS	5	4.2%	3	5.0%	4	6.7%	5	8.3%	17	5.7%
THYROID GLAND	.	.	1	1.7%	.	.	1	1.7%	2	0.7%
TONGUE	2	1.7%	2	3.3%	.	.	1	1.7%	5	1.7%
URETER	1	0.8%	.	.	2	3.3%	.	.	3	1.0%
URINARY BLADDER	3	2.5%	1	1.7%	4	6.7%	3	5.0%	11	3.7%
UTERUS: BODY/HORNS	2	1.7%	.	.	.	.	.	.	2	0.7%
UTERUS: CERVIX	2	1.7%	.	.	.	.	.	.	2	0.7%
VAGINA	2	1.7%	.	.	.	.	.	.	2	0.7%

Reference ID: 3158913

Table 2.20

Organs reported as unexamined
NDA 202992
Animal carcinogenicity study
Male Rats

Organ or tissue name	Control(count)	Control(%)	Low dose(count)	Low dose(%)	Mid dose(count)	Mid dose(%)	High dose(count)	High dose(%)	Total(count)	Total(%)
BODY CAV: ABDOMINA	120	100%	60	100%	60	100%	59	98%	299	100%
BONE MARROW: FEMUR	.	.	.	.	.	.	2	3.3%	2	0.7%
BONE: FEMUR	.	.	.	.	.	.	2	3.3%	2	0.7%
BONE: JAW	120	100%	60	100%	60	100%	60	100%	300	100%
BONE: SKULL	120	100%	60	100%	60	100%	59	98%	299	100%
BRAIN	1	0.8%	.	.	.	.	.	.	1	0.3%
ESOPHAGUS	.	.	.	.	3	5.0%	.	.	3	1.0%
EYE	.	.	.	.	1	1.7%	1	1.7%	2	0.7%
HARDERIAN GLAND	.	.	.	.	1	1.7%	.	.	1	0.3%
INTESTINE: GALT	.	.	.	.	1	1.7%	.	.	1	0.3%
JOINT: FEMOROTIBIA	.	.	.	.	.	.	2	3.3%	2	0.7%
LACRIMAL GLAND	1	0.8%	.	.	1	1.7%	.	.	2	0.7%
LN: ILIAC	120	100%	60	100%	59	98%	60	100%	299	100%
LN: MEDIASTINAL	.	.	1	1.7%	.	.	.	.	1	0.3%
LN: SUBMANDIBULAR	3	2.5%	1	1.7%	2	3.3%	1	1.7%	7	2.3%
M: QUADRICEPS	.	.	1	1.7%	.	.	.	.	1	0.3%
MAMMARY GLAND	34	28%	13	22%	16	27%	14	23%	77	26%
MESENTERIC TISSUE	120	100%	59	98%	59	98%	59	98%	297	99%
NERVE: OPTIC	7	5.8%	1	1.7%	2	3.3%	3	5.0%	13	4.3%
NERVE: SCIATIC	1	0.8%	.	.	.	.	.	.	1	0.3%
NOSE	119	99%	60	100%	60	100%	60	100%	299	100%
PARATHYROID GLAND	5	4.2%	2	3.3%	4	6.7%	1	1.7%	12	4.0%
PITUITARY GLAND	1	0.8%	.	.	.	.	1	1.7%	2	0.7%
PREPUTIAL GLAND	9	7.5%	4	6.7%	5	8.3%	3	5.0%	21	7.0%
SALIV.GLD: MANDIB.	3	2.5%	1	1.7%	2	3.3%	.	.	6	2.0%
SALIV.GLD: PAROTID	4	3.3%	1	1.7%	2	3.3%	.	.	7	2.3%
SALIV.GLD: SUBLIN.	3	2.5%	1	1.7%	2	3.3%	.	.	6	2.0%

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Table 2.20

Organs reported as unexamined
NDA 202992
Animal carcinogenicity study
Male Rats

Organ or tissue name	*Control(count)*	*Control(%)*	*Low dose(count)*	*Low dose(%)*	*Mid dose(count)*	*Mid dose(%)*	*High dose(count)*	*High dose(%)*	*Total(count)*	*Total(%)*
SKELETAL MUSCLE	120	100%	60	100%	59	98%	59	98%	298	99%
SPINAL CORD: LUMBA	2	1.7%	2	3.3%	2	3.3%	1	1.7%	7	2.3%
SPINAL CORD: THORA	4	3.3%	.	.	.	.	.	.	4	1.3%
SYSTEMIC NEOPLASM	116	97%	56	93%	57	95%	60	100%	289	96%
TAIL	120	100%	59	98%	60	100%	59	98%	298	99%
THYMUS	3	2.5%	6	10%	5	8.3%	8	13%	22	7.3%
THYROID GLAND	1	0.8%	.	.	2	3.3%	.	.	3	1.0%
TONGUE	2	1.7%	.	.	1	1.7%	.	.	3	1.0%
TRACHEA	1	0.8%	.	.	.	.	.	.	1	0.3%
URETER	2	1.7%	.	.	.	.	2	3.3%	4	1.3%
URINARY BLADDER	2	1.7%	.	.	.	.	1	1.7%	3	1.0%

Reference ID: 3158913

Chapter 3

Assessment of the validity of a negative study

3.1 Issues of concern when selecting the dose levels

The selection of an appropriate dose level for the high dose group is made difficult by the need to satisfy two competing imperatives: on the one hand, if the dose level is insufficiently high, then genuine carcinogenicity effects may not be apparent, but on the other hand, if the dose level is too high, then there is a risk of non-carcinogenic toxic effects killing the animals before they have a chance to demonstrate a carcinogenicity effect.

Haseman [4] suggested that a satisfactory balance between these two imperatives has been found when the following two conditions are both satisfied:

1. Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?

2. Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman [4] has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80—90, would be considered as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward [3], suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80–90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward [3], the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met:

1. A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls.

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2. The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical.

3. In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls.

3.2 Assessment of the validity of the mouse study

The female mouse experiment is clearly negative. The study of male mice is more problematic; the results of the tests of adenomas and adenocarcinomas of the small intestine yield results that are significant if the tumors are considered rare, but not quite significant if this endpoint is considered common. Furthermore, while the evidence suggests that this combination type be considered common, it is by no means conclusive.

Since it is at least plausible that both the female and male experiments are negative, it is appropriate to consider whether the data provide retrospective evidence that the selected dose levels were appropriate for both experiments.

As shown in table 1.1, each group had at least 45% survival until week 90. Since this corresponds to at least 27 animals in each group, we may be satisfied that the dose levels selected did not cause excessive toxicity. However, as indicated by table 1.3, the high dose groups in both sexes did experience significantly increased mortality compared to the combined vehicle control groups. It follows that the dose levels were indeed appropriate.

3.3 Assessment of the validity of the rat study

The female rat experiment is negative, and while the results for the analysis of teh combination endpoint of hemangiomas and hemangiosarcomas in male rats does approach significance, it does not reaches the threshold required by the eCAC. It is therefore appropriate to consider whether the dose levels were appropriate in this study.

Among the female rats, at least 57% (thirty four) animals were alive in each group after ninety weeks. There is therefore no concern that the dose levels were excessive. Among male rats, only twenty one high dose animals (35%) survived to the ninetieth week. Since more than twenty animals did survive, it is reasonable to conclude that the dose levels were not quite excessive. However, such a conclusion would be somewhat tenuous, and the possibility that the high dose level was excessive must also be entertained.

Since there is no evidence of a dose related effect on survival in the female rat experiment, it is reasonable to consider the weight gain displayed by these animals. The table of mean weight change is shown in table 3.1. It is clear that the mid and high doses in both the female and male rat experiments did indeed experience a significant reduction in weight gain relative to that displayed by the respective control groups. We may thus conclude that the dose levels were sufficient.

Table 3.1: Weight changes by group (rats)

Sex	Combined vehicle control	CAR0093					
	Δ_{C_P}	Δ_L	$\frac{\Delta_L}{\Delta_{C_P}} - 1$	Δ_M	$\frac{\Delta_M}{\Delta_{C_P}} - 1$	Δ_H	$\frac{\Delta_H}{\Delta_{C_P}} - 1$
Female	335.5	354.6	6%	297.8	-11%	262.5	-22%
Male	576.9	579.9	.5%	539.5	-6%	519.3	-10%

Chapter 4

Conclusions

4.1 Mouse study

The female mouse experiment is negative. Whether the male mouse experinment is negative depends on whether the combination endpoint of adenomas and adenocarcinomas of the small intestine is considered a rare outcome; if the endpoint is considered rare, then this is a positive finding, but if the endpoint is considered common, then the results narrowly miss significance.

Although a complete assessment of the appropriateness of the dose levels is outside ths ccope of this revfiew, it should be noted that overall, the survival rates were satisfactory, but with a statistically significant increase in mortality in the high dose group, compared with the combined vehicle control.

The rates at which organs were reported as autolytic or unexamined were generally low enough that they are unlikely to negatively impact the results of the study. The exception is the gut associated lymphatic tissue in the female mice, which were reported as unexamined in sufficiently many animals that the study should be regarded as inconclusive with regards to this endpoint, rather than negative. It is also worth noting that the mammary glands of the male animals did not undergo histopathological examination.

4.2 Rat study

The rat study is a negative study. However, the test of trend for the combined endpoint of hemangiomas and hemangiosarcomas in male rats is close enough to significance to warent some further consideration.

The high mortality rate experienced by the high dose male group, and the sharply diminished weight gain experienced by the high dose female group suggest that in both cases the high doses may have excessive. However, enough high dose animals of each sex survived to the ninetieth week (twenty one male animals, and forty female animals) that it is not necessary to exclude either high dose group from the analyses.

The rates at which organs were reported as autolytic or unexamined were generally low enough that they are unlikely to negatively impact the results of the study. The only exception is in the male rat experiment, where animals for which the thymus was unexamined are disproportionately concentrated in the higher dose groups. It is also worth noting that the animals in this study did not undergo routine microscopic examination for systemic tumors.

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Appendix A

Tumor incidence tables using the water control

At the request of Richard Houghtling, PhD, additional calculations were performed, to conduct poly-3 analyses of tumor incidence when the distilled water groups were used as the control, rather than the combined vehicle control group. The same combination endpoints were used as for the main study (see table 1.9).

As can be seen in tables A.5, A.6 (mice) and A.12 A.13, A.14 and A.15 (rats), when the water control group is used in lieu of the vehicle controls, there are no results that remain significant after making an adjustment for multiplicity.

Table A.1

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLD: CORTE	Adenoma: subcapsular	P-value of test of trend or comparison	.8475	.5000	.7627	1
		Number of animals reported with tumor	1	2	1	0
		Poly-3 adjusted incidence rate	2.1%	4.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.1)	(0.5,14.3)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	48.2	48.8	50.3	37.5
ADRENAL GLD: MEDUL	Pheochromocytoma·benign	P-value of test of trend or comparison	.2047			.4430
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,8.0)	(0,7.9)	(0,7.5)	(0.07,14.9)
		Poly-3 adjusted number of animals at risk	44.4	46.0	47.5	35.4
	Pheochromocytoma·malignant	P-value of test of trend or comparison	.4826		.5217	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,8.0)	(0,7.9)	(0.05,11.1)	(0,10.0)
		Poly-3 adjusted number of animals at risk	44.4	46.0	48.0	35.3
BONE MARROW: FEMUR	Hemangioma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.1)	(0,7.5)	(0,7.1)	(0,9.7)
		Poly-3 adjusted number of animals at risk	48.2	47.7	50.3	36.7
	Hemangiosarcoma	P-value of test of trend or comparison	.4751		.5102	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0,7.5)	(0.05,10.6)	(0,9.7)
		Poly-3 adjusted number of animals at risk	48.2	47.7	50.5	36.7
BONE: FEMUR	Chondroma	P-value of test of trend or comparison	.4751		.5102	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	0.0%

Reference ID: 3158913

Table A.1

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0,7.5)	(0.05,10.6)	(0,9.7)
		Poly-3 adjusted number of animals at risk	48.2	47.7	50.3	36.7
HARDERIAN GLAND	Adenoma	P-value of test of trend or comparison	.3183	.0586	.5102	.1866
		Number of animals reported with tumor	0	4	1	2
		Poly-3 adjusted incidence rate	0.0%	8.2%	2.0%	5.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(2.27,20.0)	(0.05,10.6)	(0.64,18.2)
		Poly-3 adjusted number of animals at risk	48.2	48.8	50.2	38.0
HEART	Hemangiosarcoma	P-value of test of trend or comparison	.4780		.5102	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0,7.5)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	48.2	47.8	50.5	37.5
INTESTINE: COLON	Adenoma	P-value of test of trend or comparison	.7374	.5053		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0.05,11.1)	(0,7.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	47.3	49.0	48.4	37.0
INTESTINE: DUODENU	Adenoma	P-value of test of trend or comparison	.9296	.7416	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	2.1%	2.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0.06,12.0)	(0,7.4)	(0,10.3)
		Poly-3 adjusted number of animals at risk	47.0	44.0	48.5	34.8
KIDNEY	Carcinoma: renal tubule	P-value of test of trend or comparison	.7377	.5000		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0.05,11.1)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	48.2	48.8	50.3	37.5
LIVER	Carcinoma: hepatocyte	P-value of test of trend or comparison	.7262	1	.7627	1

Reference ID: 3158913

Table A.1

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.1)	(0,7.4)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	48.3	48.8	50.3	37.5
	Hemangioma	P-value of test of trend or comparison	.0400	.2526		.0787
		Number of animals reported with tumor	0	2	0	3
		Poly-3 adjusted incidence rate	0.0%	4.1%	0.0%	8.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0.49,14.0)	(0,7.1)	(1.66,21.9)
		Poly-3 adjusted number of animals at risk	48.2	49.1	50.3	37.5
	Hemangiosarcoma	P-value of test of trend or comparison	.4507	.1250	.2577	.4353
		Number of animals reported with tumor	0	3	2	1
		Poly-3 adjusted incidence rate	0.0%	6.0%	3.9%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(1.25,16.9)	(0.48,13.7)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	48.2	49.7	50.9	37.6
LN: MESENTERIC	Hemangiosarcoma	P-value of test of trend or comparison	.4863		.5065	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.5%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,9.3)	(0,9.5)	(0.06,13.5)	(0,10.9)
		Poly-3 adjusted number of animals at risk	38.6	37.3	39.5	32.1
LUNG	Adenoma: bronchioloalveolar	P-value of test of trend or comparison	.7300	.7474	.3163	1
		Number of animals reported with tumor	1	1	3	0
		Poly-3 adjusted incidence rate	2.0%	2.1%	6.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.9)	(0.05,11.1)	(1.23,16.5)	(0,9.5)
		Poly-3 adjusted number of animals at risk	49.1	48.8	50.3	37.5
	Carcinoma: bronchioloalveolar	P-value of test of trend or comparison	.8045	.5147	.1706	.8931
		Number of animals reported with tumor	5	6	10	2
		Poly-3 adjusted incidence rate	10%	12%	19%	5.3%

Reference ID: 3158913

Table A.1

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(3.4,22.7)	(4.53,24.8)	(9.44,32.5)	(0.64,18.2)
		Poly-3 adjusted number of animals at risk	48.4	49.6	52.2	37.5
MAMMARY GLAND	Adenocarcinoma	P-value of test of trend or comparison	.5821	.5000	.5102	
		Number of animals reported with tumor	0	1	1	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0.05,11.1)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	48.2	48.4	50.3	37.5
	Adenoma	P-value of test of trend or comparison	.2577	.5000		.4353
		Number of animals reported with tumor	0	1	0	1
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0.05,11.1)	(0,7.1)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	48.2	48.5	50.3	37.5
OVARY	Adenocarcinoma: tubulostromal	P-value of test of trend or comparison	.7443	.5109		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0.05,11.3)	(0,7.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	45.3	47.0	48.7	36.1
	Cystadenoma	P-value of test of trend or comparison	.5208	1	1	.8337
		Number of animals reported with tumor	2	0	0	1
		Poly-3 adjusted incidence rate	4.4%	0.0%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.53,15.1)	(0,7.7)	(0,7.4)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	45.8	46.8	48.7	36.6
	Hemangioma	P-value of test of trend or comparison	.4826	.9412	.9477	.7631
		Number of animals reported with tumor	5	2	2	3
		Poly-3 adjusted incidence rate	11%	4.3%	4.1%	8.1%
		95% CI for poly-3 adjusted incidence rate (%)	(3.47,23.1)	(0.52,14.8)	(0.5,14.3)	(1.7,22.5)
		Poly-3 adjusted number of animals at risk	47.0	46.8	48.9	36.9

Reference ID: 3158913

Table A.1

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Hemangiosarcoma	P-value of test of trend or comparison	.7429	.5055		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0.05,11.5)	(0,7.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	45.3	47.0	48.7	36.1
	Luteoma·benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,11.8)	(0,7.7)	(0,7.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	45.3	46.8	48.7	36.1
	Osteosarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,11.8)	(0,7.7)	(0,7.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	45.9	46.8	48.7	36.1
	Tumor·benign: granulosa cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,11.8)	(0,7.7)	(0,7.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	45.3	46.8	48.7	36.1
	Tumor·malignat: granulosa cell	P-value of test of trend or comparison	.5208	1	1	.8337
		Number of animals reported with tumor	2	0	0	1
		Poly-3 adjusted incidence rate	4.4%	0.0%	0.0%	2.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.53,15.1)	(0,7.7)	(0,7.4)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	45.3	46.8	48.7	36.1
PANCREAS	Adenoma: islet cell	P-value of test of trend or comparison	.6770	.2579	.5104	
		Number of animals reported with tumor	0	2	1	0

Reference ID: 3158913

Table A.1

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	0.0%	4.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0.49,14.0)	(0.05,10.9)	(0,10.0)
		Poly-3 adjusted number of animals at risk	47.3	49.1	49.4	35.2
PITUITARY GLAND	Adenoma: pars·distalis	P-value of test of trend or comparison	.6811	.2527	.5054	
		Number of animals reported with tumor	0	2	1	0
		Poly-3 adjusted incidence rate	0.0%	4.2%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.51,14.5)	(0.05,11.3)	(0,10.0)
		Poly-3 adjusted number of animals at risk	47.0	47.8	47.5	35.0
	Carcinoma: pars· intermedia	P-value of test of trend or comparison	.7386	.5106		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.05,11.1)	(0,7.5)	(0,10.0)
		Poly-3 adjusted number of animals at risk	47.0	48.2	47.5	35.0
SKIN/SUBCUTIS	Carcinoma: squamous cell	P-value of test of trend or comparison	.4754		.5102	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0,7.4)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	48.2	48.8	51.0	37.5
	Fibrosarcoma	P-value of test of trend or comparison	.7400	.3585	.3585	.8249
		Number of animals reported with tumor	2	4	4	1
		Poly-3 adjusted incidence rate	4.1%	8.0%	7.9%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.5,14.3)	(2.18,19.2)	(2.18,19.2)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	48.4	50.0	50.8	37.5
	Leiomyosarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.1)	(0,7.4)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	48.3	48.8	50.3	37.5

Reference ID: 3158913

Table A.1

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Schwanoma: benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.1)	(0,7.4)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	48.7	48.8	50.3	37.5
SPLEEN	Hemangioma	P-value of test of trend or comparison	.7377	.5000		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0.05,11.1)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	48.2	48.8	50.3	37.5
	Hemangiosarcoma	P-value of test of trend or comparison	.7262	1	.7627	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.1)	(0,7.4)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	48.7	48.8	50.5	37.5
SYSTEMIC NEOPLASM	Lymphoma·malignant	P-value of test of trend or comparison	.9175	.0077	.9143	.6021
		Number of animals reported with tumor	10	23	6	8
		Poly-3 adjusted incidence rate	20%	44%	12%	20%
		95% CI for poly-3 adjusted incidence rate (%)	(9.82,33.7)	(29.8,58.7)	(4.44,24.3)	(8.82,35.6)
		Poly-3 adjusted number of animals at risk	50.1	52.0	50.7	40.9
	Sarcoma: histiocytic	P-value of test of trend or comparison	.5107	.7365	.7488	.6753
		Number of animals reported with tumor	7	6	6	5
		Poly-3 adjusted incidence rate	14%	12%	12%	13%
		95% CI for poly-3 adjusted incidence rate (%)	(5.82,27.2)	(4.44,24.3)	(4.35,23.9)	(4.3,28.1)
		Poly-3 adjusted number of animals at risk	49.5	50.4	51.8	38.7
THYMUS	Thymoma·benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%

Reference ID: 3158913

Table A.1

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,12.3)	(0,8.0)	(0,8.6)	(0,15.4)
		Poly-3 adjusted number of animals at risk	43.4	44.7	41.1	22.9
THYROID GLAND	Adenoma: follicular cell	P-value of test of trend or comparison	.5845	.5053	.5104	
		Number of animals reported with tumor	0	1	1	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0.05,11.1)	(0.05,10.9)	(0,9.5)
		Poly-3 adjusted number of animals at risk	47.3	48.8	49.3	37.1
UTERUS	Adenocarcinoma: endometrium	P-value of test of trend or comparison	.7418	.5053		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0.05,11.1)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	47.2	48.8	50.3	37.5
	Fibroma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.3)	(0,7.4)	(0,7.1)	(0,9.5)
		Poly-3 adjusted number of animals at risk	47.2	48.4	50.3	37.5
	Hemangioma	P-value of test of trend or comparison	.8052	.7579	.7678	1
		Number of animals reported with tumor	1	1	1	0
		Poly-3 adjusted incidence rate	2.1%	2.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.3)	(0.05,11.1)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	47.2	48.4	50.3	37.5
	Hemangiosarcoma	P-value of test of trend or comparison	.2033			.4405
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0,7.4)	(0,7.1)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	47.2	48.4	50.3	37.6

Reference ID: 3158913

Table A.1

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Leiomyoma	P-value of test of trend or comparison	.8683	.0611	.5155	
		Number of animals reported with tumor	0	4	1	0
		Poly-3 adjusted incidence rate	0.0%	8.2%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(2.27,20.0)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	47.2	48.8	50.7	37.5
	Leiomyosarcoma	P-value of test of trend or comparison	.5862	.5053	.5155	
		Number of animals reported with tumor	0	1	1	0
		Poly-3 adjusted incidence rate	0.0%	2.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0.05,11.1)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	47.2	48.4	50.3	37.5
	Polyp: endometrial stroma	P-value of test of trend or comparison	.8091	.5080	.5234	1
		Number of animals reported with tumor	1	2	2	0
		Poly-3 adjusted incidence rate	2.1%	4.1%	4.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.3)	(0.5,14.3)	(0.48,13.7)	(0,9.5)
		Poly-3 adjusted number of animals at risk	47.2	48.4	50.5	37.5
	Polyp: glandular	P-value of test of trend or comparison	.9795	.2900	.8851	.9736
		Number of animals reported with tumor	5	8	3	1
		Poly-3 adjusted incidence rate	11%	16%	6.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(3.47,23.1)	(7.32,30.2)	(1.23,16.5)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	47.4	48.6	50.3	37.5
	Sarcoma: endometrial	P-value of test of trend or comparison	.6911	.2526	.5155	
		Number of animals reported with tumor	0	2	1	0
		Poly-3 adjusted incidence rate	0.0%	4.1%	2.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0.5,14.3)	(0.05,10.6)	(0,9.5)
		Poly-3 adjusted number of animals at risk	47.2	48.5	51.0	37.5
	Tumor·benign: granular cell	P-value of test of trend or comparison	.1514		.2631	.4405
		Number of animals reported with tumor	0	0	2	1

Reference ID: 3158913

Table A.1

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	0.0%	0.0%	4.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0,7.4)	(0.48,13.7)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	47.2	48.4	50.4	37.5
UTERUS: CERVIX	Leiomyosarcoma	P-value of test of trend or comparison	.0386			.1868
		Number of animals reported with tumor	0	0	0	2
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	5.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,8.0)	(0,8.2)	(0,7.1)	(0.7,19.7)
		Poly-3 adjusted number of animals at risk	44.3	43.4	50.3	34.3
	Polyp: endometrial stroma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,12.0)	(0,8.2)	(0,7.1)	(0,10.6)
		Poly-3 adjusted number of animals at risk	44.3	43.4	50.3	33.7
VAGINA	Papilloma: squamous cell	P-value of test of trend or comparison	.7943	.2527		
		Number of animals reported with tumor	0	2	0	0
		Poly-3 adjusted incidence rate	0.0%	4.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0.52,14.8)	(0,7.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	45.2	46.3	50.0	33.2

Reference ID: 3158913

Table A.2

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLD: CORTE	Adenoma: cortex	P-value of test of trend or comparison	.9165	.1425	.7366	1
		Number of animals reported with tumor	1	4	1	0
		Poly-3 adjusted incidence rate	2.0%	9.3%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.9)	(2.53,22.1)	(0.05,11.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.9	43.1	46.8	33.0
	Adenoma: subcapsular	P-value of test of trend or comparison	.7178	.7128	.4761	1
		Number of animals reported with tumor	1	1	2	0
		Poly-3 adjusted incidence rate	2.0%	2.4%	4.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.9)	(0.06,12.6)	(0.52,14.8)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.4	42.5	46.8	33.0
ADRENAL GLD: MEDUL	Pheochromocytoma·benign	P-value of test of trend or comparison	.7030	.4494		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.5%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0.06,13.2)	(0,8.0)	(0,10.9)
		Poly-3 adjusted number of animals at risk	49.4	40.5	45.0	32.3
BONE MARROW: FEMUR	Hemangiosarcoma	P-value of test of trend or comparison	.9148	.4517	1	1
		Number of animals reported with tumor	1	2	0	0
		Poly-3 adjusted incidence rate	2.0%	4.5%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.6)	(0.54,15.5)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	50.3	44.2	47.4	33.2
BONE MARROW: STERN	Hemangioma	P-value of test of trend or comparison	.7135	.4615		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0.06,12.6)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.1	42.5	47.3	33.4
	Hemangiosarcoma	P-value of test of trend or comparison	.1930			.4024
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.0%

Reference ID: 3158913

Table A.2

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0,8.4)	(0,7.5)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	49.1	42.5	47.3	33.4
GALL BLADDER	Adenoma	P-value of test of trend or comparison	.7170	.4828		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0.06,12.6)	(0,8.6)	(0,11.2)
		Poly-3 adjusted number of animals at risk	45.8	42.5	41.4	31.3
HARDERIAN GLAND	Adenoma	P-value of test of trend or comparison	.7780	.1292	.6033	.6901
		Number of animals reported with tumor	5	9	5	3
		Poly-3 adjusted incidence rate	9.9%	20%	10%	8.9%
		95% CI for poly-3 adjusted incidence rate (%)	(3.26,21.8)	(9.58,35.3)	(3.4,22.7)	(1.86,24.3)
		Poly-3 adjusted number of animals at risk	50.4	44.0	48.3	33.7
HEART	Hemangiosarcoma	P-value of test of trend or comparison	.4651		.4896	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.9	43.5	47.8	33.4
INTESTINE: CECUM	Adenocarcinoma	P-value of test of trend or comparison	.4643		.4947	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0,8.4)	(0.05,11.3)	(0,11.2)
		Poly-3 adjusted number of animals at risk	48.0	42.8	47.1	31.5
INTESTINE: DUODENU	Adenocarcinoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,11.8)	(0,8.8)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	45.6	40.4	43.9	31.5
	Adenoma	P-value of test of trend or comparison	.4206	1	.6747	.7925

Reference ID: 3158913

Table A.2

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	2	0	2	1
		Poly-3 adjusted incidence rate	4.3%	0.0%	4.5%	3.1%
		95% CI for poly-3 adjusted incidence rate (%)	(0.52,14.8)	(0,8.8)	(0.54,15.5)	(0.08,16.7)
		Poly-3 adjusted number of animals at risk	46.3	40.4	44.2	31.8
INTESTINE: JEJUNUM	Adenocarcinoma	P-value of test of trend or comparison	.1941			.4074
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0,8.4)	(0,7.5)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	48.1	43.0	47.4	33.4
	Adenoma	P-value of test of trend or comparison	.4326	.7184	1	.6519
		Number of animals reported with tumor	1	1	0	1
		Poly-3 adjusted incidence rate	2.1%	2.3%	0.0%	3.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.1)	(0.06,12.6)	(0,7.5)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	48.1	43.0	47.4	33.4
KIDNEY	Adenoma: renal tubule	P-value of test of trend or comparison	.2379	.4674		.4024
		Number of animals reported with tumor	0	1	0	1
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	2.9%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0.06,12.3)	(0,7.5)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	49.9	43.5	47.4	33.9
LIVER	Adenoma: hepatocyte	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
		Poly-3 adjusted incidence rate	4.0%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.48,13.7)	(0,8.2)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	50.1	43.5	47.4	33.4
	Carcinoma: hepatocyte	P-value of test of trend or comparison	.7375	.6028	.4487	.8372
		Number of animals reported with tumor	7	6	8	3
		Poly-3 adjusted incidence rate	14%	14%	17%	8.8%
		95% CI for poly-3 adjusted incidence rate (%)	(5.59,26.3)	(5.17,27.9)	(7.32,30.2)	(1.86,24.3)

Reference ID: 3158913

Table A.2

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	51.3	43.9	48.1	34.0
	Cholangioma	P-value of test of trend or comparison	.4651		.4896	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.9	43.5	47.7	33.4
	Hemangioma	P-value of test of trend or comparison	.0636	.4674		.1590
		Number of animals reported with tumor	0	1	0	2
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	6.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0.06,12.3)	(0,7.5)	(0.72,20.2)
		Poly-3 adjusted number of animals at risk	49.9	43.8	47.4	33.6
	Hemangiosarcoma	P-value of test of trend or comparison	.8403	.2606	.4842	1
		Number of animals reported with tumor	1	3	2	0
		Poly-3 adjusted incidence rate	2.0%	6.9%	4.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.9)	(1.43,19.1)	(0.51,14.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.9	43.8	47.8	33.4
LN: MESENTERIC	Hemangiosarcoma	P-value of test of trend or comparison	.7132	.4800		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,9.0)	(0.07,14.5)	(0,10.6)	(0,12.3)
		Poly-3 adjusted number of animals at risk	39.7	36.3	33.9	28.7
LUNG	Adenoma: bronchioloalveolar	P-value of test of trend or comparison	.8416	.4281	.9335	.8747
		Number of animals reported with tumor	3	4	1	1
		Poly-3 adjusted incidence rate	6.0%	8.9%	2.1%	3.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.23,16.5)	(2.48,21.7)	(0.05,11.3)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	50.4	44.7	47.4	33.4
	Carcinoma: bronchioloalveolar	P-value of test of trend or comparison	.4407	.1880	1	.3604
		Number of animals reported with tumor	5	8	0	5

Reference ID: 3158913

Table A.2

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	9.8%	18%	0.0%	15%
		95% CI for poly-3 adjusted incidence rate (%)	(3.2,21.4)	(8,32.7)	(0,7.5)	(4.81,31.1)
		Poly-3 adjusted number of animals at risk	51.0	44.4	47.4	34.1
	Hemangiosarcoma	P-value of test of trend or comparison	.4651		.4896	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.9	43.5	47.8	33.4
PANCREAS	Adenocarcinoma: acinar cell	P-value of test of trend or comparison	.4678		.4896	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0,8.4)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.9	42.8	47.4	33.4
PITUITARY GLAND	Adenoma: pars-distalis	P-value of test of trend or comparison	.7714	.7064	.7191	1
		Number of animals reported with tumor	1	1	1	0
		Poly-3 adjusted incidence rate	2.0%	2.4%	2.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.9)	(0.06,12.9)	(0.06,12.3)	(0,10.9)
		Poly-3 adjusted number of animals at risk	49.2	41.7	43.1	32.9
PROSTATE GLAND	Hemangiosarcoma	P-value of test of trend or comparison	.7212	.4831		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.06,12.3)	(0,7.9)	(0,11.2)
		Poly-3 adjusted number of animals at risk	47.0	43.5	45.7	31.7
SALIV.GLD: MANDIB.	Myoepithelioma: malignant	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.0%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.9)	(0,8.2)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.6	43.5	47.4	33.4

Reference ID: 3158913

Table A.2

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
SKIN/SUBCUTIS	Fibrosarcoma	P-value of test of trend or comparison	.7011	.4390	.8671	.7867
		Number of animals reported with tumor	2	3	1	1
		Poly-3 adjusted incidence rate	4.0%	6.7%	2.1%	3.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.48,13.7)	(1.4,18.7)	(0.05,11.3)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	50.2	44.8	47.6	33.4
	Mast cell tumor·malignant	P-value of test of trend or comparison	.4678		.4947	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	48.9	43.5	47.4	33.4
	Sarcoma: not other specified	P-value of test of trend or comparison	.4678		.4947	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	48.9	43.5	47.5	33.4
SPLEEN	Hemangiosarcoma	P-value of test of trend or comparison	.9228	.0465		
		Number of animals reported with tumor	0	4	0	0
		Poly-3 adjusted incidence rate	0.0%	9.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(2.48,21.7)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.9	44.4	47.4	33.4
STOMACH: GLANDULAR	Tumor·malignant: neuroendocrine	P-value of test of trend or comparison	.7151	.4674		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0.06,12.3)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.9	43.5	47.4	33.4
STOMACH: NONGLANDU	Papilloma: squamous cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.0%	0.0%	0.0%	0.0%

Reference ID: 3158913

Table A.2

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.6)	(0,8.2)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	50.6	43.5	47.4	33.4
SYSTEMIC NEOPLASM	Lymphoma·malignant	P-value of test of trend or comparison	.3073	.1765	1	.2398
		Number of animals reported with tumor	7	11	0	8
		Poly-3 adjusted incidence rate	14%	23%	0.0%	22%
		95% CI for poly-3 adjusted incidence rate (%)	(5.7,26.7)	(12,38.0)	(0,7.5)	(9.83,39.2)
		Poly-3 adjusted number of animals at risk	51.0	47.6	47.4	36.5
	Sarcoma: histiocytic	P-value of test of trend or comparison	.0593	.7191	.7421	.1848
		Number of animals reported with tumor	1	1	1	3
		Poly-3 adjusted incidence rate	2.0%	2.3%	2.1%	8.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.9)	(0.06,12.3)	(0.05,11.3)	(1.8,23.7)
		Poly-3 adjusted number of animals at risk	49.9	43.5	47.5	34.2
TESTIS	Adenoma: Leydig cell	P-value of test of trend or comparison	.7201	.7839	.8059	.8789
		Number of animals reported with tumor	3	2	2	1
		Poly-3 adjusted incidence rate	6.1%	4.5%	4.2%	3.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.25,16.9)	(0.54,15.5)	(0.51,14.5)	(0.07,15.8)
		Poly-3 adjusted number of animals at risk	49.1	44.5	47.4	33.4
	Adenoma: rete testis	P-value of test of trend or comparison	.4678		.4947	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0,8.2)	(0.05,11.3)	(0,10.6)
		Poly-3 adjusted number of animals at risk	48.9	43.5	47.4	33.4
THYMUS	Thymoma·benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
		Poly-3 adjusted incidence rate	4.6%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.56,15.8)	(0,10.9)	(0,9.5)	(0,14.2)
		Poly-3 adjusted number of animals at risk	43.1	32.2	37.1	24.7
THYROID GLAND	Adenoma: follicular cell	P-value of test of trend or comparison	.4615		.4842	

Reference ID: 3158913

Table A.2

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0,8.4)	(0.05,11.5)	(0,10.9)
		Poly-3 adjusted number of animals at risk	49.9	42.5	46.1	33.0

Reference ID: 3158913

Table A.3

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
Adenomas and adenocarcinomas of the small intestine	P-value of test of trend or comparison	.9323	.7526	1	1
	Number of animals reported with tumor	1	1	0	0
	Poly-3 adjusted incidence rate	2.0%	2.1%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.1)	(0.05,11.1)	(0,7.1)	(0,9.5)
	Poly-3 adjusted number of animals at risk	48.8	48.8	50.3	37.5
All pheochromocytomas	P-value of test of trend or comparison	.1547		.5217	.4430
	Number of animals reported with tumor	0	0	1	1
	Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	2.8%
	95% CI for poly-3 adjusted incidence rate (%)	(0,8.0)	(0,7.9)	(0.05,11.1)	(0.07,14.9)
	Poly-3 adjusted number of animals at risk	44.4	46.0	48.0	35.4
Bronchioloalveolar tumors	P-value of test of trend or comparison	.8524	.5000	.0823	.9316
	Number of animals reported with tumor	6	7	13	2
	Poly-3 adjusted incidence rate	12%	14%	25%	5.3%
	95% CI for poly-3 adjusted incidence rate (%)	(4.53,24.8)	(5.82,27.2)	(13.8,38.9)	(0.64,18.2)
	Poly-3 adjusted number of animals at risk	49.3	49.6	52.2	37.5
Fibrosarcomas and Sarcomas (NOS) of the skin	P-value of test of trend or comparison	.8312	.2092	.2092	.8271
	Number of animals reported with tumor	4	8	8	2
	Poly-3 adjusted incidence rate	8.2%	16%	16%	5.3%
	95% CI for poly-3 adjusted incidence rate (%)	(2.27,20.0)	(6.88,28.6)	(6.88,28.6)	(0.64,18.2)
	Poly-3 adjusted number of animals at risk	48.6	51.3	51.2	37.5
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.4721	.3976	.8167	.4913
	Number of animals reported with tumor	8	10	6	7
	Poly-3 adjusted incidence rate	16%	20%	12%	18%
	95% CI for poly-3 adjusted incidence rate (%)	(7.02,29.1)	(9.82,33.7)	(4.35,23.9)	(7.54,34.3)
	Poly-3 adjusted number of animals at risk	50.5	50.1	51.7	38.4
Hepatocellular tumors	P-value of test of trend or comparison	.7262	1	.7627	1
	Number of animals reported with tumor	1	0	1	0

Reference ID: 3158913

Table A.3

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted incidence rate	2.1%	0.0%	2.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.1)	(0,7.4)	(0.05,10.6)	(0,9.5)
	Poly-3 adjusted number of animals at risk	48.3	48.8	50.3	37.5
Lipomas and liposarcomas	P-value of test of trend or comparison	.4754		.5102	
	Number of animals reported with tumor	0	0	1	0
	Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0,7.4)	(0.05,10.6)	(0,9.5)
	Poly-3 adjusted number of animals at risk	48.2	48.8	50.5	37.5
Lipomas, lipomasarcomas and hibernomas	P-value of test of trend or comparison	.4754		.5102	
	Number of animals reported with tumor	0	0	1	0
	Poly-3 adjusted incidence rate	0.0%	0.0%	2.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0,7.4)	(0.05,10.6)	(0,9.5)
	Poly-3 adjusted number of animals at risk	48.2	48.8	50.5	37.5
Luteomas and ovarian granulosa cell tumors	P-value of test of trend or comparison	.6524	1	1	.9104
	Number of animals reported with tumor	3	0	0	1
	Poly-3 adjusted incidence rate	6.6%	0.0%	0.0%	2.8%
	95% CI for poly-3 adjusted incidence rate (%)	(1.37,18.3)	(0,7.7)	(0,7.4)	(0.07,14.5)
	Poly-3 adjusted number of animals at risk	45.3	46.8	48.7	36.1
Mammary adenocarcinomas and adenocanthomas	P-value of test of trend or comparison	.5821	.5000	.5102	
	Number of animals reported with tumor	0	1	1	0
	Poly-3 adjusted incidence rate	0.0%	2.1%	2.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0.05,11.1)	(0.05,10.6)	(0,9.5)
	Poly-3 adjusted number of animals at risk	48.2	48.4	50.3	37.5
Mammary adenomas and fibroadenomas	P-value of test of trend or comparison	.2577	.5000		.4353
	Number of animals reported with tumor	0	1	0	1
	Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	2.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0.05,11.1)	(0,7.1)	(0.07,14.2)

Table A.3

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted number of animals at risk	48.2	48.5	50.3	37.5
Mammary tumors	P-value of test of trend or comparison	.3409	.2474	.5102	.4353
	Number of animals reported with tumor	0	2	1	1
	Poly-3 adjusted incidence rate	0.0%	4.1%	2.0%	2.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0.5,14.3)	(0.05,10.6)	(0.07,14.2)
	Poly-3 adjusted number of animals at risk	48.2	48.5	50.3	37.5
Ovarian tubulostromal adenocarcinomas and cystadenomas	P-value of test of trend or comparison	.6160	.8870	1	.8337
	Number of animals reported with tumor	2	1	0	1
	Poly-3 adjusted incidence rate	4.4%	2.1%	0.0%	2.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.53,15.1)	(0.05,11.3)	(0,7.4)	(0.07,14.5)
	Poly-3 adjusted number of animals at risk	45.8	47.0	48.7	36.6
Pancreatic islet and acinar-islet cell tumors	P-value of test of trend or comparison	.6770	.2579	.5104	
	Number of animals reported with tumor	0	2	1	0
	Poly-3 adjusted incidence rate	0.0%	4.1%	2.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0.49,14.0)	(0.05,10.9)	(0,10.0)
	Poly-3 adjusted number of animals at risk	47.3	49.1	49.4	35.2
Pancreatic islet cell tumors	P-value of test of trend or comparison	.6770	.2579	.5104	
	Number of animals reported with tumor	0	2	1	0
	Poly-3 adjusted incidence rate	0.0%	4.1%	2.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.5)	(0.49,14.0)	(0.05,10.9)	(0,10.0)
	Poly-3 adjusted number of animals at risk	47.3	49.1	49.4	35.2
Pituitary pars distalis tumors	P-value of test of trend or comparison	.6811	.2527	.5054	
	Number of animals reported with tumor	0	2	1	0
	Poly-3 adjusted incidence rate	0.0%	4.2%	2.1%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.51,14.5)	(0.05,11.3)	(0,10.0)
	Poly-3 adjusted number of animals at risk	47.0	47.8	47.5	35.0
Pituitary pars intermedia tumors	P-value of test of trend or comparison	.7386	.5106		

Reference ID: 3158913

Table A.3

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Number of animals reported with tumor	0	1	0	0
	Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.05,11.1)	(0,7.5)	(0,10.0)
	Poly-3 adjusted number of animals at risk	47.0	48.2	47.5	35.0
Renal tubule tumors	P-value of test of trend or comparison	.7377	.5000		
	Number of animals reported with tumor	0	1	0	0
	Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0.05,11.1)	(0,7.1)	(0,9.5)
	Poly-3 adjusted number of animals at risk	48.2	48.8	50.3	37.5
Uterine adenocarcinomas and glandular polyps	P-value of test of trend or comparison	.9989	.1383	.9342	.9938
	Number of animals reported with tumor	10	16	6	2
	Poly-3 adjusted incidence rate	21%	33%	12%	5.3%
	95% CI for poly-3 adjusted incidence rate (%)	(10.5,35.7)	(19.9,48.4)	(4.44,24.3)	(0.64,18.2)
	Poly-3 adjusted number of animals at risk	47.6	48.8	50.3	37.5
Vaginal squamous cell tumors and polyps	P-value of test of trend or comparison	.7943	.2527		
	Number of animals reported with tumor	0	2	0	0
	Poly-3 adjusted incidence rate	0.0%	4.3%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0.52,14.8)	(0,7.3)	(0,10.6)
	Poly-3 adjusted number of animals at risk	45.2	46.3	50.0	33.2

Reference ID: 3158913

Table A.4

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
Adenomas and adenocarcinomas of the small intestine	P-value of test of trend or comparison	.2665	.9592	.8831	.5802
	Number of animals reported with tumor	4	1	2	3
	Poly-3 adjusted incidence rate	7.9%	2.3%	4.2%	8.9%
	95% CI for poly-3 adjusted incidence rate (%)	(2.18,19.2)	(0.06,12.3)	(0.51,14.5)	(1.86,24.3)
	Poly-3 adjusted number of animals at risk	50.7	43.5	47.7	33.6
All pheochromocytomas	P-value of test of trend or comparison	.7030	.4494		
	Number of animals reported with tumor	0	1	0	0
	Poly-3 adjusted incidence rate	0.0%	2.5%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0.06,13.2)	(0,8.0)	(0,10.9)
	Poly-3 adjusted number of animals at risk	49.4	40.5	45.0	32.3
Bronchioloalveolar tumors	P-value of test of trend or comparison	.6791	.1423	.9981	.5182
	Number of animals reported with tumor	8	12	1	6
	Poly-3 adjusted incidence rate	16%	26%	2.1%	18%
	95% CI for poly-3 adjusted incidence rate (%)	(6.88,28.6)	(14.3,41.9)	(0.05,11.3)	(6.56,34.5)
	Poly-3 adjusted number of animals at risk	51.4	45.6	47.4	34.1
Fibrosarcomas and Sarcomas (NOS) of the skin	P-value of test of trend or comparison	.7458	.3060	.6078	.7650
	Number of animals reported with tumor	4	6	4	2
	Poly-3 adjusted incidence rate	7.8%	13%	8.3%	6.0%
	95% CI for poly-3 adjusted incidence rate (%)	(2.14,18.9)	(4.83,26.3)	(2.27,20.0)	(0.72,20.2)
	Poly-3 adjusted number of animals at risk	51.5	46.2	48.0	33.4
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.4850	.0531	.6677	.3088
	Number of animals reported with tumor	2	7	2	3
	Poly-3 adjusted incidence rate	4.0%	16%	4.2%	8.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0.48,13.7)	(6.49,30.1)	(0.51,14.5)	(1.86,24.3)
	Poly-3 adjusted number of animals at risk	50.3	44.7	47.8	33.6
Hepatocellular tumors	P-value of test of trend or comparison	.8373	.7781	.6529	.9250
	Number of animals reported with tumor	9	6	8	3

Reference ID: 3158913

Table A.4

Table of reported tumors in Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted incidence rate	17%	14%	17%	8.8%
	95% CI for poly-3 adjusted incidence rate (%)	(8.23,30.9)	(5.17,27.9)	(7.32,30.2)	(1.86,24.3)
	Poly-3 adjusted number of animals at risk	51.5	43.9	48.1	34.0
Pancreatic acinar and acinar-islet cell tumors	P-value of test of trend or comparison	.4678		.4896	
	Number of animals reported with tumor	0	0	1	0
	Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0,8.4)	(0.05,11.3)	(0,10.6)
	Poly-3 adjusted number of animals at risk	49.9	42.8	47.4	33.4
Pancreatic acinar cell tumors	P-value of test of trend or comparison	.4678		.4896	
	Number of animals reported with tumor	0	0	1	0
	Poly-3 adjusted incidence rate	0.0%	0.0%	2.1%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0,8.4)	(0.05,11.3)	(0,10.6)
	Poly-3 adjusted number of animals at risk	49.9	42.8	47.4	33.4
Pituitary pars distalis tumors	P-value of test of trend or comparison	.7714	.7064	.7191	1
	Number of animals reported with tumor	1	1	1	0
	Poly-3 adjusted incidence rate	2.0%	2.4%	2.3%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,10.9)	(0.06,12.9)	(0.06,12.3)	(0,10.9)
	Poly-3 adjusted number of animals at risk	49.2	41.7	43.1	32.9
Renal tubule tumors	P-value of test of trend or comparison	.2379	.4674		.4024
	Number of animals reported with tumor	0	1	0	1
	Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	2.9%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(0.06,12.3)	(0,7.5)	(0.07,15.8)
	Poly-3 adjusted number of animals at risk	49.9	43.5	47.4	33.9

Table A.5

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
LIVER	Hemangioma	P-value of test of trend or comparison	.0400	.2526		.0787
		Number of animals reported with tumor	0	2	0	3
		Poly-3 adjusted incidence rate	0.0%	4.1%	0.0%	8.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.4)	(0.49,14.0)	(0,7.1)	(1.66,21.9)
		Poly-3 adjusted number of animals at risk	48.2	49.1	50.3	37.5
SYSTEMIC NEOPLASM	Lymphoma-malignant	P-value of test of trend or comparison	.9175	.0077	.9143	.6021
		Number of animals reported with tumor	10	23	6	8
		Poly-3 adjusted incidence rate	20%	44%	12%	20%
		95% CI for poly-3 adjusted incidence rate (%)	(9.82,33.7)	(29.8,58.7)	(4.44,24.3)	(8.82,35.6)
		Poly-3 adjusted number of animals at risk	50.1	52.0	50.7	40.9
UTERUS: CERVIX	Leiomyosarcoma	P-value of test of trend or comparison	.0386			.1868
		Number of animals reported with tumor	0	0	0	2
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	5.8%
		95% CI for poly-3 adjusted incidence rate (%)	(0,8.0)	(0,8.2)	(0,7.1)	(0.7,19.7)
		Poly-3 adjusted number of animals at risk	44.3	43.4	50.3	34.3

Reference ID: 3158913

Table A.6

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202992 (water control)
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
SPLEEN	Hemangiosarcoma	P-value of test of trend or comparison	.9228	.0465		
		Number of animals reported with tumor	0	4	0	0
		Poly-3 adjusted incidence rate	0.0%	9.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.3)	(2.48,21.7)	(0,7.5)	(0,10.6)
		Poly-3 adjusted number of animals at risk	49.9	44.4	47.4	33.4

Reference ID: 3158913

Table A.7 ***Tumor counts for organs reported widely unanalyzed***
NDA 202992 (water control)
Animal carcinogenicity study
Mice

Species and Sex	*Organ or tissue name*	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
Mice - Female	BODY CAV: ABDOMINA	Osteosarcoma	Number of tumors found	1	0	0	0
			Number of animals examined	1	0	0	0
	BODY CAVITY	Hemangioma	Number of tumors found	1	0	0	0
			Number of animals examined	1	0	2	0
		Liposarcoma	Number of tumors found	0	0	1	0
			Number of animals examined	1	0	2	0
	MESENTERY	Fibrosarcoma	Number of tumors found	1	0	0	0
			Number of animals examined	3	5	2	4

Table A.8

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLAND	Adenoma: cortex	P-value of test of trend or comparison	.5914	.7348	.9413	.7348
		Number of animals reported with tumor	5	4	2	4
		Poly-3 adjusted incidence rate	11%	8.9%	4.4%	9.1%
		95% CI for poly-3 adjusted incidence rate (%)	(3.55,23.6)	(2.48,21.7)	(0.53,15.1)	(2.48,21.7)
		Poly-3 adjusted number of animals at risk	46.9	44.9	45.6	44.0
	Carcinoma: cortex	P-value of test of trend or comparison	.1453	1	1	.4744
		Number of animals reported with tumor	1	0	0	2
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	4.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.0)	(0,7.9)	(0.56,15.8)
		Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.8
	Pheochromocytoma·benign	P-value of test of trend or comparison	.9343	.4831	1	1
		Number of animals reported with tumor	1	2	0	0
		Poly-3 adjusted incidence rate	2.1%	4.5%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0.54,15.5)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	46.5	44.6	45.6	43.4
BONE: STERNUM	Osteoma	P-value of test of trend or comparison	.2416			.4831
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0,8.0)	(0,7.9)	(0.06,12.3)
		Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.4
BRAIN	Astrocytoma·benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	46.8	44.5	45.6	43.0
	Granular cell tumor	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%

Reference ID: 3158913

Table A.8

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	46.9	44.5	45.6	43.0
HEART	Schwannoma-benign: endocardial	P-value of test of trend or comparison	.1837		.4945	.4889
		Number of animals reported with tumor	0	0	1	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0,8.0)	(0.06,11.8)	(0.06,12.0)
		Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	44.4
INTESTINE: COLON	Lipoma	P-value of test of trend or comparison	.4915		.4945	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0,8.0)	(0.06,11.8)	(0,8.4)
		Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	42.4
INTESTINE: DUODENU	Adenoma	P-value of test of trend or comparison	.2416			.4831
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0,8.0)	(0,7.9)	(0.06,12.3)
		Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.9
LIVER	Adenoma: hepatocyte	P-value of test of trend or comparison	.1802		.4945	.4831
		Number of animals reported with tumor	0	0	1	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0,8.0)	(0.06,11.8)	(0.06,12.3)
		Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.4
	Cholangioma	P-value of test of trend or comparison	.7458	1	.7473	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	46.6	44.5	45.6	43.4
M: QUADRICEPS	Sarcoma: not otherwise specified	P-value of test of trend or comparison	1	1	1	1

Reference ID: 3158913

Table A.8

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,11.8)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	45.6	44.1	45.6	43.2
MAMMARY GLAND	Adenocarcinoma	P-value of test of trend or comparison	.4217	.8468	.4781	.6385
		Number of animals reported with tumor	10	7	11	9
		Poly-3 adjusted incidence rate	21%	15%	23%	20%
		95% CI for poly-3 adjusted incidence rate (%)	(10.2,35.0)	(6.07,28.3)	(12,38.0)	(9.36,34.6)
		Poly-3 adjusted number of animals at risk	48.1	47.4	47.1	45.2
	Adenoma	P-value of test of trend or comparison	.8573	.1193	.0789	.8663
		Number of animals reported with tumor	2	6	7	1
		Poly-3 adjusted incidence rate	4.3%	13%	15%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.52,14.8)	(5.05,27.4)	(6.2,28.9)	(0.06,12.3)
		Poly-3 adjusted number of animals at risk	46.9	44.9	46.7	43.4
	Fibroadenoma	P-value of test of trend or comparison	.9350	.7474	.5578	.9576
		Number of animals reported with tumor	30	26	28	19
		Poly-3 adjusted incidence rate	57%	52%	56%	41%
		95% CI for poly-3 adjusted incidence rate (%)	(41.4,70.2)	(36.6,66.3)	(41.3,71.2)	(26.4,56.8)
		Poly-3 adjusted number of animals at risk	53.0	50.4	49.8	46.1
NASAL TISSUE	Adenoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.3)	(0,8.0)	(0,8.0)	(0,8.2)
		Poly-3 adjusted number of animals at risk	47.2	44.5	44.6	43.0
	Sarcoma: not otherwise specified	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.3)	(0,8.0)	(0,8.0)	(0,8.2)

Reference ID: 3158913

Table A.8

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	47.2	44.5	44.6	43.0
NERVE: SCIATIC	Schwannoma·benign: endocardial	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.4
OVARY	Tumor·benign: granulosa cell	P-value of test of trend or comparison	.7458	1	.7473	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.4
OVIDUCT	Sarcoma: smooth muscle	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.4
PANCREAS	Adenoma: islet cell	P-value of test of trend or comparison	.9214	.1737	.4917	1
		Number of animals reported with tumor	1	4	2	0
		Poly-3 adjusted incidence rate	2.1%	8.9%	4.4%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(2.42,21.2)	(0.53,15.1)	(0,8.2)
		Poly-3 adjusted number of animals at risk	46.5	45.1	45.6	43.4
	Carcinoma: islet cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.3)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	47.1	44.5	45.6	43.4
	Lipoma	P-value of test of trend or comparison	.4944		.4945	
		Number of animals reported with tumor	0	0	1	0

Reference ID: 3158913

Table A.8

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.4
PARATHYROID GLAND	Adenoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,11.8)	(0,8.6)	(0,8.4)	(0,8.6)
		Poly-3 adjusted number of animals at risk	45.5	41.8	42.4	41.0
PITUITARY GLAND	Adenoma: pars·distalis	P-value of test of trend or comparison	.9357	.9503	.5645	.9824
		Number of animals reported with tumor	40	33	41	27
		Poly-3 adjusted incidence rate	73%	61%	74%	56%
		95% CI for poly-3 adjusted incidence rate (%)	(59,85.0)	(45.9,74.1)	(59.7,85.3)	(40.2,70.5)
		Poly-3 adjusted number of animals at risk	54.6	54.3	55.1	48.6
	Adenoma: pars·intermedia	P-value of test of trend or comparison	.5657	.4831	.1874	.7296
		Number of animals reported with tumor	1	2	4	1
		Poly-3 adjusted incidence rate	2.1%	4.5%	8.5%	2.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0.54,15.5)	(2.32,20.4)	(0.06,12.6)
		Poly-3 adjusted number of animals at risk	46.9	44.9	47.0	42.3
	Carcinoma: pars·distalis	P-value of test of trend or comparison	.5799	.7643	.8933	.7444
		Number of animals reported with tumor	4	3	2	3
		Poly-3 adjusted incidence rate	8.4%	6.6%	4.3%	6.8%
		95% CI for poly-3 adjusted incidence rate (%)	(2.32,20.4)	(1.37,18.3)	(0.52,14.8)	(1.43,19.1)
		Poly-3 adjusted number of animals at risk	47.6	45.4	46.1	43.9
SALIV.GLD: MANDIB.	Adenoma	P-value of test of trend or comparison	.4972		.5000	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	45.5	44.4	45.6	43.0

Reference ID: 3158913

Table A.8

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
SKIN	Carcinoma: squamous cell	P-value of test of trend or comparison	.6099	.4831	.4889	
		Number of animals reported with tumor	0	1	1	0
		Poly-3 adjusted incidence rate	0.0%	2.3%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.06,12.3)	(0.06,12.0)	(0,8.4)
		Poly-3 adjusted number of animals at risk	46.2	43.8	44.9	42.4
	Fibroma	P-value of test of trend or comparison	.7757	.7416	.4917	1
		Number of animals reported with tumor	1	1	2	0
		Poly-3 adjusted incidence rate	2.2%	2.3%	4.4%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0.06,12.0)	(0.53,15.1)	(0,8.4)
		Poly-3 adjusted number of animals at risk	46.2	44.1	45.0	42.4
	Hemangioma	P-value of test of trend or comparison	.7428	1	.7416	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.2)	(0.06,12.0)	(0,8.4)
		Poly-3 adjusted number of animals at risk	46.2	43.5	44.6	42.4
	Histiocytoma: fibrous-malignant	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.2)	(0,8.0)	(0,8.4)
		Poly-3 adjusted number of animals at risk	46.3	43.5	44.6	42.4
	Lipoma	P-value of test of trend or comparison	.4914		.4889	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0,8.2)	(0.06,12.0)	(0,8.4)
		Poly-3 adjusted number of animals at risk	46.2	43.5	44.6	42.4
	Papilloma: squamous cell	P-value of test of trend or comparison	.4943		.4945	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%

Table A.8

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0,8.2)	(0.06,11.8)	(0,8.4)
		Poly-3 adjusted number of animals at risk	46.2	43.5	45.4	42.4
	Rhabdomyosarcoma	P-value of test of trend or comparison	.7371	.4831		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.06,12.3)	(0,8.0)	(0,8.4)
		Poly-3 adjusted number of animals at risk	46.2	43.5	44.6	42.4
	Sarcoma: fibrosarcoma	P-value of test of trend or comparison	.2347	.7357	1	.4655
		Number of animals reported with tumor	1	1	0	2
		Poly-3 adjusted incidence rate	2.2%	2.3%	0.0%	4.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0.06,12.3)	(0,8.0)	(0.57,16.2)
		Poly-3 adjusted number of animals at risk	46.2	43.7	44.6	42.6
	Sarcoma: not otherwise specified	P-value of test of trend or comparison	.2400			.4773
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0,8.2)	(0,8.0)	(0.06,12.6)
		Poly-3 adjusted number of animals at risk	46.2	43.5	44.6	42.5
	Tumor-benign: basal cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.2)	(0,8.0)	(0,8.4)
		Poly-3 adjusted number of animals at risk	46.2	43.5	44.6	42.4
THYROID GLAND	Adenoma: C-cell	P-value of test of trend or comparison	.1182	.6969	.3371	.2375
		Number of animals reported with tumor	10	9	13	14
		Poly-3 adjusted incidence rate	22%	20%	28%	31%
		95% CI for poly-3 adjusted incidence rate (%)	(10.9,37.1)	(9.36,34.6)	(15.6,43.5)	(17.7,46.6)
		Poly-3 adjusted number of animals at risk	45.8	45.5	46.3	45.6
	Carcinoma: C-cell	P-value of test of trend or comparison	.5701	1	.8832	.8707

Table A.8

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	2	0	1	1
		Poly-3 adjusted incidence rate	4.4%	0.0%	2.2%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.53,15.1)	(0,8.0)	(0.05,11.5)	(0.06,12.3)
		Poly-3 adjusted number of animals at risk	45.7	44.4	46.1	43.0
UTERUS: BODY/HORNS	Carcinoma: adenosquamous	P-value of test of trend or comparison	.4972		.5000	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	45.5	44.5	45.7	43.4
	Polyp: endometrial stroma	P-value of test of trend or comparison	.3170	.6209	.5169	.4470
		Number of animals reported with tumor	6	6	7	7
		Poly-3 adjusted incidence rate	13%	13%	15%	16%
		95% CI for poly-3 adjusted incidence rate (%)	(4.83,26.3)	(4.83,26.3)	(6.07,28.3)	(6.64,30.7)
		Poly-3 adjusted number of animals at risk	46.8	46.2	47.6	43.6
	Sarcoma: smooth muscle	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,11.8)	(0,8.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	45.5	44.5	45.6	43.4
VAGINA	Carcinoma: squamous cell	P-value of test of trend or comparison	.7458	.4944		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.2%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,7.9)	(0.06,12.0)	(0,7.9)	(0,8.2)
		Poly-3 adjusted number of animals at risk	45.5	45.0	45.6	43.4
	Polyp: vagina	P-value of test of trend or comparison	.4279	1	1	.7414
		Number of animals reported with tumor	1	0	0	1
		Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	2.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,11.8)	(0,8.0)	(0,7.9)	(0.06,12.3)

Reference ID: 3158913

Table A.8

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	45.8	44.5	45.6	43.9
	Tumor-benign: granular cell	P-value of test of trend or comparison	.7486	1	.7528	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	2.2%	0.0%	2.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.06,11.8)	(0,8.0)	(0.06,11.8)	(0,8.2)
		Poly-3 adjusted number of animals at risk	45.7	44.5	45.8	43.4

Reference ID: 3158913

Table A.9

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLAND	Adenoma: cortex	P-value of test of trend or comparison	.4839		.5000	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	33.8	31.0	29.8
	Pheochromocytoma·benign	P-value of test of trend or comparison	.8436	.9221	.9754	.9399
		Number of animals reported with tumor	8	5	3	4
		Poly-3 adjusted incidence rate	24%	14%	9.6%	13%
		95% CI for poly-3 adjusted incidence rate (%)	(11.1,43.4)	(4.67,30.3)	(1.98,25.8)	(3.51,29.8)
		Poly-3 adjusted number of animals at risk	33.0	35.7	31.2	31.9
	Pheochromocytoma·malignant	P-value of test of trend or comparison	.3007	.5231	.2459	.4918
		Number of animals reported with tumor	0	1	2	1
		Poly-3 adjusted incidence rate	0.0%	2.9%	6.4%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0.07,15.3)	(0.77,21.4)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	31.4	34.1	31.1	30.3
BRAIN	Astrocytoma·benign	P-value of test of trend or comparison	.0436	1	1	.2937
		Number of animals reported with tumor	1	0	0	3
		Poly-3 adjusted incidence rate	3.2%	0.0%	0.0%	9.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0,11.6)	(2.04,26.5)
		Poly-3 adjusted number of animals at risk	31.6	33.8	30.7	30.9
	Carcinoma: Pineal Gland	P-value of test of trend or comparison	.7500	.5231		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0.07,15.3)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	34.1	30.7	29.8
	Ependymoma·benign	P-value of test of trend or comparison	.2358			.4833
		Number of animals reported with tumor	0	0	0	1

Reference ID: 3158913

Table A.9

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	31.4	33.8	30.7	30.0
	Granular cell tumor	P-value of test of trend or comparison	.0570			.2377
		Number of animals reported with tumor	0	0	0	2
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	6.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0,11.6)	(0.79,22.1)
		Poly-3 adjusted number of animals at risk	31.4	33.8	30.7	30.2
	Oligodendroglioma·benign	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	3.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.2)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	32.1	33.8	30.7	29.8
EYE	Invasion: squamous cell carcinom	P-value of test of trend or comparison	.4839		.5000	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	33.8	31.5	29.2
	Schwannoma· benign	P-value of test of trend or comparison	.2358			.4833
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	31.4	33.8	30.7	29.4
HEART	Hemangioma	P-value of test of trend or comparison	.4839		.5000	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0.08,16.7)	(0,11.9)

Table A.9

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	31.4	33.8	31.2	29.8
	Schwannoma-malignant: endocardia	P-value of test of trend or comparison	.4839		.5000	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	33.8	31.1	29.8
INTESTINE: ILEUM	Adenocarcinoma	P-value of test of trend or comparison	.2358			.4833
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	31.4	33.8	30.7	30.0
KIDNEY	Adenoma: renal tubule	P-value of test of trend or comparison	.2419			.4918
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	31.4	33.8	30.7	30.2
	Carcinoma: renal tubule	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	3.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.7	33.8	30.7	29.8
	Liposarcoma: renal	P-value of test of trend or comparison	.8008	.2697		
		Number of animals reported with tumor	0	2	0	0
		Poly-3 adjusted incidence rate	0.0%	5.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0.7,19.7)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	34.2	30.7	29.8
LIVER	Adenoma: hepatocyte	P-value of test of trend or comparison	.5359	.7693	1	.7459
		Number of animals reported with tumor	1	1	0	1

Reference ID: 3158913

Table A.9

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	3.2%	2.9%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0.07,15.8)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	31.6	34.0	30.7	30.6
	Carcinoma: hepatocyte	P-value of test of trend or comparison	.5333	.7764	1	.7459
		Number of animals reported with tumor	1	1	0	1
		Poly-3 adjusted incidence rate	3.2%	2.9%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0.07,15.3)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	31.6	34.1	30.7	30.5
	Hemangioma	P-value of test of trend or comparison	.4797		.4918	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0.08,17.2)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	33.8	30.9	29.8
	Histiocytoma: fibrous-malignant	P-value of test of trend or comparison	.2358			.4833
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	31.4	33.8	30.7	30.0
LN: MESENTERIC	Hemangiosarcoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	3.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.7	33.8	30.7	29.8
LN: SUBMANDIBULAR	Metastasis: carcinoma-not otherw	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	3.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.6	33.7	30.1	29.6

Reference ID: 3158913

Table A.9

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
M: QUADRICEPS	Sarcoma: fibrosarcoma	P-value of test of trend or comparison	.4836		.4918	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.9)	(0.08,17.2)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	33.0	30.9	29.8
MAMMARY GLAND	Fibroadenoma	P-value of test of trend or comparison	.9610	.8494	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	5.8%	3.8%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.14,28.7)	(0.09,19.6)	(0,16.1)	(0,16.8)
		Poly-3 adjusted number of animals at risk	17.2	26.1	21.6	20.5
NASAL TISSUE	Invasion: squamous cell carcinom	P-value of test of trend or comparison	.2358			.4833
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	31.4	33.8	30.7	30.0
PANCREAS	Adenoma: acinar cell	P-value of test of trend or comparison	.7313	1	.7459	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	3.1%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0.08,17.2)	(0,11.9)
		Poly-3 adjusted number of animals at risk	32.0	33.8	30.8	29.8
	Adenoma: ductal cell	P-value of test of trend or comparison	.2419			.4918
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	31.4	33.8	30.7	30.2
	Adenoma: islet cell	P-value of test of trend or comparison	.6760	.7278	.3357	.8686
		Number of animals reported with tumor	2	2	4	1
		Poly-3 adjusted incidence rate	6.3%	5.8%	13%	3.3%

Table A.9

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0.77,21.4)	(0.7,19.7)	(3.51,29.8)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	31.7	34.5	31.7	30.0
	Carcinoma: islet cell	P-value of test of trend or comparison	.3039	.5231		.4918
		Number of animals reported with tumor	0	1	0	1
		Poly-3 adjusted incidence rate	0.0%	2.9%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0.07,15.3)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	31.4	34.3	30.7	30.3
PARATHYROID GLAND	Adenoma	P-value of test of trend or comparison	.3774	1	.3060	.7458
		Number of animals reported with tumor	1	0	3	1
		Poly-3 adjusted incidence rate	3.2%	0.0%	10%	3.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,17.2)	(0,10.9)	(2.04,26.5)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	30.9	32.3	30.0	29.6
PITUITARY GLAND	Adenoma: pars·distalis	P-value of test of trend or comparison	.2544	.3048	.7341	.2488
		Number of animals reported with tumor	28	34	25	34
		Poly-3 adjusted incidence rate	66%	73%	61%	75%
		95% CI for poly-3 adjusted incidence rate (%)	(49.1,80.4)	(57.4,85.7)	(44.5,77.3)	(58.9,87.1)
		Poly-3 adjusted number of animals at risk	42.4	46.8	40.8	45.6
	Adenoma: pars·intermedia	P-value of test of trend or comparison	.4895	.7693	.7459	.7373
		Number of animals reported with tumor	1	1	1	1
		Poly-3 adjusted incidence rate	3.2%	2.9%	3.2%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0.07,15.8)	(0.08,17.2)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	31.6	34.0	31.0	29.9
	Carcinoma: pars·distalis	P-value of test of trend or comparison	.4797		.4918	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0.08,17.2)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	33.8	30.9	29.5
	Oligodendroglioma·benign	P-value of test of trend or comparison	.4839		.5000	

Reference ID: 3158913

Table A.9

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	33.8	31.0	29.5
PROSTATE GLAND	Adenocarcinoma	P-value of test of trend or comparison	.4839		.5000	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	33.8	31.3	29.8
SKIN	Carcinoma: sebaceous cell	P-value of test of trend or comparison	.7500	.5231		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	2.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0.07,15.3)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	34.1	30.7	29.8
	Fibroma	P-value of test of trend or comparison	.9967	.9806	.8810	1
		Number of animals reported with tumor	8	3	5	0
		Poly-3 adjusted incidence rate	24%	8.7%	16%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(10.7,42.3)	(1.8,23.7)	(5.11,32.8)	(0,11.9)
		Poly-3 adjusted number of animals at risk	33.7	34.5	32.0	29.8
	Hemangioma	P-value of test of trend or comparison	.2419			.4918
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0,11.6)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	31.4	33.8	30.7	30.2
	Histiocytoma: fibrous·malignant	P-value of test of trend or comparison	.9205	.8971	.8811	1
		Number of animals reported with tumor	2	1	1	0
		Poly-3 adjusted incidence rate	6.3%	2.9%	3.2%	0.0%

Reference ID: 3158913

Table A.9

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		95% CI for poly-3 adjusted incidence rate (%)	(0.77,21.4)	(0.07,15.3)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.9	34.2	31.0	29.8
	Keratoacanthoma	P-value of test of trend or comparison	.8925	.7074	1	.9355
		Number of animals reported with tumor	3	3	0	1
		Poly-3 adjusted incidence rate	9.4%	8.7%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(1.98,25.8)	(1.8,23.7)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	31.9	34.4	30.7	30.0
	Lipoma	P-value of test of trend or comparison	.5204	.7615	1	.7290
		Number of animals reported with tumor	1	1	0	1
		Poly-3 adjusted incidence rate	3.1%	2.9%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.2)	(0.07,15.8)	(0,11.6)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	32.1	34.0	30.7	30.0
	Papilloma: squamous cell	P-value of test of trend or comparison	.9963	.9501	1	1
		Number of animals reported with tumor	3	1	0	0
		Poly-3 adjusted incidence rate	9.3%	2.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.92,25.0)	(0.07,15.3)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	32.3	34.5	30.7	29.8
	Sarcoma: hemangiosarcoma	P-value of test of trend or comparison	.4839		.5000	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0.08,16.7)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.4	33.8	31.6	29.8
	Tumor-benign: basal cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	3.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.6	33.8	30.7	29.8

Reference ID: 3158913

Table A.9

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
TESTIS	Adenoma: Leydig cell	P-value of test of trend or comparison	.8485	.6926	.8128	.9311
		Number of animals reported with tumor	3	3	2	1
		Poly-3 adjusted incidence rate	9.3%	8.7%	6.4%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(1.92,25.0)	(1.8,23.7)	(0.77,21.4)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	32.4	34.5	31.0	30.0
	Tumor·benign: Sertoli cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	3.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.6	33.8	30.7	29.8
THYMUS	Thymoma·benign	P-value of test of trend or comparison	.4732		.4821	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.6%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.9)	(0,11.6)	(0.09,19.0)	(0,13.2)
		Poly-3 adjusted number of animals at risk	29.5	30.2	27.7	26.3
THYROID GLAND	Adenoma: C-cell	P-value of test of trend or comparison	.2121	.1730	.1066	.1686
		Number of animals reported with tumor	4	9	9	8
		Poly-3 adjusted incidence rate	12%	24%	27%	24%
		95% CI for poly-3 adjusted incidence rate (%)	(3.4,29.0)	(11.4,41.2)	(13.3,46.7)	(11.1,43.4)
		Poly-3 adjusted number of animals at risk	32.5	37.0	33.0	33.0
	Adenoma: follicular cell	P-value of test of trend or comparison	.9668	.3806	.8689	1
		Number of animals reported with tumor	2	4	1	0
		Poly-3 adjusted incidence rate	6.2%	11%	3.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.74,20.8)	(3.11,26.7)	(0.08,17.2)	(0,11.9)
		Poly-3 adjusted number of animals at risk	32.3	35.7	30.7	29.8
	Carcinoma: C-cell	P-value of test of trend or comparison	.1802	.2697	.4918	.2377
		Number of animals reported with tumor	0	2	1	2

Reference ID: 3158913

Table A.9

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	0.0%	5.8%	3.3%	6.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0.7,19.7)	(0.08,17.2)	(0.79,22.1)
		Poly-3 adjusted number of animals at risk	31.4	34.3	30.6	30.6
	Carcinoma: follicular cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	2	0	0	0
		Poly-3 adjusted incidence rate	6.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.77,21.4)	(0,10.6)	(0,11.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	31.9	33.8	30.4	29.8
URINARY BLADDER	Carcinoma: transitional cell	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-3 adjusted incidence rate	3.1%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.2)	(0,10.6)	(0,11.6)	(0,12.3)
		Poly-3 adjusted number of animals at risk	32.3	33.8	30.7	29.0

Reference ID: 3158913

Table A.10

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
Adenomas and adenocarcinomas of the small intestine	P-value of test of trend or comparison	.2416			.4831
	Number of animals reported with tumor	0	0	0	1
	Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0,8.0)	(0,7.9)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.9
Adenomas and carcinomas of the adrenal cortex	P-value of test of trend or comparison	.5739	.6949	.9836	.6949
	Number of animals reported with tumor	7	6	2	6
	Poly-3 adjusted incidence rate	15%	13%	4.4%	14%
	95% CI for poly-3 adjusted incidence rate (%)	(6.2,28.9)	(5.05,27.4)	(0.53,15.1)	(5.05,27.4)
	Poly-3 adjusted number of animals at risk	46.9	45.0	45.6	44.3
All lipomas	P-value of test of trend or comparison	.3339	.4889	.1168	.4831
	Number of animals reported with tumor	0	1	3	1
	Poly-3 adjusted incidence rate	0.0%	2.2%	6.6%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.06,12.0)	(1.37,18.3)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.6
All pheochromocytomas	P-value of test of trend or comparison	.9343	.4831	1	1
	Number of animals reported with tumor	1	2	0	0
	Poly-3 adjusted incidence rate	2.1%	4.5%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0.54,15.5)	(0,7.9)	(0,8.2)
	Poly-3 adjusted number of animals at risk	46.5	44.6	45.6	43.4
Astrocytomas	P-value of test of trend or comparison	1	1	1	1
	Number of animals reported with tumor	1	0	0	0
	Poly-3 adjusted incidence rate	2.1%	0.0%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.0)	(0,7.9)	(0,8.2)
	Poly-3 adjusted number of animals at risk	46.8	44.5	45.6	43.4
Fibrosarcomas and Sarcomas (NOS) of the skin	P-value of test of trend or comparison	.0205	.6658	1	.1056
	Number of animals reported with tumor	2	2	0	6

Reference ID: 3158913

Table A.10

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted incidence rate	4.3%	4.5%	0.0%	14%
	95% CI for poly-3 adjusted incidence rate (%)	(0.52,14.8)	(0.56,15.8)	(0,8.0)	(5.3,28.5)
	Poly-3 adjusted number of animals at risk	46.2	44.0	44.6	42.9
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.7458	1	.7473	1
	Number of animals reported with tumor	1	0	1	0
	Poly-3 adjusted incidence rate	2.1%	0.0%	2.2%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.0)	(0.06,11.8)	(0,8.2)
	Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.4
Hepatocellular tumors	P-value of test of trend or comparison	.1802		.4945	.4831
	Number of animals reported with tumor	0	0	1	1
	Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0,8.0)	(0.06,11.8)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.4
Lipomas and hibernomas	P-value of test of trend or comparison	.3339	.4889	.1168	.4831
	Number of animals reported with tumor	0	1	3	1
	Poly-3 adjusted incidence rate	0.0%	2.2%	6.6%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.06,12.0)	(1.37,18.3)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.6
Lipomas and liposarcomas	P-value of test of trend or comparison	.3339	.4889	.1168	.4831
	Number of animals reported with tumor	0	1	3	1
	Poly-3 adjusted incidence rate	0.0%	2.2%	6.6%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.06,12.0)	(1.37,18.3)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.6
Lipomas, lipomasarcomas and hibernomas	P-value of test of trend or comparison	.3339	.4889	.1168	.4831
	Number of animals reported with tumor	0	1	3	1
	Poly-3 adjusted incidence rate	0.0%	2.2%	6.6%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.06,12.0)	(1.37,18.3)	(0.06,12.3)

Reference ID: 3158913

Table A.10

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.6
Luteomas and ovarian granulosa cell tumors	P-value of test of trend or comparison	.7458	1	.7473	1
	Number of animals reported with tumor	1	0	1	0
	Poly-3 adjusted incidence rate	2.1%	0.0%	2.2%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.0)	(0.06,11.8)	(0,8.2)
	Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	43.4
Mammary adenocarcinomas and adenocanthomas	P-value of test of trend or comparison	.4217	.8468	.4781	.6385
	Number of animals reported with tumor	10	7	11	9
	Poly-3 adjusted incidence rate	21%	15%	23%	20%
	95% CI for poly-3 adjusted incidence rate (%)	(10.2,35.0)	(6.07,28.3)	(12,38.0)	(9.36,34.6)
	Poly-3 adjusted number of animals at risk	48.1	47.4	47.1	45.2
Mammary adenomas and fibroadenomas	P-value of test of trend or comparison	.9711	.5989	.4358	.9720
	Number of animals reported with tumor	31	29	31	19
	Poly-3 adjusted incidence rate	58%	57%	62%	41%
	95% CI for poly-3 adjusted incidence rate (%)	(43.2,71.9)	(42.2,71.8)	(46.1,75.3)	(26.4,56.8)
	Poly-3 adjusted number of animals at risk	53.1	50.8	50.0	46.1
Mammary tumors	P-value of test of trend or comparison	.9615	.7087	.5260	.9710
	Number of animals reported with tumor	36	33	34	23
	Poly-3 adjusted incidence rate	66%	63%	67%	49%
	95% CI for poly-3 adjusted incidence rate (%)	(51.4,78.9)	(47.9,76.4)	(52.1,80.5)	(34.1,65.1)
	Poly-3 adjusted number of animals at risk	54.2	52.1	51.0	46.7
Pancreatic islet and acinar-islet cell tumors	P-value of test of trend or comparison	.9566	.3178	.6750	1
	Number of animals reported with tumor	2	4	2	0
	Poly-3 adjusted incidence rate	4.2%	8.9%	4.4%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.51,14.5)	(2.42,21.2)	(0.53,15.1)	(0,8.2)
	Poly-3 adjusted number of animals at risk	47.1	45.1	45.6	43.4
Pancreatic islet cell tumors	P-value of test of trend or comparison	.9566	.3178	.6750	1

Reference ID: 3158913

Table A.10

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Number of animals reported with tumor	2	4	2	0
	Poly-3 adjusted incidence rate	4.2%	8.9%	4.4%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.51,14.5)	(2.42,21.2)	(0.53,15.1)	(0,8.2)
	Poly-3 adjusted number of animals at risk	47.1	45.1	45.6	43.4
Pituitary pars distalis tumors	P-value of test of trend or comparison	.9645	.9735	.6801	.9932
	Number of animals reported with tumor	44	36	43	30
	Poly-3 adjusted incidence rate	79%	65%	77%	60%
	95% CI for poly-3 adjusted incidence rate (%)	(65.6,89.6)	(50.4,77.8)	(63.6,88.2)	(44.2,73.6)
	Poly-3 adjusted number of animals at risk	55.6	55.2	55.6	50.3
Pituitary pars intermedia tumors	P-value of test of trend or comparison	.5657	.4831	.1874	.7296
	Number of animals reported with tumor	1	2	4	1
	Poly-3 adjusted incidence rate	2.1%	4.5%	8.5%	2.4%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0.54,15.5)	(2.32,20.4)	(0.06,12.6)
	Poly-3 adjusted number of animals at risk	46.9	44.9	47.0	42.3
Schwannomas	P-value of test of trend or comparison	.3859	1	.7473	.7416
	Number of animals reported with tumor	1	0	1	1
	Poly-3 adjusted incidence rate	2.1%	0.0%	2.2%	2.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0.05,11.5)	(0,8.0)	(0.06,11.8)	(0.06,12.0)
	Poly-3 adjusted number of animals at risk	46.5	44.5	45.6	44.4
Squamous cell papillomas and carcinomas of the skin	P-value of test of trend or comparison	.6284	.4889	.2473	
	Number of animals reported with tumor	0	1	2	0
	Poly-3 adjusted incidence rate	0.0%	2.2%	4.3%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,7.7)	(0.06,12.0)	(0.52,14.8)	(0,8.2)
	Poly-3 adjusted number of animals at risk	46.5	44.8	46.7	43.4
Vaginal squamous cell tumors and polyps	P-value of test of trend or comparison	.5372	.7472	1	.7414
	Number of animals reported with tumor	1	1	0	1
	Poly-3 adjusted incidence rate	2.2%	2.2%	0.0%	2.3%

Reference ID: 3158913

Table A.10

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	95% CI for poly-3 adjusted incidence rate (%)	(0.06,11.8)	(0.06,12.0)	(0,7.9)	(0.06,12.3)
	Poly-3 adjusted number of animals at risk	45.8	45.0	45.6	43.9

Reference ID: 3158913

Table A.11

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
Adenomas and adenocarcinomas of the small intestine	P-value of test of trend or comparison	.2358			.4833
	Number of animals reported with tumor	0	0	0	1
	Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0,11.6)	(0.08,17.8)
	Poly-3 adjusted number of animals at risk	31.4	33.8	30.7	30.0
Adenomas and carcinomas of the adrenal cortex	P-value of test of trend or comparison	.7691	.8623	.8175	.8934
	Number of animals reported with tumor	8	6	6	5
	Poly-3 adjusted incidence rate	24%	17%	19%	15%
	95% CI for poly-3 adjusted incidence rate (%)	(11.1,43.4)	(6.37,33.6)	(6.98,36.4)	(5.11,32.8)
	Poly-3 adjusted number of animals at risk	33.0	36.0	32.1	32.4
All lipomas	P-value of test of trend or comparison	.5982	.8314	.9313	.7916
	Number of animals reported with tumor	3	2	1	2
	Poly-3 adjusted incidence rate	9.0%	5.8%	3.2%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(1.86,24.3)	(0.7,19.7)	(0.08,17.2)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	33.2	34.2	30.9	30.2
All pheochromocytomas	P-value of test of trend or comparison	.7728	.8623	.8816	.8934
	Number of animals reported with tumor	8	6	5	5
	Poly-3 adjusted incidence rate	24%	17%	16%	15%
	95% CI for poly-3 adjusted incidence rate (%)	(11.1,43.4)	(6.37,33.6)	(5.28,33.7)	(5.11,32.8)
	Poly-3 adjusted number of animals at risk	33.0	36.0	31.7	32.4
Astrocytomas	P-value of test of trend or comparison	.0436	1	1	.2937
	Number of animals reported with tumor	1	0	0	3
	Poly-3 adjusted incidence rate	3.2%	0.0%	0.0%	9.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0,11.6)	(2.04,26.5)
	Poly-3 adjusted number of animals at risk	31.6	33.8	30.7	30.9
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.1525	1	.5000	.4875
	Number of animals reported with tumor	1	0	2	2

Reference ID: 3158913

Table A.11

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted incidence rate	3.2%	0.0%	6.4%	6.5%
	95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0.77,21.4)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	31.7	33.8	31.3	30.7
Hepatocellular tumors	P-value of test of trend or comparison	.4949	.7278	1	.6938
	Number of animals reported with tumor	2	2	0	2
	Poly-3 adjusted incidence rate	6.3%	5.8%	0.0%	6.4%
	95% CI for poly-3 adjusted incidence rate (%)	(0.77,21.4)	(0.7,19.7)	(0,11.6)	(0.77,21.4)
	Poly-3 adjusted number of animals at risk	31.7	34.3	30.7	31.3
Lipomas and hibernomas	P-value of test of trend or comparison	.5982	.8314	.9313	.7916
	Number of animals reported with tumor	3	2	1	2
	Poly-3 adjusted incidence rate	9.0%	5.8%	3.2%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(1.86,24.3)	(0.7,19.7)	(0.08,17.2)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	33.2	34.2	30.9	30.2
Lipomas and liposarcomas	P-value of test of trend or comparison	.5982	.8314	.9313	.7916
	Number of animals reported with tumor	3	2	1	2
	Poly-3 adjusted incidence rate	9.0%	5.8%	3.2%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(1.86,24.3)	(0.7,19.7)	(0.08,17.2)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	33.2	34.2	30.9	30.2
Lipomas, lipomasarcomas and hibernomas	P-value of test of trend or comparison	.5982	.8314	.9313	.7916
	Number of animals reported with tumor	3	2	1	2
	Poly-3 adjusted incidence rate	9.0%	5.8%	3.2%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(1.86,24.3)	(0.7,19.7)	(0.08,17.2)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	33.2	34.2	30.9	30.2
Mammary adenomas and fibroadenomas	P-value of test of trend or comparison	.9610	.8494	1	1
	Number of animals reported with tumor	1	1	0	0
	Poly-3 adjusted incidence rate	5.8%	3.8%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.14,28.7)	(0.09,19.6)	(0,16.1)	(0,16.8)

Table A.11

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted number of animals at risk	17.2	26.1	21.6	20.5
Mammary tumors	P-value of test of trend or comparison	.9610	.8494	1	1
	Number of animals reported with tumor	1	1	0	0
	Poly-3 adjusted incidence rate	5.8%	3.8%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.14,28.7)	(0.09,19.6)	(0,16.1)	(0,16.8)
	Poly-3 adjusted number of animals at risk	17.2	26.1	21.6	20.5
Pancreatic acinar and acinar-islet cell tumors	P-value of test of trend or comparison	.7313	1	.7459	1
	Number of animals reported with tumor	1	0	1	0
	Poly-3 adjusted incidence rate	3.1%	0.0%	3.2%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0.08,17.2)	(0,11.9)
	Poly-3 adjusted number of animals at risk	32.0	33.8	30.8	29.8
Pancreatic acinar cell tumors	P-value of test of trend or comparison	.7313	1	.7459	1
	Number of animals reported with tumor	1	0	1	0
	Poly-3 adjusted incidence rate	3.1%	0.0%	3.2%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0.08,17.2)	(0,11.9)
	Poly-3 adjusted number of animals at risk	32.0	33.8	30.8	29.8
Pancreatic islet and acinar-islet cell tumors	P-value of test of trend or comparison	.5483	.5446	.3357	.6813
	Number of animals reported with tumor	2	3	4	2
	Poly-3 adjusted incidence rate	6.3%	8.6%	13%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(0.77,21.4)	(1.8,23.7)	(3.51,29.8)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	31.7	35.0	31.7	30.5
Pancreatic islet cell tumors	P-value of test of trend or comparison	.5483	.5446	.3357	.6813
	Number of animals reported with tumor	2	3	4	2
	Poly-3 adjusted incidence rate	6.3%	8.6%	13%	6.6%
	95% CI for poly-3 adjusted incidence rate (%)	(0.77,21.4)	(1.8,23.7)	(3.51,29.8)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	31.7	35.0	31.7	30.5
Pituitary pars distalis tumors	P-value of test of trend or comparison	.2540	.3048	.6525	.2488

Reference ID: 3158913

Table A.11

Table of reported tumors in Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
	Number of animals reported with tumor	28	34	26	34
	Poly-3 adjusted incidence rate	66%	73%	63%	75%
	95% CI for poly-3 adjusted incidence rate (%)	(49.1,80.4)	(57.4,85.7)	(46.9,79.4)	(58.9,87.1)
	Poly-3 adjusted number of animals at risk	42.4	46.8	41.0	45.6
Pituitary pars intermedia tumors	P-value of test of trend or comparison	.4895	.7693	.7459	.7373
	Number of animals reported with tumor	1	1	1	1
	Poly-3 adjusted incidence rate	3.2%	2.9%	3.2%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0.07,15.8)	(0.08,17.2)	(0.08,17.8)
	Poly-3 adjusted number of animals at risk	31.6	34.0	31.0	29.9
Renal tubule tumors	P-value of test of trend or comparison	.4268	1	1	.7459
	Number of animals reported with tumor	1	0	0	1
	Poly-3 adjusted incidence rate	3.2%	0.0%	0.0%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0,11.6)	(0.08,17.2)
	Poly-3 adjusted number of animals at risk	31.7	33.8	30.7	30.2
Schwannomas	P-value of test of trend or comparison	.1711		.5000	.4833
	Number of animals reported with tumor	0	0	1	1
	Poly-3 adjusted incidence rate	0.0%	0.0%	3.2%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0,11.2)	(0,10.6)	(0.08,16.7)	(0.08,17.8)
	Poly-3 adjusted number of animals at risk	31.4	33.8	31.1	30.0
Squamous cell papillomas and carcinomas of the skin	P-value of test of trend or comparison	.9963	.9501	1	1
	Number of animals reported with tumor	3	1	0	0
	Poly-3 adjusted incidence rate	9.3%	2.9%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(1.92,25.0)	(0.07,15.3)	(0,11.6)	(0,11.9)
	Poly-3 adjusted number of animals at risk	32.3	34.5	30.7	29.8

Reference ID: 3158913

Table A.12

Table of tumors reported significant in at least one arm - Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
SYSTEMIC NEOPLASM	Sarcoma: histiocytic	P-value of test of trend or comparison	.0238	1	.3333	.0714
		Number of animals reported with tumor	1	0	1	3
		Poly-3 adjusted incidence rate	19%	0.0%	100%	100%
		95% CI for poly-3 adjusted incidence rate (%)	(0.42,71.6)	(0,97.5)	(2.5,100)	(29.2,100)
		Poly-3 adjusted number of animals at risk	5.3	1.0	1.0	3.0

Reference ID: 3158913

Table A.13

Table of tumors reported significant in at least one arm - Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
BRAIN	Astrocytoma·benign	P-value of test of trend or comparison	.0436	1	1	.2937
		Number of animals reported with tumor	1	0	0	3
		Poly-3 adjusted incidence rate	3.2%	0.0%	0.0%	9.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0,11.6)	(2.04,26.5)
		Poly-3 adjusted number of animals at risk	31.6	33.8	30.7	30.9

Reference ID: 3158913

Table A.14

Table of tumors reported significant in at least one arm - Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
Fibrosarcomas and Sarcomas (NOS) of the skin	P-value of test of trend or comparison	.0205	.6658	1	.1056
	Number of animals reported with tumor	2	2	0	6
	Poly-3 adjusted incidence rate	4.3%	4.5%	0.0%	14%
	95% CI for poly-3 adjusted incidence rate (%)	(0.52,14.8)	(0.56,15.8)	(0,8.0)	(5.3,28.5)
	Poly-3 adjusted number of animals at risk	46.2	44.0	44.6	42.9

Reference ID: 3158913

Table A.15

Table of tumors reported significant in at least one arm - Rat Study
NDA 202992 (water control)
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
Astrocytomas	P-value of test of trend or comparison	.0436	1	1	.2937
	Number of animals reported with tumor	1	0	0	3
	Poly-3 adjusted incidence rate	3.2%	0.0%	0.0%	9.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.08,16.7)	(0,10.6)	(0,11.6)	(2.04,26.5)
	Poly-3 adjusted number of animals at risk	31.6	33.8	30.7	30.9

Reference ID: 3158913

Table A.16 ***Tumor counts for organs reported widely unanalyzed***
NDA 202992 (water control)
Animal carcinogenicity study
Rats

Species and Sex	*Organ or tissue name*	*Tumor name*	*Quantity*	*Water*	*Low dose*	*Mid dose*	*High dose*
Rats - Female	BODY CAV: ABDOMINA	Lipoma	Number of tumors found	0	0	0	1
			Number of animals examined	0	1	0	2
		Sarcoma: fibrosarcoma	Number of tumors found	0	1	0	0
			Number of animals examined	0	1	0	2
	BONE: JAW	Carcinoma: squamous cell	Number of tumors found	1	0	0	1
			Number of animals examined	1	0	0	1
	MESENTERIC TISSUE	Lipoma	Number of tumors found	0	1	0	0
			Number of animals examined	1	1	2	0
	SYSTEMIC NEOPLASM	Leukemia: granulocytic	Number of tumors found	3	0	0	0
			Number of animals examined	7	1	1	3
		Lymphoma-malignant	Number of tumors found	3	1	0	0
			Number of animals examined	7	1	1	3
		Sarcoma: histiocytic	Number of tumors found	1	0	1	3
			Number of animals examined	7	1	1	3
Rats - Male	BODY CAV: ABDOMINA	Fibroma	Number of tumors found	0	0	0	1
			Number of animals examined	0	0	0	1
	BONE: SKULL	Osteosarcoma	Number of tumors found	1	0	0	0
			Number of animals examined	1	0	0	1
		Sarcoma: fibrosarcoma	Number of tumors found	0	0	0	1
			Number of animals examined	1	0	0	1
	LN: ILIAC	Sarcoma: not otherwise specified	Number of tumors found	1	0	0	0
			Number of animals examined	1	0	1	0
	MESENTERIC TISSUE	Lipoma	Number of tumors found	2	1	1	1
			Number of animals examined	3	1	1	1
		Sarcoma: not otherwise specified	Number of tumors found	1	0	0	0
			Number of animals examined	3	1	1	1
	SKELETAL MUSCLE	Hemangiosarcoma	Number of tumors found	0	0	0	1
			Number of animals examined	0	0	1	1
		Sarcoma: fibrosarcoma	Number of tumors found	0	0	1	0
			Number of animals examined	0	0	1	1
	SYSTEMIC NEOPLASM	Leukemia: granulocytic	Number of tumors found	2	2	2	0
			Number of animals examined	2	4	3	0
		Lymphoma-malignant	Number of tumors found	0	2	1	0
			Number of animals examined	2	4	3	0

Appendix B

Tumor incidence tables excluding the high dose rat groups

The survival rates and weight gain levels displayed by the high dose groups in the rat studies suggest that these dose levels may have been excessive. Accordingly, it is appropriate to consider the results of the poly-3 analyses of the various tumor types and combination endpoints with these dose groups excluded. Note that the p-values of pairwise tests conducted in this appendix will be the same as those displayed in the corresponding tables in Chapter 2; only the tests of trend can yield new values.

Reference ID: 3158913

Table B.1

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
ADRENAL GLAND	Adenoma: cortex	P-value of test of trend or comparison	.5546	.2585	.6689
		Number of animals reported with tumor	4	4	2
	Carcinoma: cortex	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
	Pheochromocytoma·benign	P-value of test of trend or comparison	.8217	.4120	1
		Number of animals reported with tumor	2	2	0
	Pheochromocytoma·malignant	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	3	0	0
BRAIN	Astrocytoma·benign	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	4	0	0
CLITORAL GLAND	Tumor·benign: basal cell	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
HEART	Schwannoma·benign: endocardial	P-value of test of trend or comparison	.2557		.3409
		Number of animals reported with tumor	0	0	1
INTESTINE: COLON	Lipoma	P-value of test of trend or comparison	.2557		.3409
		Number of animals reported with tumor	0	0	1
INTESTINE: DUODENU	Fibroma	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
INTESTINE: JEJUNUM	Leiomyoma	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
KIDNEY	Lipoma: renal	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
LIVER	Adenoma: hepatocyte	P-value of test of trend or comparison	.4471	1	.5673
		Number of animals reported with tumor	1	0	1
	Cholangioma	P-value of test of trend or comparison	.2557		.3409
		Number of animals reported with tumor	0	0	1
LN: MESENTERIC	Histiocytoma: fibrous·malignant	P-value of test of trend or comparison	1	1	1

Reference ID: 3158913

Table B.1

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
		Number of animals reported with tumor	1	0	0
MAMMARY GLAND	Adenocarcinoma	P-value of test of trend or comparison	.3482	.8403	.4119
		Number of animals reported with tumor	18	7	11
	Adenoma	P-value of test of trend or comparison	.2434	.3945	.2975
		Number of animals reported with tumor	9	6	7
	Fibroadenoma	P-value of test of trend or comparison	.5967	.8313	.6434
		Number of animals reported with tumor	57	26	28
NASAL TISSUE	Invasion: squamous cell carcinom	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
OVARY	Tumor·benign: granulosa cell	P-value of test of trend or comparison	.2557		.3409
		Number of animals reported with tumor	0	0	1
PANCREAS	Adenoma: acinar-islet cell	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
	Adenoma: islet cell	P-value of test of trend or comparison	.3374	.1026	.4210
		Number of animals reported with tumor	2	4	2
	Lipoma	P-value of test of trend or comparison	.2557		.3409
		Number of animals reported with tumor	0	0	1
	Sarcoma: not otherwise specified	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
PARATHYROID GLAND	Adenoma	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
PITUITARY GLAND	Adenoma: pars·distalis	P-value of test of trend or comparison	.6443	.9879	.7013
		Number of animals reported with tumor	83	33	41
	Adenoma: pars·intermedia	P-value of test of trend or comparison	.0317	.2610	.0511
		Number of animals reported with tumor	1	2	4
	Carcinoma: pars·distalis	P-value of test of trend or comparison	.8048	.7099	.8724
		Number of animals reported with tumor	7	3	2

Reference ID: 3158913

Table B.1

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
SALIV.GLD: MANDIB.	Adenoma	P-value of test of trend or comparison	.2571		.3435
		Number of animals reported with tumor	0	0	1
SALIV.GLD: SUBLIN.	Lipoma	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
SKIN	Carcinoma: squamous cell	P-value of test of trend or comparison	.4019	.5608	.5676
		Number of animals reported with tumor	1	1	1
	Fibroma	P-value of test of trend or comparison	.3087	.7139	.4257
		Number of animals reported with tumor	2	1	2
	Hemangioma	P-value of test of trend or comparison	.4473	1	.5676
		Number of animals reported with tumor	1	0	1
	Lipoma	P-value of test of trend or comparison	.2558		.3411
		Number of animals reported with tumor	0	0	1
	Papilloma: squamous cell	P-value of test of trend or comparison	.2601		.3462
		Number of animals reported with tumor	0	0	1
	Rhabdomyosarcoma	P-value of test of trend or comparison	.5058	.3359	
		Number of animals reported with tumor	0	1	0
	Sarcoma: fibrosarcoma	P-value of test of trend or comparison	.7572	.5608	1
		Number of animals reported with tumor	1	1	0
	Sarcoma: hemangiosarcoma	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
THYMUS	Hibernoma	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
	Thymoma·benign	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
THYROID GLAND	Adenoma: C-cell	P-value of test of trend or comparison	.0370	.2874	.0487
		Number of animals reported with tumor	13	9	13
	Carcinoma: C-cell	P-value of test of trend or comparison	.6089	1	.7201

Reference ID: 3158913

Table B.1

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
		Number of animals reported with tumor	2	0	1
UTERUS: BODY/HORNS	Carcinoma: adenosquamous	P-value of test of trend or comparison	.2586		.3462
		Number of animals reported with tumor	0	0	1
	Polyp: endometrial stroma	P-value of test of trend or comparison	.4761	.6622	.5473
		Number of animals reported with tumor	12	6	7
UTERUS: CERVIX	Carcinoma: squamous cell	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
VAGINA	Carcinoma: squamous cell	P-value of test of trend or comparison	.5115	.3411	
		Number of animals reported with tumor	0	1	0
	Polyp: vagina	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
	Tumor-benign: granular cell	P-value of test of trend or comparison	.7358	1	.8217
		Number of animals reported with tumor	3	0	1

Reference ID: 3158913

Table B.2

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
ADRENAL GLAND	Adenoma: cortex	P-value of test of trend or comparison	.6812	1	.7673
		Number of animals reported with tumor	3	0	1
	Carcinoma: cortex	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
	Pheochromocytoma·benign	P-value of test of trend or comparison	.9486	.8801	.9642
		Number of animals reported with tumor	16	5	3
	Pheochromocytoma·malignant	P-value of test of trend or comparison	.2502	.6951	.3544
		Number of animals reported with tumor	2	1	2
BRAIN	Astrocytoma·benign	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	2	0	0
	Carcinoma: Pineal Gland	P-value of test of trend or comparison	.4776	.3269	
		Number of animals reported with tumor	0	1	0
	Granular cell tumor	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	2	0	0
	Meningioma·malignant	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
	Reticulosis·malignant	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
EYE	Invasion: squamous cell carcinom	P-value of test of trend or comparison	.2313		.3069
		Number of animals reported with tumor	0	0	1
HEART	Hemangioma	P-value of test of trend or comparison	.2313		.3069
		Number of animals reported with tumor	0	0	1
	Schwannoma·malignant: endocardia	P-value of test of trend or comparison	.2313		.3069
		Number of animals reported with tumor	0	0	1
KIDNEY	Liposarcoma: renal	P-value of test of trend or comparison	.4619	.1047	
		Number of animals reported with tumor	0	2	0
LIVER	Adenoma: hepatocyte	P-value of test of trend or comparison	.7249	.5403	1

Reference ID: 3158913

Table B.2

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
		Number of animals reported with tumor	1	1	0
	Carcinoma: hepatocyte	P-value of test of trend or comparison	.8575	.6951	1
		Number of animals reported with tumor	2	1	0
	Cholangioma	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
	Hemangioma	P-value of test of trend or comparison	.2256		.3000
		Number of animals reported with tumor	0	0	1
LUNG/BRONCHI	Metastasis: sarcoma-not otherwis	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
M: QUADRICEPS	Sarcoma: fibrosarcoma	P-value of test of trend or comparison	.2273		.3000
		Number of animals reported with tumor	0	0	1
MAMMARY GLAND	Adenocarcinoma	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	2	0	0
	Adenoma	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
	Fibroadenoma	P-value of test of trend or comparison	.8750	.7332	1
		Number of animals reported with tumor	2	1	0
PANCREAS	Adenocarcinoma: acinar cell	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
	Adenoma: acinar cell	P-value of test of trend or comparison	.3989	1	.5079
		Number of animals reported with tumor	1	0	1
	Adenoma: acinar-islet cell	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
	Adenoma: islet cell	P-value of test of trend or comparison	.3525	.8502	.4333
		Number of animals reported with tumor	7	2	4
	Carcinoma: islet cell	P-value of test of trend or comparison	.8575	.6951	1
		Number of animals reported with tumor	2	1	0

Reference ID: 3158913

Table B.2

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
PARATHYROID GLAND	Adenoma	P-value of test of trend or comparison	.1591	1	.2565
		Number of animals reported with tumor	3	0	3
PITUITARY GLAND	Adenoma: pars-distalis	P-value of test of trend or comparison	.3223	.0500	.3872
		Number of animals reported with tumor	51	34	25
	Adenoma: pars-intermedia	P-value of test of trend or comparison	.1623	.3204	.3000
		Number of animals reported with tumor	0	1	1
	Carcinoma: pars-distalis	P-value of test of trend or comparison	.5495	1	.6570
		Number of animals reported with tumor	2	0	1
	Oligodendroglioma-benign	P-value of test of trend or comparison	.2313		.3069
		Number of animals reported with tumor	0	0	1
PROSTATE GLAND	Adenocarcinoma	P-value of test of trend or comparison	.2313		.3069
		Number of animals reported with tumor	0	0	1
SALIV.GLD: SUBLIN.	Adenoma	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
SKIN	Carcinoma: sebaceous cell	P-value of test of trend or comparison	.7290	.5491	1
		Number of animals reported with tumor	1	1	0
	Fibroma	P-value of test of trend or comparison	.3570	.8032	.4306
		Number of animals reported with tumor	9	3	5
	Histiocytoma: fibrous-malignant	P-value of test of trend or comparison	.3550	.5449	.5176
		Number of animals reported with tumor	1	1	1
	Keratoacanthoma	P-value of test of trend or comparison	.9606	.5985	1
		Number of animals reported with tumor	6	3	0
	Lipoma	P-value of test of trend or comparison	.9610	.8584	1
		Number of animals reported with tumor	4	1	0
	Papilloma: squamous cell	P-value of test of trend or comparison	.9266	.7967	1
		Number of animals reported with tumor	3	1	0
	Sarcoma: fibrosarcoma	P-value of test of trend or comparison	1	1	1

Reference ID: 3158913

Table B.2

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
		Number of animals reported with tumor	3	0	0
	Sarcoma: hemangiosarcoma	P-value of test of trend or comparison	.2313		.3069
		Number of animals reported with tumor	0	0	1
	Tumor·benign: basal cell	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
SPINAL CORD: CERVI	Astrocytoma·benign	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
STOMACH	Leiomyoma:	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
TESTIS	Adenoma: Leydig cell	P-value of test of trend or comparison	.7348	.6815	.8182
		Number of animals reported with tumor	7	3	2
	Seminoma·benign	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	1	0	0
THYMUS	Thymoma·benign	P-value of test of trend or comparison	.2160		.2842
		Number of animals reported with tumor	0	0	1
THYROID GLAND	Adenoma: C-cell	P-value of test of trend or comparison	.1295	.2744	.1657
		Number of animals reported with tumor	13	9	9
	Adenoma: follicular cell	P-value of test of trend or comparison	.2437	.0110	.3000
		Number of animals reported with tumor	0	4	1
	Carcinoma: C-cell	P-value of test of trend or comparison	.4701	.3902	.6570
		Number of animals reported with tumor	2	2	1
	Ganglioneuroma	P-value of test of trend or comparison	1	1	1
		Number of animals reported with tumor	2	0	0

Reference ID: 3158913

Table B.3

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
Adenomas and carcinomas of the adrenal cortex	P-value of test of trend or comparison	.9148	.4530	.9571
	Number of animals reported with tumor	10	6	2
All lipomas	P-value of test of trend or comparison	.4484	.9192	.5540
	Number of animals reported with tumor	5	1	3
All pheochromocytomas	P-value of test of trend or comparison	.9685	.7438	1
	Number of animals reported with tumor	5	2	0
Astrocytomas	P-value of test of trend or comparison	1	1	1
	Number of animals reported with tumor	4	0	0
Fibrosarcomas and Sarcomas (NOS) of the skin	P-value of test of trend or comparison	.8219	.4121	1
	Number of animals reported with tumor	2	2	0
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.4471	1	.5673
	Number of animals reported with tumor	1	0	1
Hepatocellular tumors	P-value of test of trend or comparison	.4471	1	.5673
	Number of animals reported with tumor	1	0	1
Lipomas and hibernomas	P-value of test of trend or comparison	.5546	.9476	.6481
	Number of animals reported with tumor	6	1	3
Lipomas and liposarcomas	P-value of test of trend or comparison	.4484	.9192	.5540
	Number of animals reported with tumor	5	1	3
Lipomas, lipomasarcomas and hibernomas	P-value of test of trend or comparison	.5546	.9476	.6481
	Number of animals reported with tumor	6	1	3
Luteomas and ovarian granulosa cell tumors	P-value of test of trend or comparison	.2557		.3409
	Number of animals reported with tumor	0	0	1
Mammary adenocarcinomas and adenocanthomas	P-value of test of trend or comparison	.3482	.8403	.4119
	Number of animals reported with tumor	18	7	11
Mammary adenomas and fibroadenomas	P-value of test of trend or comparison	.6578	.8425	.7045
	Number of animals reported with tumor	63	29	31
Mammary tumors	P-value of test of trend or comparison	.7263	.9033	.7699

Reference ID: 3158913

Table B.3

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
	Number of animals reported with tumor	73	33	34
Pancreatic acinar and acinar-islet cell tumors	P-value of test of trend or comparison	1	1	1
	Number of animals reported with tumor	1	0	0
Pancreatic islet and acinar-islet cell tumors	P-value of test of trend or comparison	.4479	.1792	.5567
	Number of animals reported with tumor	3	4	2
Pancreatic islet cell tumors	P-value of test of trend or comparison	.3374	.1026	.4210
	Number of animals reported with tumor	2	4	2
Pituitary pars distalis tumors	P-value of test of trend or comparison	.6881	.9912	.7437
	Number of animals reported with tumor	90	36	43
Pituitary pars intermedia tumors	P-value of test of trend or comparison	.0317	.2610	.0511
	Number of animals reported with tumor	1	2	4
Schwannomas	P-value of test of trend or comparison	.4471	1	.5673
	Number of animals reported with tumor	1	0	1
Squamous cell papillomas and carcinomas of the skin	P-value of test of trend or comparison	.1795	.5607	.2745
	Number of animals reported with tumor	1	1	2
Vaginal squamous cell tumors and polyps	P-value of test of trend or comparison	.7599	.5641	1
	Number of animals reported with tumor	1	1	0

Reference ID: 3158913

Table B.4

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
Adenomas and carcinomas of the adrenal cortex	P-value of test of trend or comparison	.8683	.9273	.8900
	Number of animals reported with tumor	21	6	6
All lipomas	P-value of test of trend or comparison	.7143	.6359	.8356
	Number of animals reported with tumor	4	2	1
All pheochromocytomas	P-value of test of trend or comparison	.8457	.8557	.8773
	Number of animals reported with tumor	18	6	5
Astrocytomas	P-value of test of trend or comparison	1	1	1
	Number of animals reported with tumor	3	0	0
Fibrosarcomas and Sarcomas (NOS) of the skin	P-value of test of trend or comparison	1	1	1
	Number of animals reported with tumor	6	0	0
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.0522		.0921
	Number of animals reported with tumor	0	0	2
Hepatocellular tumors	P-value of test of trend or comparison	.8672	.5230	1
	Number of animals reported with tumor	3	2	0
Lipomas and hibernomas	P-value of test of trend or comparison	.7143	.6359	.8356
	Number of animals reported with tumor	4	2	1
Lipomas and liposarcomas	P-value of test of trend or comparison	.7143	.6359	.8356
	Number of animals reported with tumor	4	2	1
Lipomas, lipomasarcomas and hibernomas	P-value of test of trend or comparison	.7143	.6359	.8356
	Number of animals reported with tumor	4	2	1
Mammary adenocarcinomas and adenocanthomas	P-value of test of trend or comparison	1	1	1
	Number of animals reported with tumor	2	0	0
Mammary adenomas and fibroadenomas	P-value of test of trend or comparison	.9389	.8309	1
	Number of animals reported with tumor	3	1	0
Mammary tumors	P-value of test of trend or comparison	.9849	.9306	1
	Number of animals reported with tumor	5	1	0
Pancreatic acinar and acinar-islet cell tumors	P-value of test of trend or comparison	.6715	1	.7579

Reference ID: 3158913

Table B.4

Table of reported tumors in Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
	Number of animals reported with tumor	3	0	1
Pancreatic acinar cell tumors	P-value of test of trend or comparison	.5461	1	.6526
	Number of animals reported with tumor	2	0	1
Pancreatic islet and acinar-islet cell tumors	P-value of test of trend or comparison	.5164	.8096	.5924
	Number of animals reported with tumor	9	3	4
Pancreatic islet cell tumors	P-value of test of trend or comparison	.5164	.8096	.5924
	Number of animals reported with tumor	9	3	4
Pituitary pars distalis tumors	P-value of test of trend or comparison	.2864	.0706	.3494
	Number of animals reported with tumor	53	34	26
Pituitary pars intermedia tumors	P-value of test of trend or comparison	.1623	.3204	.3000
	Number of animals reported with tumor	0	1	1
Schwannomas	P-value of test of trend or comparison	.2313		.3069
	Number of animals reported with tumor	0	0	1
Squamous cell papillomas and carcinomas of the skin	P-value of test of trend or comparison	.9611	.8619	1
	Number of animals reported with tumor	4	1	0

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Table B.5

Table of tumors reported significant in at least one arm - Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
PITUITARY GLAND	Adenoma: pars-intermedia	P-value of test of trend or comparison	.0317	.2610	.0511
		Number of animals reported with tumor	1	2	4
THYROID GLAND	Adenoma: C-cell	P-value of test of trend or comparison	.0370	.2874	.0487
		Number of animals reported with tumor	13	9	13

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Table B.6

Table of tumors reported significant in at least one arm - Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
PITUITARY GLAND	Adenoma: pars-distalis	P-value of test of trend or comparison	.3223	.0500	.3872
		Number of animals reported with tumor	51	34	25
THYROID GLAND	Adenoma: follicular cell	P-value of test of trend or comparison	.2437	.0110	.3000
		Number of animals reported with tumor	0	4	1

Reference ID: 3158913

Table B.7

Table of tumors reported significant in at least one arm - Rat Study
NDA 202992 (high dose rats excluded)
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low Dose*	*Mid Dose*
Pituitary pars intermedia tumors	P-value of test of trend or comparison	.0317	.2610	.0511
	Number of animals reported with tumor	1	2	4

Reference ID: 3158913

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/s/

MATTHEW T JACKSON
07/13/2012

KARL K LIN
07/13/2012
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 Serial Number:	202,992 /000
Drug Name:	Teriflunomide
Indication(s):	Multiple Sclerosis
Applicant:	Sanofi Aventis
Date(s):	Date of Submission: August 15, 2011
	PDUFA Due Date: June 15, 2012
Review Priority:	Standard Review
Biometrics Division:	Division I
Statistical Reviewer:	Sharon Yan, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader
	Kooros Mahjoob, Ph.D., Deputy Director
Medical Division:	Neurology
Clinical Team:	Jody Green, M.D., Clinical Reviewer
	Evelyn Mentari, M.D., Safety Reviewer
	Lourdes Villalba, M.D., Safety Reviewer
	Billy Dunn, M.D., Team Leader
	Eric Bastings, M.D., Deputy Director
	Russell Katz, M.D., Director
Project Manager:	Hamet Toure, Pharm.D., Lt.

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1 EXECUTIVE SUMMARY

The demonstration of the efficacy of Teriflunomide in reducing the relapse rate in the treatment of relapsing MS as monotherapy is based on the robust and consistent results of the pivotal Study EFC5049/TEMSO and supported by limited interim results of the ongoing pivotal Study EFC10531/TOWER.

In Study TEMSO conducted in 1086 patients, both 7 mg and 14 mg doses of Teriflunomide significantly reduced relapse rate in patients with relapsing MS. The model adjusted annualized relapse rate (ARR) was 0.539 in the placebo group, 0.370 in the Teriflunomide 7 mg group, and 0.369 in the Teriflunomide 14 mg group (Table 5). These results corresponded to a relative risk reduction of 31.2% (p=0.0002) in the Teriflunomide 7 mg group and 31.5% (p=0.0005) in the Teriflunomide 14 mg group compared to placebo.

Disability progression (key secondary endpoint) was statistically significantly reduced in the Teriflunomide 14 mg group compared to the placebo group (p=0.0279) but not in the 7 mg dose group (p=0.0835). The estimated percentage of patients with 12-week sustained disability progression at Week 108 was 27.3%, 21.7%, and 20.2% in the placebo group, the Teriflunomide 7 mg group, and the Teriflunomide 14 mg group, respectively (Table 7).

In the examination of EDSS score change, which the determination of disability progression was based on, the data suggested no or little treatment difference at Week 48 and Week 108 (Table 8). The mean change in EDSS score for the placebo group was slightly better than both active treatments at Week 48 but slightly worse than the Teriflunomide 14 mg at the Week 108.

The trend of time to disability progression turned into opposite direction in the region of Americas, in which both dose groups of Teriflunomide observed more patients reaching progression than the placebo group (Table 19). The region of Americas consisted of 245 (22.6%) patients with majority of them Canadians.

In a similarly designed Study TOWER conducted in 1092 patients, both 7 mg and 14 mg Teriflunomide significantly reduced relapse rate based on interim data. The adjusted ARR was 0.531 in the placebo group, 0.371 in the Teriflunomide 7 mg group, and 0.321 in the Teriflunomide 14 mg group. These results corresponded to a relative risk reduction of 30.2% (p=0.0072) in the Teriflunomide 7 mg group and 39.6% (p=0.0002) in the Teriflunomide 14 mg group compared to placebo. No other efficacy variables were analyzed for this study due to the ongoing nature of the study.

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2 INTRODUCTION

2.1 Overview

Teriflunomide (HMR1726) is a novel immunomodulator targeting the immunoinflammatory basis of multiple sclerosis. Teriflunomide is currently developed for the treatment of patients with relapsing forms of multiple sclerosis (b) (4)

The development of the monotherapy program consisted of one phase 2 study (Protocol 2001) and two phase 3 pivotal studies (TEMSO and TOWER). The statistical evaluation of efficacy of Teriflunomide is based on data collected from TEMSO study and limited interim data of TOWER study, which is still ongoing. The two studies are similarly designed with the same primary endpoint of annual relapse rate. The phase 2 Study 2001 was conducted using an MRI variable as a primary endpoint with much shorter duration (36 weeks), and is therefore not included in this review.

Study EFC6049/TEMSO (referred as TEMSO thereafter) is a randomized, double-blind, placebo controlled, parallel-group, multinational phase 3 trial conducted in 21 countries in Europe and Americas, including 4 sites in the United States. The study randomized 1088 subjects with relapsing forms of multiple sclerosis (MS) to receive Teriflunomide 7 mg, 14 mg, or placebo for duration of approximately 2 years.

Study EFC10531/TOWER (referred as TOWER thereafter) has a similar design to TEMSO except that the duration of treatment is variable. The study is to end when the last patient enrolled completes the 48 weeks of treatment. The study randomized 1096 subjects in 26 countries in Europe, Asia, Africa, Australia, and Americas, including 39 sited in the United States. The study is currently ongoing.

The submission of the interim results of TOWER is based on an agreement reached between FDA and Sanofi-Aventis at the pre-NDA meeting. The interim analysis is to provide additional evidence on the benefit/risk of Teriflunomide for regulatory purposes. The unblinded interim analysis was conducted by an independent group within Sanofi-Aventis that had no involvement in this study or in the Teriflunomide project. Specific steps were taken to maintain the blind of the study to all those involved in the conduct and analysis of the study.

A summary of the two studies is presented in the following table.

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Table 1 List of studies included in this review

Study	Phase and Design	Duration of treatment	Dosage	Comparator	# of Subjects randomized	Study Population
EFC6049/ TEMSO	Phase 3, randomized, 3-arm, placebo controlled	2 years	7 mg and 14 mg	Placebo	1088	Relapsing-remitting, secondary progressive
EFC10531/ TOWER	Phase 3, randomized, 3-arm, placebo controlled	48 weeks from the last subject randomized	7 mg and 14 mg	Placebo	1096	Relapsing MS

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form, in eCTD format. The electronic files are compatible with eCTD viewer software Global Summit. Both raw and derived datasets are included in the submission. The SAS programs for primary and secondary analyses are also included. The path to CDER Electronic Document Room for documents of this NDA is listed below:

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No major data quality issues were identified.

3.2 Evaluation of Efficacy

3.2.1 Evaluation of TEMSO Study

3.2.1.1 Study Design and Endpoints

3.2.1.1.1 Study Design

The primary objective of the TEMSO study was to determine the effect of Teriflunomide in reducing the frequency of relapses in subjects with relapsing MS.

This was a multicenter, multinational, randomized, placebo-controlled, double-blind, parallel-group study.

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After a screening phase of up to 4 weeks, the patients were randomized in 1:1:1 ratio to one of the three treatment groups to receive daily doses of placebo, Teriflunomide 7 mg, or Teriflunomide 14 mg. Randomization was stratified, based on center and by patient's EDSS score (≤ 3.5 or > 3.5). The duration of the study was approximately 2 years. Patients who had successfully completed the study treatment were offered the opportunity to enter an optional long-term extension study under a different protocol.

The study enrolled patients who aged 18 to 55, met McDonald's criteria for MS diagnosis, exhibited a relapsing clinical course with or without progression (relapsing remitting, secondary progressive, or progressive relapsing), experienced at least 1 relapse over the 1 year preceding the trial or at least 2 relapses over the 2 years preceding the trial, and had EDSS score of 5.5 or less.

Approximately 1080 patients were planned to complete the study. A total of 1088 patients were actually randomized. The study was carried out in 126 sites in 21 countries in Europe and Americas, including 4 sites in the United States.

3.2.1.1.2 Efficacy Endpoints

The primary efficacy variable was the annualized relapse rate (ARR), defined as the number of confirmed relapses per patient-year.

A relapse was defined as the appearance of a new clinical sign/symptom or clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persisted for a minimum of 24 hours in the absence of fever. Each episode of relapse was to be confirmed by the treating neurologist (unblinded), based on objective assessments by an independent examining neurologist (blinded) documenting increases in either functional system (FS) or EDSS score that met the criteria for a confirmed relapse.

The key secondary efficacy variable was time to disability progression, which was defined as the time to at least 1 point increase on EDSS score from baseline (if the baseline EDSS score was ≤ 5.5) or time to at least 0.5 point increase on EDSS score from baseline (if the baseline EDSS score was >5.5) and this increase in EDSS score was to be persistent for at least 12 weeks.

Other secondary efficacy variables were:

- Proportion of patients free of disability progression at 6 months, 1 year, and 2 years
- Fatigue Impact Scale (FIS) total score and domain scores
- Magnetic resonance imaging (MRI) variables

The key MRI secondary variable was the burden of disease. Burden of disease (BOD) was defined as the total volume of all abnormal brain tissue (calculated as the sum of the total volume of T2 lesion component and T1 hypointense lesion component).

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Other MRI secondary variables were the total number of T1 Gd-enhancing lesions per MRI scan, the total volume of T1 Gd-enhancing lesions per MRI scan, the volume of hypointense post-Gd T1 lesions (black holes), and the volume of T2 lesion component.

3.2.1.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.1.2.1 Patient Disposition

A total of 1338 patients were screened and 1088 patients were randomized. Two screen failure patients were randomized but were not treated with the study medications. These two patients are not included in the efficacy analyses.

Among the 1086 treated patients, 290 patients (placebo: 104 [28.7%]; 7 mg Teriflunomide: 91 [24.9%]; 14 mg Teriflunomide: 95 [26.5%]) did not complete the study treatments. The most frequent reasons for the study treatment discontinuations were AEs, the subjects did not wish to continue with the study, and lack of efficacy. A summary of patient disposition is presented in Table 2.

Table 2 Patient disposition – randomized patients - TEMSO

	Placebo N=363	Teriflunomide 7 mg N=366	Teriflunomide 14 mg N=359
Randomized and not treated		1 (0.3%)	1 (0.3%)
Randomized and treated	363 (100%)	365 (99.7%)	358 (99.7%)
Completed treatment period	259 (71.3%)	274 (74.9%)	263 (73.3%)
Completed study	290 (79.9%)	296 (80.9%)	283 (78.8%)
Did not complete treatment period	104 (28.7%)	91 (24.9%)	95 (26.5%)
Reason for treatment discontinuation			
Adverse event	29 (8.0%)	37 (10.1%)	38 (10.6%)
Lack of efficacy	24 (6.6%)	14 (3.8%)	17 (4.7%)
Protocol violation	3 (0.8%)	2 (0.5%)	5 (1.4%)
Lost of follow-up	4 (1.1%)	0	2 (0.6%)
Progressive disease	11 (3.0%)	4 (1.1%)	2 (0.6%)
Subject did not wish to continue	33 (9.1%)	32 (8.7%)	26 (7.2%)
Other	0	2 (0.5%)	5 (1.4%)

(Source: Selected from Table 10 in the TEMSO study report)

Reviewer's Comments: *The treatment discontinuation rate in this study is quite high. Other than the reason of adverse event, a large number of patients discontinued treatment for reason of "subjects did not wish to continue" or "lack of efficacy". Some patients discontinued study at the time of blind broken, although it is not clear whether or not the discontinuation was due to unblinding.*

A total of 40 randomization codes were broken during this study. Of these 40 cases, 18 codes (9 in placebo, 6 in 7 mg Teriflunomide, and 3 in 14 mg Teriflunomide) were broken due to medical

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and accidental reasons at the local level and 29 codes (9 in placebo, 10 in 7 mg Teriflunomide, and 10 in 14 mg Teriflunomide) were broken for regulatory purposes. There were 7 patients whose codes were broken for both medical and regulatory purposes.

The sponsor provided a list of reasons for blind broken after FDA's request. Some reasons do not appear to justify the necessity of blind broken in the reviewer's opinion. For example, the listed reasons included: no information available (1 subject), switching to alternative therapy (5 subjects), partner pregnancy (1 subject), and MS relapse (2 subjects). These subjects were listed in the category of medical/accidental reasons at local level. Seven subjects completed study after being unblinded; three of them continued in the study for about a year after being unblinded and completed the study. Two subjects (1 in the placebo group and 1 in the Teriflunomide 7 mg group) had confirmed progression that occurred after being unblinded.

In summary, the large number of blind broken and treatment discontinuation, particularly treatment discontinuation due to "subjects did not wish to continue" is of concern that the quality of the study conduct might be in question.

The intent-to-treat (ITT) population was used for the analyses of all efficacy variables. The ITT population was defined as all randomized patients who had at least 1 day of study medication exposure. All patients were analyzed in the treatment group to which they were randomized. The ITT patient population for this study consisted of 1086 subjects.

A total of 27 patients in the ITT population (10 in the placebo group, 9 in 7 mg Teriflunomide group and 8 in 14 mg Teriflunomide group) were excluded from the per-protocol patient population due to various protocol violations.

3.2.1.2.2 Patient Demographic and Baseline Characteristics

The baseline demographic characteristics of the randomized population were generally comparable across the treatment groups (Table 3). The study population was primarily Caucasian (97.5%) with a mean age of 38 years. As expected, the majority of the patients were female (72.2%).

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Table 3 Demographic and baseline characteristics - TEMSO

		Teriflunomide	
	Placebo N=363	**7 mg N=366**	**14 mg N=359**
Age (years)			
Mean (SD)	38.4 (9.0)	37.4 (9.0)	37.8 (8.2)
Median	39.0	38.5	38.0
Sex [n (%)]			
Male	88 (24.2%)	111 (30.3%)	104 (29.0%)
Female	275 (75.8%)	255 (69.7%)	255 (71.0%)
Race [n (%)]			
Caucasian / White	356 (98.3%)	355 (97.3%)	347 (96.9%)
Other	6 (1.7%)	10 (2.7%)	11 (3.1%)
Region [n (%)]			
Americas	82 (22.6%)	83 (22.7%)	81 (22.6%)
Eastern Europe	114 (31.4%)	116 (31.7%)	108 (30.1%)
Western Europe	167 (46.0%)	167 (45.6%)	170 (47.4%)

(Source: Selected from Table 14 in TEMSO study report)

The baseline disease characteristics for all randomized patients were generally well balanced between the treatment groups (Table 4). The median time since first diagnosis of MS was 3.50 years and the median time since first symptoms of MS was 6.83 years. A total of 794 patients (73.0%) were not treated with any MS medications within 2 years prior to randomization. The majority of the patients (91.5%) in the randomized population had relapsing-remitting MS with a median baseline EDSS score of 2.50. The number of relapses (median) within the past 2 years was reported to be 2. At baseline, the median BOD for the study population was 13.02 mL.

Reference ID: 3127800

Table 4 Baseline disease characteristics - TEMSO

		Teriflunomide	
	Placebo N=363	**7 mg N=366**	**14 mg N=359**
Time since first diagnosis (years)			
Mean (SD)	5.13 (5.59)	5.28 (5.36)	5.58 (5.48)
Median	3.25	3.75	3.67
Number of relapses within 2 years			
Mean (SD)	2.2 (1.0)	2.3 (1.2)	2.2 (1.0)
Median	2.0	2.0	2.0
MS subtype [n (%)]			
Relapsing remitting	329 (90.6%)	333 (91.0%)	333 (92.8%)
Secondary progressive	22 (6.1%)	17 (4.6%)	12 (3.3%)
Progressive relapsing	12 (3.3%)	16 (4.4%)	14 (3.9%)
Treated in last 2 years [n (%)]			
Yes	90 (24.8%)	102 (27.9%)	102 (28.4%)
No	273 (75.2%)	264 (72.1%)	257 (71.6%)
Baseline EDSS score			
Mean (SD)	2.68 (1.34)	2.68 (1.34)	2.67 (1.24)
Median	2.50	2.50	2.50
$\leq$ 3.5	287 (79.1%)	281 (76.8%)	277 (77.2%)
> 3.5	76 (20.9%)	85 (23.2%)	82 (22.8%)
Number of Gd-enhancing lesions			
Mean (SD)	1.66 (3.55)	1.50 (3.96)	1.81 (5.17)
Median	0.0	0.0	0.0
Baseline burden of disease (ml)			
Mean (SD)	19.34 (18.94)	20.37 (20.59)	18.08 (17.49)
Median	12.75	13.96	12.39

(Source: Selected from Table 2 in TEMSO study report Appendix)

3.2.1.3 Statistical Methodologies

Analysis of Primary Endpoint

As specified in the SAP, the primary analysis for the ARR was to be performed using a Poisson regression model with robust error variance to accommodate the potential over-dispersed data. The model was to include the total number of confirmed relapses as response variable, a 3-level treatment group, EDSS strata (baseline EDSS score $\leq$ 3.5 versus >3.5) and region as covariates. To account for different study durations among patients, the log-transformed standardized study duration from the randomization date to the last dose date was to be included in the model as an "offset" variable. The robust error variances were to be estimated by specifying the patient identifier in the repeated statement using SAS PROC GENMOD, which is equivalent to the Generalized Estimating Equation (GEE) model.

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Two-sided 95% confidence intervals (CI) of the rate ratio were to be provided for the comparisons of each active treatment versus placebo. The estimated relapse rate and its 2-sided 95% CIs and the gross estimate of ARR were to be provided for each treatment group.

Analysis of Key Secondary Endpoint

The time to disability progression was to be analyzed using the log-rank test with time to disability progression as the dependent variable, the treatment group as test variable, and region and baseline EDSS strata as stratification factors. The Kaplan-Meier method was to be used to estimate the time to disability progression rate for each group. The main analysis was the time to disability progression confirmed for at least 12 weeks. The supportive analyses were to be performed using time to disability progression confirmed for at least 24 weeks and disability progression based on the PP population.

Analyses of Other Secondary Endpoints

The change from baseline in MRI variable BOD was to be analyzed using a mixed-effect model with repeated measures (MMRM) on cubic root transformed volume data. The model was to include fixed effects for treatment, EDSS strata, region, visit, treatment-by-visit interaction, baseline value (cubic root transformed), and baseline-by-visit interaction. An unstructured correlation matrix was to be used to model the within-patient errors. The parameters were to be estimated using the restricted maximum likelihood method with the Newton-Raphson algorithm and the denominator degrees of freedom were to be estimated using Satterthwaite's approximation.

The number of Gd-enhancing T1 lesions per MRI scan was to be compared between the treatment groups using the same model as for the ARR. The model was to include the total number of Gd-enhancing T1 lesions as response variable and treatment group, EDSS strata, region, and baseline number of Gd-enhancing T1 lesions as covariates. To account for the different numbers of scans performed among the patients, the log-transformed number of scans was to be included in the model as an offset variable.

Change from baseline at Week 108 in FIS total score and 3 subscales were to be analyzed using the same model as described for BOD. No data transformation was needed.

Multiplicity Adjustment

Multiplicity adjustment was made for testing 2 doses on the primary and key secondary endpoints for testing a family of the following hypotheses:

- H1: no treatment difference between Teriflunomide 14 mg and placebo on ARR
- H2: no treatment difference between Teriflunomide 7 mg and placebo on ARR
- S1: no treatment difference between Teriflunomide 14 mg and placebo on disability progression

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- S2: no treatment difference between Teriflunomide 7 mg and placebo on disability progression

To strongly control Type-I error rate for this family, a step down testing procedure was to be applied in the order specified above. Each hypothesis was to be formally tested only if the preceding one was significant at 5% level.

If all hypothesis tests described above were significant at 5% level, a step down testing procedure was to be applied to the following secondary endpoints in the order specified below within each dose at 2.5% significance level, i.e., within a dose each hypothesis was formally tested only if the preceding one was significant at the 2.5% level:

- Change from baseline in total score of fatigue impact scale at Week 108
- Total number of Gd-enhancing T1-lesions per MRI scan over the treatment period
- Change from baseline in MRI burden of disease at Week 108

By applying the multiplicity adjustment approach described above for a family of hypotheses of 5 endpoints and 2 doses, Type-1 error rate was strongly controlled for the entire family.

3.2.1.4 Results and Conclusions

3.2.1.4.1 Analysis of the Primary Endpoint

The results in analysis of confirmed ARR reported by the sponsor were confirmed by the reviewer and presented in Table 5. Analysis of all relapses, confirmed and non-confirmed, was performed by the reviewer and included in Table 5.

Of the 1086 patients in the ITT population analyzed for MS relapse, 184 patients (50.7%) in the placebo group, 154 patients (42.2%) in the Teriflunomide 7 mg group, and 141 patients (39.4%) in the Teriflunomide 14 mg group experienced at least 1 MS relapse during the treatment.

The total numbers of confirmed MS relapses recorded in the ITT population between the date of randomization and the date of last dose were 335 relapses in the placebo group, 233 relapses in the Teriflunomide 7 mg group, and 227 relapses in the Teriflunomide 14 mg group.

The adjusted ARR was 0.539 (95% CI: 0.466 to 0.623) in the placebo group, 0.370 (95% CI: 0.318 to 0.432) in the Teriflunomide 7 mg group, and 0.369 (95% CI: 0.308 to 0.441) in the Teriflunomide 14 mg group. These results corresponded to a relative risk reduction of 31.2% (p=0.0002) in the Teriflunomide 7 mg group and 31.5% (p=0.0005) in the Teriflunomide 14 mg group compared to placebo. Results from analysis of all relapses, confirmed and unconfirmed, are consistent with the results from analysis of confirmed relapses. Time to first confirmed relapse is plotted in Figure 1.

Reference ID: 3127800

Table 5 Analysis of MS relapse - TEMSO

	Placebo N=363	Teriflunomide	
		7 mg N=365	14 mg N=358
Confirmed relapses			
Number of relapses			
0	179 (49.3%)	211 (57.8%)	217 (60.6%)
1	97 (26.7%)	92 (25.2%)	86 (24.0%)
2	48 (13.2%)	49 (13.4%)	33 (9.2%)
3	22 (6.1%)	10 (2.7%)	16 (4.5%)
4	11 (3.0%)	2 (0.5%)	4 (1.1%)
≥ 5	6 (1.7%)	1 (0.3%)	2 (0.6%)
Unadjusted group relapse rate	.534	0.368	0.369
Adjusted annualized relapse rate	0.539 (0.466, 0.623)	0.370 (0.318, 0.432)	0.369 (0.308, 0.441)
Estimated ARR (95% CI)		0.688 (0.563, 0.839)	0.685 (0.554, 0.847)
Relative risk (95% CI)		0.0002	0.0005
p-value			
Individual patient ARR	0.731 (1.553)	0.646 (2.240)	0.597 (2.163)
Mean (SD)	0.475	0.0	0.0
Median			
All relapses (confirmed & unconfirmed)			
Adjusted relapse rate (95% CI)	0.636	0.453 (0.394, 0.855)	0.441 (0.375, 0.518)
Relative risk (95% CI)		0.713 (0.594, 0.855)	0.693 (0.571, 0.840)
Nominal p-value		0.0003	0.0002

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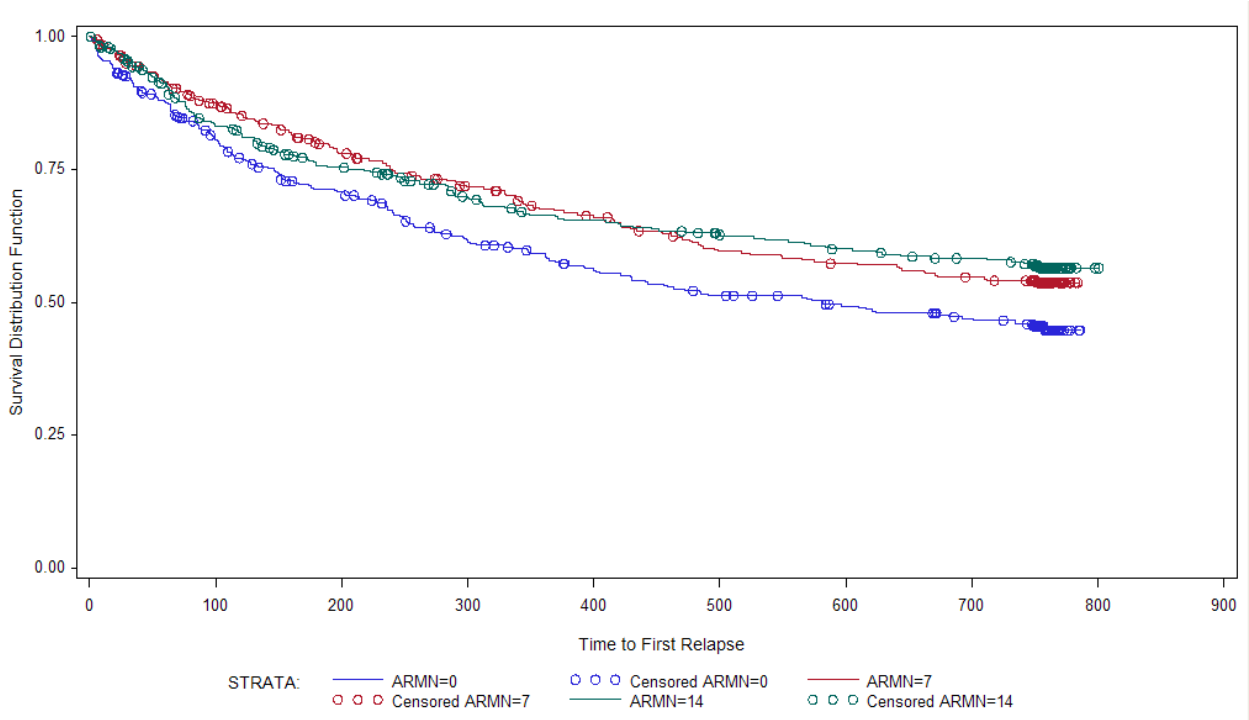

Figure 1 Time to first confirmed relapse – TEMSO (Source: produced by the reviewer)

Results from analysis on PP patient population are similar. No large discrepancies were found in subgroup populations. Analyses of relapse rate by subgroups are discussed in details in Section 4.

Sensitivity analysis was performed to evaluate the impact of 40 subjects who were blind broken during the study. The following table provides a summary of these subjects and estimated relapse rates after excluding these 40 subjects from the analysis. The analysis results were little changed from the primary analysis.

Table 6 Analysis of relapse rate excluding subjects who had blind broken

		Teriflunomide	
	Placebo N=363	**7 mg N=365**	**14 mg N=358**
Blind broken subjects			
N	15	13	12
Mean number of relapses	1.47	1.38	0.25
Mean duration in study (days)	399	525	353
Excluding subjects above			
Adjusted relapse rate	0.517	0.353	0.372
Risk ratio		0.557	0.581
Nominal p-value		0.0003	0.0027

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3.2.1.4.2 Analysis of Time to disability progression

Results presented in Table 7 are reported by the sponsor and confirmed by the reviewer.

The estimated percentage of patients with 12-week sustained disability progression at Week 108 using the Kaplan-Meier method was 27.3%, 21.7%, and 20.2% in the placebo group, the Teriflunomide 7 mg group, and the Teriflunomide 14 mg group, respectively (Table 7). The treatment difference carried a p-value of 0.0835 for Teriflunomide 7 mg vs. placebo and 0.0279 for Teriflunomide 14 mg vs. placebo from the log-rank test.

The hazard ratio estimated from Cox model was 0.762 for the Teriflunomide 7 mg versus placebo (p=0.0962) and 0.702 for the Teriflunomide 14 mg versus placebo (p=0.0337).

Although the effect of the 7-mg Teriflunomide dose showed a similar trend, it did not reach statistical significance.

Table 7 Analysis of time to disability progression sustained for 12 weeks – TEMSO

		teriflunomide	
	Placebo (N=363)	**7 mg (N=365)**	**14 mg (N=358)**
Number of patients with disability progression	86 (23.7%)	68 (18.6%)	62 (17.3%)
Number of patients who were censored	277 (76.3%)	297 (81.4%)	296 (82.7%)
Probability of disability progression (95% CI) at[a]			
24 weeks	0.086 (0.057, 0.116)	0.058 (0.033, 0.083)	0.062 (0.036, 0.088)
48 weeks	0.160 (0.121, 0.200)	0.131 (0.094, 0.167)	0.113 (0.079, 0.148)
108 weeks	0.273 (0.223, 0.323)	0.217 (0.171, 0.263)	0.202 (0.156, 0.247)
Hazard ratio (95% CI)[b]		0.763 (0.555, 1.049)	0.702 (0.506, 0.973)
P-value[c]		0.0835	0.0279

Note: The time-to-event variable is defined as the time (days) from the date of randomization to the date of the first disability progression. For patients who have no disability progression on or before last during treatment EDSS evaluation, it will be censored at the date of last during-treatment EDSS evaluation.

[a] Derived from Kaplan-Meier estimates

[b] Derived using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

[c] Derived from log-rank test with stratification of EDSS strata at baseline and region

PGM=PRODOPS/HMR1726/EFC6049/CSR/REPORT/PGM/eff_time2event_i_t.sas OUT=REPORT/OUTPUT/eff_dp_i_t_i.rtf (18AUG2010 - 18:22)

(Source: Table 20 in TEMSO study report)

The Kaplan-Meier plot of time to disability progression sustained for 12 weeks in the ITT population is presented in Figure 2.

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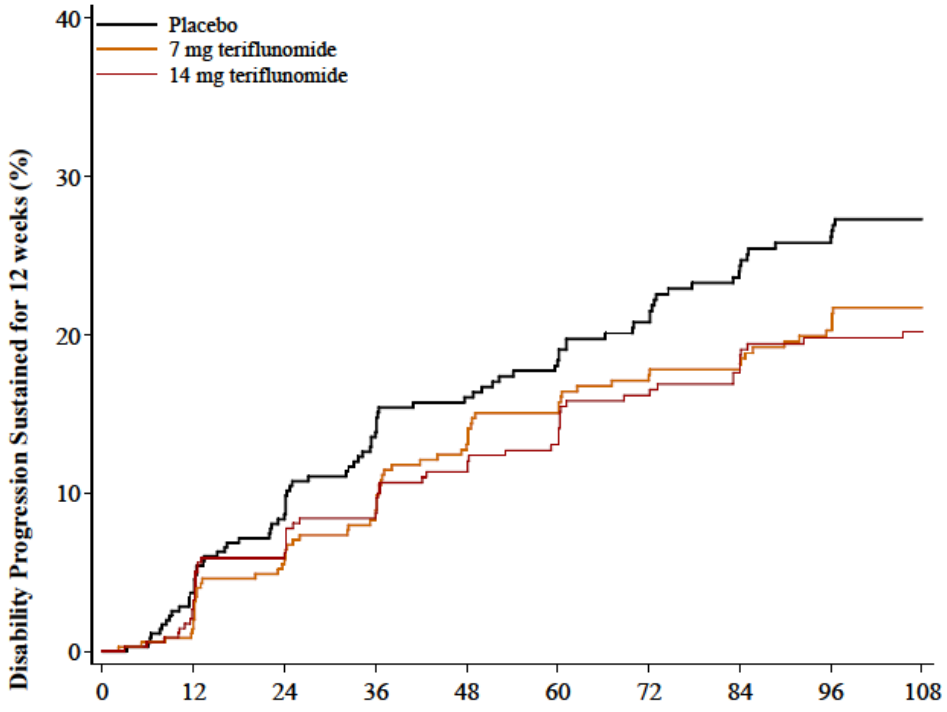

Number at Risk										
Placebo	363	336	306	279	258	242	224	211	200	160
7 mg teriflunomide	365	343	309	290	266	252	238	234	224	178
14 mg teriflunomide	358	329	302	285	262	251	234	227	217	175

Figure 2 Kaplan-Meier estimate of time to disability progression - TEMSO
(Source: Figure 2 in TEMSO study report)

Results from analysis of disability progression sustained for 12 weeks on PP patient population are similar with effect of Teriflunomide 14 mg reaching the significance level (p=0.0258) and Teriflunomide 7 mg failing to reach the significance level (p=0.1144).

The estimated percentage of patients with 24-week sustained disability progression at Week 108 was 18.7%, 13.9%, and 13.8% in the placebo, Teriflunomide 7 mg, and Teriflunomide 14 mg groups, respectively. No statistically significant treatment effects were found.

Discrepancy of treatment difference in disability progression was found in the region of Americas in which more Teriflunomide-treated patients progressed. Analyses of disability progression by subgroups are discussed in details in Section 4.

Additional Analysis Performed by the Reviewer

Results of disability progression were little changed when two patients who progressed after being unblinded were excluded from the analysis. The analysis resulted in a p-value of 0.0830 from comparison of Teriflunomide 7 mg versus placebo and a p-value of 0.0329 from Teriflunomide 14 mg versus placebo. The analysis after excluding all 40 subjects who had blind broken resulted in a p-value of 0.0619 from comparison of Teriflunomide 7 mg versus placebo and a p-value of 0.0420 from Teriflunomide 14 mg versus placebo.

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Changes from baseline in EDSS scores are analyzed since disability progression was determined by EDSS score change. The average EDSS scores at baseline EDSS were similar among the treatment groups. The treatment appeared to have little or no effect on EDSS scores at Week 48 or Week 108. Note that many patients did not have Week 48 EDSS scores available. Therefore, the Week 48 EDSS means were based on smaller number of patients across all treatment groups. No inferential analyses were performed.

Table 8 Change from baseline in EDSS - TEMSO

		Teriflunomide	
	Placebo N=363	**7 mg N=365**	**14 mg N=358**
Baseline			
N	363	365	358
Mean (SD)	2.68 (1.34)	2.69 (1.33)	2.67 (1.25)
Week 48 change			
N	303	302	292
Mean (SD)	0.04 (0.90)	0.08 (0.86)	0.06 (0.75)
Week 108 change			
N	339	352	349
Mean (SD)	0.23 (1.05)	0.26 (1.00)	0.19 (0.95)

3.2.1.4.3 Analysis of Other Secondary Endpoints

Based on pre-specified multiplicity adjustment for type-I error control, no statistical significance could be claimed for efficacy variables other than the ARR and disability progression regardless of p-values obtained due to the insignificance of the treatment difference between Teriflunomide 7 mg and placebo in disability progression.

Fatigue Impact Scale

The sponsor reported that no statistically significant treatment difference was observed in the FIS score at Week 108 (p=0.3861 for the Teriflunomide 7 mg group compared with the placebo group and p=0.0871 for the Teriflunomide 14 mg group compared with the placebo group).

Burden of Disease

The sponsor reported that the mean cubic root transformed volumes of abnormal brain tissue detected on MRI at baseline were similar across the treatment groups.

At Week 108, the mean change in absolute value of cubic root transformed BOD from baseline was 0.111 for the placebo group, 0.072 for the Teriflunomide 7 mg group and 0.045 for the Teriflunomide 14 mg group (Table 9). The model adjusted least square mean difference from

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baseline was -0.053 for the Teriflunomide 7 mg group and -0.089 for the Teriflunomide 14 mg group with the corresponding p-values of 0.0317 and 0.0003 respectively.

Table 9 MMRM analysis of burden of disease using cubic root volume data - TEMSO

		Teriflunomide	
	Placebo N=363	**7 mg N=365**	**14 mg N=355**
Baseline			
N	358	359	355
Mean (SD)	2.383 (0.892)	2.437 (0.890)	2.359 (0.825)
Median	2.336	2.409	2.314
Week 108			
N	258	265	261
Mean (SD)	2.465 (0.873)	2.503 (0.862)	2.383 (0.801)
Median	2.471	2.518	2.385
Change from baseline (MMRM)[1]			
N	256	262	260
LS Mean (SE)	0.132 (0.018)	0.080 (0.018)	0.043 (0.018)
LS mean difference vs. placebo		-0.053	-0.089
p-value		0.0317	0.0003

1. MMRM analysis used data at Weeks 24, 48, 72 and 108.

Gadolinium Enhancing T1 Lesions

A summary of cumulative number of Gd-enhancing T1 lesions is presented in Table 10.

Table 10 Analysis of Gd-enhancing T1 lesions - TEMSO

	Placebo	**Teriflunomide**	
	N=346	**7 mg N=350**	**14 mg N=340**
Baseline			
N	343	344	338
Number with ≥ 1 Gd T1 lesions			
Yes	133 (38.8%)	119 (34.6%)	116 (34.3%)
No	210 (61.2%)	225 (65.4%)	222 (65.7%)
Mean (SD)	1.69 (3.58)	1.46 (3.94)	1.81 (5.27)
Post-baseline			
N	346	350	340
Number with ≥ 1 Gd T1 lesions			
Yes	211 (61.0%)	170 (48.6%)	122 (35.9%)
No	135 (39.0%)	180 (51.4%)	218 (64.1%)
Mean (SD)	1.81 (6.39)	0.65 (1.48)	0.42 (1.09)
Adjusted Gd T1 lesions per scan			
Estimated (95% CI)	1.33 (1.06, 1.67)	0.57 (0.43, 0.75)	0.26 (0.17, 0.41)
Relative risk (95% CI)		0.43 (0.31, 0.59)	0.20 (0.12, 0.32)
p-value		<.0001	<.0001

(Source: Selected from Table 24 in TEMSO study report)

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3.2.1.4.4 Conclusions

It was evident that both doses of Teriflunomide had a statistically significant effect in reducing the relapse rate. The results are consistent and robust across PP population and subgroup populations (discussed in details in Section 4), in confirmed and all relapses, and with relapse rate and time to first relapse.

The evidence of the effect of Teriflunomide 14 mg in reducing the disability progression, though reached statistical significance, was weakened by the conflicting observation in the region of Americas and by EDSS score change. The effect in reducing disability progression for Teriflunomide 7 mg, although showing a positive trend numerically, was not established in this study. Positive results from another study are needed to confirm and to establish a significant treatment effect in reducing disability progression.

3.2.2 Evaluation of TOWER Study

The data presented in this section are the results of an interim analysis. The interim analysis was performed to provide additional evidence on the safety profile of Teriflunomide and supportive data of the beneficial effect on relapse rate for regulatory purpose. This interim analysis was initially unplanned. There was no plan to stop the study based on interim efficacy data, i.e., the study will continue to its planned end. A full clinical study report will be prepared when the study reaches completion.

Specific steps were taken to maintain the blind of the study to all those involved in the conduct and analysis of the study and to protect the overall blinding and integrity of the study data given the interim analysis. The sponsor reported that the unblinded interim analysis was conducted by an independent group within Sanofi-Aventis that had no involvement in this study or in the Teriflunomide project. Unblinded analysis data and outputs were stored in a secure, restricted location not accessible by study team members. Each person involved in the analysis and reporting of the interim data was required to sign a confidentiality agreement, and these were the only people with access to patient level data and the unblinded report.

The interim analysis was performed on all patients randomized in the study as of November 30, 2010. Patient data through February 28, 2011 are included such that the last patient included in the analysis had approximately 3 months of follow-up as a minimum, and the expected average exposure was 1 year. The database for this interim analysis report was locked on May 13, 2011.

The interim efficacy analysis was performed for the primary endpoint, ARR. No formal statistical tests were performed to compare the treatment groups by the sponsor.

3.2.2.1 Study Design and Endpoints

3.2.2.1.1 Study Design

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The primary objective of the TOWER study was to assess the effect of 2 doses of Teriflunomide in comparison to placebo on frequency of MS relapses in patients with relapsing MS.

This was a multicenter, multinational, randomized, double-blind, parallel-group (3 groups), placebo-controlled study. The treatment duration was 48 weeks from the last patient recruited. The treatment period had a fixed end for all patients so that all patients were to have the end-of-treatment (EOT) visit within 6 weeks prior or 6 weeks after the EOT visit for the last patient randomized. The minimum duration on treatment for any patient not withdrawing prematurely was 48 weeks.

It was planned that a total of approximately 1110 patients would be randomized into the trial to receive Teriflunomide 7 mg, Teriflunomide 14 mg, or placebo in a ratio of 1:1:1. A total of 1096 patients were actually randomized. For inclusion in the study patients were required to have a relapsing form of MS meeting McDonald's criteria for MS diagnosis and an EDSS score ≤5.5 at the screening visit. In addition, patients were required to have had at least 1 relapse in the 12 months preceding randomization, or at least 2 relapses in the 24 months preceding the randomization visit.

3.2.2.1.2 Efficacy Endpoints

The primary efficacy variable was the annualized relapse rate (ARR). Only this primary endpoint was analyzed at the interim analysis.

The key secondary endpoint was the time to disability progression confirmed at 12 weeks. Other secondary efficacy variables included change from baseline in the total score and 3 sub-scores of fatigue impact scale (FIS) at Week 48, time to first confirmed relapse, proportion of patients without relapse, proportion of patients free of disability progression at 6 months, 1 year, and 2 years, and change from baseline in EDSS.

Refer to Section 3.2.1.1.2 for definition of relapse and disability progression.

3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.2.1 Patient Disposition

A total of 1418 patients were screened in this study and 1096 were randomized as the cut-off date for inclusion in this interim analysis. Within the 1096 patients randomized 4 patients were screen failures and were not treated with the study medications. These 4 patients were not included in the ITT patient population.

Among the patients who were randomized and treated, 72 patients from the placebo group (19.7%), 85 patients from the Teriflunomide 7 mg group (22.4%), and 74 patients from the

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Teriflunomide 14 mg group (21.1%) discontinued from the study. The most frequent reasons for the study treatment discontinuations were AEs (96 patients), other reasons (68 patients), and lack of efficacy (48 patients) (Table 11). Investigator comments associated with "other reasons" indicated that many of these discontinuations resulted from patient decision.

For all patients who discontinued treatment prematurely for any reason, the Investigator recorded whether the discontinuation was at the patient's request. A total of 144 patients requested treatment discontinuation. The sponsor stated that the frequency of patients who requested treatment discontinuation was similar between treatment groups.

Table 11 Patient disposition - TOWER

		teriflunomide	
	Placebo (N=366)	**7 mg (N=379)**	**14 mg (N=351)**
Randomized and not treated	1 (0.3%)	1 (0.3%)	2 (0.6%)
Reason for not treated	1 (0.3%)	1 (0.3%)	2 (0.6%)
Adverse event	0	0	0
Lack of efficacy	0	0	0
Poor compliance to protocol	0	1 (0.3%)	1 (0.3%)
Lost to follow-up	0	0	0
Other reason	1 (0.3%)	0	1 (0.3%)
Randomized and treated	365 (99.7%)	378 (99.7%)	349 (99.4%)
Ongoing	293 (80.1%)	293 (77.3%)	275 (78.3%)
Did not complete study treatment period	72 (19.7%)	85 (22.4%)	74 (21.1%)
Patient's request for treatment discontinuation	46 (12.6%)	53 (14.0%)	45 (12.8%)
Reason for study treatment discontinuation			
Adverse event[a]	16 (4.4%)	40 (10.6%)	40 (11.4%)
Lack of efficacy	24 (6.6%)	17 (4.5%)	7 (2.0%)
Poor compliance to protocol	12 (3.3%)	2 (0.5%)	3 (0.9%)
Lost to follow-up	0	0	2 (0.6%)
Other reason	20 (5.5%)	26 (6.9%)	22 (6.3%)

Note: Percentages are calculated using the number of randomized patients as denominator.

a AEs leading to discontinuation of study medication were recorded on the AE CRF but there was no information provided on the End-of-Trial CRF for 1 patient in the placebo group, 4 patients in the teriflunomide group and 4 patients in the teriflunomide 14 mg group.

(Source: Table 4 in TOWER study report)

As of the cut-off date for this interim analysis (28 February 2011), treatment was ongoing for 861 patients.

A total of 27 patients (6 in the placebo group, 6 in the 7 mg Teriflunomide group and 15 in the 14 mg Teriflunomide group) with major efficacy related protocol deviations were identified in this study. These patients were excluded from the PP patient population.

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Reviewer's Comments: *It should be noted that the average treatment duration for the 861 patients whose treatment is ongoing is approximately one year. Therefore, it is expected that final count of treatment discontinuation could be substantially higher. Again, the large number of treatment discontinuation by patient decision raises concern of the quality of in study conduct.*

3.2.2.2.2 Patient Demographic and Baseline Characteristics

The baseline demographic characteristics of the randomized population were comparable across the treatment groups (Table 12). The study population was primarily Caucasian (83.5%) with a mean age of 37.9 years. As expected, the majority of the patients were female (71.0%).

Table 12 Patient demographic characteristics - TOWER

		Teriflunomide	
	Placebo N=366	**7 mg N=379**	**14 mg N=351**
Age (years)			
Mean (SD)	38.1 (9.2)	37.4 (9.4)	38.1 (9.5)
Median	39.0	38.0	38.0
Sex [n (%)]			
Male	113 (30.9%)	99 (26.1%)	106 (30.2%)
Female	253 (69.1%)	280 (73.9%)	245 (69.8%)
Race [n (%)]			
Caucasian / White	306 (83.6%)	311 (82.1%)	298 (84.9%)
Asian	50 (13.7%)	52 (13.7%)	45 (12.8%)
Other	10 (2.7%)	16 (4.2%)	8 (2.3%)
Region [n (%)]			
Americas	82 (22.4%)	88 (23.2%)	75 (21.4%)
Eastern Europe	112 (30.6%)	115 (30.3%)	114 (32.5%)
Western Europe	116 (31.7%)	119 (31.4%)	112 (31.9%)
Asian and Australia	56 (15.3%)	57 (15.0%)	50 (14.2%)

(Source: Selected from Table 8 in TOWER study report)

The baseline disease characteristics for all randomized patients were generally similar across the treatment groups (Table 13). The median time since first diagnosis of MS was 3.17 years. The majority of the patients (97.4%) in the randomized population had relapsing-remitting MS with a median baseline EDSS score of 2.50. The number of relapses (median) within the past 2 years was reported to be 2.0. Among the 360 patients (32.8%) who had taken previous MS medications, the distributions of patients within each type of previous treatment were similar across the study treatment groups.

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Table 13 Patient baseline disease characteristics - randomized patients - TOWER

	Placebo N=366	7 mg N=379	14 mg N=351
Time since first diagnosis (years)			
Mean (SD)	4.87 (5.69)	5.30 (5.41)	5.26 (5.76)
Median	2.79	3.50	3.25
Number of relapses within 2 years			
Mean (SD)	2.1 (1.2)	2.1 (1.1)	2.1 (1.2)
Median	2.0	2.0	2.0
MS subtype [n (%)]			
Relapsing remitting	356 (97.3%)	365 (96.3%)	346 (98.9%)
Secondary progressive	4 (1.1%)	3 (0.8%)	2 (0.6%)
Progressive relapsing	6 (1.6%)	11 (2.9%)	2 (0.6%)
Treated in last 2 years [n (%)]			
Yes	125 (34.2%)	115 (30.3%)	120 (34.2%)
No	241 (65.8%)	264 (69.7%)	231 (65.8%)
Baseline EDSS score			
Mean (SD)	2.66 (1.34)	2.74 (1.36)	2.70 (1.35)
Median	2.50	2.50	2.50
$\leq$ 3.5	284 (77.6%)	284 (74.9%)	258 (73.5%)
> 3.5	82 (22.4%)	95 (25.1%)	93 (26.5%)

(Source: Selected from Appendix of TOWER study report)

3.2.2.3 Statistical Methodologies

The analysis of ARR followed the same method of the TEMSO study as described in Section 3.2.1.3.

Analyses of the secondary efficacy variables will be conducted at the end of the study and presented in the full clinical study report and will not be presented in this interim analysis report.

3.2.2.4 Results and conclusions

The results from analysis of ARR are presented in Table 14, which include results reported by the sponsor and confirmed by the reviewer and p-values from inferential comparisons performed by the reviewer. The sponsor did not conduct inferential comparisons between the treatment groups.

Of the 1092 patients in the ITT population analyzed for MS relapse, 124 patients (34.0%) in the placebo group, 89 patients (23.5%) in the Teriflunomide 7 mg group, and 80 patients (22.9%) in the Teriflunomide 14 mg group experienced at least 1 MS relapse during the treatment (Table 14).

The adjusted ARR was 0.531 in the placebo group, 0.371 in the Teriflunomide 7 mg group, and 0.321 in the Teriflunomide 14 mg group. These results corresponded to a relative risk reduction

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of 30.2% (p=0.0072) in the Teriflunomide 7 mg group and 39.6% (p=0.0002) in the Teriflunomide 14 mg group compared to placebo.

Table 14 Analysis of relapse rate - TOWER

	Placebo N=365	Teriflunomide	
		7 mg N=378	14 mg N=349
Number with ≥ 1 relapse			
Yes	124 (34.0%0	89 (23.5%)	80 (22.9%)
No	241 (66.0%)	289 (76.5%)	269 (77.1%)
Unadjusted group relapse rate	0.507	0.359	0.303
Adjusted annualized relapse rate			
Estimated ARR (95% CI)	0.531 (0.444, 0.636)	0.371 (0.300, 0.459)	0.321 (0.258, 0.400)
Relative risk (95% CI)		0.698 (0.538, 0.907)	0.604 (0.462, 0.789)
p-value		0.0072	0.0002
Individual patient ARR			
Mean (SD)	0.674 (1.470)	0.454 (1.226)	0.459 (2.559)
Median	0	0	0

3.3 Evaluation of Safety

Refer to Clinical Review by Dr. Jody Green and Safety Review by Dr. Evelyn Mentari and Dr. Lourdes Villalba for Evaluation of Safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Analyses of the primary endpoint on gender and age group were performed. The relapse rate for the younger age group (< 38 years of age) appears to be much higher than the older age group across all treatment groups in both studies (Table 15 for TEMSO study and Table 16 for TOWER study). The Teriflunomide groups all showed numerically lower relapse rate than the placebo group. No analyses were performed on race sub-populations since most subjects (97%) were White.

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Table 15 Analysis of ARR by age and gender - TEMSO

TEMSO	Placebo N=363	Teriflunomide 7 mg N=365	Teriflunomide 14 mg N=358
Gender			
Male			
N	88	111	104
Adjusted ARR	0.454	0.373	0.357
Relative risk		0.822	0.786
Nominal p-value		0.3100	0.2578
Female			
N	275	254	254
Adjusted ARR	0.540	0.354	0.360
Relative risk		0.655	0.667
Nominal p-value		0.0005	0.0014
Age Group			
< 38			
N	156	170	173
Adjusted ARR	0.729	0.451	0.465
Relative risk		0.619	0.638
Nominal p-value		0.0008	0.0042
≥ 38			
N	207	195	185
Adjusted ARR	0.425	0.313	0.305
Relative risk		0.737	0.719
Nominal p-value		0.0342	0.0229

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Table 16 Analysis of ARR by age and gender - TOWER

TOWER	Placebo N=363	Teriflunomide	
		7 mg N=366	14 mg N=359
Gender			
Male			
N	112	99	105
Adjusted ARR	0.576	0.299	0.331
Relative risk		0.520	0.575
Nominal p-value		0.0158	0.0240
Female			
N	253	279	244
Adjusted ARR	0.527	0.401	0.317
Relative risk		0.761	0.602
Nominal p-value		0.0715	0.0020
Age Group			
< 38			
N	166	186	164
Adjusted ARR	0.703	0.492	0.378
Relative risk		0.699	0.537
Nominal p-value		0.0423	0.0008
≥ 38			
N	199	192	185
Adjusted ARR	0.419	0.296	0.290
Relative risk		0.705	0.691
Nominal p-value		0.0814	0.0657

4.2 Other Special/Subgroup Populations

Analyses of relapse rate by region, MS type, and previous MS treatment were performed (Table 17 for TEMSO and Table 18 for TOWER). Relapse rates are lower across treatment groups in the region of Americas in both studies.

Only 8 US patients were included in the TEMSO study while in the TOWER study the Americas mainly consisted of US patients (204 of the 245 patients). Therefore, analysis of relapse rate for US versus non-US was not performed.

There were only 28 patients that had progressive relapsing or secondary progressive MS in the TOWER study, and relapse rate could not be estimated.

Relapse rates were higher in patients who were previously treated with MS drugs than the relapse rates in naïve patients across treatment groups in both studies. In the TOWER study, the relapse rate of previously treated patients in Teriflunomide 7 mg group was slightly higher than the relapse rate in the placebo group. But the number of patients is small and no conclusion could be made.

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Table 17 Analysis of ARR by region and MS type - TEMSO

TEMSO	Placebo N=363	Teriflunomide 7 mg N=366	Teriflunomide 14 mg N=359
Region			
Americas			
N	82	83	80
Adjusted ARR	0.306	0.205	0.274
Relative risk		0.668	0.896
Nominal p-value		0.1144	0.6775
Eastern Europe			
N	114	116	108
Adjusted ARR	0.520	0.416	0.416
Relative risk		0.800	0.800
Nominal p-value		0.2087	0.2443
Western Europe			
N	167	166	170
Adjusted ARR	0.712	0.447	0.398
Relative risk		0.628	0.559
Nominal p-value		0.0010	<.0001
Type of MS			
Relapsing Remitting			
N	329	332	332
Adjusted ARR	0.537	0.371	0.355
Relative risk		0.691	0.661
Nominal p-value		0.0005	0.0002
Prog relapsing or Sec Progressive			
N	34	33	26
Adjusted ARR	0.478	0.305	0.471
Relative risk		0.639	0.985
Nominal p-value		0.2096	0.9708
Previous MS Treatment			
Yes			
N	90	102	102
Adjusted ARR	0.781	0.497	0.470
Relative risk		0.637	0.602
Nominal p-value		0.0069	0.0038
No			
N	273	263	256
Adjusted ARR	0.448	0.307	0.314
Relative risk		0.686	0.702
Nominal p-value		0.0029	0.0091

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Table 18 Analysis of ARR by region and MS type - TOWER

TOWER	Placebo N=363	Teriflunomide 7 mg N=366	Teriflunomide 14 mg N=359
Region			
Americas			
N	82	88	75
Adjusted ARR	0.375	0.224	0.273
Relative risk		0.598	0.728
Nominal p-value		0.1574	0.2964
Asian & Australia			
N	56	57	49
Adjusted ARR	0.776	0.448	0.199
Relative risk		0.577	0.256
Nominal p-value		0.0706	0.0016
Eastern Europe			
N	111	115	113
Adjusted ARR	0.438	0.353	0.341
Relative risk		0.805	0.778
Nominal p-value		0.3960	0.2859
Western Europe			
N	116	118	112
Adjusted ARR	0.658	0.481	0.371
Relative risk		0.732	0.563
Nominal p-value		0.1313	0.0169
Type of MS			
Relapsing Remitting			
N	355	364	344
Adjusted ARR	0.515	0.371	0.307
Relative risk		0.721	0.596
Nominal p-value		0.0162	0.0002
Prog relapsing or Sec Progressiv			
N	10	14	4
Adjusted ARR	NA	NA	NA
Previous MS Treatment			
Yes			
N	125	115	120
Adjusted ARR	0.572	0.585	0.402
Relative risk		1.023	0.704
Nominal p-value		0.9118	0.0803
No			
N	240	265	229
Adjusted ARR	0.494	0.278	0.265
Relative risk		0.563	0.537
Nominal p-value		0.0009	0.0006

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In Study TEMSO, there appeared to have opposite directions in treatment difference in disability progression in the region of Americas, which was composed of mainly Canadians. It was found that more subjects in Teriflunomide 7 mg group and Teriflunomide 14 mg group progressed than in the placebo group. Further analysis was performed to investigate whether or not it was due to the imbalance in EDSS scores at baseline. In the analysis presented in the following table, post-baseline EDSS score was taken at patient's disability progression or at the last treatment assessment if the patient did not have progression.

The data showed that in the region of Americas, placebo-treated patients had almost no increase in EDSS scores in average, while both dose groups of Teriflunomide showed worsening measured by EDSS scores and number of patients who had disability progression. The average number of days before progression was longer in Teriflunomide 14 mg than the Teriflunomide 7 mg group and the placebo group. There appeared to have no baseline imbalance. No inferential testing was performed.

Table 19 Disability progression in the region of Americas - TEMSO

TEMSO	Placebo N=363	Teriflunomide 7 mg N=365	Teriflunomide 14 mg N=358
Overall EDSS mean			
N	363	365	358
Baseline mean (SD)	2.68 (1.34)	2.69 (1.33)	2.67 (1.25)
Mean change from baseline	0.30 (1.02)	0.32 (1.00)	0.22 (0.91)
Americas			
N	82	83	80
Baseline mean (SD)	2.61 (1.25)	2.57 (1.23)	2.68 (1.11)
Mean change from baseline	0.02 (0.98)	0.28 (1.03)	0.20 (0.81)
Number progressed Americas			
N	13	18	14
Baseline mean (SD)	1.85 (1.55)	1.92 (1.44)	2.00 (0.83)
Mean change from baseline	1.31 (0.43)	1.56 (0.82)	1.25 (0.38)
Mean # days to progression	220	254	314

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Two issues arose. One is the unblinding of 40 patients in TEMSO study, and the reasons provided do not appear to justify the need of unblinding. The other is the high dropout rate in both TEMSO and TOWER with a large number of patients requested discontinuation.

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Regardless of the two issues, the evidence of the effect of Teriflunomide in reducing the relapse rate appears to be solid.

5.2 Conclusions and Recommendations

Study TEMSO and interim data from the ongoing study TOWER have provided sufficient evidence that Teriflunomide is efficacious in reducing the relapse rate in patients with relapsing forms of MS. Both 7 mg and 14 mg Teriflunomide have demonstrated treatment effect in reducing the relapse rate as compared to placebo (Table 5). The results are generally consistent in terms of direction and size of the treatment difference across various patient populations as in PP population and subgroup populations.

The effect of treatment in delaying disability progression is only showed in Teriflunomide 14 mg in the TEMSO study, as Teriflunomide 7 mg failed to reach statistical significance as compared to placebo. In the region of Americas, the placebo group had fewer patients reaching disability progression than either dose groups of Teriflunomide. Disability progression was not analyzed for TOWER study since only the ARR was provided in the interim data.

In conclusion, the effect of Teriflunomide in reducing the relapse rate is clearly established based on data from TEMSO and TOWER. The evidence of effect of Teriflunomide in delaying the physical disability is not strong enough to allow a definitive conclusion, and should be determined when the TOWER study completes. No other efficacy endpoints have been demonstrated to be effective.

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/s/

XIAORONG YAN
05/08/2012

KUN JIN
05/08/2012
I concur with the review.

KOOROS MAHJOOB
05/09/2012
I concure with this review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202-992 **Applicant: Sanofi-Aventis** **Stamp Date: 8/12/2011**

Drug Name: Teriflunomide **NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			x	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.				We don't know yet. It will be reviewed.

Reference ID: 3021965

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician Date

Supervisor/Team Leader Date

Reference ID: 3021965

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/s/

XIAORONG YAN
09/28/2011

KUN JIN
09/28/2011