CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #/Serial #:	202-155
DRUG NAME:	Apixaban
INDICATION:	Stroke or Systemic Embolism Prevention in Atrial Fibrillation
APPLICANT:	Bristol-Myers Squibb
DATE OF RECEIPT:	09/23/2011
REVIEW PRIORITY:	Priority
BIOMETRICS DIVISION:	Division of Biometrics I
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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The conclusion and reviewer's recommendation on Apixaban are solely based on the findings of Study CV185030, which was designed to evaluate the efficacy and safety of Apixaban versus warfarin (INR target range 2.0-3.0) in subjects with non-valvular AF. The findings of this study are sufficient to conclude Apixaban is superior to warfarin for the prevention of 1) stroke (hemorrhagic or ischemic) and SE, 2) ISTH major bleeding and 3) death due to any cause.

However, there are a large number of medication errors had been uncovered during the final stage of the review process, see section 1.4. The significant findings of the Apixaban can not be concluded unless various aspects of the medication errors can be addressed by the sponsor.

1.2 Brief Overview of Clinical Study

The two Phase 3 studies were active-controlled, randomized, multi-national, multi-center, double-blind, parallel-group studies with independent, blinded adjudication of efficacy and safety endpoints by an external Events Adjudication Committee. The Treatment Period of each study was to be completed after a pre-specified number of subjects (448 subjects in CV185030 and 226 subjects in CV185048) had a primary efficacy endpoint. The CV185048 study was stopped early because a planned interim analysis by an independent DMC demonstrated evidence of a clinically important reduction in stroke and SE in subjects in this AF population who had received Apixaban in comparison with ASA. The primary efficacy endpoint in both Phase 3 studies was the composite of stroke or SE. These two studies were global studies and included 18,201 and 5,598, respectively, subjects from Europe, North America, Asia/Pacific, and Latin America.

1.3 Statistical Issues and Findings

The primary objective of CV185030 was to demonstrate NI for Apixaban as compared to warfarin, and the 4 key objectives of the study (including, in addition to the primary objective, assessments of superiority for primary efficacy endpoint, superiority for ISTH major bleeding, and superiority for all-cause death) were tested following a hierarchical testing strategy to preserve the overall type I error at a significance level adjusted for the formal interim test for superiority (the adjustment was small and did not impact the results). Overall type I error was preserved at $\leq$5%.

Apixaban was superior to warfarin for the prevention of composite endpoint of stroke (any type), and SE (HR=0.79 with two-sided p=0.0114). Apixaban reduced the risk of stroke or SE by 21% from 1.60 to 1.27% per year compared to warfarin. Numerical decreases in stroke/SE event rates were observed across all levels of INR control. Similar trend was observed across all countries, and US finding (HR=0.794) is consistent with the overall result. During the trial, the protocol specified very small portion of the subjects who were at higher risk of bleeding to be assigned to the lower strength of Apixaban, 2.5 mg BID. Apixaban showed robust and consistent effects in reducing stroke/SE compared to warfarin within both the lower and higher dosage groups.

Since the superiority of Apixaban compared to warfarin was demonstrated for the primary efficacy endpoint, subsequently according to the sequential testing strategy outlined in the statistical analysis plan, Apixaban was superior to warfarin with regard to ISTH major bleeding (HR=0.69. two-sided p-value <0.0001) and for the reduction of all-cause death (HR =0.89, two-sided p=0.0465).

1.4 Medication Errors in CV185030

The CV185030 study report indicated that 664 (7.3%) and 109 patients (1.2%) in the Apixaban and warfarin arms, respectively, had medication errors. During a 31-Jan-2012 teleconference, we asked the sponsor to explain the large discrepancy between the study arms. Medication errors involve the dispensing of the wrong type of study medication to a patient. In this study, patients in the Apixaban arm were to receive active Apixaban and warfarin placebo, and those in the warfarin arm were to receive active warfarin and Apixaban placebo. Thus, errors in dispensing could conceivably result in a patient receiving concomitantly:

1. Two different active products (warfarin and Apixaban)
2. Two placebos
3. Two bottles of active warfarin or two bottles of active Apixaban
4. Wrong active medication and a placebo

Please refer to the clinical review for detailed information on various aspects of the medication error data.

On February 6, 2012, the sponsor indicated that the discrepancy were due to fact that cases where placebo was provided in error were not counted as errors. After counted erroneous dispensing of active or placebo, increased but balanced number, 8.6% and 7.9%, of patients in the Apixaban and warfarin arms, respectively, that had medication errors, see Table 1.

Table 1 Summary of Containers Dispensed of the Incorrect Type, by Treatment Group - Treated Subjects

APIXABAN ARM	**Subjects Treated (S=9088)**	**Bottles dispensed (B=224,271)**
Active-Warfarin Dispensed in Error, n (%)	664 (7.3)	723 (0.32)
Placebo-Apixaban Dispensed in Error, n (%)	134 (1.5)	136 (0.06)
Total Errors, n (%)	**784 (8.6)**	**859 (0.38)**
WARFARIN ARM	**Subjects Treated (S=9052)**	**Bottles dispensed (B=211,911)**
Placebo-Warfarin Dispensed in Error, n (%)	629 (6.9)	684 (0.32)
Active-Apixaban Dispensed in Error, n (%)	109 (1.2)	111 (0.05)
Total Errors, n (%)	**719 (7.9)**	**795 (0.38)**

The sponsor performed sensitivity analyses excluding endpoints after a subject first received an incorrect medication and censoring subjects who did not have an endpoint prior to first receiving an incorrect medication. The results of primary efficacy endpoint, ISTH major bleeding and all-cause death are summarized below.

- Primary efficacy endpoint: HR (95% CI) = 0.78 (0.65, 0.94) and p-value=0.0093
- ISTH major bleeding: HR (95% CI) = 0.68 (0.59, 0.79) and p-value<0.0001
- All-cause death: HR (95% CI) = 0.88 (0.79, 0.98) and p-value<0.0260

Hence, the sponsor argues that the results of the sensitivity analyses show that these medication errors did not impact the conclusions drawn in the study. The effect of Apixaban compared to warfarin on the 3 key endpoints of the study (stroke/systemic embolism, ISTH major bleeding and all-cause death) was not inflated by the medication errors given that the point estimates for HR and p-values were just slightly lower when data after medication errors were excluded compared to when they were all included.

However, depending on whether the true state of nature is either that Apixaban is more effective than warfarin or otherwise, the sensitivity analyses as proposed by censoring the events that occurred after a medication error automatically assume that such events are not associated with the treatment assigned to. In addition, the medication error resulting in patient's taking the treatment not assigned to further complicates the issue of how the events occurring after the error should be treated in terms of which treatment arm that should be associated with. The bottom line is that the proposed sensitivity analyses hinge on the assumption this reviewer is not willing to make and cannot verify, which may yield a bias either for or against Apixaban. Therefore, the claim that the observed medication errors did not impact the effectiveness of the Apixaban should not be concluded lightly.

FDA also requested one additional concern on further quantification of medication errors to assess whether the proportion of previously reported could have been markedly under-estimated. The sponsor performed a series of assumption-based modeling analyses of key endpoint results to explore how many medication errors would likely be needed to nullify the significant results of the efficacy and safety analyses. The sponsor assumed a series of per-bottle error rates higher than the observed error rate of 0.38%. Assumed error rates assumed ranged from 0.5% to 1% at increments of 0.1%, then 1% to 5% at increments of 1%, and finally, an assumed error rate of 10%. In the simulations, for each assumed rate of treatment assignment errors, e.g., 0.5%, correct bottles were randomly selected and assigned to an incorrect treatment type. These simulated cases were combined with the 1654 known cases to achieve the overall error rate in treatment dispensations at the specified level; for each assumed error rate, 100 replications were generated and, for each replicate, sensitivity analyses on primary efficacy and ISTH major bleeding were performed. The sensitivity analyses used the observed endpoints in the study and followed the methodology used in the CSR analyses but excluding endpoints on or after a subject first received an incorrect bottle type and censoring subjects who did not have an endpoint prior to first receiving an incorrect bottle type.

The sponsor argues that the mean p-values for the primary efficacy endpoint and ISTH major bleeding did not exceed 0.05 even when overall error in treatment dispensations was simulated to be 5%, which is more than 13 times the 0.38% reported error rate in the clinical database. These simulations applied the same assumption as the original sensitivity analysis mentioned, i.e. the events occurred after the subject first received an incorrect medication are not associated with the corresponding treatment group one is assigned to. Therefore, it may still be problematic to conclude the robustness of the study based on this modeling approach.

2 INTRODUCTION

2.1 Overview

Atrial Fibrillation is the most common cardiac arrhythmia, accounting for approximately one third of hospitalizations attributed to cardiac rhythm disturbances. An estimated 2.6 million people in North America and 4.5 million people in Europe have AF. The prevalence of AF increases with age. It is estimated that 3.8% of the population in the United States (US) ≥ 60 years of age and 9.0% of the US population ≥ 80 years have AF. As the US population ages, the incidence of AF is projected to increase sharply. AF has significant morbidity, mortality, and economic cost, due to the occurrence of both hemodynamic impairment and thromboembolic events. The hemodynamic impairment and rhythm disturbances may be symptomatic and can lead to a decrease in quality of life. However, most of the mortality and functional impairment associated with AF is due to the occurrence of ischemic stroke and systemic emboli. AF patients also have concomitant coronary artery disease, for which they should normally receive acetylsalicylic acid (ASA). However due to a higher rate of bleeding when anticoagulants and ASA are co-administered, one of these agents may either be withheld or dose-adjusted in such patients.

In summary, AF is a common problem with an increasing incidence. It is associated with strokes, which frequency and severity have a substantial impact on both mortality and quality of life, and add significantly to the economic burden of the disease. New effective therapies that reduce the risk of stroke in AF patients are desirable for both clinical and economic reasons.

The current treatments to prevent stroke in AF are Vitamin K antagonists (VKAs, coumadins), typified by warfarin, and are the most widely prescribed oral anticoagulants. In several adequate and well-controlled trials, warfarin decreased the risk of stroke/systemic thromboembolism by 68% versus placebo. This class of drugs when used in patients with AF also has shown to have a higher risk of bleeding at therapeutic doses than ASA alone. VKAs have a slow onset and offset of action, high inter- and intra-individual variability in their effective plasma concentrations, and have a high potential for food and drug interactions. In addition, the management of warfarin therapy can be challenging. A warfarin dose is generally adjusted to maintain an INR between 2.0 and 3.0. Maintaining INR within the target range is often difficult, requiring frequent monitoring and lab works. Thus, there is an unmet medical need for oral anticoagulants that can be given at fixed doses without the need for laboratory monitoring, that are as affective as warfarin the reducing the risk of stroke and systemic embolism.

Dabigatran, a recently approved thrombin inhibitor, was effective in preventing stroke in the RE-LY study of AF patients eligible for warfarin therapy. In addition, patients treated with dabigatran in that study had lower rates of intracranial hemorrhage than those in the warfarin treatment group. However, several safety findings associated with dabigatran are noteworthy. The rate of major bleeding with dabigatran treatment was similar (HR of 0.93, 95% CI: 0.81, 1.07) to the rate of major bleeding with warfarin treatment in the RE-LY study. The risk of bleeding increased with age in both groups; however, patients >75 years who received dabigatran had more major bleeding compared to those treated with warfarin.

An alternative approach adopted by the sponsors was to perform 2 studies: one large study, CV185030, in a population able to take a VKA using warfarin as a comparator, and a second large study, CV185048, in a population unsuitable for warfarin. In the latter population, ASA was chosen as the comparator, as it is often employed clinically in AF patients unable or unwilling to use warfarin.

Table 2 List of pivotal studies

Study	Phase	Objectives	# of Subjects	Study Population
CV185030	Phase 3	To determine if Apixaban is noninferior to warfarin (INR target range 2.0 3.0) in the combined endpoint of stroke and systemic embolism, in subjects with AF and at least one additional risk factor for stroke	~18,140	Non-valvular AF patients
CV185048	Phase 3	To determine if Apixaban is superior to aspirin for preventing the composite outcome of stroke or systemic embolism in patients with AF and at least one additional risk factor for stroke who have failed or are unsuitable for vitamin K antagonist therapy.	5578	Non-valvular AF patients

The CV185048 was stopped early because a planned interim analysis by an independent DMC demonstrated evidence of a clinically important reduction in stroke and SE in AF subjects who had received Apixaban in comparison with ASA, see Table 3.

Table 3 Adjudicated Stroke or SE during the ITT population (CV185048)

	Apixaban	ASA
#Events/N	51/2798	112/2780
Hazard ratio (SE)	0.45 (0.17)	
95% CI	0.32, 0.63	
P-value for superiority	<0.0001	

(Source: reviewer's result)

This reviewer will focus on the efficacy evaluation of CV185030.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\Cdsesub1\evsprod\NDA202155

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The following description is based on the sponsor's clinical study report. Any discrepancy between the study report and study protocol will be discussed in the section of statistical reviewer's comments.

3.1.1 CV185030 (ARISTOTLE)

CV185030 also known as ARISTOTLE is a phase 3, Warfarin controlled, double-blind, parallel arm study to evaluate efficacy and safety of Apixaban in prevention stroke and systemic embolism in subjects with non-valvular AF.

The primary objective is to demonstrate if Apixaban was NI to Warfarin (INR target range 2.0-3.0) for the combined endpoint of stroke and SE, in subjects with AF and at least one additional risk factor for stroke. The goal of the study was to show Apixaban is non-inferior to Warfarin with NI margin of (b) (4) (The agency has recommended a margin of 1.38). If non-inferiority would be achieved, superiority would be tested.

Eligible subjects were randomized in a 1:1 ratio to either Apixaban or Warfarin. Apixaban was dosed as one tablet BID, using either the 5 mg tablets or the 2.5 mg tablets for the selected Apixaban subjects. A reduced dose of Apixaban was used for subjects deemed to be at increased risk of bleeding.

There were 1,053 sites selected from 40 countries under a uniform protocol (424 sites in Europe, 316 sites in the North America. 176 sites in Asia/Pacific, and 137 sites in Latin America). The study included 3 periods: Screening period of up to 14 days, Treatment period lasting until the earlier of a subject's treatment discontinuation or the attainment of approximately 448 primary efficacy events, and Follow-up period until the latter of 30 days after treatment discontinuation or the attainment of 448 primary efficacy events.

The primary efficacy endpoint was days from randomization to first occurrence of confirmed stroke (hemorrhagic, ischemic or of unspecified type) or SE during the intended treatment period. The Intended treatment period started on the day of randomization and ended at the efficacy cut-off date. The cut-off date is the date on which it was expected that 448 primary event have occurred.

The study included 1 planned interim analysis for efficacy. The planned interim analysis for efficacy was to be performed after 50% (224) of the primary event have been confirmed. The objective of this interim analysis was to determine whether Apixaban is superior to Warfarin for the primary efficacy endpoint. The DMC could recommend stopping the study if the one-sided

p-values associated with the superiority test for the primary efficacy endpoint is < 0.0001. The effect of the interim analysis to assess superiority for the primary efficacy endpoint has the following effect on the final tests:

- Negligible effect on the type I error for the final assessment of NI ($<5x10^{-10}$); therefore the final assessment of NI will be performed at one-sided 0.025 when using NI margin of 1.38.
- The final tests of superiority for the efficacy endpoints will be performed at one-sided 0.02499.

The primary endpoint for this study is the time from randomization to first occurrence of confirmed ischemic stroke, hemorrhagic stroke or systemic embolism.

There are two major secondary endpoints: time from first dose of study drug to first occurrence of confirmed major bleeding and all-cause death.

Time to Event Analyses

The statistical analysis plan (SAP) was finalized on May 11, 2010. The calculation of p-values and construction of point estimates and CIs for RR will be based on Cox proportional hazard models. Site and prior Warfarin/VKA status will be included in the model as stratification factors.

Rule for Combining Sites

This study included more than 1,000 investigative sites, most randomizing both experienced and naive subjects, leading to a total of more than 1,800 possible strata if both prior warfarin/VKA status and actual investigative site are included as stratification factors in the model. On the other hand, the study includes 40 countries randomizing both experienced and naive subjects, leading to a total of 80 possible strata if both prior warfarin/VKA status and investigative site pooled to the country level are included as stratification factors in the model. With a target 448 primary efficacy events, the large number of strata in either approach produces very sparse data and, therefore, the baseline hazard within each stratum would be poorly estimated with such models. For this reason, when using a Cox proportional hazards model stratified by prior warfarin/VKA status and investigative site, site will be pooled to the Geographic Region level.

Testing Strategy

A hierarchical testing strategy will be followed:

- If NI for the primary efficacy endpoint (using a NI margin of 1.38) is demonstrated, then superiority for primary efficacy endpoint will be tested at the one-sided α=0.025.
- If superiority for the primary efficacy endpoint is demonstrated then superiority for major bleeding will be tested at the one-sided α=0.025.
- If superiority for major bleeding is demonstrated then superiority for all-cause death will be tested at the one-sided α= 0.025.

3.1.1.1 Patient Disposition, Demographic and Baseline Characteristics

A total of 20,998 subjects were enrolled in the study. Of these subjects, 18,201 (86.7%) were randomized to receive study treatment. The disposition of patients is listed in the Table 4. There are fewer subjects discontinued study drug in the Apixaban group than in the Warfarin group. The subject's request is the most common reasons for the discontinuation.

Table 4 End of Treatment Period Subject Status Summary

	Apixaban (N =9120) n (%)	Warfarin (N =9081) n (%)
Number subjects discontinued	2310 (25.3)	2493 (27.5)
Reason for discontinuation		
Death	331 (3.6)	349 (3.8)
Adverse Event	679 (7.4)	738 (8.1)
Stroke	75 (0.8)	108 (1.2)
SSE	14 (0.2)	8 (<0.1)
MI	24 (0.3)	15 (0.2)
Bleeding	154 (1.7)	190 (2.1)
Other	424 (4.6)	438 (4.8)
Not Reported	1 (<0.1)	0
Subject requested discontinuation	921 (10.1)	989 (10.9)
Lost to follow-up	51 (0.6)	39 (0.4)
Non-compliance	57 (0.6)	77 (0.8)
Pregnancy	1 (<0.1)	0
Subjects no long meet study criteria	87 (1.0)	100 (1.1)
Admin Reason by sponsor	11 (0.1)	8 (<0.1)
Other	81 (0.9)	89 (1.0)

(Source: Clinical Study Report CV185030, Table 5.1, page 93)

Table 5 summaries the baseline demographics information of the ITT population. The treatment groups were well balanced for baseline demographic characteristics and physical measurements. Approximately 70% of the population was elderly (over 65 years). Over 82% of the population was White. Almost 65% of the subjects were male.

Table 5 Baseline Demographic Information

	Apixaban N=9120	**Warfarin N=9081**	**Total N=18201**
Age			
<65	2731 (29.9)	2740 (30.2)	5471 (30.1)
65-<75	3539 (38.8)	3513 (38.7)	7052 (38.7)
>=75	2850 (31.3)	2828 (31.1)	5678 (31.2)
Mean (SD)	69.1 (9.61)	69.0 (9.74)	69.1 (9.68)
Median (Q1, Q3)	70 (63, 76)	70 (63, 76)	70 (63, 76)
Min, Max	21, 95	19, 97	19, 97
Sex, n(%)			
Male	5886 (64.5)	5899 (65.0)	11785 (64.7)
Female	3234 (35.5)	3182 (35.0)	6416 (35.3)
Race, n (%)			
White	7536 (82.6)	7493 (82.5)	15029 (82.6)
Black	125 (1.4)	102 (1.1)	227 (1.2)
Asian	1310 (14.4)	1332 (14.7)	2642 (14.5)
Other	149 (1.6)	154 (1.7)	303 (1.7)

Weight (kg)			
Mean (SD)	83.9 (20.7)	84.1 (20.6)	84.0 (20.7)
Median	82.0	82.0	82.0
Height (cm)			
Mean (SD)	168.7 (10.7)	168.7 (10.7)	168.7 (10.7)
Median	170.0	169.0	169.0
BMI (kg/m^2)			
Mean (SD)	29.3 (5.9)	29.4 (6.1)	29.4 (6.0)
Median	28.6	28.4	28.5

(Source: Clinical Study Report CV185030, Table 5.3.1, page 98-100)

The treatment groups were well balanced for the baseline disease characteristics, see Table 6.

Table 6 Selected Baseline Disease Characteristics

	Apixaban N=9120	Warfarin N=9081	Total N=18201
Level of Renal Impairment			
Severe (%)	137 (1.5)	133 (1.5)	270 (1.5)
Moderate (%)	1365 (15.0)	1382 (15.2)	2747 (15.1)
Mild (%)	3817 (41.9)	3770 (41.5)	7587 (41.7)
Normal (%)	3761 (41.2)	3757 (41.4)	7518 (41.3)
Not Reported (%)	40 (0.4)	39 (0.4)	79 (0.4)
Prior StrokeEM/TIA (%)	1748 (19.2)	1790 (19.7)	3538 (19.4)
CHF within 3 months (5)	3235 (35.5)	3216 (35.4)	6451 (35.4)
Prior VKA Used			
No	3912 (42.9)	3888 (42.8)	7800 (42.9)
Yes	5208 (57.1)	5193 (57.2)	10401 (57.1)
CHADS2			
0	54 (0.6)	58 (0.6)	112 (0.6)
1	3046 (33.4)	3025 (33.3)	6071 (33.4)
2	3262 (35.8)	3254 (35.8)	6516 (35.8)
3	1681 (18.4)	1598 (17.6)	3279 (18.0)
4	767 (8.4)	814 (9.0)	1581 (8.7)
5	273 (3.0)	289 (3.2)	562 (3.1)
6	37 (0.4)	43 (0.5)	80 (0.4)
Hypertension	7962 (87.3)	7954 (87.6)	15916 (87.4)

(Source: Clinical Study Report CV185030)

3.1.1.2 Primary Efficacy Results

The primary objective in this study was to determine if Apixaban was non-inferior to warfarin in reducing the occurrence of stroke or Systemic Embolism. Comparisons between treatment groups for stroke/SE were performed using a Cox regression analysis with treatment in the model. Descriptive statistics, such as event numbers and Kaplan-Meier plots (see Figure 1), are also presented. The NI and superiority of Apixaban versus Warfarin for prevention of stroke or SE was both demonstrated, see Table 7.

Table 7 Hazard ratios and CIs for stroke/SEE, randomized set.

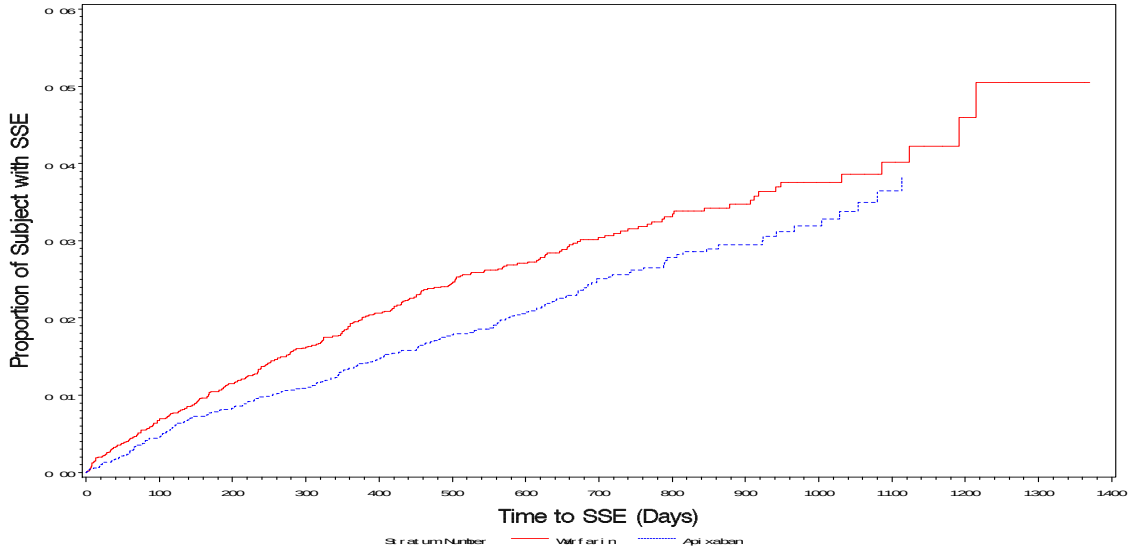
	Apixaban	Warfarin
#Events/N	212/9120	265/9081
Event rate (%/Yr)	1.27	1.60
Hazard ratio (SE)	0.79 (0.09)	

95% CI	0.66, 0.95
P-value for NI using 1.38	0.0001
P-value for superiority	0.0114

(Source: Reviewer's results)

Figure 1 captured the Kaplan-Meier curves of the two treatment groups and it showed clear separation between the two groups soon after randomization and maintained the separation throughout the duration of the trial.

Figure 1 Kaplan-Meier Plot for Stroke or Systemic Embolism During the ITT



(Source: Reviewer's Result)

Table 8 presented the detailed breakdown of the different types of strokes.

Table 8 Summary of Adjudicated Stroke/SEE during ITT

	Apixaban N=9120	Warfarin N=9081
Stroke/Systemic Embolism	212 (2.32%)	265 (2.92%)
Ischemic or unspecified Stroke	162 (1.77%)	175 (1.93%)
Hemorrhagic stroke	40 (0.44%)	78 (0.86%)
Systemeic Embolism	15 (0.16%)	17 (0.18%)

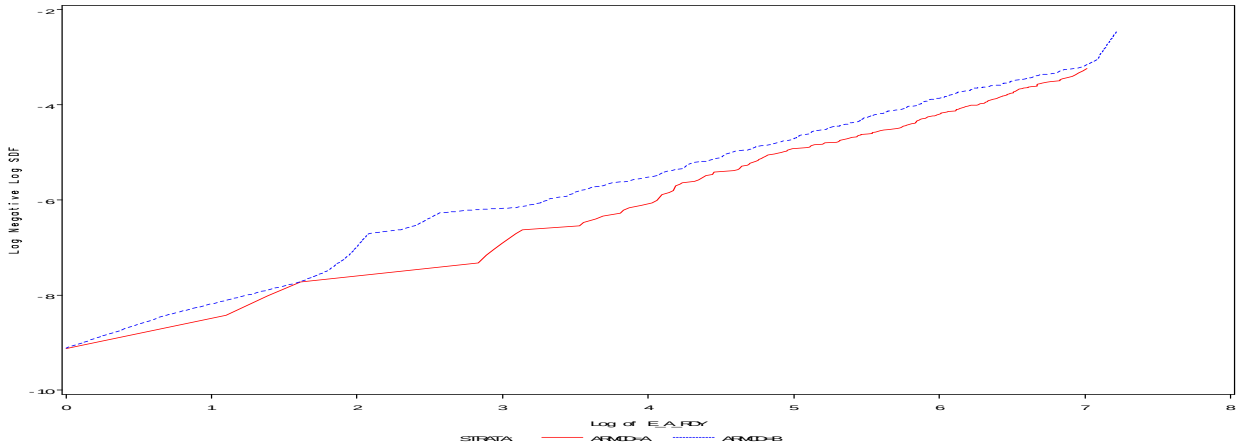
(Source: reviewer's results)

3.1.1.3 Reviewer's Results

Validation of the Proportional Hazard Assumption: The basic Cox Model assumes that the hazard functions for two different levels of a covariate are proportional for all values of time, t. For example, if men have twice the risk of heart attack compared to women at age 50, they also have twice the risk of heart attack at age 60, or any other age. The underlying risk of heart attack as a function of age can have any form. Therefore, the validity of the Cox regression findings hinges on the proportional hazard assumption. A simple and common approach to check this

assumption is through the plot of log(-log(S(t))) vs. log(t). However, the interpretation of the plot is subjective. In general, we can conclude PH unless a distinct pattern of non-parallelism (e.g. crossing) is seen. Hence, Figure 2 shows reasonable fit to the PH assumption.

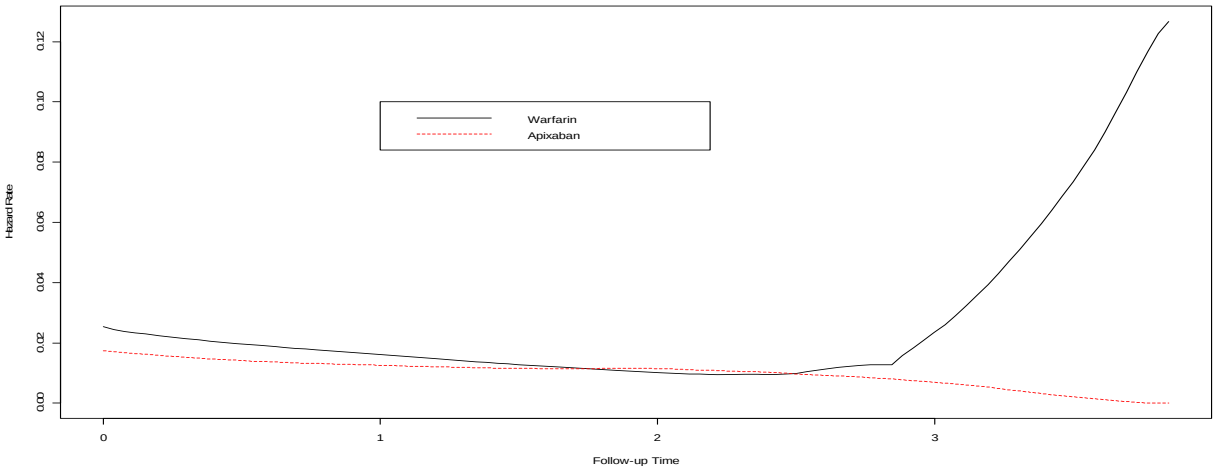
Figure 2 Log(-Log(Survival)) vs. Log(Time) Plot



(Source: Reviewer's Result)

In addition, I also produced a smooth estimate of the hazard function for both treatment arms. The smooth curves are from the estimated hazard functions for each day. Suppose, we first split the time to event into intervals of 3 months, then the number of events in each group in the corresponding time window divided by the number of patient years within this time window will be one way to estimate the hazard function for each of those 3 months time window. Now, suppose we refine the time window down to everyday, then the estimate hazard function on each day can be computed. However, we can not see any meaningful trend in Figure 3.

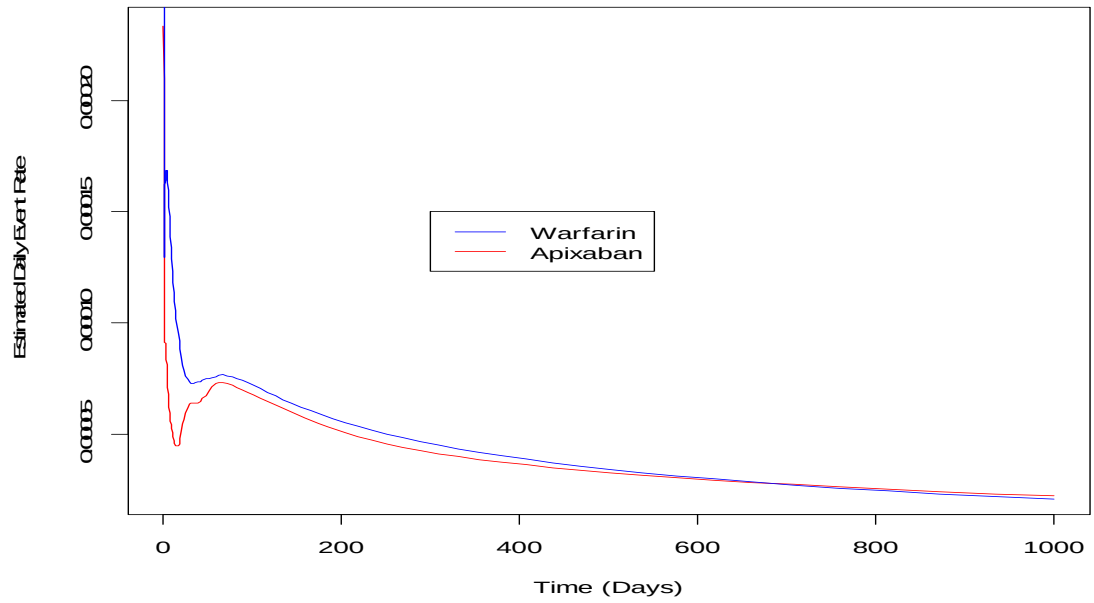
Figure 3 Estimated Hazard functions over time (year)



(Source: Reviewer's Result)

There is a big jump in the warfarin arm's hazard function right around year 3 due to the occurrence of 4 primary events. Further, only 5% of total patients remained at risk at the time of the first of those 4 events. Therefore, I made a cut off at the year 3 and produced Figure 4, which suggested that the estimated event rates go down over the first 3 years (in both groups). The difference between groups in the hazard functions seems larger in the earlier days.

Figure 4 Estimated Event Rates (Cutoff at year 3) for the primary endpoint

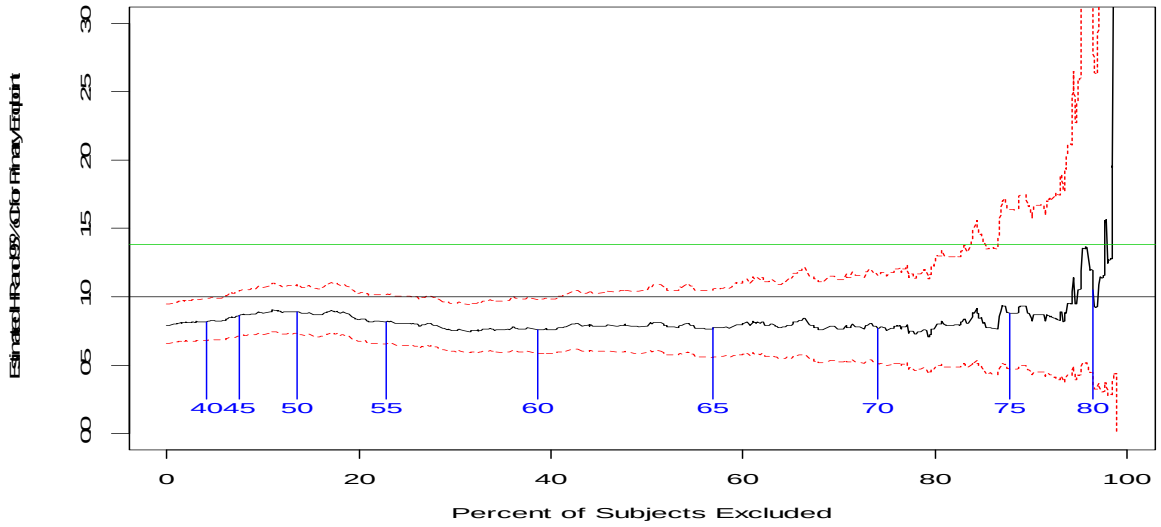


(Source: Reviewer's Result)

Analyses by INR control

The subjects on warfarin had their INR level measured throughout the whole trial and the mean percent of time of INR in 2-3 were computed for each warfarin subject as well. The efficacy of warfarin is highly dependent of the time in therapeutic range (TTR). For each subject in the warfarin arm, the TTR is defined as the proportion of time the INR is between 2 and 3. Even though Apixaban does not require INR monitoring, it is important to assess the effect of Apixaban relative to warfarin according to INR-based properties for warfarin. However, it is not feasible to match Apixaban-treated subjects to corresponding warfarin-treated subjects at the subject level. Therefore, the reviewer assessed the robustness of the efficacy findings of Apixaban in terms of TTR in Figure 5. For each site, the site level TTR is the average of the TTR for the warfarin subjects in that site. This figure shows that the estimated hazard ratio (black curve) for sites with TTR above different cutoff values. The x-axis shows the percent of the total subjects are excluded (from sites with warfarin TTR lower than the corresponding marked cutoff value). The upper and lower red curves are the upper and lower bound of the 95% confidence intervals. The curves started at all data included, which is same as the Hazard ratio and its' confidence interval of the primary endpoint. The curves at the far right side of the figure only included very small amount of data. For example, if we set the TTR cutoff level at 80%, then only less than 5% of trial population is included in this analysis. The point estimates curve resided under the superiority margin of 1.0 throughout except far right end of the figure.

Figure 5 Estimated Hazard ratio for the primary endpoint among sites with TTR above different marked cutoff levels.



(Source: Reviewer's Result)

Comparisons of Apixaban to warfarin within quartiles of INR control were made Table 9. It is not feasible to match Apixaban treated subjects to corresponding warfarin treated subjects at the subject level. Therefore, the clinical sites were ranked and allocated into one of the 4 quartiles intervals based on their median warfarin TTR. Apixaban treated subjects from the corresponding sites were then compared with the warfarin treated subjects. Consistent with the primary efficacy results, Apixaban demonstrated a reduction in stroke/SE compared to warfarin for study sites with INR control in each of the 4 quartile intervals. The point estimates are consistently below 1.0, and ranged from 0.76 to 0.85. All 95% confidence interval upper bounds are below the margin of 1.38.

Table 9 Summary of Adjudicated SSE during the ITT by level of INR control

Center TTR (%)	APIXABAN	WARFARIN
< 55.2763, n/N (%)	69/2197 (3.14)	88/2178 (4.04)
EVENT RATE (%/YR)	1.78	2.35
HAZARD RATIO (APIXABAN/WARFARIN)	0.76	
95% CI FOR HAZARD RATIO	(0.55 , 1.04)	
55.2763 - < 64.6208, n/N (%)	72/2842 (2.53)	86/2865 (3.00)
EVENT RATE (%/YR)	1.39	1.65
HAZARD RATIO (APIXABAN/WARFARIN)	0.85	
95% CI FOR HAZARD RATIO	(0.62 , 1.17)	
64.6208 - < 72.7020, n/N (%)	41/2394 (1.71)	55/2418 (2.27)
EVENT RATE (%/YR)	0.90	1.20
HAZARD RATIO (APIXABAN/WARFARIN)	0.75	
95% CI FOR HAZARD RATIO	(0.50 , 1.12)	
>= 72.7020, n/N (%)	29/1637 (1.77)	36/1613 (2.23)
EVENT RATE (%/YR)	0.95	1.19
HAZARD RATIO (APIXABAN/WARFARIN)	0.79	
95% CI FOR HAZARD RATIO	(0.49 , 1.30)	

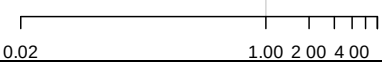
(Source: Sponsor's Response to requests for information #10, page 11)

Analysis on the Impact of Individual Country

The study was conducted in 40 countries. The number of patients per country ranged from 6 to 3,417. Among these countries, Apixaban was numerically superior to warfarin in the many countries (see Figure 6). It failed to demonstrate the superiority in United States. However, the point estimate (HR=0.794) is consistent with the overall study. The point estimate in the most of countries is below the non-inferiority margin of 1.38. Furthermore, the upper bound of hazard ratio was below the margin in United States.

Figure 6 The Forest Plots of Hazard ratio and 95% CI for stroke/SEE comparing Apixaban to warfarin by countries

Country	#events/N (Apixaban)	#events/N (Warfarin)	HR	(95% CI)
ARGEN	20/786	20/775	0.979	(0.5264 , 1.819)
AUS	1/17	1/17	1	(0.0625 , 15.988)
AUSTL	2/166	4/156	0.472	(0.0864 , 2.584)
BRAZ	5/353	11/347	0.42	(0.1460 , 1.210)
CAN	11/529	17/528	0.668	(0.3126 , 1.427)
CHILE	4/128	2/130	1.969	(0.3598 , 10.775)
CHINA	28/422	26/421	1.08	(0.6331 , 1.841)
COLOM	1/54	5/57	0.194	(0.0226 , 1.670)
CZR	1/83	1/82	1.093	(0.0680 , 17.562)
DEN	3/169	2/170	1.402	(0.2319 , 8.471)
GER	4/431	7/423	0.566	(0.1656 , 1.932)
HKONG	3/38	1/38	3.137	(0.3261 , 30.182)
HUN	6/227	6/228	0.977	(0.3151 , 3.031)
IND	6/302	16/299	0.359	(0.1403 , 0.918)
ISR	6/170	2/174	2.891	(0.5802 , 14.408)
JAPAN	3/161	6/175	0.514	(0.1284 , 2.060)
KOREA	1/153	8/157	0.124	(0.0155 , 0.994)
MALAY	4/64	7/62	0.555	(0.1621 , 1.897)
MEX	11/310	10/299	1.066	(0.4525 , 2.511)
NETH	2/155	1/154	1.781	(0.1612 , 19.691)
PERU	2/103	4/110	0.56	(0.1024 , 3.061)
PHIL	4/103	10/102	0.381	(0.1191 , 1.222)
ROMAN	4/138	3/136	1.266	(0.2831 , 5.658)
RUSS	20/896	32/904	0.612	(0.3500 , 1.070)
SAFR	3/44	1/45	2.137	(0.2088 , 21.870)
SPAIN	4/116	2/114	1.842	(0.3364 , 10.085)
SWE	2/111	2/106	1.021	(0.1437 , 7.257)
TAIW	1/27	1/30	1.041	(0.0651 , 16.651)
UKR	14/480	10/476	1.379	(0.6124 , 3.104)
USA	31/1720	39/1697	0.794	(0.4953 , 1.272)



[Source: Reviewer's Results]

3.1.1.4 Secondary Efficacy Analysis

Analysis of Major Bleeding Endpoint per ISTH criteria

According to the sequential testing strategy outlined previously, since the superiority of Apixaban compared to warfarin was demonstrated for the primary efficacy endpoint, the superiority for ISTH major bleeding was tested. Apixaban was superior to warfarin for ISTH major bleeding (p-value < 0.0001), see Table 10.

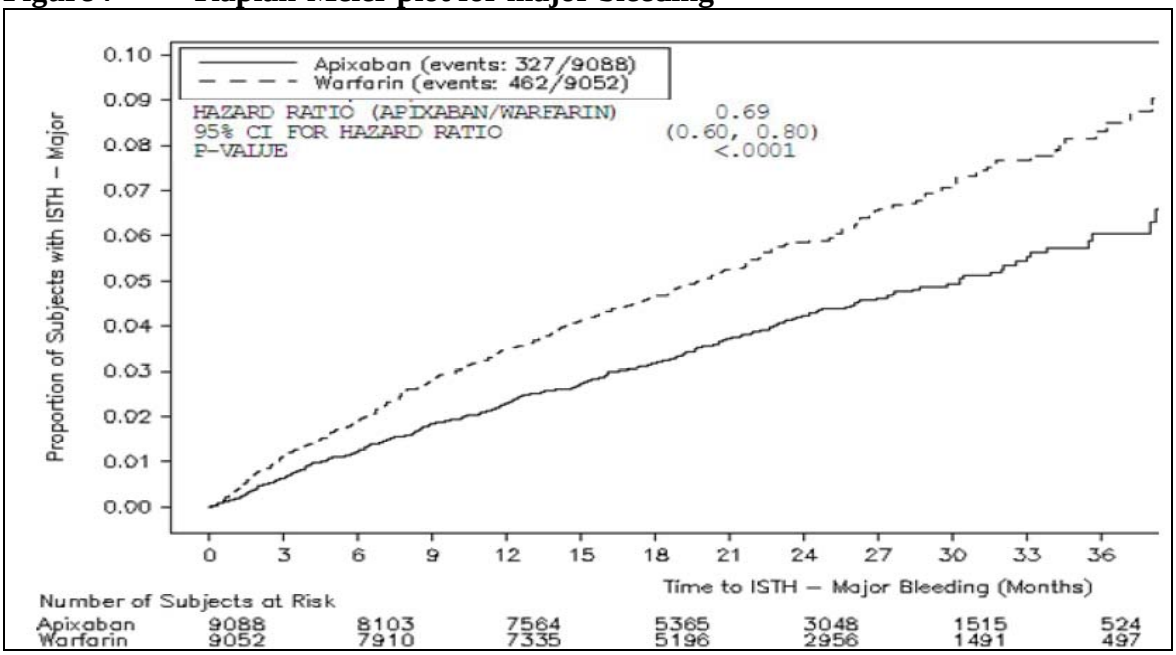
Table 10 Hazard ratios and CIs for Major Bleeding During Treatment Period.

	Apixaban	Warfarin
#Events/N	327/9088	462/9052
Hazard ratio (SE)	0.69 (0.07)	
95% CI	0.60 0.80	
P-value for superiority	<0.0001	

(Source: Reviewer's Results)

The Kaplan-Meier plot for ISTH major bleeding showed clear separation between Apixaban and warfarin shortly after the initiation of the study, see Figure 7.

Figure 7 Kaplan-Meier plot for major bleeding



(Source: Reviewer's Result)

Analysis of All-cause Death

Finally, the third endpoint tested was all-cause death, since superiority of Apixaban compared to warfarin was demonstrated for both the primary efficacy endpoint and ISTH major bleeding. Based on the pre-specified Cox proportional hazard model, Apixaban was superior to warfarin for reduction of all-cause death (HR=0.89, p-value=0.0465), see Table 11.

Table 11 Hazard ratios and CIs for All-cause Death During the Intended Treatment Period.

	Apixaban	Warfarin
#Events/N	603/9120	669/9081
Hazard ratio (SE)	0.89 (0.06)	
95% CI	0.80 0.998	
P-value for superiority	0.0465	

(Source: Reviewer's Results)

3.2 Evaluation of Safety

Safety is not evaluated in this review. Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

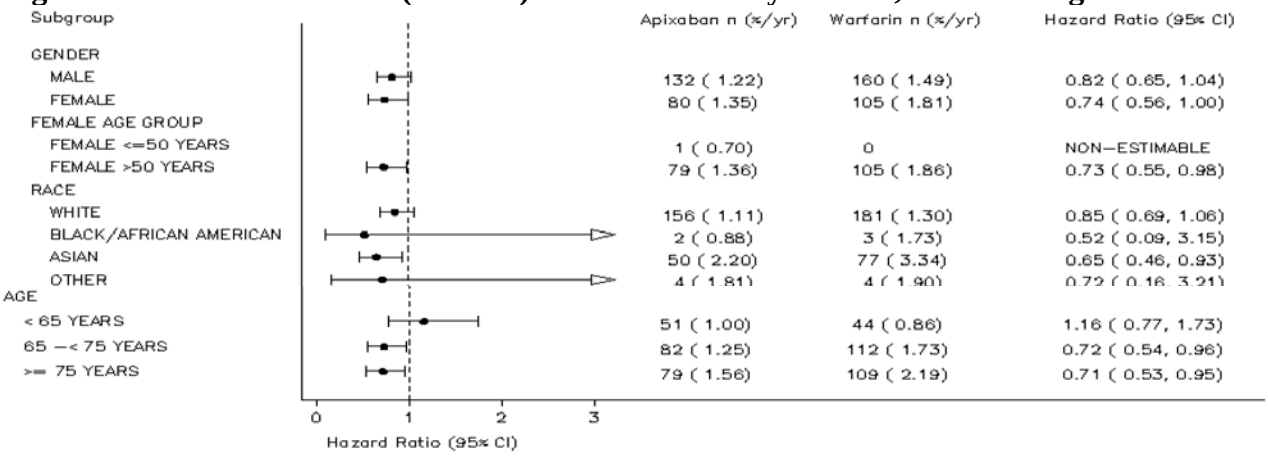
Various subgroup analyses were performed to explore whether the efficacy of Apixaban was markedly different among different subgroups compared to that observed in the primary efficacy results.

4.1 Gender, Age and Race group

There were no obvious differences in hazard ratios for the primary endpoint across either gender group. Male and female both demonstrated marginal superiority over warfarin. All four race groups' point estimates are less than 1.0, and the superiority was observed in Asians. The estimated HRs for all these subgroups was considerably less than 1.0.

Finally, the estimated hazard ratios and the upper bounds of 95% CI were <1 for both over 65 years old age groups, which suggested that the risk of stroke/SE was lower in the Apixaban group than in the warfarin group. However, Apixaban seemed less effective than warfarin for the people are younger than 65 years old. The estimated HR exceeded 1.0 and the associated upper bound of 95% CI also well exceed 1.0. See Figure 8.

Figure 8 Hazard Ratios (95% CI) for stroke/SEE by Gender, Race and Age



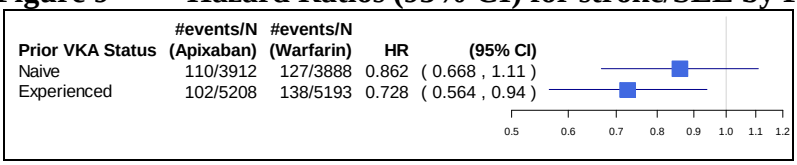
[Source: Sponsor's study report page 131-132]

4.2 Other Subgroup Populations

4.2.1 PRIOR VKA USE

Warfarin, the most widely used VKA, was chosen as the active control. Therefore, it is important to find out whether Dabigatran has any different effects depend on the patients' prior VKA usage.

Figure 9 Hazard Ratios (95% CI) for stroke/SEE by Prior VKA Usage



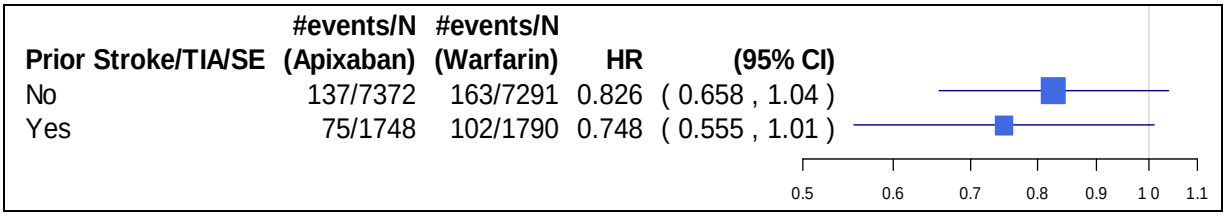
[Source: Reviewer's Results]

Based on Figure 9, the hazard ratios of stroke/SEE on Apixaban over warfarin were under 1.00 regardless of prior VKA use. It is more effective in the VKA experienced group and Apixaban also demonstrated to be statistically superior to warfarin.

4.2.2 HISTORY OF STROKE/SEE/TIA

The majority of subjects never had any episodes of Stroke/SEE/TIA in both treatment groups. Whether the subjects had history of stroke or not, Apixaban showed a robust effect in reducing stroke/SE compared to warfarin, see Figure 10.

Figure 10 Hazard Ratios (95% CI) for stroke/SEE by History of Stroke/SEE/TIA

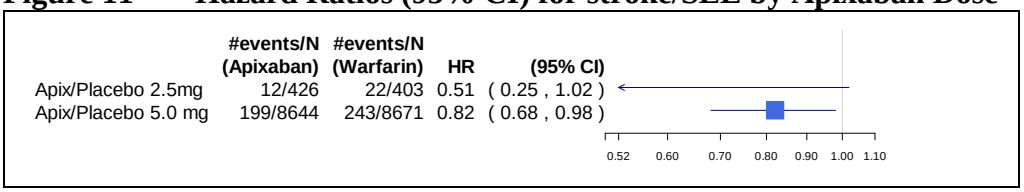


[Source: Reviewer's Results]

4.2.3 LOW DOSE VERSUS HIGH DOSE

The protocol specified that the dose of Apixaban assigned at randomization was to be 2.5 mg BID for subjects who are at higher risk of bleeding (age>80, weight < 60kg or serum creatinine >1.5mg/dL). As seen in Figure 10, the efficacy of Apixaban was maintained in the reduced dose with only 4.6% of randomized subjects. In fact, the Apixaban showed robust findings in both dosage groups.

Figure 11 Hazard Ratios (95% CI) for stroke/SEE by Apixaban Dose



[Source: Reviewer's results]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary objective of CV185030 was to demonstrate NI for Apixaban as compared to warfarin, and the 4 key objectives of the study (including, in addition to the primary objective, assessments of superiority for primary efficacy endpoint, superiority for ISTH major bleeding, and superiority for all-cause death) were tested following a hierarchical testing strategy to preserve the overall type I error at a significance level adjusted for the formal interim test for superiority (the adjustment was small and did not impact the results). Overall type I error was preserved at ≤5%.

Apixaban was superior to warfarin for the prevention of composite endpoint of stroke (any type), and SE (HR=0.79 with two-sided p=0.0114). Apixaban reduced the risk of stroke or SE by 21% from 1.60 to 1.27% per year compared to warfarin. Numerical decreases in stroke/SE event rates were observed across all levels of INR control. Similar trend was observed across all countries, and US finding (HR=0.794) is consistent with the overall result.

During the trial, the protocol specified very small portion of the subjects who were at higher risk of bleeding to be assigned to the lower strength of Apixaban, 2.5 mg BID. Apixaban showed robust and consistent effects in reducing stroke/SE compared to warfarin within both the lower and higher dosage groups.

Apixaban was superior to warfarin with regard to ISTH major bleeding (HR=0.69. two-sided p-value <0.0001) and for the reduction of all-cause death (HR =0.89, two-sided p=0.0465).

5.2 Conclusions and Recommendations

The conclusion and reviewer's recommendation on Apixaban are solely based on the findings of Study CV185030, which was designed to evaluate the efficacy and safety of Apixaban versus warfarin (INR target range 2.0-3.0) in subjects with non-valvular AF. The findings of this study are sufficient to conclude Apixaban is superior to warfarin for the prevention of 1) stroke (hemorrhagic or ischemic) and SE, 2) ISTH major bleeding and 3) death due to any cause.

However, there are a large number of medication errors had been uncovered during the final stage of the review process, see section 1.4. The significant findings of the Apixaban can not be concluded unless various aspects of the medication errors can be addressed by the sponsor.

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/s/

STEVE G BAI
05/01/2012

HSIEN MING J HUNG
05/01/2012

Statistical Review and Evaluation
CARCINOGENICITY STUDIES

IND/NDA Number: NDA 202155
Drug name: BMS-562247
Indication(s):
Applicant:
Documents Reviewed: Electronic submission
Electronically submitted dataset
Dated: 2011-09-30
Review Priority:

Biometrics Division: Division of Biometrics 6
Statistical Reviewer: Matthew Jackson, PhD
Concurring Reviewer: Karl Lin, PhD
Medical Division: Division of cardio-renal products
Reviewing Pharmacologist: Patricia Harlow, PhD
Project Manager:

Keywords: Animal Mouse Rat Carcinogenicity

Contents

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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 BMS-562247 when administered through diet, once daily at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist, Patricia Harlow, 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 comprised two experiments, one in male mice and one in female mice (in addition to a toxicokinetic study, the results of which are not considered as part of this review). The mice used were Crl:CD-1 (ICR) BR mice, and were approximately four weeks old when delivered. Three hundred mice were used in each experiment, divided into five dose groups of sixty animals each. Two groups were control groups, and received the basal diet without any BMS-562247. The remaining three groups, the low, mid, and high dose groups respectively, received various doses of BMS-562247 mixed in thir basal diet. The dose levels of the test article were 150 mg/kg in the low dose group, 500 mg/kg in the mid dose group, and 1500 mg/kg (male animals) or 3000 mg/kg (female animals) in the high dose group.

During the first year of the study, animals received cageside inspections twice daily. During these inspections, they were checked for mortality, moribundity, injury, and to ensure that they had an adequate supply of food and water. In the second year, these inspections were conducted three times per day. Detailed clinical exams were conducted weekly. After death, each animal underwent a complete necroscopy.

1.2 Sponsor's analysis

1.2.1 Survival analysis

The sponsor assessed the impact of BMS-562247 on survival by conducting a two tailed test of trend, at the 0.05 level, using the life table method. The two control groups were pooled in both female and male mice.

When considering the results for female mice, the sponsor notes that there is no sign of any one group over- or underperforming any of the others. It is noted however, that there is a significant difference ($p = 0.0329$) in survival between the two control groups.

The sponsor notes that among male mice, the high dose group does underperform the other groups, but also observes that the mid dose group overperforms the other groups, thus making the possibility of a dose related effect on survival seem remote. The statistical tests do not yield any significant results. It should be noted however, that the sponsor has only conducted tests of trend, and has not conducted the pairwise tests that would be needed to assess whether the mid or high dose groups' survival outcomes were significantly different from those of the control groups.

1.2.2 Tumor analysis

The sponsor used various versions of Peto's method [6] to test for a tumorigenic dose response for each reported tumor type. The exact method was used when the total number of tumor bearing animals (across all groups in one sex) was below twelve; otherwise the asymptotic method was

used. For tumors found exclusively after death, either the death rate or prevalance method was used, depending on whether the tumors were deemed fatal or incidental. Tumor types found through palpation were analyzed using the onset time method.

In additional to individual tumor types, several combination endpoints were considred. These are listed in table 1.1.

The threshold for significance was 0.025 for rare tumors and 0.005 for common tumors. In all cases, the control groups were combined.

Table 1.1: Combination tumor types considered by the sponsor

All hemangiomas and hemangiosarcomas
Uterine glandular polyps and adenocarcinomas
Uterine glandular and stromal polyps

The tests of two individual tumor types yielded p-values below 0.05. These were salivary schwannomas in male mice ($p = 0.0269$) and glandular endometrial polyps in female mice ($p = 0.0230$). In addition, in female mice, the combination endpoints including endpmetrial polyps also yielded p-values below 0.05 (for glandular endmetrial polyps and adenocarcinoms the p-value was 0.0081, and for glandular and stromal polyps it was 0.0263), as did the test of hemangiomas and hemangiosarcomas ($p = 0.0487$). The sponsor claims that these are all common tumors, and therefore, since in no case is the p-value below 0.005, none of these results constitute positive findings.

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 1.2. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table 1.3, and the results of log-rank survival tests comparing the treated groups with the combined control group are presented in table 1.4.

Figure 1.1: Survival curves for female mice

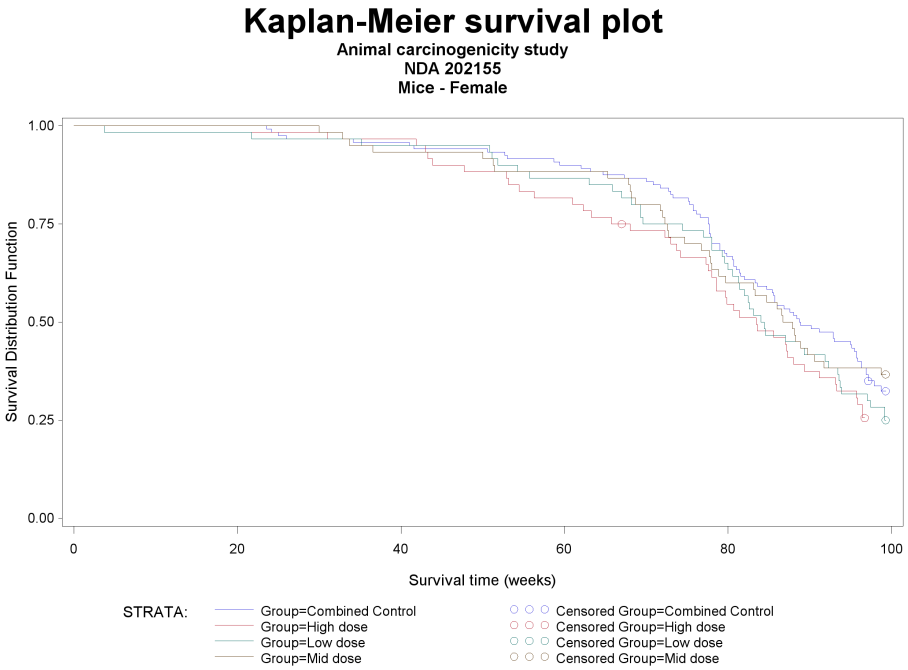

Figure 1.2: Survival curves for male mice

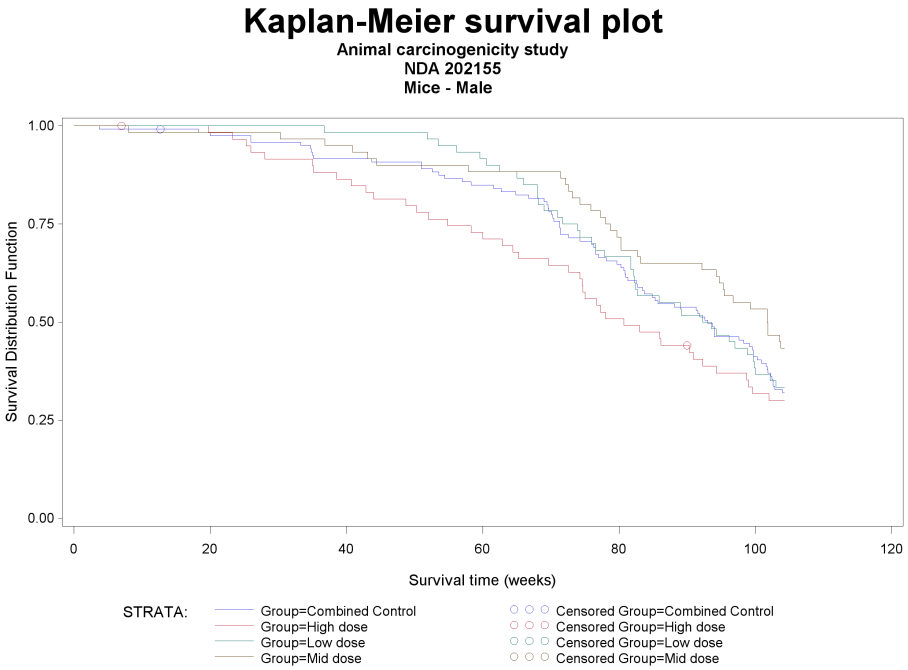

Table 1.2

Survival rates at key times
NDA 202155
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	112	93%	86	72%	59	49%	0	0.0%
	Low dose	150	60	54	90%	43	72%	25	42%	0	0.0%
	Mid dose	500	60	53	88%	39	65%	25	42%	0	0.0%
	High dose	3000	60	53	88%	37	62%	22	37%	0	0.0%
Mice - Male	Combined Control	0	120	106	88%	79	66%	64	53%	39	33%
	Low dose	150	60	58	97%	40	67%	31	52%	20	33%
	Mid dose	500	60	54	90%	46	77%	39	65%	26	43%
	High dose	1500	60	46	77%	31	52%	26	43%	17	28%

Commentry In the case of the female mice, the Kaplan-Meier curves (figure 1.1) suggest that the high dose group experienced higher mortality than the other groups. This observation is borne out by the statistical tests, which reveal a statistically significant trend of increasing mortality as dose is increased ($p = 0.0498$), although there is no significant difference in survival between the combined control group and the high dose group ($p = 0.0885$).

Among male mice, the Kaplan-Meier plots again suggest that the high dose group has underperformed the other groups, but this effect is not statistically significant (the p-value for the test of trend is 0.1625, and the p-value for the comparison test between the combined control group and the high dose group is 0.535).

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 1.5.

In the case of the female mice, there is a visible difference in survival between the control groups visible in the Kaplan-Meier plots. This difference is weakly statistically significant ($p = 0.0329$).

In the case of the male mice, there is no suggestion that the two control groups experienced different survival outcomes.

Table 1.3: Results of log-rank tests of survival across all groups

Log-rank tests of survival
NDA 202155
Animal carcinogenicity study

Species and 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*
Mice - Female	4.1070	3	4	0.2501	0.0997	0.0498
Mice - Male	5.2369	3	4	0.1553	0.3250	0.1625
Rats - Female	1.4077	3	4	0.7037	0.5625	0.2813
Rats - Male	2.4732	3	4	0.4802	0.3009	0.1504

Table 1.4: Table 1.4

Pairwise comparisons (log-rank) of survival between treated groups and controls
NDA 202155
Animal carcinogenicity study

Species and Sex	*Quantity*	*Low dose*	*Mid dose*	*High dose*
Mice - Female	Chi squared test statistic	1.4162	0.1603	2.9016
	p-value of comparison with control	0.2340	0.6889	0.0885
Mice - Male	Chi squared test statistic	0.0848	1.7008	0.3337
	p-value of comparison with control	0.7710	0.1922	0.5635
Rats - Female	Chi squared test statistic	0.0230	0.2386	0.2492
	p-value of comparison with control	0.8796	0.6252	0.6177
Rats - Male	Chi squared test statistic	0.1124	0.7149	0.4705
	p-value of comparison with control	0.7375	0.3978	0.4928

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

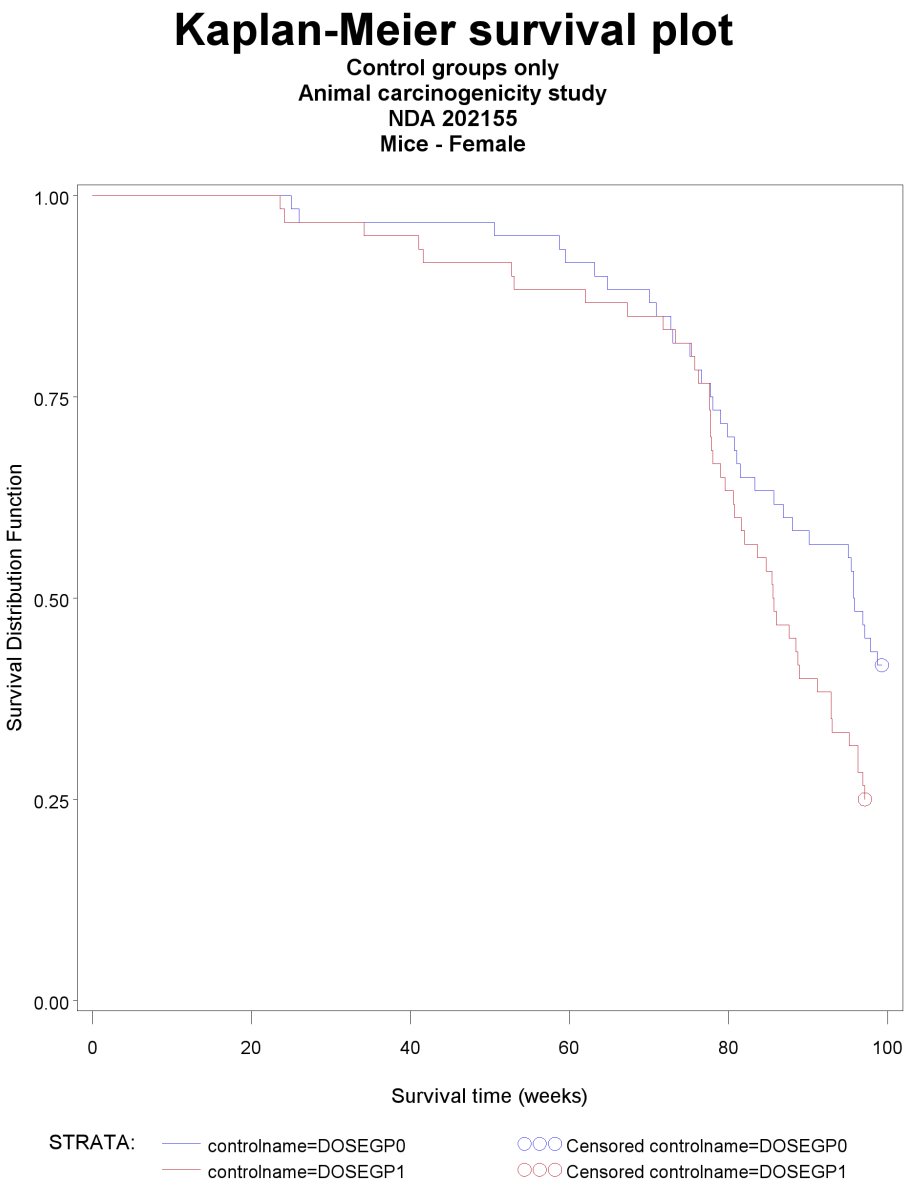

Figure 1.4: Survival curves for control groups (male mouse experiment)

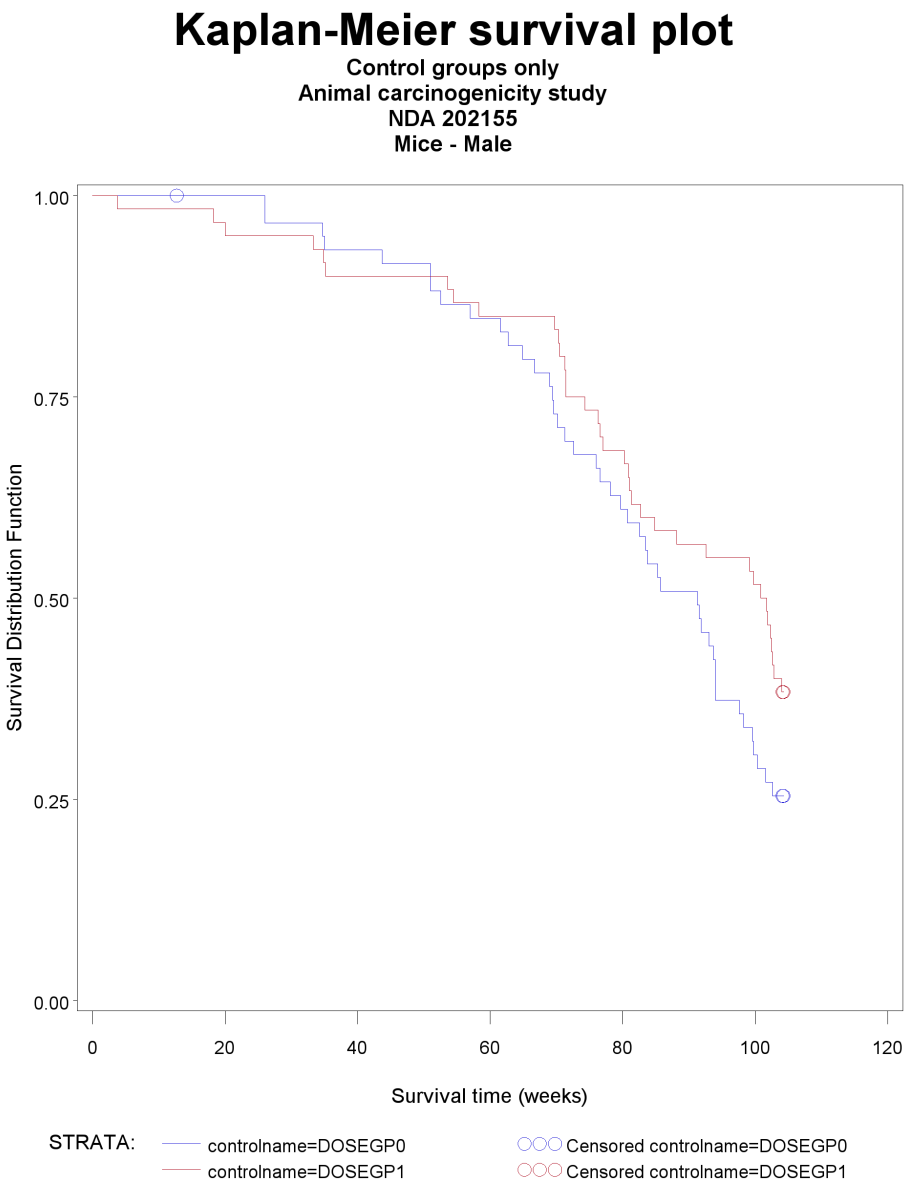

Table 1.5

Log-rank tests of heterogeneity of survival between control groups
NDA 202155
Animal carcinogenicity study

Species and Sex	*Chi^2*	*DF*	*P-value*
Mice - Female	4.5518	1	0.0329
Mice - Male	2.5866	1	0.1078
Rats - Female	0.6950	1	0.4045
Rats - Male	0.0885	1	0.7662

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 this 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 becasue 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 1.6 and 1.7.

Organ or tissue types which were examined in only a few organ types are denoted secondary.

In the mouse study, there are no secondary organs.

Each tumor type found in a primary organ of at least one animal is considered a co-primary endpoint. In addition, in consultation with Patricia Harlow, PhD, a list of combination endpoints has been drawn up. This list is presented in table 1.8.

Table 1.6

Primary organs in study of female mice
NDA 202155
Animal carcinogenicity study

Organ or tissue name
adrenal glands
aorta
bone, vertebra
cavity, abdominal
eyes, optic nerves
gallbladder
harderian glands
heart
kidneys
liver
lung
lymph node, hepatic
lymph node, iliac
lymph node, inguinal
lymph node, mandibular
lymph node, mediastinal
lymph node, mesenteric
lymph node, renal
mammary gland
multicentric neoplasm
nerve, sciatic
ovaries
pancreas
parathyroid glands
pituitary gland
skeletal muscle, diaphragm
skeletal muscle, quadriceps femoris
skin, subcutis
spleen
stomach, glandular
stomach, nonglandular
thymus gland
thyroid gland
tongue
trachea
urinary bladder
uterus with cervix
vagina

Table 1.7

Primary organs in study of male mice
NDA 202155
Animal carcinogenicity study

Organ or tissue name
adrenal glands
bone, sternum
brain
cavity, thoracic
epididymides
esophagus
eyes, optic nerves
gallbladder
harderian glands
kidneys
large intestine, colon
liver
lung
lymph node, hepatic
lymph node, mandibular
lymph node, mediastinal
lymph node, mesenteric
lymph node, renal
mammary gland
multicentric neoplasm
pancreas
parathyroid glands
pituitary gland
prostate gland
salivary gland, mandibular
seminal vesicles
skeletal muscle, diaphragm
skin, subcutis
small intestine, duodenum
spinal cord, lumbar
spleen
stomach, glandular
stomach, nonglandular
tail
testes
thymus gland
thyroid gland
tongue

Primary organs in study of male mice
NDA 202155
Animal carcinogenicity study

Organ or tissue name
trachea
urinary bladder

Table 1.8

Customized and combination endpoints analyzed
NDA 202155
Animal carcinogenicity study

Composite endpoint
Bronchiolar alveolar tumors
C-cell tumors
Cortical cell tumors
Endometrial tumors of the uterus
Follicular cell tumors
Granular cell tumors of the uterus, cervix and vagina
Granular or meningeal granular cell tumors (brain)
Harderian adenomas and adenocarcinomas
Hemangiomas and hemangiosarcomas
Hepatocellular tumors
Islet cell tumors
Leiomyomas and leiomyosarcomas of the uterus, cervix, ovaries and vagina
Leiomyomas of the uterus, cervix, ovaries and vagina
Leiomyosarcomas of the uterus, cervix, ovaries and vagina
Mammary adenomas or fibroadenomas
Mammary adenomas, adenocarcinomas or fibroadenomas
Mast cell tumors
Ovarian cystadenomas and cystadenocarcinomas
Ovarian stromal tumors
Parathyroid tumors
Pheochromocytomas
Pituitary pars distalis tumors
Skin carcinomas
Stromal tumors of the uterus or ovaries
Subcutis fibromas and fibrosarcomas
Uterine glandular polyps and adenocarcinomas
Uterine leiomyomas and leiomyosarcomas
Uterine stromal tumors

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 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 BMS-562247 with combined control, we use the thresholds for significance presented in table 1.9.

Despite the weakly significant difference in survival between the two female dose groups, there seems to be little reason to consider these groups as having had substantially different experiences in the study. Thus, for both males and females, analyses of tumor incidence have been conducted using a combined control.

Noteworthy results

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables 1.10 (female mice) and 1.11 (male mice). The results of analyses of customized endpoints (see table 1.8) are presented in tables 1.12 and 1.13.

Individual tumor types in female mice for which tests yielding p-values below 0.05 were conducted are presented in table 1.14, which is excerpted from table 1.10. Combination tumor types for which tests yielding p-values below 0.05 were conducted are presented in table 1.16, which is excerpted from table 1.12. Individual tumor types in male 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. No tests of customized or combination tumor types were conducted that yielded p-values below 0.05.

Table 1.9: 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

Uterine and cervical tumors The test of trend for the incidence of benign glandular polyps of the uterus and cervix is significant at the 0.05 level: $p = 0.0148$. The comparison between the high dose group and the control group yields a p-value of 0.0867.

When uterine adenocarcinomas are included in the endpoint, the test of trend becomes even more significant ($p = 0.0058$), and the p-value of the test of comparison between the high dose group and the combined control drops below 0.05 ($p = 0.0425$).

Assuming that these endpoints are common tumor types, none of these results meet the requirements for statistical significance. Nonetheless, the results for combined benign glandular polyps and uterine adenocarcinomas is strong enough to at least warrant further discussion.

(If these are considered rare tumors, then the situation is different, but given that the observed survival-adjusted incidence rate for benign glandular polyps is 5.4% in the control group, well above the 1% needed to consider a tumor type to be rare, it would seem a stretch to consider this to be a rare endpoint.)

Benign schwannoma of the mandibular salivary gland in male mice Only two male animals developed benign schwannomas of the mandibular salivary gland, both in the high dose group. This is enough to generate a p-value below 0.05 for the test of trend ($p = 0.0265$), but is insufficient for a statistically significant difference between the high dose group and the combined control ($p = 0.0836$). After making a multiplicity adjustment, even the test of trend misses statistical significance. Unless these are considered extremely rare tumors, this should be considered a negative finding.

1.3.3 Analysis of unexamined and autolytic organs

Unexamined animals

No animals have been reported as completely unexamined.

Organs reported autolytic

No mice were reported as having any organs autolyzed to the extent that a usable sample was not obtainable.

Organs reported as unexamined

The numbers of animals with organs reported as being unexamined are presented in tables 1.17 and 1.18.

The parathyroid has been reported as unexamined in many animals (42% of female animals and 39% of male animals). While it is not uncommon in studies such as this for there to be large numbers of animals for which the parathyroid was unexamined, it is nonetheless the case that with respect to tumors of the parathyroids, this study should be regarded as inconclusive, rather than negative.

The same situation applies (less strongly) to tumors of the thymus in female mice: 23% of the female animals did not have their thymus glands examined.

1.3.4 Tables of results

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
adrenal glands	adenoma, subcapsular cell, benign	P-value of test of trend or comparison	.5758	.3204		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,12.3)
		Poly-3 adjusted number of animals at risk	70.9	33.7	34.2	28.9
	pheochromocytoma, malignant	P-value of test of trend or comparison	.3433	.5360	1	.4980
		Number of animals reported with tumor	1	1	0	1
		Poly-3 adjusted incidence rate	1.4%	3.0%	0.0%	3.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0.07,15.8)	(0,10.3)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	71.0	33.6	34.2	29.5
aorta	carcinoma, bronchiolar alveolar, malignant	P-value of test of trend or comparison	.3795		.3269	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.1	33.2	34.6	29.7
	sarcoma, undifferentiated, malignant	P-value of test of trend or comparison	.1747			.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)	(0,10.3)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	70.1	33.2	34.2	29.9
bone, vertebra	osteosarcoma, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.5	33.2	34.2	29.7
cavity, abdominal	lipoma, benign	P-value of test of trend or comparison	.3772		.3238	
		Number of animals reported with tumor	0	0	1	0

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.3	29.7
gallbladder	adenoma, benign	P-value of test of trend or comparison	.1758			.2959
		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 (%)	(0,5.2)	(0,10.6)	(0,10.3)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	69.9	33.2	34.2	29.8
harderian glands	adenocarcinoma, malignant	P-value of test of trend or comparison	.8229	.5449	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 (%)	(0.04,7.6)	(0.07,15.3)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.4	34.0	34.2	29.7
	adenoma, benign	P-value of test of trend or comparison	.1676	.2444	.1041	.2097
		Number of animals reported with tumor	1	2	3	2
		Poly-3 adjusted incidence rate	1.4%	5.8%	8.5%	6.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0.7,19.7)	(1.75,23.1)	(0.79,22.1)
		Poly-3 adjusted number of animals at risk	71.4	34.6	35.1	30.6
	carcinoma, bronchiolar alveolar, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.5	33.2	34.2	29.7
heart	carcinoma, bronchiolar alveolar, malignant	P-value of test of trend or comparison	.3772		.3238	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.07,15.3)	(0,11.9)

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.6	29.7
	osteosarcoma, malignant	P-value of test of trend or comparison	.5749	.3173		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.4	34.2	29.7
kidneys	carcinoma, bronchiolar alveolar, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.5	33.2	34.2	29.7
	carcinoma, tubular cell, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.9	33.2	34.2	29.7
liver	adenoma, hepatocellular, benign	P-value of test of trend or comparison	.5843	.8551	.2389	.8234
		Number of animals reported with tumor	4	1	4	1
		Poly-3 adjusted incidence rate	5.5%	3.0%	11%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(1.51,13.6)	(0.07,15.8)	(3.11,26.7)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	72.5	33.3	35.4	29.9
	carcinoma, squamous cell, malignant	P-value of test of trend or comparison	.5749	.3173		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.7	34.2	29.7

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	osteosarcoma, malignant	P-value of test of trend or comparison	.8207	.5360	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	1.4%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.5	33.4	34.2	29.7
lung	adenocarcinoma, malignant	P-value of test of trend or comparison	.8776	.7887	.7967	1
		Number of animals reported with tumor	3	1	1	0
		Poly-3 adjusted incidence rate	4.2%	3.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.87,11.9)	(0.07,15.8)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.8	33.8	34.8	29.7
	adenoma, bronchiolar alveolar, benign	P-value of test of trend or comparison	.3443	.1557	.3969	.3232
		Number of animals reported with tumor	12	9	7	7
		Poly-3 adjusted incidence rate	16%	25%	19%	21%
		95% CI for poly-3 adjusted incidence rate (%)	(8.21,25.6)	(12.1,43.3)	(7.96,36.0)	(8.7,38.9)
		Poly-3 adjusted number of animals at risk	77.0	36.0	36.7	33.7
	carcinoma, bronchiolar alveolar, malignant	P-value of test of trend or comparison	.9944	.8777	.8975	1
		Number of animals reported with tumor	11	3	3	0
		Poly-3 adjusted incidence rate	15%	8.8%	8.5%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(7.66,25.4)	(1.86,24.3)	(1.75,23.1)	(0,11.9)
		Poly-3 adjusted number of animals at risk	73.6	33.9	35.2	29.7
	carcinoma, tubular cell, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.9	33.2	34.2	29.7
	osteosarcoma, malignant	P-value of test of trend or comparison	.5749	.3173		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
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 (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.4	34.2	29.7
	sarcoma, stromal, malignant	P-value of test of trend or comparison	.3772		.3238	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.9	29.7
	sarcoma, undifferentiated, malignant	P-value of test of trend or comparison	.1737			.2900
		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)	(0,10.3)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.2	29.9
	schwannoma, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.8	33.2	34.2	29.7
lymph node, iliac	leiomyosarcoma, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.8	33.2	34.2	29.7
lymph node, inguinal	leiomyosarcoma, 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)	(0,10.3)	(0,12.3)
		Poly-3 adjusted number of animals at risk	71.8	33.2	34.2	28.9
lymph node, mediastinal	adenocarcinoma, malignant	P-value of test of trend or comparison	1	1	1	1

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
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	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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.7	33.2	34.2	29.7
	carcinoma, bronchiolar alveolar, malignant	P-value of test of trend or comparison	.6164	1	.5491	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.7)	(0,10.6)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.8	33.2	34.6	29.7
	carcinoma, squamous cell, malignant	P-value of test of trend or comparison	.5783	.3204		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.6	33.7	34.2	29.7
lymph node, mesenteric	carcinoma, bronchiolar alveolar, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	70.8	33.2	34.2	29.7
mammary gland	adenocarcinoma, malignant	P-value of test of trend or comparison	.9294	.8584	.8652	1
		Number of animals reported with tumor	4	1	1	0
		Poly-3 adjusted incidence rate	5.6%	3.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.53,13.8)	(0.07,15.8)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	72.0	33.8	34.8	29.7
multicentric neoplasm	hemangioma, benign	P-value of test of trend or comparison	.2621	.9331	1	.5372
		Number of animals reported with tumor	6	1	0	3
		Poly-3 adjusted incidence rate	8.1%	3.0%	0.0%	9.4%
		95% CI for poly-3 adjusted incidence rate (%)	(3.03,17.0)	(0.07,15.8)	(0,10.3)	(1.98,25.8)

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	73.6	33.7	34.2	31.8
	hemangiosarcoma, malignant	P-value of test of trend or comparison	.0735	.5168	.1563	.1194
		Number of animals reported with tumor	3	2	4	4
		Poly-3 adjusted incidence rate	4.1%	5.9%	11%	13%
		95% CI for poly-3 adjusted incidence rate (%)	(0.86,11.7)	(0.7,19.7)	(3.11,26.7)	(3.51,29.8)
		Poly-3 adjusted number of animals at risk	72.5	34.0	35.4	31.2
	lymphoma, malignant	P-value of test of trend or comparison	.1872	.2256	.0918	.1602
		Number of animals reported with tumor	15	10	13	10
		Poly-3 adjusted incidence rate	19%	27%	32%	30%
		95% CI for poly-3 adjusted incidence rate (%)	(11.2,30.1)	(13.8,45.2)	(18.1,49.1)	(15.1,48.7)
		Poly-3 adjusted number of animals at risk	77.1	36.9	40.3	33.5
	sarcoma, histiocytic, malignant	P-value of test of trend or comparison	.9594	.7096	.9032	1
		Number of animals reported with tumor	5	2	1	0
		Poly-3 adjusted incidence rate	6.8%	5.9%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(2.2,15.1)	(0.7,19.7)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	74.0	34.1	34.3	29.7
ovaries	adenoma, tubulostromal, 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	2.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.33,9.7)	(0,10.6)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	72.0	33.2	34.2	29.7
	cystadenocarcinoma, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.5	33.2	34.2	29.7
	cystadenoma, benign	P-value of test of trend or comparison	.1737			.2900

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
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	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)	(0,10.3)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.2	29.9
	leiomyosarcoma, malignant	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 (%)	(0.33,9.7)	(0,10.6)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	72.2	33.2	34.2	29.7
	osteosarcoma, malignant	P-value of test of trend or comparison	.5749	.3173		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.4	34.2	29.7
	sarcoma, stromal, malignant	P-value of test of trend or comparison	.3772		.3238	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.9	29.7
	schwannoma, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.8	33.2	34.2	29.7
	sex-cord/stromal tumor, benign	P-value of test of trend or comparison	.3125	1	.3902	.6465

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
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	2	0	2	1
		Poly-3 adjusted incidence rate	2.8%	0.0%	5.7%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.8)	(0,10.6)	(0.7,19.7)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	71.6	33.2	34.9	29.9
pancreas	adenoma, islet 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	1.4%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.5	33.2	34.2	29.7
	sarcoma, undifferentiated, malignant	P-value of test of trend or comparison	.3772		.3238	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.9	29.7
pituitary gland	adenoma, pars distalis, benign	P-value of test of trend or comparison	.6599	1	.4135	.9107
		Number of animals reported with tumor	6	0	4	1
		Poly-3 adjusted incidence rate	8.4%	0.0%	11%	3.5%
		95% CI for poly-3 adjusted incidence rate (%)	(3.12,17.5)	(0,10.9)	(3.2,27.5)	(0.09,18.3)
		Poly-3 adjusted number of animals at risk	71.4	32.7	34.9	28.4
skeletal muscle, diaphragm	carcinoma, bronchiolar alveolar, malignant	P-value of test of trend or comparison	.6136	1	.5449	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.4%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.5	33.2	34.6	29.7

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	sarcoma, stromal, malignant	P-value of test of trend or comparison	.3772		.3238	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.9	29.7
	sarcoma, undifferentiated, malignant	P-value of test of trend or comparison	.1737			.2900
		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)	(0,10.3)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.2	29.9
skeletal muscle, quadriceps femoris	sarcoma, stromal, malignant	P-value of test of trend or comparison	.3772		.3238	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.9	29.7
skin, subcutis	carcinoma, basal cell, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.4	33.2	34.2	29.7
	carcinoma, basosquamous cell, malignant	P-value of test of trend or comparison	.1737			.2900
		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)	(0,10.3)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.2	30.0
	fibrosarcoma, malignant	P-value of test of trend or comparison	.4292	.6819	.6909	.6421
		Number of animals reported with tumor	2	1	1	1
		Poly-3 adjusted incidence rate	2.8%	3.0%	2.9%	3.3%

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
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 (%)	(0.33,9.7)	(0.07,15.8)	(0.07,15.3)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	72.1	33.7	34.9	29.9
	keratoacanthoma, benign	P-value of test of trend or comparison	.3772		.3238	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.3	29.7
	osteosarcoma, malignant	P-value of test of trend or comparison	.5749	.3173		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.4	34.2	29.7
	schwannoma, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.8	33.2	34.2	29.7
spleen	osteosarcoma, malignant	P-value of test of trend or comparison	.5749	.3173		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.0	33.4	34.2	29.7
stomach, glandular	adenoma, benign	P-value of test of trend or comparison	.5774	.3238		
		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 (%)	(0,5.1)	(0.07,15.3)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	34.1	34.2	29.7
stomach, nonglandular	carcinoma, squamous cell, malignant	P-value of test of trend or comparison	.5749	.3173		

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
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	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.7	34.2	29.7
	sarcoma, stromal, malignant	P-value of test of trend or comparison	.3772		.3238	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.9%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0,10.6)	(0.07,15.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.9	29.7
thymus gland	carcinoma, bronchiolar alveolar, malignant	P-value of test of trend or comparison	.6198	1	.5578	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.5%	0.0%	3.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,8.2)	(0,11.2)	(0.07,15.8)	(0,12.8)
		Poly-3 adjusted number of animals at risk	66.7	31.4	33.7	27.4
	schwannoma, 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	1.5%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,8.2)	(0,11.2)	(0,10.6)	(0,12.8)
		Poly-3 adjusted number of animals at risk	66.9	31.4	33.3	27.4
urinary bladder	leiomyosarcoma, 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)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.7	33.2	34.2	29.6
uterus with cervix	adenocarcinoma, malignant	P-value of test of trend or comparison	.1004		.3238	.2900
		Number of animals reported with tumor	0	0	1	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.9%	3.3%

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
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 (%)	(0,5.1)	(0,10.6)	(0.07,15.3)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.7	29.9
	carcinoma, squamous cell, malignant	P-value of test of trend or comparison	.1786			.2970
		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)	(0,10.3)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.2	30.1
	fibroma, 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	2.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.8)	(0,10.6)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.8	33.2	34.2	29.7
	fibrous histiocytoma, benign	P-value of test of trend or comparison	.1737			.2900
		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)	(0,10.3)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	71.3	33.2	34.2	30.0
	leiomyoma, benign	P-value of test of trend or comparison	.2239	.1469	1	.2399
		Number of animals reported with tumor	3	4	0	3
		Poly-3 adjusted incidence rate	4.2%	12%	0.0%	9.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.86,11.7)	(3.2,27.5)	(0,10.3)	(2.04,26.5)
		Poly-3 adjusted number of animals at risk	72.1	34.4	34.2	30.8
	leiomyosarcoma, malignant	P-value of test of trend or comparison	.8938	.6296	.6296	1
		Number of animals reported with tumor	4	2	2	0
		Poly-3 adjusted incidence rate	5.5%	5.9%	5.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.51,13.6)	(0.7,19.7)	(0.7,19.7)	(0,11.9)

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted number of animals at risk	72.5	34.0	34.4	29.7
	neuroendocrine tumor, benign	P-value of test of trend or comparison	.5749	.3173		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.7	34.2	29.7
	osteosarcoma, malignant	P-value of test of trend or comparison	.5749	.3173		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.4	34.2	29.7
	polyp, glandular, benign	P-value of test of trend or comparison	.0148	1	.8587	.0867
		Number of animals reported with tumor	4	0	1	5
		Poly-3 adjusted incidence rate	5.4%	0.0%	2.9%	16%
		95% CI for poly-3 adjusted incidence rate (%)	(1.49,13.4)	(0,10.6)	(0.07,15.3)	(5.28,33.7)
		Poly-3 adjusted number of animals at risk	73.6	33.2	34.3	31.9
	polyp, stromal, benign	P-value of test of trend or comparison	.4531	.0931	.5449	.5079
		Number of animals reported with tumor	1	3	1	1
		Poly-3 adjusted incidence rate	1.4%	8.9%	2.9%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(1.86,24.3)	(0.07,15.3)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	71.6	33.6	34.3	30.2
	sarcoma, stromal, malignant	P-value of test of trend or comparison	.3108	1	.3962	.6421
		Number of animals reported with tumor	2	0	2	1
		Poly-3 adjusted incidence rate	2.8%	0.0%	5.7%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.33,9.7)	(0,10.6)	(0.68,19.2)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	72.1	33.2	35.0	29.9

Table 1.10

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	sarcoma, undifferentiated, malignant	P-value of test of trend or comparison	.5749	.3173		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.3)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.8	34.2	29.7
vagina	carcinoma, squamous cell, malignant	P-value of test of trend or comparison	.5723	.3173		
		Number of animals reported with tumor	0	1	0	0
		Poly-3 adjusted incidence rate	0.0%	3.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.1)	(0.07,15.8)	(0,10.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	71.3	33.9	33.8	29.7
	leiomyosarcoma, malignant	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 (%)	(0.34,9.8)	(0,10.6)	(0,10.6)	(0,11.9)
		Poly-3 adjusted number of animals at risk	72.0	33.2	33.8	29.7

Table 1.11

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
adrenal glands	adenoma, cortical, benign	P-value of test of trend or comparison	.6124	.2098	1	.6398
		Number of animals reported with tumor	2	3	0	1
		Poly-3 adjusted incidence rate	2.7%	7.8%	0.0%	3.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.3)	(1.62,21.4)	(0,8.4)	(0.08,17.2)
		Poly-3 adjusted number of animals at risk	75.3	38.6	42.3	30.4
	adenoma, subcapsular cell, benign	P-value of test of trend or comparison	.2603	.2143	.2592	.3268
		Number of animals reported with tumor	2	3	3	2
		Poly-3 adjusted incidence rate	2.7%	7.8%	7.0%	6.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.4)	(1.62,21.4)	(1.43,19.1)	(0.79,22.1)
		Poly-3 adjusted number of animals at risk	74.8	38.6	43.0	30.4
	fibrosarcoma, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.3)	(0,9.3)	(0,8.4)	(0,11.6)
		Poly-3 adjusted number of animals at risk	74.8	38.6	42.3	30.4
bone, sternum	fibrosarcoma, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.1)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	76.6	39.3	43.3	31.4
brain	oligodendroglioma, malignant	P-value of test of trend or comparison	.3936		.3644	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.8)	(0,9.0)	(0.06,12.3)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.4	31.4
cavity, thoracic	fibrosarcoma, malignant	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0

Table 1.11

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.1)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	76.6	39.3	43.3	31.4
	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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
epididymides	fibrosarcoma, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
	schwannoma, malignant	P-value of test of trend or comparison	.3936		.3644	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.8)	(0,9.0)	(0.06,12.3)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
gallbladder	adenoma, benign	P-value of test of trend or comparison	.1673	.3514		.2871
		Number of animals reported with tumor	0	1	0	1
		Poly-3 adjusted incidence rate	0.0%	2.5%	0.0%	3.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0,5.0)	(0.06,13.5)	(0,8.4)	(0.08,17.8)
		Poly-3 adjusted number of animals at risk	72.4	39.3	42.4	29.7
harderian glands	adenocarcinoma, malignant	P-value of test of trend or comparison	.6310	1	.5941	1
		Number of animals reported with tumor	1	0	1	0
		Poly-3 adjusted incidence rate	1.3%	0.0%	2.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.1)	(0,9.0)	(0.06,12.3)	(0,11.2)

Table 1.11

Table of reported tumors in Mouse Study
NDA 202155
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	76.5	39.3	43.6	31.0
	adenoma, benign	P-value of test of trend or comparison	.5492	.6662	.0991	.8262
		Number of animals reported with tumor	4	2	6	1
		Poly-3 adjusted incidence rate	5.2%	5.1%	14%	3.2%
		95% CI for poly-3 adjusted incidence rate (%)	(1.43,12.9)	(0.61,17.3)	(5.17,27.9)	(0.08,16.7)
		Poly-3 adjusted number of animals at risk	76.5	39.3	43.6	31.0
kidneys	carcinoma, c-cell, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.1)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	76.2	39.3	43.3	31.4
	fibrosarcoma, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
	neoplasm, nos, malignant	P-value of test of trend or comparison	.1649			.2925
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.2%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.8)	(0,9.0)	(0,8.2)	(0.08,16.7)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.5
	papilloma, transitional cell, benign	P-value of test of trend or comparison	.1649			.2925
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.2%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.8)	(0,9.0)	(0,8.2)	(0.08,16.7)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4

Table 1.11

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
liver	adenoma, hepatocellular, benign	P-value of test of trend or comparison	.4543	.1557	.2106	.4702
		Number of animals reported with tumor	15	12	12	7
		Poly-3 adjusted incidence rate	19%	29%	27%	21%
		95% CI for poly-3 adjusted incidence rate (%)	(11,29.7)	(15.7,45.5)	(14.6,42.8)	(8.98,40.0)
		Poly-3 adjusted number of animals at risk	78.8	41.7	44.7	32.9
	carcinoma, c-cell, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.1)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	76.2	39.3	43.3	31.4
	carcinoma, hepatocellular, malignant	P-value of test of trend or comparison	.7532	.4430	.8988	.8262
		Number of animals reported with tumor	4	3	1	1
		Poly-3 adjusted incidence rate	5.2%	7.5%	2.3%	3.1%
		95% CI for poly-3 adjusted incidence rate (%)	(1.43,12.9)	(1.57,20.9)	(0.06,12.3)	(0.08,16.7)
		Poly-3 adjusted number of animals at risk	76.6	39.8	43.3	31.8
	fibrosarcoma, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
lung	adenocarcinoma, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.1)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	76.5	39.3	43.3	31.4
	adenoma, bronchiolar alveolar, benign	P-value of test of trend or comparison	.5295	.6497	.7582	.6185
		Number of animals reported with tumor	17	8	8	7
		Poly-3 adjusted incidence rate	22%	20%	18%	21%

Table 1.11

Table of reported tumors in Mouse Study
NDA 202155
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 (%)	(13.1,32.6)	(9.05,36.5)	(8,32.7)	(8.7,38.9)
		Poly-3 adjusted number of animals at risk	78.9	40.0	44.8	33.5
	carcinoma, bronchiolar alveolar, malignant	P-value of test of trend or comparison	.1769	.0940	.7779	.1381
		Number of animals reported with tumor	7	8	3	6
		Poly-3 adjusted incidence rate	9.1%	19%	6.8%	19%
		95% CI for poly-3 adjusted incidence rate (%)	(3.68,17.8)	(8.6,34.9)	(1.4,18.7)	(6.98,36.4)
		Poly-3 adjusted number of animals at risk	77.2	41.3	44.4	32.4
	carcinoma, hepatocellular, malignant	P-value of test of trend or comparison	.6011	.3421		
		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 (%)	(0,4.8)	(0.06,13.5)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
	fibrosarcoma, malignant	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	2.6%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.2)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	76.6	39.3	43.3	31.4
lymph node, mesenteric	fibrosarcoma, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.3)	(0,9.5)	(0,8.4)	(0,11.2)
		Poly-3 adjusted number of animals at risk	74.7	37.8	42.4	31.4
multicentric neoplasm	hemangioma, benign	P-value of test of trend or comparison	.1020	.5692	1	.2041
		Number of animals reported with tumor	1	1	0	2
		Poly-3 adjusted incidence rate	1.3%	2.5%	0.0%	6.3%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0.06,13.5)	(0,8.2)	(0.77,21.4)
		Poly-3 adjusted number of animals at risk	75.9	39.6	43.3	31.7
	hemangiosarcoma, malignant	P-value of test of trend or comparison	.3791	.9669	.8980	.6084

Table 1.11

Table of reported tumors in Mouse Study
NDA 202155
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	7	1	2	3
		Poly-3 adjusted incidence rate	9.0%	2.5%	4.6%	9.1%
		95% CI for poly-3 adjusted incidence rate (%)	(3.68,17.8)	(0.06,13.5)	(0.56,15.8)	(1.92,25.0)
		Poly-3 adjusted number of animals at risk	77.6	39.8	43.3	32.9
	leukemia, granulocytic, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	76.0	39.3	43.3	31.4
	lymphoma, malignant	P-value of test of trend or comparison	.8986	1	.9033	.9788
		Number of animals reported with tumor	10	0	3	1
		Poly-3 adjusted incidence rate	13%	0.0%	6.9%	3.2%
		95% CI for poly-3 adjusted incidence rate (%)	(6.16,22.0)	(0,9.0)	(1.43,19.1)	(0.08,16.7)
		Poly-3 adjusted number of animals at risk	79.2	39.3	43.3	31.4
	mast cell tumor, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
	mast cell tumor, malignant	P-value of test of trend or comparison	.3936		.3644	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.8)	(0,9.0)	(0.06,12.3)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.9	31.4
	sarcoma, histiocytic, malignant	P-value of test of trend or comparison	.7794	1	.7470	1
		Number of animals reported with tumor	2	0	1	0
		Poly-3 adjusted incidence rate	2.6%	0.0%	2.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.3)	(0,9.0)	(0.06,12.3)	(0,11.2)

Table 1.11

Table of reported tumors in Mouse Study
NDA 202155
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	76.0	39.3	43.6	31.4
parathyroid glands	adenoma, benign	P-value of test of trend or comparison	.4182		.4118	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	3.5%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,8.8)	(0,14.2)	(0.09,18.3)	(0,18.5)
		Poly-3 adjusted number of animals at risk	40.4	24.5	28.2	18.0
pituitary gland	adenoma, pars distalis, benign	P-value of test of trend or comparison	.3788	1	.7442	.6542
		Number of animals reported with tumor	2	0	1	1
		Poly-3 adjusted incidence rate	2.7%	0.0%	2.4%	3.2%
		95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.4)	(0,9.5)	(0.06,12.6)	(0.08,16.7)
		Poly-3 adjusted number of animals at risk	74.6	38.0	42.4	31.7
	carcinoma, pars intermedia, malignant	P-value of test of trend or comparison	.4000		.3675	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.9)	(0,9.5)	(0.06,12.3)	(0,11.2)
		Poly-3 adjusted number of animals at risk	74.5	38.0	43.3	31.2
salivary gland, mandibular	schwannoma, benign	P-value of test of trend or comparison	.0265			.0836
		Number of animals reported with tumor	0	0	0	2
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	6.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.8)	(0,9.0)	(0,8.2)	(0.77,21.4)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
seminal vesicles	fibrosarcoma, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
skeletal muscle, diaphragm	fibrosarcoma, malignant	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0

Table 1.11

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
skin, subcutis	fibrosarcoma, malignant	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	2.6%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.2)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	76.8	39.3	43.3	31.4
	lipoma, benign	P-value of test of trend or comparison	.1649			.2925
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	3.2%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.8)	(0,9.0)	(0,8.2)	(0.08,16.7)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.5
small intestine, duodenum	sarcoma, undifferentiated, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.1)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	76.3	39.3	43.3	31.2
tail	sarcoma, undifferentiated, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
testes	adenoma, interstitial cell, benign	P-value of test of trend or comparison	.0608	.7153	.7433	.1446
		Number of animals reported with tumor	2	1	1	3
		Poly-3 adjusted incidence rate	2.6%	2.5%	2.3%	9.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.2)	(0.06,13.5)	(0.06,12.3)	(1.98,25.8)
		Poly-3 adjusted number of animals at risk	76.6	39.3	43.3	31.7

Table 1.11

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	adenoma, rete testis, benign	P-value of test of trend or comparison	.3033	1	1	.5013
		Number of animals reported with tumor	1	0	0	1
		Poly-3 adjusted incidence rate	1.3%	0.0%	0.0%	3.2%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0,9.0)	(0,8.2)	(0.08,16.7)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4
thyroid gland	carcinoma, c-cell, malignant	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	2.6%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.3)	(0,9.0)	(0,8.2)	(0,11.6)
		Poly-3 adjusted number of animals at risk	75.8	39.3	43.3	30.4
tongue	carcinoma, squamous cell, 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.1)	(0,9.0)	(0,8.2)	(0,11.2)
		Poly-3 adjusted number of animals at risk	76.7	39.3	43.3	31.4
urinary bladder	mesenchymal tumor, benign	P-value of test of trend or comparison	.3968		.3697	
		Number of animals reported with tumor	0	0	1	0
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.8)	(0,9.0)	(0.06,12.0)	(0,11.2)
		Poly-3 adjusted number of animals at risk	75.9	39.3	44.3	31.4

Table 1.12

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Bronchiolar alveolar tumors	P-value of test of trend or comparison	.8410	.4023	.6711	.8640
	Number of animals reported with tumor	23	12	10	7
	Poly-3 adjusted incidence rate	29%	33%	27%	21%
	95% CI for poly-3 adjusted incidence rate (%)	(19.2,40.4)	(18,51.0)	(13.4,44.1)	(8.7,38.9)
	Poly-3 adjusted number of animals at risk	79.4	36.7	37.7	33.7
Harderian adenomas and adenocarcinomas	P-value of test of trend or comparison	.2908	.2004	.2004	.3421
	Number of animals reported with tumor	2	3	3	2
	Poly-3 adjusted incidence rate	2.8%	8.5%	8.5%	6.5%
	95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.8)	(1.75,23.1)	(1.75,23.1)	(0.79,22.1)
	Poly-3 adjusted number of animals at risk	71.5	35.5	35.1	30.6
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.0775	.7966	.6552	.1779
	Number of animals reported with tumor	9	3	4	7
	Poly-3 adjusted incidence rate	12%	8.7%	11%	21%
	95% CI for poly-3 adjusted incidence rate (%)	(5.64,21.8)	(1.8,23.7)	(3.11,26.7)	(8.7,38.9)
	Poly-3 adjusted number of animals at risk	74.9	34.6	35.4	33.2
Hepatocellular tumors	P-value of test of trend or comparison	.5843	.8551	.2389	.8234
	Number of animals reported with tumor	4	1	4	1
	Poly-3 adjusted incidence rate	5.5%	3.0%	11%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(1.51,13.6)	(0.07,15.8)	(3.11,26.7)	(0.08,17.8)
	Poly-3 adjusted number of animals at risk	72.5	33.3	35.4	29.9
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	1.4%	0.0%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0,10.3)	(0,11.9)
	Poly-3 adjusted number of animals at risk	71.5	33.2	34.2	29.7
Leiomyomas and leiomyosarcomas of the uterus, cervix, ovaries and vagina	P-value of test of trend or comparison	.5764	.2055	.8455	.6023
	Number of animals reported with tumor	7	6	2	3

Table 1.12

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted incidence rate	9.5%	17%	5.8%	9.7%
	95% CI for poly-3 adjusted incidence rate (%)	(3.89,18.8)	(6.37,33.6)	(0.7,19.7)	(2.04,26.5)
	Poly-3 adjusted number of animals at risk	73.3	35.2	34.4	30.8
Leiomyomas of the uterus, cervix, ovaries and vagina	P-value of test of trend or comparison	.2239	.1469	1	.2399
	Number of animals reported with tumor	3	4	0	3
	Poly-3 adjusted incidence rate	4.2%	12%	0.0%	9.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.86,11.7)	(3.2,27.5)	(0,10.3)	(2.04,26.5)
	Poly-3 adjusted number of animals at risk	72.1	34.4	34.2	30.8
Leiomyosarcomas of the uterus, cervix, ovaries and vagina	P-value of test of trend or comparison	.8938	.6296	.6296	1
	Number of animals reported with tumor	4	2	2	0
	Poly-3 adjusted incidence rate	5.5%	5.9%	5.8%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(1.51,13.6)	(0.7,19.7)	(0.7,19.7)	(0,11.9)
	Poly-3 adjusted number of animals at risk	72.5	34.0	34.4	29.7
Ovarian cystadenomas and cystadenocarcinomas	P-value of test of trend or comparison	.3180	1	1	.4980
	Number of animals reported with tumor	1	0	0	1
	Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0,10.3)	(0.08,17.8)
	Poly-3 adjusted number of animals at risk	71.5	33.2	34.2	29.9
Ovarian stromal tumors	P-value of test of trend or comparison	.5060	1	.4145	.8234
	Number of animals reported with tumor	4	0	3	1
	Poly-3 adjusted incidence rate	5.5%	0.0%	8.4%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(1.51,13.6)	(0,10.6)	(1.75,23.1)	(0.08,17.8)
	Poly-3 adjusted number of animals at risk	72.3	33.2	35.7	29.9
Pituitary pars distalis tumors	P-value of test of trend or comparison	.6599	1	.4135	.9107
	Number of animals reported with tumor	6	0	4	1
	Poly-3 adjusted incidence rate	8.4%	0.0%	11%	3.5%
	95% CI for poly-3 adjusted incidence rate (%)	(3.12,17.5)	(0,10.9)	(3.2,27.5)	(0.09,18.3)

Table 1.12

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted number of animals at risk	71.4	32.7	34.9	28.4
Skin carcinomas	P-value of test of trend or comparison	.3180	1	1	.4980
	Number of animals reported with tumor	1	0	0	1
	Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.6)	(0,10.6)	(0,10.3)	(0.08,17.8)
	Poly-3 adjusted number of animals at risk	71.4	33.2	34.2	30.0
Stromal tumors of the uterus or ovaries	P-value of test of trend or comparison	.4543	.6571	.3359	.6023
	Number of animals reported with tumor	7	3	5	3
	Poly-3 adjusted incidence rate	9.5%	8.9%	14%	9.8%
	95% CI for poly-3 adjusted incidence rate (%)	(3.89,18.8)	(1.86,24.3)	(4.67,30.3)	(2.04,26.5)
	Poly-3 adjusted number of animals at risk	73.4	33.6	35.9	30.6
Subcutis fibromas and fibrosarcomas	P-value of test of trend or comparison	.4292	.6819	.6909	.6421
	Number of animals reported with tumor	2	1	1	1
	Poly-3 adjusted incidence rate	2.8%	3.0%	2.9%	3.3%
	95% CI for poly-3 adjusted incidence rate (%)	(0.33,9.7)	(0.07,15.8)	(0.07,15.3)	(0.08,17.8)
	Poly-3 adjusted number of animals at risk	72.1	33.7	34.9	29.9
Uterine glandular polyps and adenocarcinomas	P-value of test of trend or comparison	.0058	1	.6232	.0425
	Number of animals reported with tumor	4	0	2	6
	Poly-3 adjusted incidence rate	5.4%	0.0%	5.7%	19%
	95% CI for poly-3 adjusted incidence rate (%)	(1.49,13.4)	(0,10.6)	(0.7,19.7)	(6.98,36.4)
	Poly-3 adjusted number of animals at risk	73.6	33.2	34.9	32.1
Uterine leiomyomas and leiomyosarcomas	P-value of test of trend or comparison	.5764	.2055	.8455	.6023
	Number of animals reported with tumor	7	6	2	3
	Poly-3 adjusted incidence rate	9.5%	17%	5.8%	9.7%
	95% CI for poly-3 adjusted incidence rate (%)	(3.89,18.8)	(6.37,33.6)	(0.7,19.7)	(2.04,26.5)
	Poly-3 adjusted number of animals at risk	73.3	35.2	34.4	30.8
Uterine stromal tumors	P-value of test of trend or comparison	.2027	.2785	.1563	.2399

Table 1.12

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Number of animals reported with tumor	3	3	4	3
	Poly-3 adjusted incidence rate	4.1%	8.9%	11%	9.8%
	95% CI for poly-3 adjusted incidence rate (%)	(0.86,11.7)	(1.86,24.3)	(3.11,26.7)	(2.04,26.5)
	Poly-3 adjusted number of animals at risk	72.4	33.6	35.7	30.6

Table 1.13

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Bronchiolar alveolar tumors	P-value of test of trend or comparison	.2382	.2932	.7780	.2300
	Number of animals reported with tumor	23	15	11	13
	Poly-3 adjusted incidence rate	29%	36%	24%	38%
	95% CI for poly-3 adjusted incidence rate (%)	(19.2,40.4)	(21,52.0)	(12.6,39.5)	(21.5,56.4)
	Poly-3 adjusted number of animals at risk	79.6	42.0	45.9	34.5
C-cell tumors	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	2.6%	0.0%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.3)	(0,9.0)	(0,8.2)	(0,11.6)
	Poly-3 adjusted number of animals at risk	75.8	39.3	43.3	30.4
Cortical cell tumors	P-value of test of trend or comparison	.6178	.2142	1	.6458
	Number of animals reported with tumor	2	3	0	1
	Poly-3 adjusted incidence rate	2.6%	7.6%	0.0%	3.2%
	95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.2)	(1.57,20.9)	(0,8.2)	(0.08,16.7)
	Poly-3 adjusted number of animals at risk	76.4	39.3	43.3	31.4
Harderian adenomas and adenocarcinomas	P-value of test of trend or comparison	.5939	.7501	.0835	.8761
	Number of animals reported with tumor	5	2	7	1
	Poly-3 adjusted incidence rate	6.5%	5.1%	16%	3.2%
	95% CI for poly-3 adjusted incidence rate (%)	(2.11,14.5)	(0.61,17.3)	(6.64,30.7)	(0.08,16.7)
	Poly-3 adjusted number of animals at risk	77.2	39.3	43.8	31.0
Hemangiomas and hemangiosarcomas	P-value of test of trend or comparison	.1754	.9154	.9308	.3396
	Number of animals reported with tumor	8	2	2	5
	Poly-3 adjusted incidence rate	10%	5.0%	4.6%	15%
	95% CI for poly-3 adjusted incidence rate (%)	(4.53,19.4)	(0.6,16.9)	(0.56,15.8)	(4.95,31.9)
	Poly-3 adjusted number of animals at risk	77.6	40.1	43.3	33.3
Hepatocellular tumors	P-value of test of trend or comparison	.5712	.1897	.3232	.5805
	Number of animals reported with tumor	19	14	13	8

Table 1.13

Table of reported tumors in Mouse Study
NDA 202155
Animal carcinogenicity study
Male mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted incidence rate	24%	33%	29%	24%
	95% CI for poly-3 adjusted incidence rate (%)	(14.9,35.0)	(19.1,49.5)	(16.4,45.2)	(10.7,42.3)
	Poly-3 adjusted number of animals at risk	79.5	42.2	44.7	33.4
Mast cell tumors	P-value of test of trend or comparison	.6336	1	.5980	1
	Number of animals reported with tumor	1	0	1	0
	Poly-3 adjusted incidence rate	1.3%	0.0%	2.3%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,7.2)	(0,9.0)	(0.06,12.3)	(0,11.2)
	Poly-3 adjusted number of animals at risk	75.9	39.3	43.9	31.4
Parathyroid tumors	P-value of test of trend or comparison	.4182		.4118	
	Number of animals reported with tumor	0	0	1	0
	Poly-3 adjusted incidence rate	0.0%	0.0%	3.5%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0,8.8)	(0,14.2)	(0.09,18.3)	(0,18.5)
	Poly-3 adjusted number of animals at risk	40.4	24.5	28.2	18.0
Pituitary pars distalis tumors	P-value of test of trend or comparison	.3788	1	.7442	.6542
	Number of animals reported with tumor	2	0	1	1
	Poly-3 adjusted incidence rate	2.7%	0.0%	2.4%	3.2%
	95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.4)	(0,9.5)	(0.06,12.6)	(0.08,16.7)
	Poly-3 adjusted number of animals at risk	74.6	38.0	42.4	31.7
Subcutis fibromas and fibrosarcomas	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	2.6%	0.0%	0.0%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.32,9.2)	(0,9.0)	(0,8.2)	(0,11.2)
	Poly-3 adjusted number of animals at risk	76.8	39.3	43.3	31.4

Table 1.14

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
uterus with cervix	polyp, glandular, benign	P-value of test of trend or comparison	.0148	1	.8587	.0867
		Number of animals reported with tumor	4	0	1	5
		Poly-3 adjusted incidence rate	5.4%	0.0%	2.9%	16%
		95% CI for poly-3 adjusted incidence rate (%)	(1.49,13.4)	(0,10.6)	(0.07,15.3)	(5.28,33.7)
		Poly-3 adjusted number of animals at risk	73.6	33.2	34.3	31.9

Table 1.15

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202155
Animal carcinogenicity study
Male mice

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
salivary gland, mandibular	schwannoma, benign	P-value of test of trend or comparison	.0265			.0836
		Number of animals reported with tumor	0	0	0	2
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	6.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.8)	(0,9.0)	(0,8.2)	(0.77,21.4)
		Poly-3 adjusted number of animals at risk	75.9	39.3	43.3	31.4

Table 1.16

Table of tumors reported significant in at least one arm - Mouse Study
NDA 202155
Animal carcinogenicity study
Female mice
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Uterine glandular polyps and adenocarcinomas	P-value of test of trend or comparison	.0058	1	.6232	.0425
	Number of animals reported with tumor	4	0	2	6
	Poly-3 adjusted incidence rate	5.4%	0.0%	5.7%	19%
	95% CI for poly-3 adjusted incidence rate (%)	(1.49,13.4)	(0,10.6)	(0.7,19.7)	(6.98,36.4)
	Poly-3 adjusted number of animals at risk	73.6	33.2	34.9	32.1

Table 1.17

Organs reported as unexamined
NDA 202155
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 glands	1	0.8%	.	.	.	.	1	1.7%	2	0.7%
aorta	2	1.7%	.	.	.	.	.	.	2	0.7%
eyes, optic nerves	3	2.5%	1	1.7%	.	.	2	3.3%	6	2.0%
gallbladder	3	2.5%	.	.	.	.	1	1.7%	4	1.3%
lymph node, hepatic	1	0.8%	.	.	.	.	.	.	1	0.3%
lymph node, inguinal	.	.	.	.	.	.	1	1.7%	1	0.3%
lymph node, mandibular	6	5.0%	3	5.0%	1	1.7%	4	6.7%	14	4.7%
lymph node, mediastinal	1	0.8%	.	.	.	.	.	.	1	0.3%
lymph node, mesenteric	2	1.7%	.	.	.	.	.	.	2	0.7%
lymph node, renal	.	.	.	.	1	1.7%	.	.	1	0.3%
nerve, sciatic	1	0.8%	.	.	.	.	.	.	1	0.3%
parathyroid glands	53	44%	25	42%	31	52%	18	30%	127	42%
pituitary gland	1	0.8%	1	1.7%	1	1.7%	3	5.0%	6	2.0%
spleen	2	1.7%	.	.	.	.	.	.	2	0.7%
thymus gland	8	6.7%	2	3.3%	2	3.3%	4	6.7%	16	5.3%
thyroid gland	1	0.8%	.	.	.	.	.	.	1	0.3%
tongue	1	0.8%	.	.	.	.	.	.	1	0.3%
trachea	.	.	.	.	1	1.7%	.	.	1	0.3%
urinary bladder	1	0.8%	.	.	.	.	1	1.7%	2	0.7%
vagina	.	.	.	.	1	1.7%	.	.	1	0.3%

Table 1.18

Organs reported as unexamined
NDA 202155
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 glands	2	1.7%	1	1.7%	1	1.7%	1	1.7%	5	1.7%
esophagus	1	0.8%	.	.	.	.	.	.	1	0.3%
eyes, optic nerves	8	6.7%	1	1.7%	2	3.3%	3	5.0%	14	4.7%
gallbladder	6	5.0%	.	.	3	5.0%	4	6.7%	13	4.3%
harderian glands	.	.	.	.	.	.	1	1.7%	1	0.3%
large intestine, colon	.	.	1	1.7%	.	.	.	.	1	0.3%
lymph node, hepatic	2	1.7%	.	.	.	.	.	.	2	0.7%
lymph node, mandibular	10	8.3%	1	1.7%	2	3.3%	5	8.3%	18	6.0%
lymph node, mediastinal	1	0.8%	1	1.7%	.	.	.	.	2	0.7%
lymph node, mesenteric	5	4.2%	2	3.3%	1	1.7%	.	.	8	2.7%
lymph node, renal	.	.	.	.	.	.	1	1.7%	1	0.3%
mammary gland	.	.	.	.	.	.	1	1.7%	1	0.3%
pancreas	2	1.7%	.	.	.	.	.	.	2	0.7%
parathyroid glands	48	40%	21	35%	23	38%	25	42%	117	39%
pituitary gland	4	3.3%	3	5.0%	1	1.7%	3	5.0%	11	3.7%
prostate gland	2	1.7%	1	1.7%	.	.	1	1.7%	4	1.3%
small intestine, duodenum	1	0.8%	.	.	.	.	1	1.7%	2	0.7%
spinal cord, lumbar	1	0.8%	.	.	.	.	.	.	1	0.3%
spleen	3	2.5%	.	.	.	.	.	.	3	1.0%
stomach, glandular	1	0.8%	.	.	.	.	.	.	1	0.3%
stomach, nonglandular	2	1.7%	.	.	.	.	.	.	2	0.7%
thymus gland	33	28%	11	18%	10	17%	15	25%	69	23%
thyroid gland	1	0.8%	.	.	.	.	1	1.7%	2	0.7%
trachea	1	0.8%	.	.	.	.	1	1.7%	2	0.7%

Chapter 2

Rat Study

This study comprised two experiments, one in male rats and one in female rats (in addition to a toxicokinetic study, the results of which are not considered as part of this review). The rats used were CDCrl:CD[SD]) rats, and were approximately four weeks old when delivered. Three hundred rats were used in each experiment, divided into five dose groups of sixty animals each. Two groups were control groups, and received the basal diet without any BMS-562247. The remaining three groups, the low, mid, and high dose groups respectively, received various doses of BMS-562247 mixed in thir basal diet. The dose levels of the test article were 50 mg/kg in the low dose group, 200 mg/kg in the mid dose group, and 600 mg/kg in the high dose group.

During the first year of the study, animals received cageside inspections twice daily. During these inspections, they were checked for mortality, moribundity, injury, and to ensure that they had an adequate supply of food and water. In the second year, these inspections were conducted three times per day. Detailed clinical exams were conducted weekly. After death, each animal underwent a complete necroscopy.

2.1 Sponsor's analysis

2.1.1 Survival analysis

The sponsor assessed the impact of BMS-562247 on survival by conducting a two tailed test of trend, at the 0.05 level, using the life table method. The two control groups were pooled in both female and male rats.

When analyzing the data from the female rats, the sponsor found no statistically significant evidence of a dose related trend in survival. Likewise, no significant difference was found between the two control groups.

When analyzing survival data from the male rats, the sponsor observed that survival rates were poorer among mid and high dose animals than among control or low dose animals. However, the test of trend did not generate any significant results ($p = 0.3009$). Likewise, no significant difference was found between the two control groups.

2.1.2 Tumor analysis

The sponsor used various versions of Peto's method [6] to test for a tumorigenic dose response for each reported tumor type. The exact method was used when the total number of tumor bearing animals (across all groups in one sex) was below twelve; otherwise the asymptotic method was used. For tumors found exclusively after death, either the death rate or prevalance method was used, depending on whether the tumors were deemed fatal or incidental. Tumor types found through palpation were analyzed using the onset time method.

In additional to individual tumor types, several combination endpoints were considred. These are listed in table 2.1.

The threshold for significance was 0.025 for rare tumors and 0.005 for common tumors. In all cases, the control groups were combined.

Table 2.1: Combination tumor types considered by the sponsor (rat study)

Pituitary gland tumors
C-cell adenomas and carcinomas
Hepatocellular adenomas and carcinomas (males only)
Islet cell adenomas and carcinomas (males only)
Parathyroid adenomas and carcinomas (males only)
Granular cell tumors of the brain and meninges (females only)
Mammary adenomas, fibroadenomas and adenocarcinomas (females only)
Granular tumors of the uterus, cervix and vagina

The only endpoint for which the tests generated p-values below 0.05 were malignant lymphoma in both female ($p = 0.0323$) and male ($p = 0.0370$) rats. Since these p-values are both above 0.005, the sponsor considers these to be negative findings.

2.2 Data analysis

2.2.1 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 2.2. The results of log-rank tests of heterogeneity of survival and of dose response across the groups are presented in table 1.3, and the results of log-rank survival tests comparing the treated groups with the combined control group are presented in table 1.4.

In neither the female nor male rats are there any statistically significant results suggesting a dose related increase in mortality, although the Kaplan-Meier plots of survival of female rats do suggest that the high dose group slightly underperformed the other grups.

Figure 2.1: Survival curves for female rats

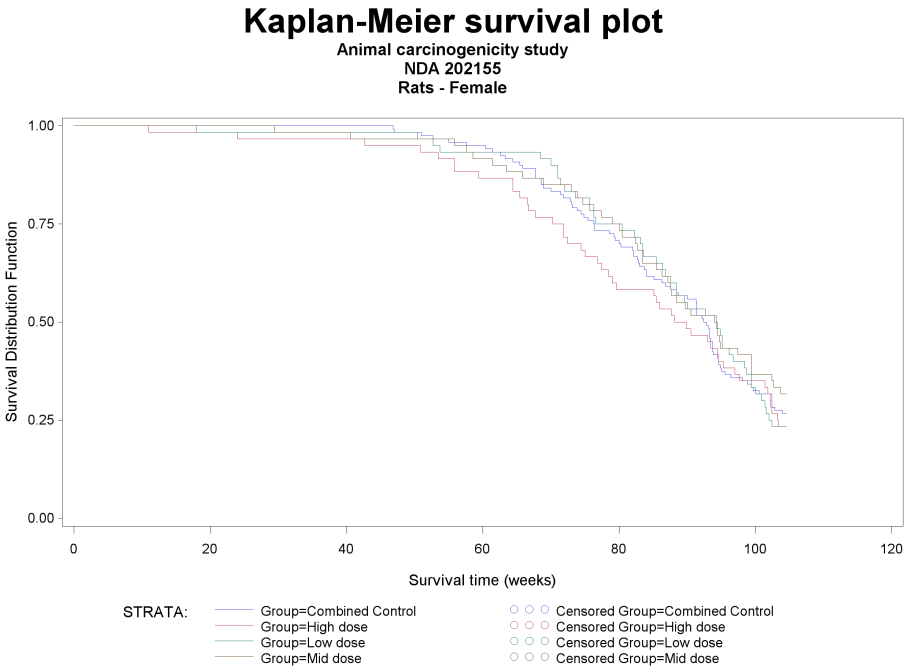

Figure 2.2: Survival curves for male rats

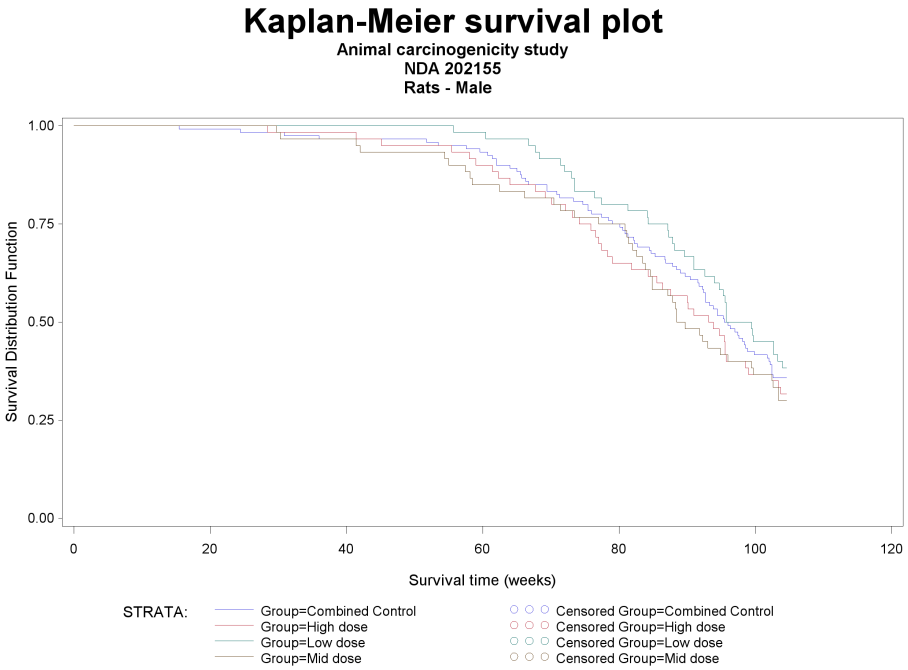

Table 2.2

Survival rates at key times
NDA 202155
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	117	98%	88	73%	68	57%	33	28%
	Low dose	50	60	58	97%	45	75%	32	53%	14	23%
	Mid dose	200	60	58	97%	46	77%	33	55%	19	32%
	High dose	600	60	56	93%	38	63%	29	48%	14	23%
Rats - Male	Combined Control	0	120	115	96%	92	77%	74	62%	43	36%
	Low dose	50	60	60	100%	48	80%	40	67%	24	40%
	Mid dose	200	60	56	93%	45	75%	29	48%	18	30%
	High dose	600	60	57	95%	41	68%	34	57%	19	32%

Commentry

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 1.5.

In neither sex is there is any suggestion that the two control groups experienced different survival outcomes.

2.2.2 Tumor analysis

Endpoints

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

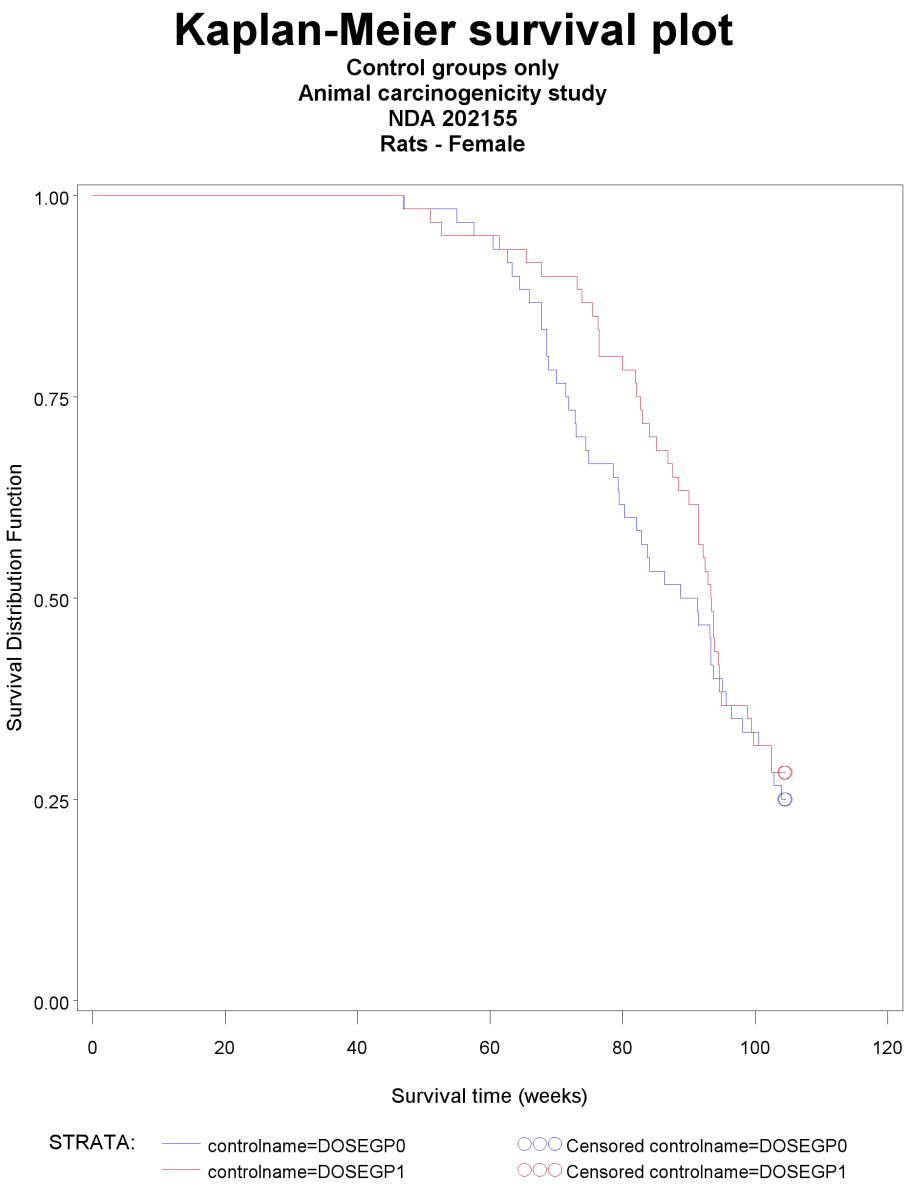

Figure 2.4: Survival curves for control groups (male rat experiment)

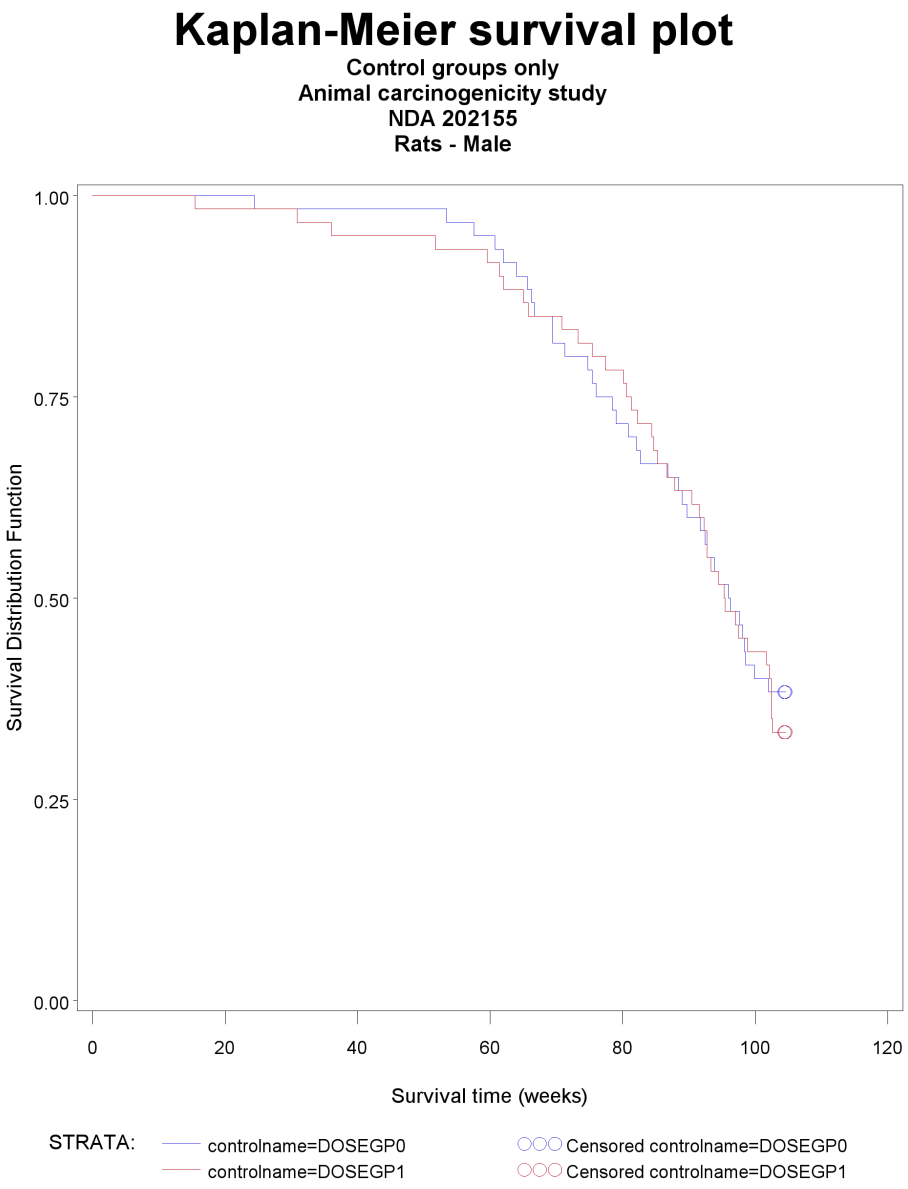

Table 2.3

Primary organs in study of female rats
NDA 202155
Animal carcinogenicity study

Organ or tissue name
ADRENAL GLAND
BRAIN
CECUM
CERVIX
COMBINED CERVIX, UTERUS & VAGINA
JEJUNUM
KIDNEY
LIVER
MAMMARY GLAND
OVARY
PANCREAS
PARATHYRO D GLAND
PITUITARY GLAND
SKIN/SUBCUTIS
STOMACH
SYSTEMIC NEOPLASMS
THYMUS
THYROID GLAND
TONGUE
UTERUS
VAGINA
ZYMBALS GLAND

Table 2.4

Primary organs in study of male rats
NDA 202155
Animal carcinogenicity study

Organ or tissue name
ADRENAL GLAND
BRAIN
CECUM
EPIDIDYMIS
HEART
JEJUNUM
KIDNEY
LIVER
MAMMARY GLAND
PANCREAS
PARATHYROID GLAND
PITUITARY GLAND
SEMINAL VESICLE
SKIN/SUBCUTIS
STOMACH
SYSTEMIC NEOPLASMS
TESTIS
THYROID GLAND
ZYMBALS GLAND

Table 2.5

Secondary organs in study of female rats
NDA 202155
Animal carcinogenicity study

Organ or tissue name
ADIPOSE TISSUE
EARS

Table 2.6

Secondary organs in study of male rats
NDA 202155
Animal carcinogenicity study

Organ or tissue name
ADIPOSE TISSUE
EARS

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 1.9.

Noteworthy results

The results of the statistical analyses of tumor incidence in primary endpoints are presented in tables 2.7 (female rats) and 2.8 (male rats). The results of analyses of customized endpoints (see table 1.8) are presented in tables 2.9 and 2.10.

Individual tumor types in female rats for which tests yielding p-values below 0.05 were conducted are presented in table 2.11, which is excerpted from table 2.7. No tests of customized or combination tumor types were conducted that yielded p-values below 0.05. Individual tumor types in male 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 2.13, which is excerpted from table 2.10.

No tumors were reported in any secondary organs.

Malignant lymphoma In both female and male rats, the tests of trend for malignant lymphoma yield p-values below 0.05 (0.0302 in the case of the female rats, and 0.0371 for the male rats). In neither case does the comparison between the high dose group and the combined control group yield a p-value below 0.05, and neither of the trend test results remain significant after adjusting for multiplicity. It follows that according to the algorithm used by the eCAC, neither of these results are considered a positive finding.

However, the test in male and female rats are independent, and the presence of near-significant results for the same tumor type in both sexes is striking; the result in one sex provides corroboratory evidence for the result in the other sex. This corroboration must be borne in mind when making a judgement about the relative likelihoods of whether these are true or false positives; they should not be viewed in isolation of one another.

To see how these two results reinforce one another, it is worth considering the results of the the standard statistical tests when the male and female rats are combined. When the sexes are combined, the p-value of the test of trend is 0.0040, and the comparison between the control and high dose group yields a p-value of 0.0140. It not appropriate to weight these results as heavily as those generated in the planned analyses; *post hoc* analyses are intrinsically biased, due to the manner of the selection of statistics to analyse. However, these results do add weight to the circumstantial case that the possible tumorigenic effect for malignant lymphomas at least receive further consideration.

Pheochromocytomas in male rats The noteworthy result for pheochromocytomas is for the comparison between the low dose group and the combined control (the survival-adjusted incidence rates are 10% in the combined control group and 26% in the low dose group, for a p-value of 0.0174). There is no sign of a dose related trend, or of elevated rates for the mid or high dose groups. This is therefore a negative finding.

Follicular cell tumors in male rats The noteworthy result for follicular cell tumors is also for the comparison between the low dose group and the combined control group (the survival-adjusted incidence rates are 1.2% in the combined control group and 1% in the low dose group, for a p-value of 0.0209). There is no sign of a dose related trend, or of elevated rates for the mid or high dose groups. This is therefore a negative finding.

2.2.3 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 2.14. The numbers of such organs found in male rats are presented in table 2.15.

Autolysis in the rat study was minimal. Thirteen animals across the two sexes experienced a total of eighteen autolytic organs, with no one animal having more than two autolytic organs. The organs most frequently reported as autolytic were the pancreas and thyroid, which were autolytic in six animals each (across the two sexes). There is no reason to think that this level of autolyis might affect the validity of the study.

Organs reported as unexamined

The numbers of animals with organs reported as being unexamined are presented in tables 1.17 and 1.18.

With the exceptions of the secondary organs (adipose tissue and ears), the only organ to have been reported as unexamined in a significant number of animals is the parathyroid, which was unexamined in 18% of female rats and 15% of male rats. These levels of of unexamined organs are low enough that they are unlikely to have impacted the validity of the study.

2.2.4 Tables of results

Table 2.7

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLAND	Adenoma: cortical cell	P-value of test of trend or comparison	.8078	.8075	.3168	1
		Number of animals reported with tumor	3	1	3	0
		Poly-3 adjusted incidence rate	3.7%	2.4%	7.4%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.77,10.6)	(0.06,13.2)	(1.54,20.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	80.9	40.8	40.8	36.8
	Carcinoma: cortical 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)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.6	40.6	40.8	36.8
	Pheochromocytoma	P-value of test of trend or comparison	.4483	.3336	1	.5007
		Number of animals reported with tumor	3	3	0	2
		Poly-3 adjusted incidence rate	3.8%	7.3%	0.0%	5.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0.78,10.7)	(1.5,19.9)	(0,8.8)	(0.66,18.7)
		Poly-3 adjusted number of animals at risk	79.9	41.1	40.8	36.9
	Pheochromocytoma: complex	P-value of test of trend or comparison	.1888			.3190
		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 (%)	(0,4.6)	(0,8.8)	(0,8.8)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	37.0
BRAIN	Astrocytoma	P-value of test of trend or comparison	.2499	1	.5574	.5262
		Number of animals reported with tumor	1	0	1	1
		Poly-3 adjusted incidence rate	1.2%	0.0%	2.5%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.8)	(0,8.8)	(0.06,13.2)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	80.0	40.6	40.8	36.8
	Granular cell tumor	P-value of test of trend or comparison	.1846			.3130
		Number of animals reported with tumor	0	0	0	1

Table 2.7

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.6)	(0,8.8)	(0,8.8)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	36.8
	Granular or Meningeal granular cell tumors	P-value of test of trend or comparison	.3359	1	1	.5300
		Number of animals reported with tumor	1	0	0	1
		Poly-3 adjusted incidence rate	1.3%	0.0%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	36.8
	Meningeal 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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	36.8
	Reticulosis	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)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	36.8
CECUM	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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	36.8
CERVIX	Carcinoma: squamous cell	P-value of test of trend or comparison	.1856			.3158

Table 2.7

Table of reported tumors in Rat Study
NDA 202155
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	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 (%)	(0,4.6)	(0,8.8)	(0,8.8)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	78.8	40.6	40.8	36.8
	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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	78.8	40.6	40.8	36.8
	Granular cell tumor	P-value of test of trend or comparison	.5828	1	1	.7827
		Number of animals reported with tumor	3	0	0	1
		Poly-3 adjusted incidence rate	3.8%	0.0%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.78,10.7)	(0,8.8)	(0,8.8)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	79.7	40.6	40.8	36.8
	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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	78.8	40.6	40.8	36.8
	Sarcoma: endometrial stromal	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)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.7	40.6	40.8	36.8
	Schwannoma	P-value of test of trend or comparison	.8371	.5612	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	1.3%	2.5%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0.06,13.2)	(0,8.8)	(0,9.7)

Table 2.7

Table of reported tumors in Rat Study
NDA 202155
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	79.6	40.7	40.8	36.8
COMBINED CERVIX, UTERUS & VAGINA	Granular cell tumor	P-value of test of trend or comparison	.4841	1	.6300	.7851
		Number of animals reported with tumor	6	0	3	2
		Poly-3 adjusted incidence rate	7.4%	0.0%	7.4%	5.3%
		95% CI for poly-3 adjusted incidence rate (%)	(2.77,15.6)	(0,8.8)	(1.54,20.4)	(0.64,18.2)
		Poly-3 adjusted number of animals at risk	80.7	40.6	40.8	37.5
JEJUNUM	Adenocarcinoma	P-value of test of trend or comparison	.5969	.3417		
		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 (%)	(0,4.6)	(0.06,12.9)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.2	41.3	40.8	36.8
KIDNEY	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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.8	40.6	40.8	36.8
	Sarcoma: anaplastic	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)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.5	40.6	40.8	36.8
LIVER	Adenoma: hepatocellular	P-value of test of trend or comparison	.8656	1	.8108	1

Table 2.7

Table of reported tumors in Rat Study
NDA 202155
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	3	0	1	0
		Poly-3 adjusted incidence rate	3.8%	0.0%	2.4%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.78,10.7)	(0,8.8)	(0.06,13.2)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.9	36.8
MAMMARY GLAND	Adenocarcinoma	P-value of test of trend or comparison	.1552	.8268	.2108	.3028
		Number of animals reported with tumor	14	5	11	9
		Poly-3 adjusted incidence rate	17%	12%	24%	22%
		95% CI for poly-3 adjusted incidence rate (%)	(9.42,26.7)	(3.98,26.2)	(12.6,39.5)	(10.6,38.5)
		Poly-3 adjusted number of animals at risk	83.6	41.8	45.5	40.9
	Adenoma	P-value of test of trend or comparison	.4804	.5114	.7114	.5396
		Number of animals reported with tumor	16	9	7	8
		Poly-3 adjusted incidence rate	19%	20%	17%	20%
		95% CI for poly-3 adjusted incidence rate (%)	(11.2,29.1)	(9.58,35.3)	(6.81,31.4)	(8.82,35.6)
		Poly-3 adjusted number of animals at risk	84.3	44.7	42.4	40.1
	Adenomas or Fibroadenomas	P-value of test of trend or comparison	.3348	.7106	.3606	.4622
		Number of animals reported with tumor	52	25	30	26
		Poly-3 adjusted incidence rate	56%	53%	61%	59%
		95% CI for poly-3 adjusted incidence rate (%)	(45.2,66.8)	(37.2,67.9)	(45.2,74.8)	(42.2,73.7)
		Poly-3 adjusted number of animals at risk	92.7	47.3	49.3	44.2
	Adenomas, Fibroadenomas or Adenocarcinomas	P-value of test of trend or comparison	.3128	.7297	.4435	.4371
		Number of animals reported with tumor	57	27	32	29
		Poly-3 adjusted incidence rate	60%	56%	63%	63%
		95% CI for poly-3 adjusted incidence rate (%)	(48.9,69.9)	(40.2,70.5)	(47,75.9)	(46.4,76.8)
		Poly-3 adjusted number of animals at risk	95.5	48.3	51.1	46.3
	Fibroadenoma	P-value of test of trend or comparison	.2274	.3567	.2026	.2672
		Number of animals reported with tumor	42	24	27	23
		Poly-3 adjusted incidence rate	47%	52%	55%	54%

Table 2.7

Table of reported tumors in Rat Study
NDA 202155
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 (%)	(36.1,58.1)	(36.1,67.1)	(40.2,70.5)	(37.7,70.2)
		Poly-3 adjusted number of animals at risk	89.1	46.6	48.7	42.5
OVARY	Fibrosarcoma	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)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.5	40.6	40.8	36.8
	Granulosa cell tumor (B)	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	2.5%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.3,8.8)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.5	40.6	40.8	36.8
	Thecoma (B)	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)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	36.8
PANCREAS	Adenoma: islet cell	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	3.8%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.78,10.7)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.7	40.6	40.8	36.8
	Carcinoma: islet cell	P-value of test of trend or comparison	.7433	.8817	1	.8595
		Number of animals reported with tumor	4	1	0	1
		Poly-3 adjusted incidence rate	5.0%	2.4%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(1.38,12.5)	(0.06,12.9)	(0,8.8)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	79.4	41.1	40.8	37.2

Table 2.7

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Schwannoma	P-value of test of trend or comparison	.5979	.3390		
		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 (%)	(0,4.6)	(0.06,13.2)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	78.9	40.8	40.8	36.8
PITUITARY GLAND	Adenoma: pars distalis	P-value of test of trend or comparison	.5735	.8717	.7128	.7299
		Number of animals reported with tumor	96	42	44	43
		Poly-3 adjusted incidence rate	85%	79%	83%	82%
		95% CI for poly-3 adjusted incidence rate (%)	(76.2,91.0)	(64.4,89.2)	(68.6,91.9)	(68,91.8)
		Poly-3 adjusted number of animals at risk	113	53.4	53.1	52.4
	Adenomas or Carcinomas	P-value of test of trend or comparison	.6055	.8394	.8483	.7477
		Number of animals reported with tumor	106	48	47	48
		Poly-3 adjusted incidence rate	92%	87%	87%	90%
		95% CI for poly-3 adjusted incidence rate (%)	(84.7,96.4)	(75.5,95.8)	(75.1,95.7)	(77.4,96.9)
		Poly-3 adjusted number of animals at risk	116	54.9	53.8	53.4
	Carcinoma: pars distalis	P-value of test of trend or comparison	.4880	.4827	.8797	.5367
		Number of animals reported with tumor	10	6	3	5
		Poly-3 adjusted incidence rate	12%	14%	7.2%	13%
		95% CI for poly-3 adjusted incidence rate (%)	(6.01,21.5)	(5.3,28.5)	(1.5,19.9)	(4.41,28.8)
		Poly-3 adjusted number of animals at risk	81.7	42.1	41.5	37.7
SKIN/SUBCUTIS	Adenoma: basal cell	P-value of test of trend or comparison	.1856	.3361		.3130
		Number of animals reported with tumor	0	1	0	1
		Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.6)	(0.06,13.2)	(0,8.8)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	79.2	40.9	40.8	36.8
	Fibroma	P-value of test of trend or comparison	.1846			.3130
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.7%

Table 2.7

Table of reported tumors in Rat Study
NDA 202155
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 (%)	(0,4.6)	(0,8.8)	(0,8.8)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	36.8
	Fibrosarcoma	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)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.6	40.6	40.8	36.8
	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	1.3%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	36.8
STOMACH	Papilloma: squamous cell	P-value of test of trend or comparison	.1897	.3361		.3190
		Number of animals reported with tumor	0	1	0	1
		Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.6)	(0.06,13.2)	(0,8.8)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	79.2	40.8	40.8	37.0
SYSTEMIC NEOPLASMS	Hemangiosarcoma	P-value of test of trend or comparison	.7771	1	.5529	1
		Number of animals reported with tumor	3	0	2	0
		Poly-3 adjusted incidence rate	3.7%	0.0%	4.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.77,10.6)	(0,8.8)	(0.58,16.5)	(0,9.7)
		Poly-3 adjusted number of animals at risk	80.2	40.6	41.3	36.8
	Histiocytic sarcoma	P-value of test of trend or comparison	.5455	1	.2686	1
		Number of animals reported with tumor	1	0	2	0
		Poly-3 adjusted incidence rate	1.3%	0.0%	4.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0.58,16.5)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.2	40.6	41.6	36.8
	Lymphoma: malignant	P-value of test of trend or comparison	.0302	.7147	.4074	.0838

Table 2.7

Table of reported tumors in Rat Study
NDA 202155
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	1	2	4
		Poly-3 adjusted incidence rate	2.5%	2.4%	4.9%	10%
		95% CI for poly-3 adjusted incidence rate (%)	(0.3,8.7)	(0.06,12.9)	(0.6,16.9)	(2.87,24.8)
		Poly-3 adjusted number of animals at risk	80.3	41.6	40.9	38.3
THYMUS	Thymoma	P-value of test of trend or comparison	.3427	1	1	.5381
		Number of animals reported with tumor	1	0	0	1
		Poly-3 adjusted incidence rate	1.3%	0.0%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	37.4
THYROID GLAND	Adenoma: C-cell	P-value of test of trend or comparison	.0879	.8669	.0818	.2159
		Number of animals reported with tumor	7	2	8	6
		Poly-3 adjusted incidence rate	8.7%	4.9%	19%	15%
		95% CI for poly-3 adjusted incidence rate (%)	(3.55,17.2)	(0.6,16.9)	(8.6,34.9)	(5.71,30.5)
		Poly-3 adjusted number of animals at risk	80.8	40.8	41.2	39.2
	Adenoma: follicular cell	P-value of test of trend or comparison	.5278	.4276	.7150	.6836
		Number of animals reported with tumor	2	2	1	1
		Poly-3 adjusted incidence rate	2.5%	4.8%	2.5%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.31,9.0)	(0.58,16.5)	(0.06,13.2)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	78.9	41.5	40.8	36.8
	C-cell Adenomas or Carcinomas	P-value of test of trend or comparison	.1217	.4630	.0772	.1828
		Number of animals reported with tumor	10	6	10	8
		Poly-3 adjusted incidence rate	12%	15%	24%	20%
		95% CI for poly-3 adjusted incidence rate (%)	(6.01,21.5)	(5.43,29.2)	(12.1,40.3)	(9.05,36.5)
		Poly-3 adjusted number of animals at risk	81.4	41.4	41.7	39.2
	Carcinoma: C-cell	P-value of test of trend or comparison	.4404	.1798	.1798	.5007
		Number of animals reported with tumor	3	4	4	2
		Poly-3 adjusted incidence rate	3.8%	9.7%	9.6%	5.4%

Table 2.7

Table of reported tumors in Rat Study
NDA 202155
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 (%)	(0.78,10.7)	(2.66,23.1)	(2.66,23.1)	(0.66,18.7)
		Poly-3 adjusted number of animals at risk	79.0	41.2	41.5	36.8
	Carcinoma: follicular cell	P-value of test of trend or comparison	.6729	.1130		
		Number of animals reported with tumor	0	2	0	0
		Poly-3 adjusted incidence rate	0.0%	4.9%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.6)	(0.6,16.9)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	78.4	40.6	40.8	36.8
TONGUE	Carcinoma: squamous cell	P-value of test of trend or comparison	.5949	.3361		
		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 (%)	(0,4.6)	(0.06,13.2)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.2	41.0	40.8	36.8
UTERUS	Adenoma: endometrial	P-value of test of trend or comparison	.5969	.3417		
		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 (%)	(0,4.6)	(0.06,12.9)	(0,8.8)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.2	41.1	40.8	36.8
	Granular cell tumor	P-value of test of trend or comparison	.3427	1	1	.5381
		Number of animals reported with tumor	1	0	0	1
		Poly-3 adjusted incidence rate	1.3%	0.0%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	79.6	40.6	40.8	37.5
	Leiomyosarcoma	P-value of test of trend or comparison	.1888			.3190
		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 (%)	(0,4.6)	(0,8.8)	(0,8.8)	(0.07,14.2)
		Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	37.2

Table 2.7

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Polyp: endometrial stromal	P-value of test of trend or comparison	.5319	.7546	.7546	.6999
		Number of animals reported with tumor	5	2	2	2
		Poly-3 adjusted incidence rate	6.2%	4.9%	4.8%	5.4%
		95% CI for poly-3 adjusted incidence rate (%)	(2.03,14.0)	(0.58,16.5)	(0.58,16.5)	(0.66,18.7)
		Poly-3 adjusted number of animals at risk	80.5	41.0	41.5	36.8
VAGINA	Granular cell tumor	P-value of test of trend or comparison	.6801	1	.2098	1
		Number of animals reported with tumor	2	0	3	0
		Poly-3 adjusted incidence rate	2.5%	0.0%	7.4%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.3,8.8)	(0,8.8)	(1.54,20.4)	(0,9.7)
		Poly-3 adjusted number of animals at risk	79.5	40.6	40.8	36.8

Table 2.8

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLAND	Adenoma: cortical cell	P-value of test of trend or comparison	.5263	.7274	1	.6851
		Number of animals reported with tumor	2	1	0	1
		Poly-3 adjusted incidence rate	2.4%	2.2%	0.0%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0.29,8.3)	(0.06,11.8)	(0,9.3)	(0.06,13.5)
		Poly-3 adjusted number of animals at risk	84.1	45.2	38.9	40.0
	Pheochromocytoma	P-value of test of trend or comparison	.7614	.0174	.4558	.6256
		Number of animals reported with tumor	9	12	5	4
		Poly-3 adjusted incidence rate	10%	26%	13%	10%
		95% CI for poly-3 adjusted incidence rate (%)	(4.84,18.9)	(14.3,41.9)	(4.19,27.4)	(2.79,24.2)
		Poly-3 adjusted number of animals at risk	86.3	45.8	40.0	39.9
BRAIN	Meningeal 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	1.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0,7.9)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.6	45.2	38.9	39.4
	Meningioma (B)	P-value of test of trend or comparison	.1893			.3171
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.3)	(0,7.9)	(0,9.3)	(0.06,13.5)
		Poly-3 adjusted number of animals at risk	84.1	45.2	38.9	39.4
	Oligodendroglioma	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)	(0,7.9)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.6	45.2	38.9	39.4
	Reticulosis	P-value of test of trend or comparison	.8219	.2749	1	1
		Number of animals reported with tumor	1	2	0	0

Table 2.8

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		Poly-3 adjusted incidence rate	1.2%	4.4%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.4)	(0.53,15.1)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	85.1	45.2	38.9	39.4
EPIDIDYMIS	Mesothelioma	P-value of test of trend or comparison	.8349	.5778	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	1.2%	2.2%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0.06,11.8)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.1	45.6	38.9	39.4
HEART	Schwannoma: 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	1.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0,7.9)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.1	45.2	38.9	39.4
	Schwannoma: intramural	P-value of test of trend or comparison	.1893			.3171
		Number of animals reported with tumor	0	0	0	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.3)	(0,7.9)	(0,9.3)	(0.06,13.5)
		Poly-3 adjusted number of animals at risk	84.1	45.2	38.9	39.4
KIDNEY	Lipoma	P-value of test of trend or comparison	.8349	.5778	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	1.2%	2.2%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0.06,11.8)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.3	45.2	38.9	39.4
LIVER	Adenoma: hepatocellular	P-value of test of trend or comparison	.9420	.6843	.8571	1
		Number of animals reported with tumor	4	2	1	0
		Poly-3 adjusted incidence rate	4.7%	4.4%	2.5%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.3,11.7)	(0.53,15.1)	(0.06,13.5)	(0,9.0)

Table 2.8

Table of reported tumors in Rat Study
NDA 202155
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	84.3	46.0	39.4	39.4
	Carcinoma: hepatocellular	P-value of test of trend or comparison	.2488	1	.7875	.5201
		Number of animals reported with tumor	3	0	1	2
		Poly-3 adjusted incidence rate	3.5%	0.0%	2.6%	5.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.73,10.1)	(0,7.9)	(0.06,13.5)	(0.6,16.9)
		Poly-3 adjusted number of animals at risk	84.6	45.2	39.2	40.3
	Hemangioma	P-value of test of trend or comparison	.8349	.5778	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	1.2%	2.2%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0.06,11.8)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.3	45.5	38.9	39.4
	Hepatocellular Adenomas or Carcinomas	P-value of test of trend or comparison	.7046	.8863	.8428	.8512
		Number of animals reported with tumor	7	2	2	2
		Poly-3 adjusted incidence rate	8.3%	4.4%	5.0%	5.0%
		95% CI for poly-3 adjusted incidence rate (%)	(3.38,16.4)	(0.53,15.1)	(0.61,17.3)	(0.6,16.9)
		Poly-3 adjusted number of animals at risk	84.8	46.0	39.7	40.3
MAMMARY GLAND	Adenoma	P-value of test of trend or comparison	.3775	.5747	1	.5390
		Number of animals reported with tumor	1	1	0	1
		Poly-3 adjusted incidence rate	1.2%	2.3%	0.0%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0.06,12.0)	(0,9.3)	(0.06,13.5)
		Poly-3 adjusted number of animals at risk	83.1	44.2	38.9	39.9
	Fibroadenoma	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)	(0,8.0)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	83.1	44.2	38.9	39.4
PANCREAS	Adenoma: acinar cell	P-value of test of trend or comparison	.1951			.3252
		Number of animals reported with tumor	0	0	0	1

Table 2.8

Table of reported tumors in Rat Study
NDA 202155
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%	0.0%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.3)	(0,8.0)	(0,9.3)	(0.06,13.2)
		Poly-3 adjusted number of animals at risk	83.7	44.9	38.7	40.1
	Adenoma: islet cell	P-value of test of trend or comparison	.4259	.8377	1	.5878
		Number of animals reported with tumor	6	2	0	3
		Poly-3 adjusted incidence rate	7.1%	4.4%	0.0%	7.6%
		95% CI for poly-3 adjusted incidence rate (%)	(2.63,14.9)	(0.53,15.1)	(0,9.3)	(1.57,20.9)
		Poly-3 adjusted number of animals at risk	84.4	45.3	38.7	39.5
	Carcinoma: islet cell	P-value of test of trend or comparison	.3798	.8878	.6210	.6210
		Number of animals reported with tumor	4	1	2	2
		Poly-3 adjusted incidence rate	4.8%	2.2%	5.0%	5.0%
		95% CI for poly-3 adjusted incidence rate (%)	(1.3,11.7)	(0.06,11.8)	(0.61,17.3)	(0.61,17.3)
		Poly-3 adjusted number of animals at risk	84.1	45.2	39.7	39.7
	Islet cell Adenomas or Carcinomas	P-value of test of trend or comparison	.3677	.8976	.9418	.5490
		Number of animals reported with tumor	10	3	2	5
		Poly-3 adjusted incidence rate	12%	6.6%	5.0%	13%
		95% CI for poly-3 adjusted incidence rate (%)	(5.79,20.8)	(1.37,18.3)	(0.61,17.3)	(4.19,27.4)
		Poly-3 adjusted number of animals at risk	84.8	45.5	39.7	39.9
PARATHYROID GLAND	Adenoma	P-value of test of trend or comparison	.1138	1	1	.2656
		Number of animals reported with tumor	1	0	0	2
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	5.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.7)	(0,11.2)	(0,10.6)	(0.66,18.7)
		Poly-3 adjusted number of animals at risk	70.8	31.6	33.5	36.8
	Adenomas or Carcinomas	P-value of test of trend or comparison	.2032	1	1	.4187
		Number of animals reported with tumor	2	0	0	2
		Poly-3 adjusted incidence rate	2.8%	0.0%	0.0%	5.4%
		95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.9)	(0,11.2)	(0,10.6)	(0.66,18.7)
		Poly-3 adjusted number of animals at risk	70.8	31.6	33.5	36.8

Table 2.8

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Carcinoma	P-value of test of trend or comparison	.3797	1	1	.5660
		Number of animals reported with tumor	1	0	0	1
		Poly-3 adjusted incidence rate	1.4%	0.0%	0.0%	2.7%
		95% CI for poly-3 adjusted incidence rate (%)	(0.04,7.7)	(0,11.2)	(0,10.6)	(0.07,14.5)
		Poly-3 adjusted number of animals at risk	70.6	31.6	33.5	36.6
PITUITARY GLAND	Adenoma: pars distalis	P-value of test of trend or comparison	.8471	.3062	.8188	.8188
		Number of animals reported with tumor	74	42	32	32
		Poly-3 adjusted incidence rate	69%	75%	64%	64%
		95% CI for poly-3 adjusted incidence rate (%)	(59.5,78.3)	(60.3,85.6)	(48.1,77.1)	(48.1,77.1)
		Poly-3 adjusted number of animals at risk	107	56.2	50.3	50.3
	Adenomas or Carcinomas	P-value of test of trend or comparison	.8030	.3514	.7850	.7850
		Number of animals reported with tumor	75	42	33	33
		Poly-3 adjusted incidence rate	70%	75%	66%	65%
		95% CI for poly-3 adjusted incidence rate (%)	(60.5,79.2)	(60.3,85.6)	(50.1,78.8)	(50.1,78.8)
		Poly-3 adjusted number of animals at risk	107	56.2	50.3	50.8
	Carcinoma: pars distalis	P-value of test of trend or comparison	.1053		.3115	.3171
		Number of animals reported with tumor	0	0	1	1
		Poly-3 adjusted incidence rate	0.0%	0.0%	2.6%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.3)	(0,7.9)	(0.06,13.8)	(0.06,13.5)
		Poly-3 adjusted number of animals at risk	84.1	45.2	38.9	39.9
	Carcinoma: pars intermedia	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)	(0,7.9)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.1	45.2	38.9	39.4
SEMINAL VESICLE	Adenocarcinoma	P-value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0

Table 2.8

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
		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)	(0,7.9)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.7	45.2	38.9	39.4
SKIN/SUBCUTIS	Adenoma: 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	1.2%	0.0%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0,7.9)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.3	45.2	38.9	39.4
	Fibroma	P-value of test of trend or comparison	.5202	.4353	.6773	.6851
		Number of animals reported with tumor	2	2	1	1
		Poly-3 adjusted incidence rate	2.4%	4.4%	2.6%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0.29,8.3)	(0.53,15.1)	(0.06,13.8)	(0.06,13.5)
		Poly-3 adjusted number of animals at risk	84.4	45.5	38.9	39.4
	Fibrosarcoma	P-value of test of trend or comparison	.6336	.5778	.2359	1
		Number of animals reported with tumor	1	1	2	0
		Poly-3 adjusted incidence rate	1.2%	2.2%	5.1%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0.06,11.8)	(0.61,17.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.1	45.3	39.5	39.4
	Keratoacanthoma	P-value of test of trend or comparison	.8057	.9267	1	.9021
		Number of animals reported with tumor	5	1	0	1
		Poly-3 adjusted incidence rate	5.8%	2.2%	0.0%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(1.91,13.2)	(0.06,11.8)	(0,9.3)	(0.06,13.5)
		Poly-3 adjusted number of animals at risk	85.7	45.5	38.9	39.4
	Lipoma	P-value of test of trend or comparison	.3744	.5778	1	.5354
		Number of animals reported with tumor	1	1	0	1
		Poly-3 adjusted incidence rate	1.2%	2.2%	0.0%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0.06,11.8)	(0,9.3)	(0.06,13.5)
		Poly-3 adjusted number of animals at risk	84.1	45.2	38.9	39.8

Table 2.8

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Liposarcoma	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)	(0,7.9)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.6	45.2	38.9	39.4
	Osteosarcoma: extraskeletal	P-value of test of trend or comparison	.8365	.5843	1	1
		Number of animals reported with tumor	1	1	0	0
		Poly-3 adjusted incidence rate	1.2%	2.2%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0.05,11.5)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.7	46.0	38.9	39.4
	Schwannoma	P-value of test of trend or comparison	.4806	1	1	.6892
		Number of animals reported with tumor	2	0	0	1
		Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(0.28,8.2)	(0,7.9)	(0,9.3)	(0.06,13.2)
		Poly-3 adjusted number of animals at risk	85.2	45.2	38.9	40.3
	Trichoepithelioma	P-value of test of trend or comparison	.9735	.8247	1	1
		Number of animals reported with tumor	3	1	0	0
		Poly-3 adjusted incidence rate	3.5%	2.2%	0.0%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.73,10.1)	(0.06,11.8)	(0,9.3)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.9	45.5	38.9	39.4
SYSTEMIC NEOPLASMS	Hemangiosarcoma	P-value of test of trend or comparison	.8796	.4770	.7814	.9344
		Number of animals reported with tumor	6	4	2	1
		Poly-3 adjusted incidence rate	7.0%	8.7%	5.1%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(2.6,14.7)	(2.42,21.2)	(0.61,17.3)	(0.06,13.5)
		Poly-3 adjusted number of animals at risk	85.7	45.8	39.4	39.4
	Histiocytic sarcoma	P-value of test of trend or comparison	.0818	.5724	.1507	.1507
		Number of animals reported with tumor	3	2	4	4
		Poly-3 adjusted incidence rate	3.5%	4.4%	9.9%	9.9%

Table 2.8

Table of reported tumors in Rat Study
NDA 202155
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 (%)	(0.73,10.1)	(0.53,15.1)	(2.72,23.7)	(2.72,23.7)
		Poly-3 adjusted number of animals at risk	84.7	45.9	40.4	40.5
	Lymphoma: malignant	P-value of test of trend or comparison	.0371	.5778	1	.0936
		Number of animals reported with tumor	1	1	0	3
		Poly-3 adjusted incidence rate	1.2%	2.2%	0.0%	7.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0.06,11.8)	(0,9.3)	(1.57,20.9)
		Poly-3 adjusted number of animals at risk	84.7	45.6	38.9	39.7
TESTIS	Adenoma: interstitial cell	P-value of test of trend or comparison	.0777	.7274	.3781	.1821
		Number of animals reported with tumor	2	1	2	3
		Poly-3 adjusted incidence rate	2.4%	2.2%	5.1%	7.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.29,8.3)	(0.06,11.8)	(0.61,17.3)	(1.57,20.9)
		Poly-3 adjusted number of animals at risk	84.3	45.2	39.4	39.4
THYROID GLAND	Adenoma: C-cell	P-value of test of trend or comparison	.2783	.5690	.9590	.3306
		Number of animals reported with tumor	15	8	3	9
		Poly-3 adjusted incidence rate	17%	17%	7.6%	22%
		95% CI for poly-3 adjusted incidence rate (%)	(9.75,26.6)	(7.65,31.4)	(1.57,20.9)	(10.3,37.6)
		Poly-3 adjusted number of animals at risk	88.1	46.7	39.2	41.8
	Adenoma: follicular cell	P-value of test of trend or comparison	.7817	.1218	.5277	1
		Number of animals reported with tumor	1	3	1	0
		Poly-3 adjusted incidence rate	1.2%	6.6%	2.6%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(1.37,18.3)	(0.06,13.8)	(0,9.0)
		Poly-3 adjusted number of animals at risk	84.1	45.7	38.8	39.4
	C-cell Adenomas or Carcinomas	P-value of test of trend or comparison	.4735	.7721	.9588	.5711
		Number of animals reported with tumor	21	9	5	10
		Poly-3 adjusted incidence rate	24%	19%	12%	23%
		95% CI for poly-3 adjusted incidence rate (%)	(15.1,33.8)	(9.15,33.9)	(4.08,26.8)	(11.8,39.5)
		Poly-3 adjusted number of animals at risk	89.1	46.9	40.2	42.6

Table 2.8

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Carcinoma: C-cell	P-value of test of trend or comparison	.8950	.9187	.7348	.9731
		Number of animals reported with tumor	8	2	3	1
		Poly-3 adjusted incidence rate	9.4%	4.4%	7.5%	2.5%
		95% CI for poly-3 adjusted incidence rate (%)	(4.1,17.7)	(0.53,15.1)	(1.57,20.9)	(0.06,13.2)
		Poly-3 adjusted number of animals at risk	85.1	45.7	39.8	40.2
	Carcinoma: follicular cell	P-value of test of trend or comparison	.5670	.1218	.3140	
		Number of animals reported with tumor	0	2	1	0
		Poly-3 adjusted incidence rate	0.0%	4.4%	2.6%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0,4.3)	(0.53,15.1)	(0.06,13.8)	(0,9.0)
		Poly-3 adjusted number of animals at risk	83.9	45.6	38.9	39.4
ZYMBALS GLAND	Adenocarcinoma	P-value of test of trend or comparison	.7197	.2939	.5262	1
		Number of animals reported with tumor	1	2	1	0
		Poly-3 adjusted incidence rate	1.2%	4.4%	2.8%	0.0%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.8)	(0.53,15.1)	(0.07,14.5)	(0,9.3)
		Poly-3 adjusted number of animals at risk	80.9	45.5	36.0	38.7

Table 2.9

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
C-cell tumors	P-value of test of trend or comparison	.1217	.4630	.0772	.1828
	Number of animals reported with tumor	10	6	10	8
	Poly-3 adjusted incidence rate	12%	15%	24%	20%
	95% CI for poly-3 adjusted incidence rate (%)	(6.01,21.5)	(5.43,29.2)	(12.1,40.3)	(9.05,36.5)
	Poly-3 adjusted number of animals at risk	81.4	41.4	41.7	39.2
Cortical cell tumors	P-value of test of trend or comparison	.8613	.8711	.4228	1
	Number of animals reported with tumor	4	1	3	0
	Poly-3 adjusted incidence rate	4.9%	2.4%	7.4%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(1.34,12.2)	(0.06,13.2)	(1.54,20.4)	(0,9.7)
	Poly-3 adjusted number of animals at risk	81.3	40.8	40.8	36.8
Endometrial tumors of the uterus	P-value of test of trend or comparison	.5849	.5492	.7546	.6999
	Number of animals reported with tumor	5	3	2	2
	Poly-3 adjusted incidence rate	6.2%	7.2%	4.8%	5.4%
	95% CI for poly-3 adjusted incidence rate (%)	(2.03,14.0)	(1.5,19.9)	(0.58,16.5)	(0.66,18.7)
	Poly-3 adjusted number of animals at risk	80.5	41.5	41.5	36.8
Follicular cell tumors	P-value of test of trend or comparison	.6713	.1058	.7150	.6836
	Number of animals reported with tumor	2	4	1	1
	Poly-3 adjusted incidence rate	2.5%	9.6%	2.5%	2.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.31,9.0)	(2.66,23.1)	(0.06,13.2)	(0.07,14.5)
	Poly-3 adjusted number of animals at risk	78.9	41.5	40.8	36.8
Granular cell tumors of the uterus, cervix and vagina	P-value of test of trend or comparison	.4841	1	.6300	.7851
	Number of animals reported with tumor	6	0	3	2
	Poly-3 adjusted incidence rate	7.4%	0.0%	7.4%	5.3%
	95% CI for poly-3 adjusted incidence rate (%)	(2.77,15.6)	(0,8.8)	(1.54,20.4)	(0.64,18.2)
	Poly-3 adjusted number of animals at risk	80.7	40.6	40.8	37.5
Granular or meningeal granular cell tumors (brain)	P-value of test of trend or comparison	.3359	1	1	.5300
	Number of animals reported with tumor	1	0	0	1

Table 2.9

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted incidence rate	1.3%	0.0%	0.0%	2.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0.07,14.5)
	Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	36.8
Hepatocellular tumors	P-value of test of trend or comparison	.8656	1	.8108	1
	Number of animals reported with tumor	3	0	1	0
	Poly-3 adjusted incidence rate	3.8%	0.0%	2.4%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.78,10.7)	(0,8.8)	(0.06,13.2)	(0,9.7)
	Poly-3 adjusted number of animals at risk	79.2	40.6	40.9	36.8
Islet cell tumors	P-value of test of trend or comparison	.9082	.9678	1	.9575
	Number of animals reported with tumor	7	1	0	1
	Poly-3 adjusted incidence rate	8.7%	2.4%	0.0%	2.7%
	95% CI for poly-3 adjusted incidence rate (%)	(3.55,17.2)	(0.06,12.9)	(0,8.8)	(0.07,14.2)
	Poly-3 adjusted number of animals at risk	80.2	41.1	40.8	37.2
Leiomyomas and leiomyosarcomas of the uterus, cervix, ovaries and vagina	P-value of test of trend or comparison	.3427	1	1	.5381
	Number of animals reported with tumor	1	0	0	1
	Poly-3 adjusted incidence rate	1.3%	0.0%	0.0%	2.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0.07,14.2)
	Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	37.2
Leiomyomas of the uterus, cervix, ovaries and vagina	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)	(0,8.8)	(0,8.8)	(0,9.7)
	Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	36.8
Leiomyosarcomas of the uterus, cervix, ovaries and vagina	P-value of test of trend or comparison	.1888			.3190
	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 (%)	(0,4.6)	(0,8.8)	(0,8.8)	(0.07,14.2)

Table 2.9

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Mammary adenomas or fibroadenomas	Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	37.2
	P-value of test of trend or comparison	.3348	.7106	.3606	.4622
	Number of animals reported with tumor	52	25	30	26
	Poly-3 adjusted incidence rate	56%	53%	61%	59%
	95% CI for poly-3 adjusted incidence rate (%)	(45.2,66.8)	(37.2,67.9)	(45.2,74.8)	(42.2,73.7)
Mammary adenomas, adenocarcinomas or fibroadenomas	Poly-3 adjusted number of animals at risk	92.7	47.3	49.3	44.2
	P-value of test of trend or comparison	.3128	.7297	.4435	.4371
	Number of animals reported with tumor	57	27	32	29
	Poly-3 adjusted incidence rate	60%	56%	63%	63%
	95% CI for poly-3 adjusted incidence rate (%)	(48.9,69.9)	(40.2,70.5)	(47,75.9)	(46.4,76.8)
Pheochromocytomas	Poly-3 adjusted number of animals at risk	95.5	48.3	51.1	46.3
	P-value of test of trend or comparison	.2345	.3336	1	.2880
	Number of animals reported with tumor	3	3	0	3
	Poly-3 adjusted incidence rate	3.8%	7.3%	0.0%	8.1%
	95% CI for poly-3 adjusted incidence rate (%)	(0.78,10.7)	(1.5,19.9)	(0,8.8)	(1.66,21.9)
Pituitary pars distalis tumors	Poly-3 adjusted number of animals at risk	79.9	41.1	40.8	37.2
	P-value of test of trend or comparison	.6055	.8394	.8483	.7477
	Number of animals reported with tumor	106	48	47	48
	Poly-3 adjusted incidence rate	92%	87%	87%	90%
	95% CI for poly-3 adjusted incidence rate (%)	(84.7,96.4)	(75.5,95.8)	(75.1,95.7)	(77.4,96.9)
Stromal tumors of the uterus or ovaries	Poly-3 adjusted number of animals at risk	116	54.9	53.8	53.4
	P-value of test of trend or comparison	.5319	.7546	.7546	.6999
	Number of animals reported with tumor	5	2	2	2
	Poly-3 adjusted incidence rate	6.2%	4.9%	4.8%	5.4%
	95% CI for poly-3 adjusted incidence rate (%)	(2.03,14.0)	(0.58,16.5)	(0.58,16.5)	(0.66,18.7)
Subcutis fibromas and fibrosarcomas	Poly-3 adjusted number of animals at risk	80.5	41.0	41.5	36.8
	P-value of test of trend or comparison	.3359	1	1	.5300

Table 2.9

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Female rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Uterine leiomyomas and leiomyosarcomas	Number of animals reported with tumor	1	0	0	1
	Poly-3 adjusted incidence rate	1.3%	0.0%	0.0%	2.7%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.9)	(0,8.8)	(0,8.8)	(0.07,14.5)
	Poly-3 adjusted number of animals at risk	79.6	40.6	40.8	36.8
	P-value of test of trend or comparison	.1888			.3190
Uterine stromal tumors	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 (%)	(0,4.6)	(0,8.8)	(0,8.8)	(0.07,14.2)
	Poly-3 adjusted number of animals at risk	79.2	40.6	40.8	37.2
	P-value of test of trend or comparison	.5319	.7546	.7546	.6999
Uterine tumors	Number of animals reported with tumor	5	2	2	2
	Poly-3 adjusted incidence rate	6.2%	4.9%	4.8%	5.4%
	95% CI for poly-3 adjusted incidence rate (%)	(2.03,14.0)	(0.58,16.5)	(0.58,16.5)	(0.66,18.7)
	Poly-3 adjusted number of animals at risk	80.5	41.0	41.5	36.8

Table 2.10

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
C-cell tumors	P-value of test of trend or comparison	.4735	.7721	.9588	.5711
	Number of animals reported with tumor	21	9	5	10
	Poly-3 adjusted incidence rate	24%	19%	12%	23%
	95% CI for poly-3 adjusted incidence rate (%)	(15.1,33.8)	(9.15,33.9)	(4.08,26.8)	(11.8,39.5)
	Poly-3 adjusted number of animals at risk	89.1	46.9	40.2	42.6
Cortical cell tumors	P-value of test of trend or comparison	.5263	.7274	1	.6851
	Number of animals reported with tumor	2	1	0	1
	Poly-3 adjusted incidence rate	2.4%	2.2%	0.0%	2.5%
	95% CI for poly-3 adjusted incidence rate (%)	(0.29,8.3)	(0.06,11.8)	(0,9.3)	(0.06,13.5)
	Poly-3 adjusted number of animals at risk	84.1	45.2	38.9	40.0
Follicular cell tumors	P-value of test of trend or comparison	.8604	.0209	.2286	1
	Number of animals reported with tumor	1	5	2	0
	Poly-3 adjusted incidence rate	1.2%	11%	5.1%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(3.55,23.6)	(0.63,17.7)	(0,9.0)
	Poly-3 adjusted number of animals at risk	84.1	46.0	38.9	39.4
Granular or meningeal granular cell tumors (brain)	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)	(0,7.9)	(0,9.3)	(0,9.0)
	Poly-3 adjusted number of animals at risk	84.6	45.2	38.9	39.4
Hepatocellular tumors	P-value of test of trend or comparison	.7046	.8863	.8428	.8512
	Number of animals reported with tumor	7	2	2	2
	Poly-3 adjusted incidence rate	8.3%	4.4%	5.0%	5.0%
	95% CI for poly-3 adjusted incidence rate (%)	(3.38,16.4)	(0.53,15.1)	(0.61,17.3)	(0.6,16.9)
	Poly-3 adjusted number of animals at risk	84.8	46.0	39.7	40.3
Islet cell tumors	P-value of test of trend or comparison	.3677	.8976	.9418	.5490
	Number of animals reported with tumor	10	3	2	5

Table 2.10

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
	Poly-3 adjusted incidence rate	12%	6.6%	5.0%	13%
	95% CI for poly-3 adjusted incidence rate (%)	(5.79,20.8)	(1.37,18.3)	(0.61,17.3)	(4.19,27.4)
	Poly-3 adjusted number of animals at risk	84.8	45.5	39.7	39.9
Mammary adenomas or fibroadenomas	P-value of test of trend or comparison	.5302	.7244	1	.6888
	Number of animals reported with tumor	2	1	0	1
	Poly-3 adjusted incidence rate	2.4%	2.3%	0.0%	2.5%
	95% CI for poly-3 adjusted incidence rate (%)	(0.29,8.4)	(0.06,12.0)	(0,9.3)	(0.06,13.5)
	Poly-3 adjusted number of animals at risk	83.1	44.2	38.9	39.9
Mammary adenomas, adenocarcinomas or fibroadenomas	P-value of test of trend or comparison	.5302	.7244	1	.6888
	Number of animals reported with tumor	2	1	0	1
	Poly-3 adjusted incidence rate	2.4%	2.3%	0.0%	2.5%
	95% CI for poly-3 adjusted incidence rate (%)	(0.29,8.4)	(0.06,12.0)	(0,9.3)	(0.06,13.5)
	Poly-3 adjusted number of animals at risk	83.1	44.2	38.9	39.9
Parathyroid tumors	P-value of test of trend or comparison	.2032	1	1	.4187
	Number of animals reported with tumor	2	0	0	2
	Poly-3 adjusted incidence rate	2.8%	0.0%	0.0%	5.4%
	95% CI for poly-3 adjusted incidence rate (%)	(0.34,9.9)	(0,11.2)	(0,10.6)	(0.66,18.7)
	Poly-3 adjusted number of animals at risk	70.8	31.6	33.5	36.8
Pheochromocytomas	P-value of test of trend or comparison	.7614	.0174	.4558	.6256
	Number of animals reported with tumor	9	12	5	4
	Poly-3 adjusted incidence rate	10%	26%	13%	10%
	95% CI for poly-3 adjusted incidence rate (%)	(4.84,18.9)	(14.3,41.9)	(4.19,27.4)	(2.79,24.2)
	Poly-3 adjusted number of animals at risk	86.3	45.8	40.0	39.9
Pituitary pars distalis tumors	P-value of test of trend or comparison	.7744	.3062	.7478	.7478
	Number of animals reported with tumor	74	42	33	33
	Poly-3 adjusted incidence rate	69%	75%	66%	65%
	95% CI for poly-3 adjusted incidence rate (%)	(59.5,78.3)	(60.3,85.6)	(50.1,78.8)	(50.1,78.8)

Table 2.10

Table of reported tumors in Rat Study
NDA 202155
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Subcutis fibromas and fibrosarcomas	Poly-3 adjusted number of animals at risk	107	56.2	50.3	50.8
	P-value of test of trend or comparison	.6381	.3485	.2845	.7875
	Number of animals reported with tumor	3	3	3	1
	Poly-3 adjusted incidence rate	3.6%	6.6%	7.6%	2.5%
	95% CI for poly-3 adjusted incidence rate (%)	(0.73,10.1)	(1.37,18.3)	(1.57,20.9)	(0.06,13.5)
	Poly-3 adjusted number of animals at risk	84.4	45.6	39.5	39.4

Table 2.11

Table of tumors reported significant in at least one arm - Rat Study
NDA 202155
Animal carcinogenicity study
Female rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
SYSTEMIC NEOPLASMS	Lymphoma: malignant	P-value of test of trend or comparison	.0302	.7147	.4074	.0838
		Number of animals reported with tumor	2	1	2	4
		Poly-3 adjusted incidence rate	2.5%	2.4%	4.9%	10%
		95% CI for poly-3 adjusted incidence rate (%)	(0.3,8.7)	(0.06,12.9)	(0.6,16.9)	(2.87,24.8)
		Poly-3 adjusted number of animals at risk	80.3	41.6	40.9	38.3

Table 2.12

Table of tumors reported significant in at least one arm - Rat Study
NDA 202155
Animal carcinogenicity study
Male rats

Organ or tissue name	*Tumor name*	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
ADRENAL GLAND	Pheochromocytoma	P-value of test of trend or comparison	.7614	.0174	.4558	.6256
		Number of animals reported with tumor	9	12	5	4
		Poly-3 adjusted incidence rate	10%	26%	13%	10%
		95% CI for poly-3 adjusted incidence rate (%)	(4.84,18.9)	(14.3,41.9)	(4.19,27.4)	(2.79,24.2)
		Poly-3 adjusted number of animals at risk	86.3	45.8	40.0	39.9
SYSTEMIC NEOPLASMS	Lymphoma: malignant	P-value of test of trend or comparison	.0371	.5778	1	.0936
		Number of animals reported with tumor	1	1	0	3
		Poly-3 adjusted incidence rate	1.2%	2.2%	0.0%	7.6%
		95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(0.06,11.8)	(0,9.3)	(1.57,20.9)
		Poly-3 adjusted number of animals at risk	84.7	45.6	38.9	39.7

Table 2.13

Table of tumors reported significant in at least one arm - Rat Study
NDA 202155
Animal carcinogenicity study
Male rats
Composite endpoints

Composite endpoint	*Quantity*	*Control*	*Low dose*	*Mid dose*	*High dose*
Follicular cell tumors	P-value of test of trend or comparison	.8604	.0209	.2286	1
	Number of animals reported with tumor	1	5	2	0
	Poly-3 adjusted incidence rate	1.2%	11%	5.1%	0.0%
	95% CI for poly-3 adjusted incidence rate (%)	(0.03,6.5)	(3.55,23.6)	(0.63,17.7)	(0,9.0)
	Poly-3 adjusted number of animals at risk	84.1	46.0	38.9	39.4
Pheochromocytomas	P-value of test of trend or comparison	.7614	.0174	.4558	.6256
	Number of animals reported with tumor	9	12	5	4
	Poly-3 adjusted incidence rate	10%	26%	13%	10%
	95% CI for poly-3 adjusted incidence rate (%)	(4.84,18.9)	(14.3,41.9)	(4.19,27.4)	(2.79,24.2)
	Poly-3 adjusted number of animals at risk	86.3	45.8	40.0	39.9

Table 2.14

Organs reported as autolytic
NDA 202155
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(%)*
PANCREAS	1	0.8%	.	.	.	.	.	.	1	0.3%
THYROID GLAND	2	1.7%	1	1.7%	.	.	.	.	3	1.0%

Table 2.15

Organs reported as autolytic
NDA 202155
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(%)*
CECUM	1	0.8%	.	.	.	.	.	.	1	0.3%
JEJUNUM	1	0.8%	.	.	.	.	1	1.7%	2	0.7%
PANCREAS	3	2.5%	.	.	1	1.7%	1	1.7%	5	1.7%
STOMACH	1	0.8%	.	.	1	1.7%	1	1.7%	3	1.0%
THYROID GLAND	2	1.7%	.	.	1	1.7%	.	.	3	1.0%

Table 2.16

Organs reported as unexamined
NDA 202155
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(%)*
ADIPOSE TISSUE	104	87%	55	92%	57	95%	53	88%	269	90%
CERVIX	1	0.8%	.	.	.	.	.	.	1	0.3%
EARS	118	98%	59	98%	59	98%	60	100%	296	99%
PARATHYROID GLAND	21	18%	13	22%	8	13%	12	20%	54	18%
ZYMBALS GLAND	4	3.3%	3	5.0%	4	6.7%	1	1.7%	12	4.0%

Table 2.17

Organs reported as unexamined
NDA 202155
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(%)*
ADIPOSE TISSUE	113	94%	57	95%	56	93%	55	92%	281	94%
EARS	120	100%	60	100%	60	100%	59	98%	299	100%
MAMMARY GLAND	1	0.8%	1	1.7%	.	.	.	.	2	0.7%
PANCREAS	.	.	1	1.7%	.	.	.	.	1	0.3%
PARATHYROID GLAND	18	15%	17	28%	7	12%	3	5.0%	45	15%
ZYMBALS GLAND	6	5.0%	1	1.7%	6	10%	2	3.3%	15	5.0%

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.

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

Table 3.1: Weight changes by group (mice)

Sex	Combined control	BMS-562247					
	Δ_C	Δ_L	$\frac{\Delta_L}{\Delta_C} - 1$	Δ_M	$\frac{\Delta_M}{\Delta_C} - 1$	Δ_H	$\frac{\Delta_H}{\Delta_C} - 1$
Female	17.73	16.29	−8.6%	19.22	+8.4%	18.41	+3.8%
Male	15.16	16.04	+5.8%	16.27	+7.3%	18.33	+20.9%

3.2.1 Female mouse experiment

Although survival rates at 90 weeks were below 50% in all groups, the number of surviving animals was in each case above 20 (see table 1.2). We may therefore conclude that the the number and longevity of the animals in this experiment was sufficient to meet our usual standards.

There is evidence of a dose related increase in mortality (see table 1.3), so we may conclude that the doses did indeed pose an adequate tumor challenge to the animals.

3.2.2 Male mouse experiment

Survival rates at 90 weeks were above 50% for each group except the high dose group, and even for that group, twenty six animals animals were still alive. It follows that we can conclude that the number and longevity of the animals in this experiment was sufficient to meet our usual standards.

However, there is no evidence of either a dose related increase in mortality or a dose related reduction in weight gain. The determination of whether the high dose level was adequately close to the MTD must therefore be made by the reviewing pharmacologist, on the basis of clinical signs of toxicity. It should be noted however, that the high dose group experienced sharply *higher* levels of weight gain than the combined control groups.

3.3 Assessment of the validity of the rat study

Table 3.2: Weight changes by group (rats)

Sex	Combined control	BMS-562247					
	Δ_C	Δ_L	$\frac{\Delta_L}{\Delta_C} - 1$	Δ_M	$\frac{\Delta_M}{\Delta_C} - 1$	Δ_H	$\frac{\Delta_H}{\Delta_C} - 1$
Female	300.4	306.9	+2.2%	333.5	+11.0%	304.1	+1.2%
Male	544.6	496.7	−8.8%	557.8	+2.4%	467.4	−14.2%

In both male and female rats, survival at 90 weeks was good; at least 29 animals (and at least 48%) in each group. There is thus no concern that toxicity effects were excessive. There is no statistically significant evidence of a dose related reduction in survival in either sex. However, in the female rats, the Kaplan-Meier plots do suggest that the high dose group experienced slightly higher mortality than the other groups. In the male rat group, there is evidence of diminished weight gain, relative to the combined control, in the high dose group. It follows that it is reasonable

to conclude that both experiments posed an adequately strong tumor challenge to the high dose animals, although this evidence is weak in the case of the female rats.

Chapter 4

Conclusions

4.1 Mouse study

This is a negative study.

Both the male and female mouse experiments are negative. However, the result for uterine glandular polyps and adenocarcinomas (combined) is strongly suggestive of a tumorigenic effect; the test of trend just misses the threshold for significance for a common tumor type ($p = 0.0058$), although the comparison between the high dose and control group is not close to significance ($p = 0.0425$). This possible finding is worthy of some further discussion before being definitively classed as negative.

The high rates at which the parathyroid (both sexes) and thymus (female mice only) were reported as unexamined mean that the study should be considered inconclusive rather than negative for these endpoints. There was no problem with autolysis in this study (in fact, there was not even a single organ which was reported as being autolyzed to the extent that a usable sample could not be obtained).

Although mortality was fairly high in this study, sufficient animals lived a sufficiently long time to conclude that we need not be too concerned about having an inappropriately small sample size. There was a dose related increase in mortality in the female mice, so for this experiment we may also conclude that the dose level was close to the MTD. However, for the male mice, there is no evidence of either a dose related reduction in survival or weight gain. Therefore, absent clinical signs of toxicity, we must consider the possibility that dose levels in the male mouse experiment were too low.

4.2 Rat study

This is a negative study.

However, the test of trend for malignant lymphoma yielded p-values below 0.05 in *both* the male and female rat experiments. Taken together, these independent results buttress each other, meaning that despite the fact that the results are not significant after making an adjustment for multiple testing, they should still be considered strongly as a possible effect.

There was no problem with unexamined or autolytic organs in this study.

Dose levels appear in retrospect to have been appropriate. Mortality was not excessive, and the high dose male rats experienced substantial diminished weight gain compared with the combined control. The evidence that the female rats experienced diminished survival is weak - the result is not statistically significant, but the Kaplan-Meier plots (figure 2.1) suggest that the high dose female group experienced lower rates of survival than the other groups.

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Concur with review