CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 202,439/N000
Drug Name:	Xarelto (rivaroxaban 20 mg IR tablets)
Indication(s):	Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
Applicant:	Ortho-McNeil-Janssen Pharmaceuticals
Date(s):	Received date: Jan 5, 2011
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Keywords:

active control/non-inferiority, Cox regression, benefit-risk, logrank test, survival analysis

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1. EXECUTIVE SUMMARY

Rivaroxaban was non-inferior to warfarin, as warfarin was used in the study, on the primary endpoint. When analyzing the data up to 2 days after last dose, the confidence interval for the hazard ratio is entirely below 1 (point estimate 0.79, 95% CI (0.66, 0.96)). There is a question about whether warfarin was used optimally in the study (the median TTR across sites was 59). For superiority, the ITT analysis is preferred. In the ITT analysis, the confidence interval does not exclude 1 (point estimate 0.91, 95% CI (0.77, 1.08)). Rivaroxaban was not superior on all cause mortality by either the on-treatment or ITT analysis.

2. INTRODUCTION

This is a statistical review for NDA 202439/N000 investigating the efficacy of rivaroxaban as a prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

2.1 Overview

According to the sponsor, rivaroxaban (BAY 59-7939) is a potent and highly selective direct Factor Xa (FXa) inhibitor. Rivaroxaban is currently being co-developed for the prevention and treatment of multiple thrombosis-mediated conditions through a joint collaboration between Bayer Schering Pharma (Bayer) and Johnson & Johnson Pharmaceutical Research and Development, LLC (J&JPRD). Rivaroxaban (10 mg tablet) is currently marketed as Xarelto in over 100 countries worldwide for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or know replacement surgery.

In this submission, the sponsor is seeking approval for rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). According to the sponsor, atrial fibrillation is the most common cardiac arrhythmia of clinical significance and is an important independent risk factor for stroke. It is estimated that AF is currently affecting 6 millions patients in Europe and approximately 2.3 millions in the United States and this patient population is growing rapidly.

Vitamin K antagonists and warfarin in particular have been established as the most effective therapy for the prevention of cardioembolic events in patients with AF. However, the management of warfarin therapy can be challenging. A warfarin dose is generally adjusted to maintain an International Normalized Ratio (INR) between 2.0 and 3.0, inclusive. As an INR increases above this range, the risk of hemorrhagic complications also increases. As an INR decreases below this range, the risk of embolic complications increases. 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.

The efficacy and safety of rivaroxaban as a prevention of stroke and systemic embolism in patients with non-valvular AF have been studied in two studies. They are listed below.

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Table 1. List of all studies included in analysis

Study	Phase	Treatment Period	# of Subjects per Arm	Study Population
ROCKET-AF	Phase 3	Estimated to be 14 32 months depending upon reaching the target number of events	~7130 subjects	Non-valvular AF patients
J-ROCKET	Phase 3	Estimated to be 31 months depending upon reach the target number of events	640 subjects	Non-valvular AF patients

Both studies were randomized, double-blind, double-dummy, prospective, multicenter, parallel-group, warfarin-comparator, non-inferiority studies. ROCKET-AF was the pivotal study while J-ROCKET was supposed to be supportive. J-ROCKET was designed primarily to evaluate the safety of rivaroxabain in Japanese patients. It was not supposed to be a stand alone pivotal trial for the U.S. registration. There was no efficacy hypothesis tested in J-ROCKET. The primary safety hypothesis in J-ROCKET was to test whether rivaroxaban was non-inferior to warfarin for major and non-major clinically relevant bleeding.

This review will focus on the efficacy evaluation of ROCKET-AF.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\Cdsesub1\evsprod\NDA202439\0000\m5\datasets. Data for the pivotal study (ROCKET-AF) were submitted in SDTM format and associated SAS programs were also provided for the pivotal study (ROCKET-AF).

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No statistical issues with the data or analysis quality. The data files were in SAS transport format. Some of the files were larger than recommended by the FDA guidance document (50 magebytes).

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study ROCKET-AF (also known as JNJ39039039 AFL3001)

ROCKET-AF (**R**ivaroxaban **O**nce Daily Oral Direct Factor Xa Inhibition **C**ompared with Vitamin **K** Antagonism for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation) was a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multi-center study. Forty-five (45) countries participated in this study and each country was assigned to 1 of 5 regions as follows:

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• **Asia Pacific**: Australia, China, Hong Kong, India, Korea, Malaysia, *New Zealand*, Philippines, Singapore, Taiwan, Thailand
• **East Europe**: Bulgaria, Czech Republic, Greece, Hungary, Lithuania, Poland, Romania, Russia, Turkey, Ukraine
• **Latin America**: Argentina, Brazil, Chile, Colombia, Mexico, Panama, Peru, Venezuela
• **North America**: Canada, United States
• **West Europe**: Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, *South Africa*, Spain, Sweden, Switzerland, United Kingdom

The study consisted of three periods: a screening period, a double-blind treatment period, and a post treatment observation period (about 30 days in duration). The duration of the double-blind period depended of the time needed to reach 290 primary efficacy endpoint events. The investigated dose was rivaroxaban 20 mg once daily given orally. In patients with creatinine clearance between 30 and 49 mL/min, the dose was decreased to 15 mg once daily. The active control was warfarin with the dose adjusted to the target INR of 2.5 (range between 2 and 3).

The primary efficacy variable was the composite of stroke and non-CNS systemic embolism in subjects with non-valvular atrial fibrillation. The primary objective of the study was to show rivaroxaban is non-inferior to warfarin with the non-inferiority margin of 1.46 (The Agency has recommended a non-inferiority of 1.38). If non-inferiority would be achieved, superiority would be tested.

There were two major secondary efficacy variables: 1) the composite of stroke, non-CNS systemic embolism, and vascular death in subjects with non-valvular atrial fibrillation and 2) the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death in subjects with non-valvular atrial fibrillation. In addition, all-cause mortality was also examined. The diagram of multiple testing procedure is as follows:

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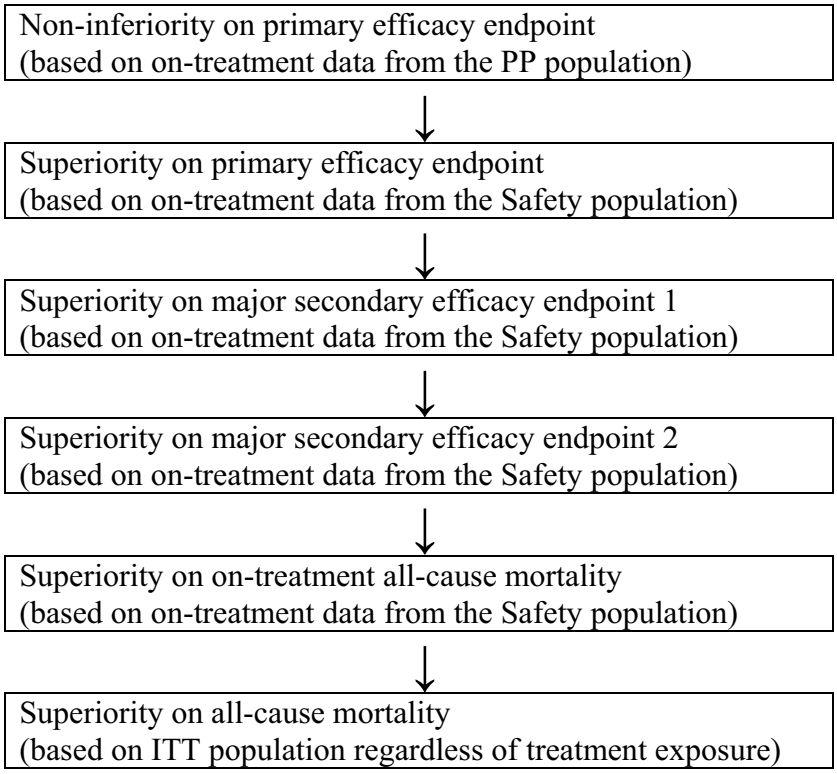

Figure 1. ROCKET-AF: Diagram of multiple testing procedure

The statistical analysis plan (SAP) was originated on Nov 27, 2007, with amendment 1 on June 30, 2009, and amendment 2 on Oct 1, 2010. In the SAP, several analysis sets were stipulated. They are:

- The intent-to-treat (ITT) population which consists of all randomized unique subjects.
- The safety population which consists of all ITT subjects who take at least one dose of study medication after randomization during the double-blind treatment period.
- The per-protocol (PP) population which consists of all ITT subjects excluding those who have specific pre-defined major protocol deviations that occur by the time of enrollment into the study or during the trial.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.1 Study ROCKET-AF

A total of 14,264 subjects were randomized to either rivaroxaban (7,131 subjects) or warfarin (7,133 subjects). This disposition of subjects is summarized in Table 2.

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Table 2. ROCKET-AF: Disposition of subjects

	Rivaroxaban (N 7111) n (%)	Warfarin (N 7125) n (%)	Total (N 14236) n (%)
Completed study medication	4591 (64.56)	4657 (65.36)	9248 (64.96)
Early study medication discontinuation	2520 (35.44)	1468 (34.64)	4988 (35.04)
Adverse event	993 (13.96)	919 (12.90)	1912 (13.43)
- Bleeding	304 (4.28)	219 (3.07)	523 (3.67)
- Non-bleeding	689 (9.69)	699 (9.81)	1388 (9.75)
- Missing/Incomplete data	0	1 (0.01)	1 (0.01)
Non-compliant with study medication	134 (1.88)	164 (2.30)	298 (2.90)
Consent withdrawn	671 (9.44)	673 (9.45)	1344 (9.44)
Investigator decision, not protocol-related	191 (2.69)	178 (2.50)	369 (2.59)
Lost to follow-up	6 (0.08)	8 (0.11)	14 (0.10)
Protocol violation	142 (2.00)	124 (1.74)	266 (1.87)
Clinical efficacy endpoint reached	300 (4.22)	332 (4.66)	632 (4.44)
Study terminated by sponsor	82 (1.15)	69 (0.97)	151 (1.06)
Missing/incomplete data	1 (0.01)	1 (0.01)	2 (0.01)

(Source: Clinical Study Report 39039039AFL3001, Table 7, Page 108)

Table 3 summarizes the baseline demographics information of the ITT population. Approximately 60% of the subjects were male. The majority of the patients were white (approximately 83%). Asians accounted for about 13% of the patients. The average age was about 71 years with approximately 45% of the subjects over the age of 75 years. The distribution of the demographics appeared balanced between the two arms.

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Table 3. ROCKET-AF: Demographics and Baseline Characteristics (ITT analysis set)

	Rivaroxaban (N 7131)	Warfarin (N 7133)	Total (N 14264)
Sex, n (%)			
Female	2830 (39.69)	2830 (39.67)	5660 (39.68)
Male	4301 (60.31)	4303 (60.33)	8604 (60.32)
Race, n (%)			
White	5922 (83.05)	5957 (83.51)	11879 (83.28)
Black	94 (1.32)	86 (1.21)	180 (1.26)
Asian	897 (12.58)	889 (12.46)	1786 (12.52)
Others	218 (3.06)	201 (2.82)	419 (2.94)
Age			
18 - < 65	1651 (23.15)	1643 (23.03)	3294 (23.09)
65 - < 75	2360 (33.09)	2381 (33.38)	4741 (33.24)
≥ 75	3120 (43.75)	3109 (43.59)	6229 (44.83)
Mean (SD)	71.21 (9.46)	71.18 (9.39)	71.19 (9.42)
Median (Q1, Q3)	73 (65, 78)	73 (65, 78)	73 (65, 78)
Min, Max	25, 97	28, 95	25, 97
Baseline weight (kg)			
N	7129	7132	14261
Mean (SD)	82.07 (19.13)	81.64 (18.92)	81.85 (19.04)
Median (Q1, Q3)	80 (69, 92.6)	80 (69, 92)	80 (69, 92)
Min, Max	36, 209	30, 227	30, 227
Baseline height (cm)			
N	7126	7129	14255
Mean (SD)	167.67 (10.01)	167.73 (10.22)	167.70 (10.12)
Median (Q1, Q3)	168 (160, 175)	168 (160, 175)	168 (160, 175)
Min, Max	120, 207	62.6, 209.6	62.6, 209.6
Baseline BMI (kg/m^2)			
N	7126	7129	14255
Mean (SD)	29.06 (5.70)	28.95 (7.24)	29.00 (6.51)
Median (Q1, Q3)	28.31 (25.15, 32.05)	28.07 (25.06, 31.83)	28.17 (25.10, 31.98)
Min, Max	15.23, 65.17	13.91, 403.19	13.91, 403.19

(Source: Clinical Study Report 39039039AFL3001, Table 8, Pages 109-110)

Table 4 summarizes selected baseline disease characteristics of the ITT population. Two-third of the patients have used vitamin K antagonist previously. The majority of the patients had hypertension at baseline. The majority of the patients had persistent AF type (lasting greater than 7 days at any time). Slightly more than half of the patients had prior stroke, transient ischemic attack, TIA, or non-CNS systemic embolism.

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Table 4. ROCKET-AF: Selected Baseline Disease Characteristics (ITT analysis set)

	Rivaroxaban (N 7131)	Warfarin (N 7133)	Total (N 14264)
Congestive heart failure			
No	2663 (37.4%)	2691 (37.7%)	5354 (37.5%)
Yes	4467 (62.7%)	4441 (62.3%)	8908 (62.5%)
Prior VKA used			
No	2688 (37.7%)	2672 (37.5%)	5360 (37.6%)
Yes	4443 (62.31%)	4461 (62.5%)	8904 (62.4%)
Prior Stroke/EM/TIA			
No	3215 (45.1%)	3238 (45.4%)	6453 (45.2%)
Yes	3916 (54.9%)	3895 (54.6%)	7811 (54.8%)
Prior MI			
No	5949 (83.4%)	5847 (82.0%)	11796 (82.7%)
Yes	1182 (16.6%)	1286 (18.0%)	2468 (17.3%)
CHADS2			
1	1 (0.01%)	2 (0.03%)	3 (0.02%)
2	925 (13.0%)	934 (13.1%)	1859 (13.0%)
3	3058 (42.9%)	3158 (44.3%)	6216 (43.6%)
4	2092 (29.3%)	1999 (28.0%)	4091 (28.7%)
5	932 (13.1%)	881 (12.4%)	1813 (12.7%)
6	123 (1.7%)	159 (2.2%)	282 (2.0%)
Hypertension			
No	695 (9.8%)	659 (9.2%)	1354 (9.5%)
Yes	6436 (90.3%)	6474 (90.8%)	12910 (90.5%)
AF type			
Newly diagnosed/onset	100 (1.4%)	102 (1.4%)	202 (1.4%)
Paroxysmal	1245 (17.5%)	1269 (17.8%)	2514 (17.6%)
Persistent	5786 (81.1%)	5762 (80.8%)	11548 (81.0%)

(Source: Clinical Study Report 39039039AFL3001, Tables 8-9, Pages 109-112)

3.2.3 Statistical Methodologies

3.2.3.1 Study ROCKET-AF

The primary efficacy variable is the time from randomization to the first occurrence of the composite of stroke and non-CNS systemic embolism based on the Clinical Endpoint Committee (CEC) adjudication. The primary analysis set is the per-protocol set which consists of all randomized subjects excluding those who have specific pre-defined major protocol deviations that occur by the time of enrollment into the study or during the trial. The analysis window is from the randomization up to the last dose + 2 days. The primary analysis is the Cox proportional hazards model with treatment as a factor. The objective of the primary analysis is to show that rivaroxaban is non-inferior to warfarin. Non-inferiority is achieved when the upper limit of the 2-sided 95% confidence interval of the hazard ratio (rivaroxaban/warfarin) is less than the margin 1.46. It

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is noted that the Agency has recommended the margin of 1.38 on several occasions (e.g., Feb 11, 2008 letter to the sponsor).

If non-inferiority is achieved, then the superiority of rivaroxaban over warfarin on the time from randomization to the first occurrence of the composite of stroke and non-CNS systemic embolism would be tested. The analysis model is the Cox proportional hazards model with treatment as a factor. If the upper limit of the 2-sided 95% confidence interval is below 1, then superiority of rivaroxaban over warfarin on the primary efficacy variable is declared.

A number of secondary endpoints were also planned to be tested. The first major secondary endpoint is the time from randomization to the first event of the composite of stroke, non-CNS systemic embolism, and vascular death.

The second major secondary endpoint is the time from randomization to the first event of the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death.

3.2.4 Results and Conclusions

3.2.4.1 Study ROCKET-AF: Sponsor's results

The sponsor's overall results on the efficacy evaluation are summarized in Figure 2 and in Table 5. Rivaroxaban was statistically significant to warfarin on the primary efficacy measure (the composite of stroke and non-CNS systemic embolism). Rivaroxaban was statistically significant to warfarin on the first major secondary efficacy measure (the composite of stroke, non-CNS systemic embolism, and vascular death) and on the second major secondary efficacy measure (the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death).

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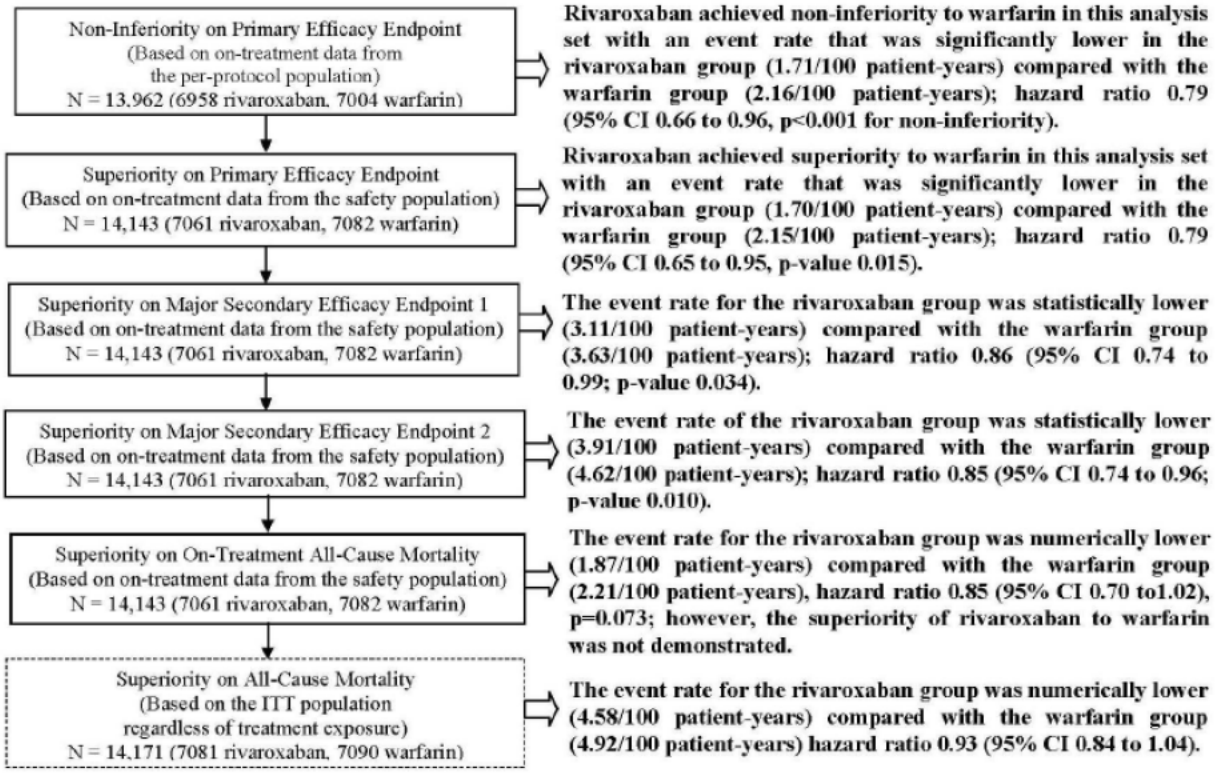

Figure 2. ROCKET-AF: Sponsor's results on prespecified hierarchy of multiple testing procedure for efficacy
(Source: Clinical Study Report 39039039AFL3001, Figure 8, Page 131)

Table 5. ROCKET-AF: Sponsor's efficacy results

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)	P-value
Per protocol – Non-inferiority				
Composite of stroke and non-CNS systemic embolism	241/7004 (3.4%)	188/6958 (2.7%)	0.79 (0.66, 0.96)	<0.001
Safety/on-treatment – Superiority				
- Composite of stroke and non-CNS systemic embolism	243/7082 (3.5%)	189/7061 (2.7%)	0.79 (0.65, 0.96)	0.014
- Composite of stroke, non-CNS embolism, and vascular death	410/7082 (5.8%)	346/7061 (4.9%)	0.86 (0.74, 0.99)	0.033
- Composite of stroke, non-CNS embolism, MI, and vascular death	519/7082 (7.3%)	433/7061 (6.1%)	0.85 (0.74, 0.96)	0.010
- All cause mortality	250/7082 (3.5%)	208/7061 (2.9%)	0.85 (0.70, 1,02)	0.072
ITT/regardless of treatment exposure – Superiority				
- All cause mortality	667/7090 (9.4%)	621/7081 (8.8%)	0.93 (0.84, 1.04)	0.204

(Source: Clinical Study Report: Study ROCKET-AF; Table 25, page 132)

The sponsor performed several sensitivity analyses assessing the robustness of the results.

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Kaplan-Meier Curve: Figure 3 captures the Kaplan-Meier curves for the two treatment groups based on the per-protocol analysis set excluding site 042012. The curves showed a separation between the treatment groups from after about one month to the end of the study.

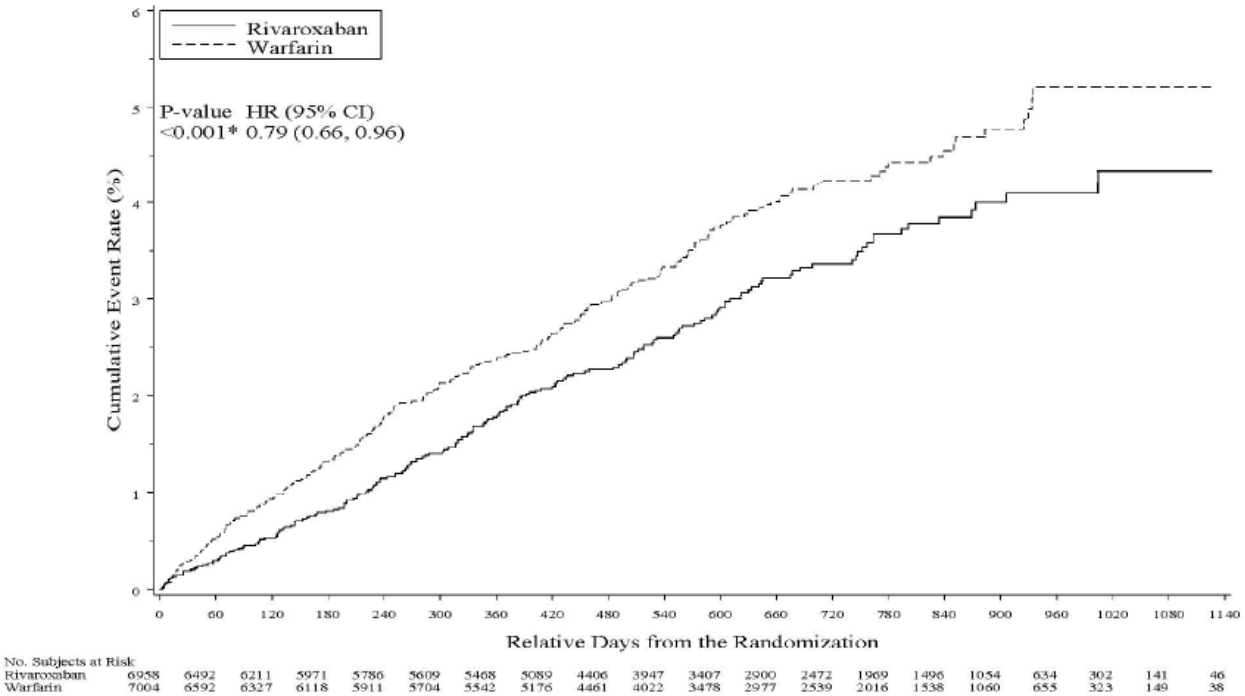

Figure 3. ROCKET-AF: Kaplan-Meier curves for the time from randomization to the first occurrence of the primary efficacy endpoint (adjudicated by CEC) while on treatment (up to last dose + 2 days)
(Source: Clinical Study Report: Study ROCKET-AF; Figure 9, page 133)

3.2.4.2 Study ROCKET-AF: Reviewer's results

Table 6 summarizes various sensitivity analyses for the primary efficacy endpoint for various analysis sets and various censoring dates. The largest upper bound of the 95% confidence interval was 1.08, far below the 1.38 non-inferiority margin.

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Table 6. ROCKET-AF: Reviewer's non-inferiority sensitivity analyses on the composite of stroke and non-CNS systemic embolism

Analysis set	Epoch	Censor at	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)	P value[#]
Per protocol[1] (out.hypo11)	Randomization to first primary efficacy endpoint	last dose + 2 days	241/7004 (3.4%)	188/6958 (2.7%)	0.79 (0.66, 0.96)	0.018
Per protocol[2] (out.hypo12)	Randomization to first primary efficacy endpoint	last dose + 2 days	242/7046 (3.4%)	190/7008 (2.7%)	0.80 (0.66, 0.97)	0.020
ITT[1] (out.hypo13)	Randomization to first primary efficacy endpoint	last dose + 2 days	243/7090 (3.4%)	189/7081 (2.7%)	0.79 (0.65, 0.95)	0.014
ITT[2] (out.hypo15)	Randomization to first primary efficacy endpoint	last dose + 2 days	244/7133 (3.4%)	191/7131 (2.7%)	0.79 (0.66, 0.96)	0.017
Per protocol[1] (out.hypo16)	Randomization to first primary efficacy endpoint	last dose + 7 days	253/7004 (3.6%)	219/6958 (3.1%)	0.88 (0.74, 1.06)	0.170
ITT[1] (out.hypo17)	Randomization to first primary efficacy endpoint	last dose + 7 days	255/7090 (3.6%)	220/7081 (3.1%)	0.88 (0.73, 1.05)	0.147
Per protocol[1] (out.hypo18)	Randomization to first primary efficacy endpoint	last dose + 14 days	269/7004 (3.8%)	233/6958 (3.3%)	0.88 (0.74, 1.05)	0.158
ITT[1] (out.hypo19)	Randomization to first primary efficacy endpoint	last dose + 14 days	271/7090 (3.8%)	235/7081 (3.3%)	0.88 (0.74, 1.05)	0.149
Per protocol[1] (out.hypo110)	Randomization to first primary efficacy endpoint	last dose + 30 days	279/7004 (4.0%)	247/6958 (3.5%)	0.90 (0.76, 1.07)	0.229
ITT[1] (out.hypo111)	Randomization to first primary efficacy endpoint	last dose + 30 days	281/7090 (4.0%)	251/7081 (3.%)	0.91 (0.76, 1.07)	0.251
Per protocol[1] (out.hypo117)	From randomization up to follow up visit	Follow up visit	283/7004 (4.0%)	252/6958 (3.6%)	0.90 (0.76, 1.07)	0.244
ITT[1] (out.hypo114)	From randomization up to follow up visit	Follow up visit	285/7090 (4.0%)	257/7081 (3.6%)	0.91 (0.77, 1.08)	0.285
Per protocol[1] (out.hypo118)	From randomization up to the notification of site date	Site notification	303/7004 (4.3%)	263/6958 (3.8%)	0.87 (0.74, 1.03)	0.101
ITT[1] (out.hypo115)	From randomization up to the notification of site date	Site notification	306/7090 (4.3%)	269/7081 (3.8%)	0.88 (0.74, 1.03)	0.116
Per protocol[1] (out.hypo119)	From randomization up to reference end date[**]	Reference end date	317/7004 (4.5%)	285/6958 (4.1%)	0.90 (0.77, 1.06)	0.205
ITT[1] (out.hypo116)	From randomization up to reference end date[**]	Reference end date	320/7090 (4.5%)	293/7081 (4.1%)	0.91 (0.78, 1.07)	0.263

(Source (in order of analyses): Clinical Study Report: Study ROCKET-AF;
Table 26 (page 136),
Attachment 6.1 (page 818),
Reviewer's results,
Reviewer's results,
Table 28 (page140),
Reviewer's results,
Table 28 (page 140),
Reviewer's results,
Table 28 (page 140),
Reviewer's results,
Reviewer's results,
Table 28 (page 140),
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Table 28 (page 140),
Reviewer's results,
Table 28 (page 140))

[1] Excluding site 042012 due to non-compliance

[2] Including site 042012

[**] Reference end date is the last date of all study-related visits (scheduled and unscheduled)

[#] Log-rank p-value for H_0: HR = 1 (superior)

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Proportional hazard assumption: The Cox model relies on the proportional hazard assumption. To examine this assumption, a log(-log (survival)) curve was produced. Figure 4 plots the log(-log(survival (month))) versus log(month). The proportional hazard assumption would be reasonable in the case where the two curves are parallel. Figure 4 suggests that the two lines were not parallel. They appear to be farthest apart around month 6 (log 6≈1.8) and then seem to get closer together for later time points. The proportional hazard assumption appeared violated over all. Thus, the hazard ratio seen in Table 4 can be interpreted as an average of the hazard ratios across time. Despite the possible violation of the proportional hazard assumption, p-values from the likelihood ratio test (p 0.018), the score test (p 0.018), and the Wald test (p 0.018) were consistent with the log-rank test p-value (p 0.018).

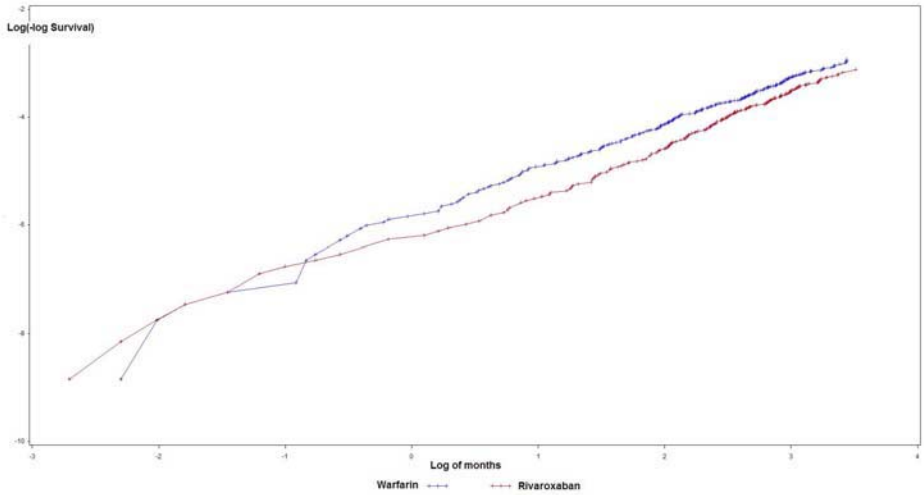

Figure 4. ROCKET-AF: Log(-Log(Survival)) curve for the primary efficacy endpoint

Another way of looking at the proportional hazards assumption is to estimate the hazard functions directly. I split the time into intervals of 6 months. The last time interval is larger than 6 months and includes all events after month 24. I counted the number of events in each group in each time window and the number of patient years of exposure in that time window. The estimated hazard function for each time period within each treatment arm is {# events}/{# patient years of exposure}. Events are counted up to last study dose plus day 2 as in the primary analysis. Similarly, I estimated the hazard function on each day (similar to above, but time period is one day). I then used locally polynomial regression to fit a curve through those estimates for each day. It weights each day according to the amount of information and then combines the information from nearby days to get a better estimate of the hazard function each day. The points in Figure 5 are the points from the estimated hazard functions over 6 month time periods. The smooth curves are

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from the estimated hazard functions for each day. The figure suggests that the risk goes down over time (in both groups) and that there is a larger difference between groups in the hazard functions in the earlier time points.

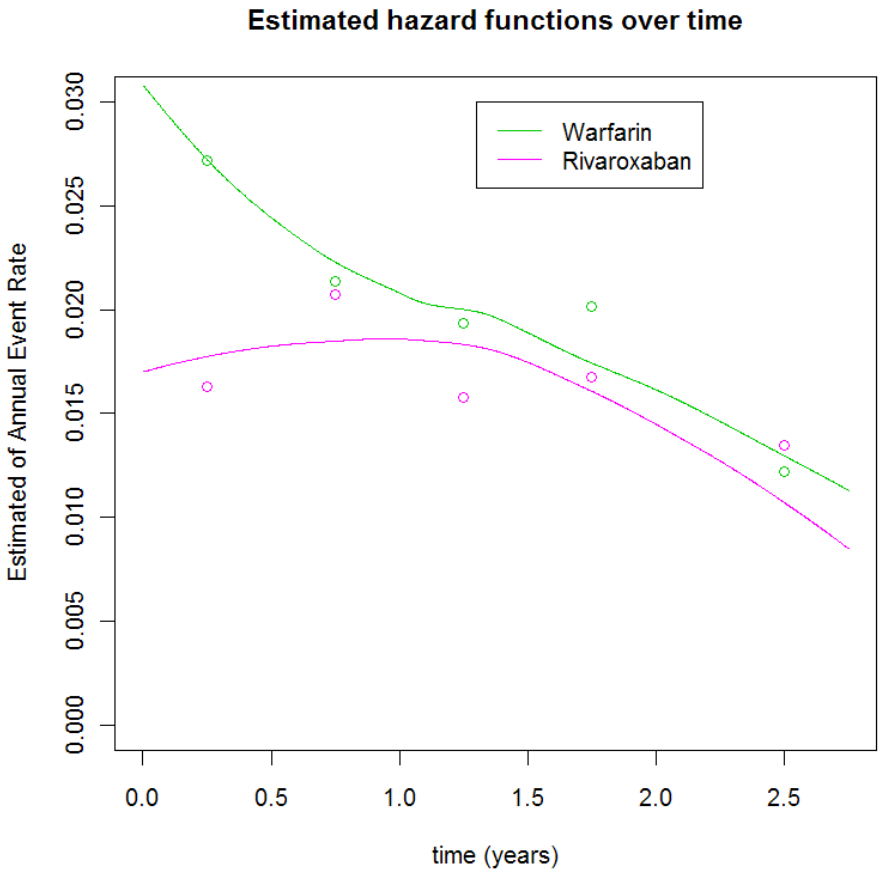

Figure 5. Estimated hazard functions for the primary efficacy endpoint

Distribution of time to censoring: The distribution of the time to censoring for the primary efficacy endpoint appeared balanced between warfarin and rivaroxaban, as shown in Table 7.

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Table 7. ROCKET-AF: Distribution of time to censoring for the primary efficacy endpoint (safety sample, excluding site 042012)

		Warfarin N 7082	Rivaroxaban N 7061
Primary events		243	189
Time to censoring (days)	Max	1265	1265
	99th %tile	1117	1120
	95th	1015	1011
	90th	957	956
	75th	814	813
	50th	612	598
	Mean	592.3	582.3
	25th	421	409.5
	10th	141	113
	5th	51	37
	1st	9	7
	Min	0	2

(Source: Reviewer's results)

Time in Therapeutic Range The efficacy of warfarin is highly dependent on 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 (excluding time periods where the subject was not taking warfarin). For each site, the site level TTR is the average of the TTR for the subjects in that site. Figure 6 shows the distribution of TTR on the subject level and on the site level. The median TTR for all subjects was 58 and the median TTR for all sites was 59.

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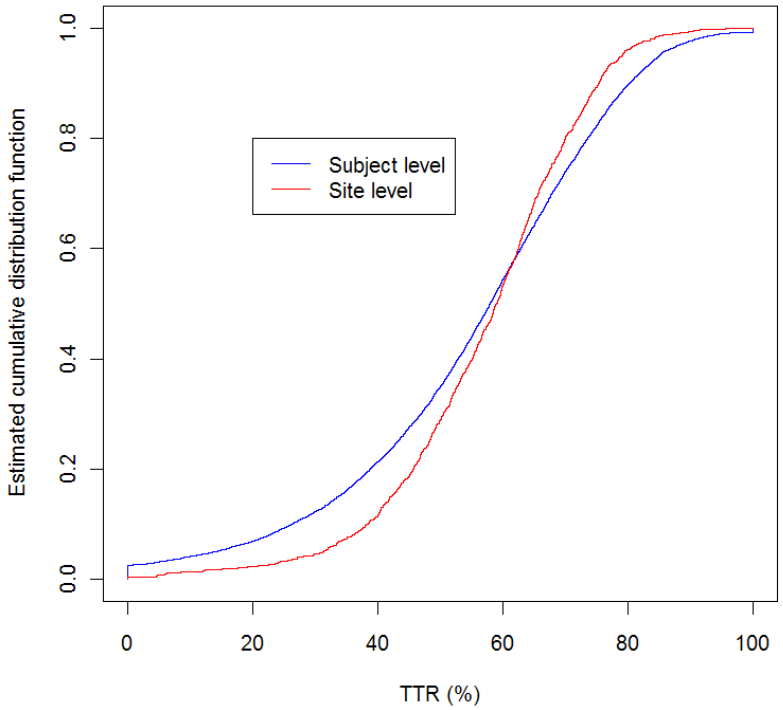

Figure 6. Distribution of TTR across subjects and sites

Figure 7 shows the estimated hazard ratio for sites with TTR above different cutoff values. The x-axis shows what percent of the total subjects are excluded (from sites with TTR lower than the cutoff value). The upper and lower curves are the upper and lower bound of the pointwise 95% confidence intervals. The curves start using all the data, which is the same point estimate and confidence interval as for the primary endpoint, i.e. 0.79 and (0.66, 0.96). The curves at the far right side of the figure are based on a small amount of data (less than 20% of the subjects), but the curves appear to show the point estimate is closer to 1, and in some cases larger than 1 when including sites with high TTR (e.g. greater than 70%).

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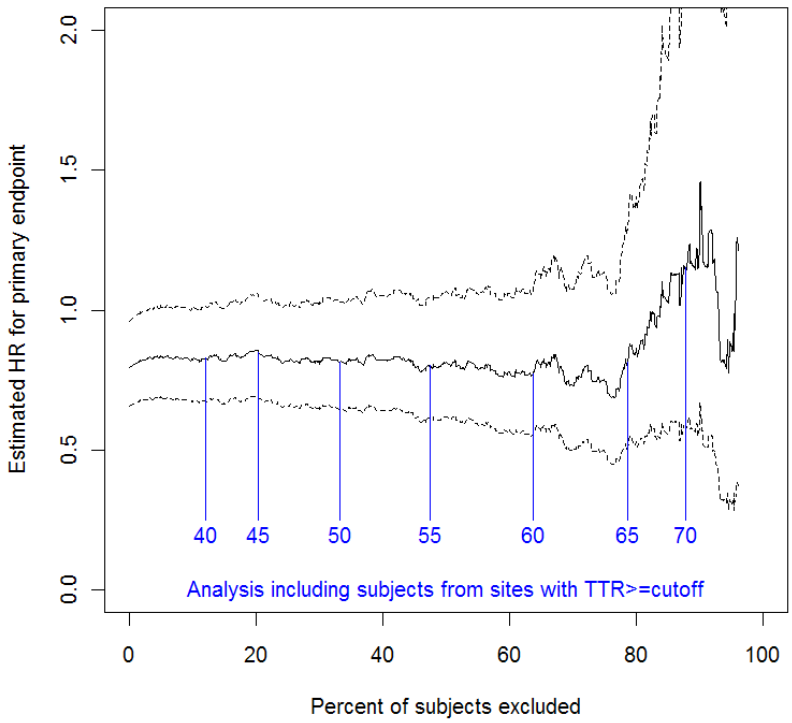

Figure 7. Estimated hazard ratio for primary endpoint among sites with TTR above different cutoff levels.

3.3 Evaluation of Safety

A safety evaluation was not performed. Please refer to the clinical review for the safety evaluation and report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Study ROCKET-AF

4.1.1.1 Gender

Male patients in this study accounted for about 60% of the sample. Table 8 summarizes efficacy results by sex for the primary and key secondary efficacy measures. It appears that the efficacy was consistent for both sexes.

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Table 8. ROCKET-AF: Reviewer's efficacy results by sex

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)
Male			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	135/4236 (3.2%)	102/4201 (2.4%)	0.78 (0.61, 1.01)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	136/4283 (3.2%)	103/4270 (2.4%)	0.78 (0.60, 1.01)
- Composite of stroke, non-CNS embolism, and vascular death	265/4283 (6.2%)	221/4270 (5.2%)	0.86 (0.72, 1.03)
- Composite of stroke, non-CNS embolism, MI, and vascular death	341/4283 (8.0%)	282/4270 (6.6%)	0.85 (0.73, 1.00)
Female			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	106/2768 (3.8%)	86/2757 (3.1%)	0.80 (0.60, 1.07)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	107/2799 (3.8%)	86/2791 (3.1%)	0.80 (0.60, 1.06)
- Composite of stroke, non-CNS embolism, and vascular death	145/2799 (5.2%)	125/2791 (4.5%)	0.85 (0.67, 1.08)
- Composite of stroke, non-CNS embolism, MI, and vascular death	178/2799 (6.4%)	151/2791 (5.4%)	0.84 (0.68, 1.04)

(Source: FDA analysis)

4.1.1.2 Race

White patients accounted for about 83% of the sample. For this analysis, race is dichotomized into white versus non-white (other races). Table 9 summarizes the efficacy results by race. Numerical improvements were observed in both white and non-white patients.

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Table 9. ROCKET-AF: Reviewer's efficacy results by race

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)
White			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	192/5846 (3.3%)	151/5772 (2.6%)	0.81 (0.65, 1.00)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	194/5909 (3.3%)	151/5856 (2.6%)	0.80 (0.64, 0.99)
- Composite of stroke, non-CNS embolism, and vascular death	335/5909 (5.7%)	274/5856 (4.7%)	0.84 (0.71, 0.98)
- Composite of stroke, non-CNS embolism, MI, and vascular death	429/5909 (7.3%)	344/5856 (5.9%)	0.82 (0.71, 0.94)
Others			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	49/1158 (4.2%)	37/1186 (3.1%)	0.73 (0.48, 1.12)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	49/1173 (4.2%)	38/1205 (3.2%)	0.75 (0.49, 1.15)
- Composite of stroke, non-CNS embolism, and vascular death	75/1173 (6.4%)	72/1205 (6.0%)	0.93 (0.67, 1.29)
- Composite of stroke, non-CNS embolism, MI, and vascular death	90/1173 (7.7%)	89/1205 (7.4%)	0.96 (0.72, 1.29)

(Source: FDA analysis)

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4.1.1.3 Age

Age was grouped into less than 65 years, 65 to 75 years, and greater than 76 years. Table 10 summarizes the efficacy results by age. It appears that rivaroxaban was not efficacious against warfarin for patients < 65 years of age.

Table 10. ROCKET-AF: Reviewer's efficacy results by age

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)
Age < 65 years			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	41/1614 (2.5%)	43/1617 (2.7%)	1.06 (0.69, 1.63)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	42/1636 (2.6%)	43/1642 (2.6%)	1.04 (0.68, 1.58)
- Composite of stroke, non-CNS embolism, and vascular death	81/1636 (5.0%)	75/1642 (4.6%)	0.94 (0.68, 1.28)
- Composite of stroke, non-CNS embolism, MI, and vascular death	99/1636 (6.1%)	91/1642 (5.5%)	0.93 (0.70, 1.24)
Age in [65 – 75] years			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	98/2742 (3.6%)	76/2729 (2.8%)	0.79 (0.58, 1.06)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	98/2768 (3.5%)	77/2767 (2.8%)	0.79 (0.59, 1.07)
- Composite of stroke, non-CNS embolism, and vascular death	161/2768 (5.8%)	140/2767 (5.1%)	0.88 (0.70, 1.10)
- Composite of stroke, non-CNS embolism, MI, and vascular death	199/2768 (7.2%)	173/2767 (6.3%)	0.88 (0.71, 1.07)
Age > 76 years			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	102/2648 (3.9%)	69/2612 (2.6%)	0.69 (0.51, 0.93)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	103/2678 (3.8%)	69/2652 (2.6%)	0.68 (0.50, 0.92)
- Composite of stroke, non-CNS embolism, and vascular death	168/2678 (6.3%)	131/2652 (4.9%)	0.79 (0.63, 0.99)
- Composite of stroke, non-CNS embolism, MI, and vascular death	221/2678 (8.3%)	169/2652 (6.4%)	0.78 (0.63, 0.95)

(Source: FDA analysis)

4.1.1.4 Geographical Region

Table 11 summarizes the efficacy by U.S. versus non-U.S. Greater treatment effects were observed in U.S. patients versus non-U.S. patients.

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Table 11. ROCKET-AF: Reviewer's efficacy results by U.S. versus non-U.S.

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)
United States (U.S.) sites			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	29/956 (3.0%)	15/950 (1.6%)	0.54 (0.29, 1.01)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	29/964 (3.0%)	15/962 (1.6%)	0.54 (0.29, 1.01)
- Composite of stroke, non-CNS embolism, and vascular death	46/964 (4.8%)	30/962 (3.1%)	0.68 (0.43, 1.08)
- Composite of stroke, non-CNS embolism, MI, and vascular death	70/964 (7.3%)	50/962 (5.2%)	0.74 (0.51, 1.06)
Non-U.S. sites			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	212/6048 (3.5%)	173/6008 (2.9%)	0.83 (0.68, 1.01)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	214/6118 (3.5%)	174/6099 (2.9%)	0.82 (0.67, 1.00)
- Composite of stroke, non-CNS embolism, and vascular death	364/6118 (5.9%)	316/6099 (5.2%)	0.88 (0.75, 1.02)
- Composite of stroke, non-CNS embolism, MI, and vascular death	449/6118 (7.3%)	383/6099 (6.3%)	0.86 (0.75, 0.99)

(Source: FDA analysis)

Figure 8 presents the primary efficacy and principal safety measures by region and country. The primary efficacy measure is the composite of CEC-adjudicated stroke and non-CNS embolism. The principal safety measure is the composite of all CEC-adjudicated major and non-major clinically relevant bleeding events. In the figure, the average percentage of INR in [2-3] range as well as the average percentages of INR higher and lower than the [2-3] range are also presented for warfarin patients. The averages are over all patients in a particular group. The overall time in therapeutic range was 48.6% and for U.S. patients was 56%. The efficacy hazard ratio for the U.S. patients was 0.54 and the principal safety hazard ratio was 1.28.

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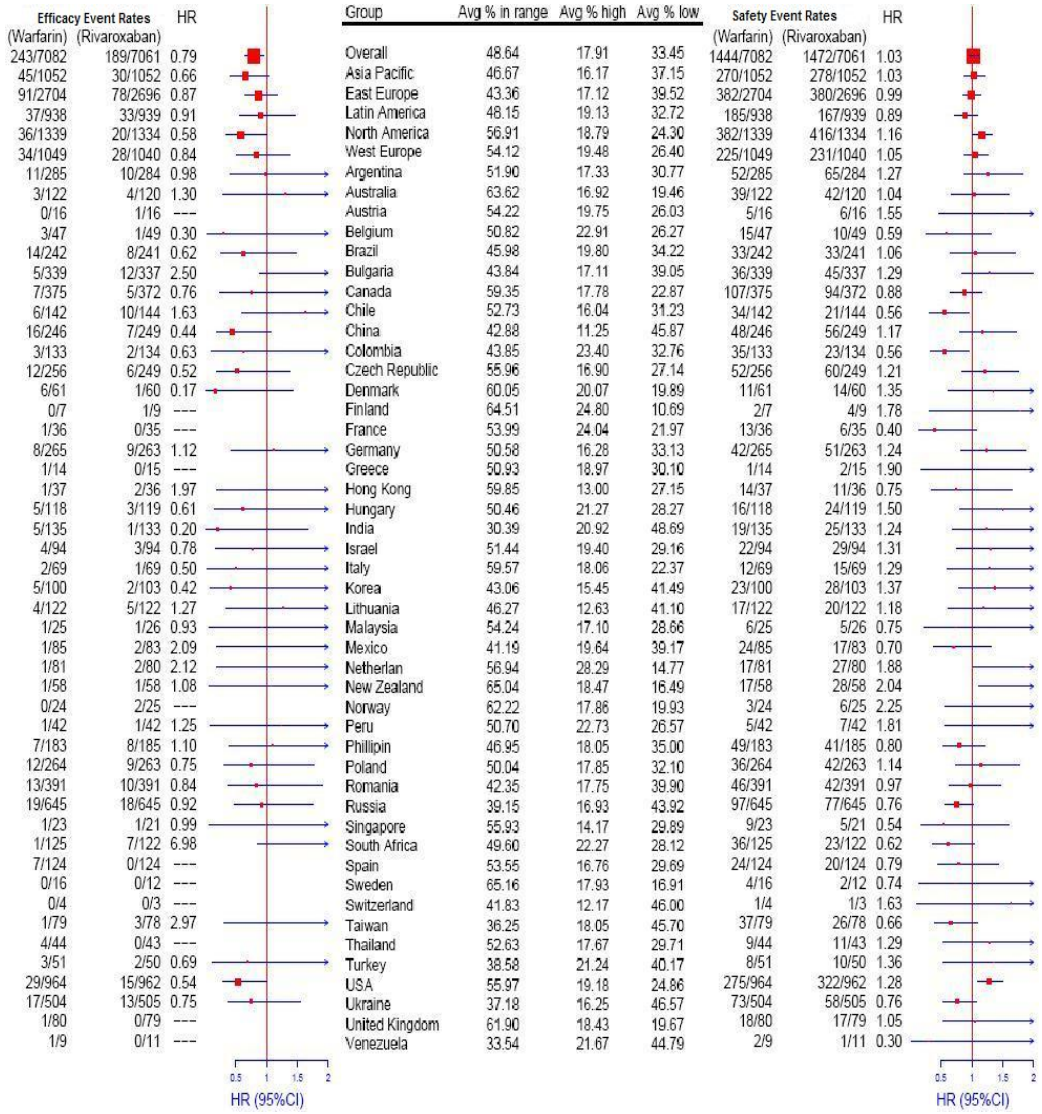

Figure 8. ROCKET-AF: Efficacy and Safety Results by regions/countries

* Efficacy is based on the primary efficacy endpoint (composite of strokes and non CNS embolism, CEC adjudicated), from randomization to the first primary efficacy endpoint (or last dose + 2 days) in the safety analysis set (excluding site 042012)

* Safety is based on the principal safety endpoint (composite of all major and non major clinically relevant bleeding events, CEC adjudicated), from first dose to first occurrence of principal safety endpoint (or last dose + 2 days), in the safety analysis set (excluding site 042012).

* Avg % in range, Avg % high, and Avg % low are the average percentages of INR in, higher, and lower than [2 3] INR range for patients in warfarin arm.

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4.2 Other Special/Subgroup Populations

4.2.1 Study ROCKET-AF

4.2.1.1 Baseline CHADS2 score

Table 12. ROCKET-AF: Reviewer's **efficacy results by baseline CHADS2 score**

Event	Warfarin # of event/N	Rivaroxaban # of event/N	Hazard ratio (95% CI)
CHADS2 in (0, 1, 2)			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	24/924 (2.6%)	20/900 (2.2%)	0.89 (0.49, 1.62)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	24/933 (2.6%)	21/923 (2.3%)	0.92 (0.51, 1.65)
- Composite of stroke, non-CNS embolism, and vascular death			
- Composite of stroke, non-CNS embolism, MI, and vascular death			
CHADS2 in (3, 4)			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	174/5060 (3.4%)	127/5030 (2.5%)	0.74 (0.59, 0,93)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	175/5119 (3.4%)	127/5098 (2.5%)	0.73 (0.58, 0.92)
- Composite of stroke, non-CNS embolism, and vascular death			
- Composite of stroke, non-CNS embolism, MI, and vascular death			
CHADS2 in (5, 6)			
Per protocol – Non-inferiority			
Composite of stroke and non-CNS systemic embolism	43/1020 (4.2%)	41/1028 (4.0%)	0.96 (0.63, 1.48)
Safety/on-treatment – Superiority			
- Composite of stroke and non-CNS systemic embolism	44/1030 (4.3%)	41/1040 (3.9%)	0.94 (0.61, 1.44)
- Composite of stroke, non-CNS embolism, and vascular death			
- Composite of stroke, non-CNS embolism, MI, and vascular death			

(Source: FDA analysis)

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

One of the issues in any active control study with a non-inferiority design is whether the active control was used correctly. If it was not used correctly, the constancy assumption may be in doubt. It need not have been used optimally, but at a minimum should be used in a way comparably to how it was used in the historical studies used as the basis of the non-inferiority margin. In this case, the historical studies (comparing warfarin to placebo) are fairly old and it is difficult to say whether warfarin was used in this study as well as it was in those studies. Other issues that might affect the constancy assumption include the populations studied and the background therapy. It is difficult to compare those factors in the current study to the historical studies. Some statistical analyses can help with looking into these issues, but ultimately it is up to the clinical reviewers to decide.

Another important issue for active control noninferiority studies is the definition of the analysis population. Some would say that for the noninferiority analysis, the on-treatment or per-protocol population may be the more important analysis, but others would say the ITT is still important. If there were big difference in results for the two, it would be necessary to look into the reasons for that. However, there was not a big difference in this application as far as testing noninferiority is concerned. For testing superiority, the ITT analysis is preferred.

5.2 Conclusions and Recommendations

Rivaroxaban was non-inferior to warfarin, as warfarin was used in the study, on the primary endpoint. When analyzing the data up to 2 days after last dose, the confidence interval for the hazard ratio is entirely below 1 (point estimate 0.79, 95% CI (0.66, 0.96)). There is a question about whether warfarin was used optimally in the study (the median TTR across sites was 59). For superiority, the ITT analysis is preferred. In the ITT analysis, the confidence interval does not exclude 1 (point estimate 0.91, 95% CI (0.77, 1.08)). Rivaroxaban was not superior on all cause mortality by either the on-treatment or ITT analysis.

Reference ID: 2979595

CHECK LIST

Number of Pivotal Studies: 1.

Trial Specification

Specify for each trial: ROCKET-AF

Protocol Number (s): 39039039AFL3001

Protocol Title (optional): A prospective, randomized, double-blind, double-dummy, parallel-group, multicenter, event-driven, non-inferiority study comparing the efficacy and safety of once daily oral rivaroxaban (BAY 59-7939) with adjusted-dose oral warfarin for the prevention of stroke and non-central nervous system systemic embolism in subjects with non-valvular atrial fibrillation.

Phase: 3

Control: Active Control

Blinding: Double-Blind

Number of Centers: 1172

Region(s) (Country): 45 countries

- Asia Pacific: Australia, China, Hong Kong, India, Korea, Malaysia, New Zealand, Philippines, Singapore, Taiwan, Thailand
- East Europe: Bulgaria, Czech Republic, Greece, Hungary, Lithuania, Poland, Romania, Russia, Turkey, Ukraine
- Latin America: Argentina, Brazil, Chile, Colombia, Mexico, Panama, Peru, Venezuela
- North America: Canada, United States
- West Europe: Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, South Africa, Spain, Sweden, Switzerland, United Kingdom

Duration: Event-driven trial, initiated on Dec 18, 2006 and completed on Sept 7, 2010

Treatment Arms: Rivaroxaban

Treatment Schedule: 20 mg orally once daily or warfarin (orally once daily, titrated to the INR of 2.5 [range 2.0 to 3.0, inclusive])

Randomization: Yes

Ratio: 1:1

Method of Randomization: stratification

If stratified, then the Stratification Factors: country, prior VKA use, and history of prior stroke, TIA, or non-CNS systemic embolism

Primary Endpoint: Time from randomization to the first occurrence of stroke or non-CNS systemic embolism

Primary Analysis Population: Per-protocol

Statistical Design: Non-Inferiority/Superiority

If non-inferiority or equivalence: Was the non-inferiority margin calculated based on historical data?

Margin = 1.38

%Retained = 50%

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Adaptive Design: No

Primary Statistical Methodology: Cox proportional hazard model

Interim Analysis: Yes (mainly for futility consideration)

If yes:

No. of Times: 1 (at midpoint)

Method: Cox model

α Adjustment: Yes

α Spending Function: Haybittle-Peto

DSMB: Yes

Sample Size: 405 primary efficacy events (14,000 randomized patients)

Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes/No

Statistic = log-rank

Power= 95%

Δ= to rule out the non-inferiority margin of 1.46

α = 0.05

- Was there an Alternative Analysis in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation: Several sensitivity analyses are planned
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No.
- Were the Covariates pre-specified in the protocol? No.
- Did the Applicant perform Sensitivity Analyses? Yes.
- How were the Missing Data handled? Subjects were censored when lost to followup or 2 days after last study dose administered. Censoring was assumed non-informative in the log-rank test.
- Was there a Multiplicity involved? Yes

  If yes,

  Multiple Arms (Yes/No)? No.

  Multiple Endpoints (Yes/No)? Yes.

  Which method was used to control for type I error? Endpoints were tested sequentially in a pre-specified order.
- Multiple Secondary Endpoints: Are they being included in the label? If yes, method to control for type 1 error: Yes. Sequential testing.

Were Subgroup Analyses Performed (Yes/No)? Yes.

- Were there any Discrepancies between the protocol/statistical analysis plan vs. the study report? No.
- Overall, was the study positive (Yes/No)? Yes.

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/s/

JOHN P LAWRENCE
07/28/2011

HSIEN MING J J HUNG
07/28/2011
concur

Statistical Review and Evaluation
CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 202439
Drug name: BAY 59-7939 (Rivaroxaban)	
Indication(s): Anticoagulant	
Applicant:	
Documents Reviewed:	Electronic submission Dated 2010-12-30 Electronically submitted dataset Dated 2010-12-30
Review Priority:	Medium
Biometrics Division:	Division of Biometrics 6
Statistical Reviewer:	Matthew Jackson, PhD
Concurring Reviewer:	Karl Lin, PhD
Medical Division: DCRP	
Reviewing Pharmacologist:	Patricia Harlow, PhD
Project Manager:	
Keywords:	Animal Mouse Rat Carcinogenicity

Reference ID: 2944884

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0.1 Background

In this submission the sponsor included reports of two animal carcinogenicity studies; one in mice and one in rats. These studies were intended to assess the carcinogenic potential of Rivaroxaban when administered by gavage, once daily at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist, Patricia Harlow.

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.

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Chapter 1

Mouse study

1.1 Overview

Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups and one vehicle control group. Each of these four groups was randomly assigned sixty animals, for a total of two hundred and forty animals of each sex. The animals used were Crl:CD-1(ICR)BR mice.

The vehicle for the test was ethanol/Solutol HS 15/tap water in a 10:40:50 ratio. It is not clear from the report whether this was a solution or a mixture. The quantity of vehicle administered was 10 mL/kg per day. The test item was administered as a suspension in the vehicle.

The low, mid, and high dose animals of both sexes were treated with daily dose levels of 10, 20, and 60 mg/kg respectively.

Animals were inspected for morbidity and mortality twice a day (once a day on weekends and public holidays), and detailed clinical observations were performed weekly. Animals that were euthanized *in extremis* or sacrificed at the scheduled end of the study underwent necroscopy, and their organs were subjected to gross pathological examination. Animals found dead were necroscopsied soon as possible.

1.2 Data analysis

1.2.1 Sponsor's analyses

Survival analysis

The sponsor reports the number of mice to have died before week 104. The sponsor claims that these deaths are largely attributable to "severe amyloidosis and malignant lymphoma", which are described as "well-known systemic diseases in aging mice". The sponsor also concludes that "A treatment-related effect on the survival (sic.) is not inferred from these data". However, it appears that no time-to-event data were considered when assessing the animals' mortality, and that no formal survival analysis has been conducted.

Tumor data analysis

The organs were planned to be examined in all animals are listed in table 1.1:

Each type of tumor found in one of the organs listed in table 1.1 was considered as a separate endpoint. For each such endpoint, either four or five statistical tests were conducted: Fisher's exact test was used to test incidence between each of the three treated groups and the control group, and a "conventional Peto test" was used to test for a dose response relationship. In addition, when the trend test was found to have generated a significant result, an "exact stratified linear rank test" (see

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Table 1.1: Sponsor's list of primary endpoints

Abnormalities	Adrenal glands	Aorta
Brain (cerebrum)	Brain (cerebellum)	Brain (brain stem)
Cecum	Clitoral gland	Colon
Duodenum	Epididymides	Esophagus
Eyes	Exorbital lacrimal glands	Femur (with joint)
Gallbladder	Harderian glands	Heart
Ileum	Jejunum	Kidneys
Larynx	Liver	Lungs
Lymph nodes, mandibular	Lymph nodes, mesenteric	Nasal cavity/nasopharynx
Optic nerves	Ovaries	Oviducts
Pancreas	Pituitary gland	Preputial gland
Prostate	Rectum	Salivary glands (parotid)
Salivary gland (submandibular)	Salivary gland (sublingual)	Sciatic nerve
Seminal vesicles	Skeletal muscle (thigh)	Skin (mammary region)
Spinal chord (cervical)	Spinal chord (thoracic)	Spinal chord (lumbar)
Spleen	Sternum with bone marrow	stomach
Testes	Thymus	Thyroid glands (with parathyroids)
Tongue	Trachea	Ureters
Urinary bladder	Uterus (with cervix)	Vagina
Zymbal's glands		

Ali [1] or Mehta et. al. [5][1]) was used to confirm the result, the thinking being that a conventional Peto test, being an asymptotic method, was insufficiently conservative. Why the sponsor did not use only the putatively more conservative exact test of trend is not clear. In addition, the combined endpoint of hepatocellular tumors was tested for a significant trend, (using both the asymptotic and exact methods). However, the pairwise tests against control were not applied to this endpoint.

The above trend tests, use Peto's method with the *ad hoc* run procedure (see Peto [8]). However, it should also be noted that the test used for pairwise comparisons, Fisher's exact test, is not a survival adjusted method.

Tumor types for which the sponsor reported at least one test with a p-value below 0.05 are presented in table 1.2. It is important to note that the p-values for the test of trend are tested against the null hypothesis of no dose dependence. In the case of hepatocellular tumors in female mice, the observed trend was negative. The p-value is therefore a measurement of discordance of the observed data compared with the null hypothesis of no *protective* effect (and not against the null hypothesis of no tumorigenic effect).

Table 1.2: p-values for tumor types reported as significant by the sponsor

Organ/tissue	Tumor	Sex	p-value				
			Trend tests		Pairwise comparison with control		
			Conventional Peto	Exact Peto	Low Dose	Mid Dose	High Dose
Single tumor types							
Liver	Hepatocellular Carcinoma	Female	0.1093	0.2005	0.7605	.	.
		Male	0.0465	0.0562	0.3559	0.0812	0.0771
Ovaries	Cystadenoma	Female	0.0323	0.0581	.	0.5000	0.2478
Combined tumor types							
Hepatocellular tumors		Female	0.1094				
		Male	0.0076	0.0089			

[1]Note that the pathology report for the mouse study did not include a references section, and while this citation was included in the references section in the pathology report for the rat study, the citation was incomplete, missing the article title and part of the journal name.

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Hepatocellular carcinomas, and hepatocellular tumors The sponsor argues that the p-value for the test of trend for hepatocellular carcinomas is not significant after adjusting for multiplicity (see table 1.5). In the case of hepatocellular adenomas and carcinomas combined, the sponsor claims again (correctly) that the p-value of 0.0089 does not meet the threshold for statistical significance in common tumors, and that precursor lesions are not found to be subject to a dose related response.

More worthy of concern is the sponsor's suggestion that "liver cell neoplasms often display a large spontaneous variability among control and dosed groups within the same study and without any relation to treatment". If this claim is true, it would follow that this study, and others administered by the same sponsor, cannot be held to have been properly controlled - the implication being that either the randomization process had broken down or that some environmental conditions affected some dose groups more than others.[2] In either case, a pattern of results such as the sponsor describes (on page 1207 of the report) would raise serious questions about the sponsor's ability to administer animal carcinogenicity studies. Fortunately, it seems likely that no such pattern exists, and the sponsor is simply reporting anecdotes here.

Ovarian cystadenomas The sponsor concluded that since ovarian cystadenomas are common, the observed p-values do not constitute statistical significance after making an adjustment for multiplicity. Additionally, the sponsor claims that there is no indication of a dose related increase in incidence of other ovarian tumors or lesions, and also that the observed incidence rates in the high dose groups are consistent with historical controls. The sponsor concludes that "a relation to the test compound is not assumed".

1.2.2 Reviewer's analysis

To verify the sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in theses analyses were provided by the sponsor electronically.

Survival Analysis

Figures 1.1 and 1.2 show the Kaplan-Meier plots for male and female mice respectively. The results of log-rank tests of survival are presented in table 1.3. Intercurrent mortality data are presented in table 1.4. The plots show no sign of any dose related mortality, and the statistical tests indicate no significant results.

[2] While spontaneous variability among groups is understandable in a single study, a pattern of such variability across trials is a different matter entirely. It is precisely to prevent such patterns, and thereby ensure that the randomness in a study is well understood and accounted for, that the concept of the randomized controlled trial was developed.

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Figure 1.1: Survival plot for male mice

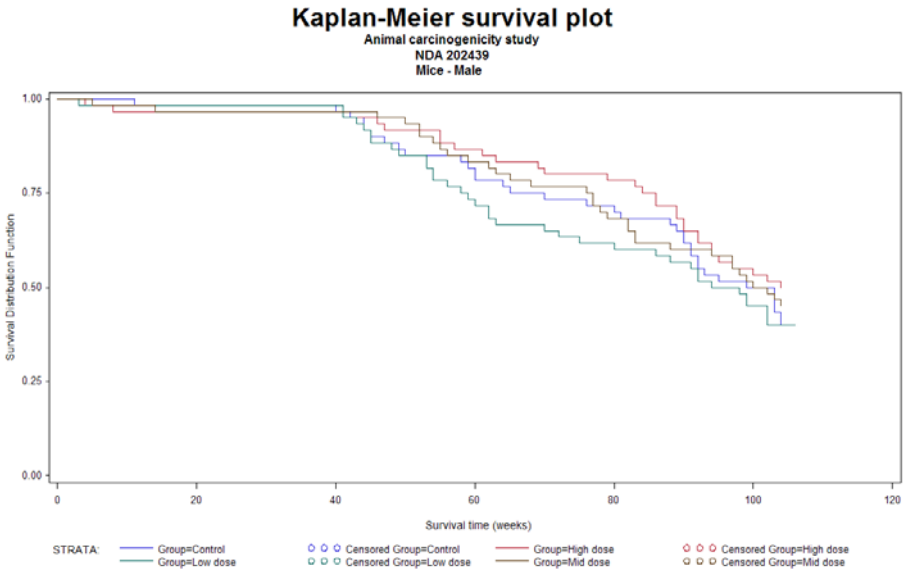

Figure 1.2: Survival plot for female mice

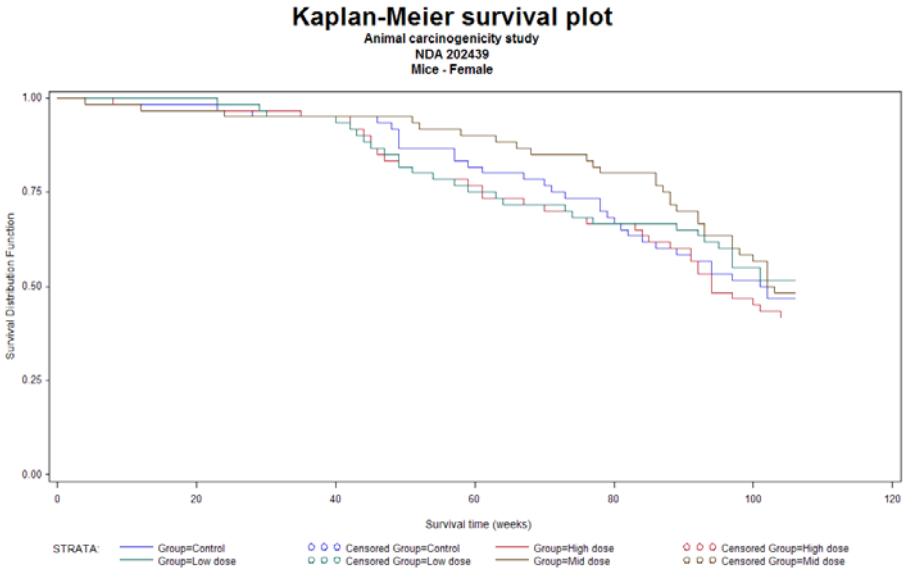

Table 1.3: Results of log-rank tests of survival — Mice

Species and Sex	Number of Groups	Test of homogeneity			Test of trend	
		χ^2 statistic	df	p-value	Two tailed p-value	One tailed p-value
Mice — Female	4	2.0120	3	0.5699	0.2873	0.1437
Mice — Male	4	1.8333	3	0.6077	0.2153	0.8923

Table 1.4: Survival rates at key times — mice

Species and Sex	Dose Group	Dose (mg per kg)	Number and percentage alive								
			Start	52 weeks	(%)	78 weeks	(%)	90 weeks	(%)	Termination	(%)
Mice — Female	Control	0	60	52	87%	44	73%	35	58%	28	47%
	Low dose	10	60	48	80%	40	67%	39	65%	31	52%
	Mid dose	20	60	56	93%	49	82%	42	70%	29	48%
	High dose	60	60	48	80%	40	67%	36	60%	26	43%
Mice — Male	Control	0	60	51	85%	43	72%	39	65%	26	43%
	Low dose	10	60	51	85%	37	62%	34	57%	24	40%
	Mid dose	20	60	56	93%	43	72%	36	60%	28	47%
	High dose	60	60	55	92%	48	80%	41	68%	31	52%

Tumor data analysis

Theoretical underpinnings The tumor data were analyzed for dose response relationships and pairwise comparisons of tumor incidence in each of the treated groups versus the vehicle control (placebo) 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[2] and developed in the paper of Bieler and Williams[3]. 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. The tumor rates and the p-values of the tested tumor types are listed Table 1.9.

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, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with one or two species.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman [7]. In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin [9] 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 we use the thresholds for significance presented in table 1.5.

Table 1.5: 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

Analysis of tumor data It appears from the data that two types of organ were considered. The first type, which shall be called *Primary* organ types, comprises those organs which were examined in the vast majority of animals. The second type, which shall be called "secondary", are those organs which were only examined in a small number of animals. In fact, the nature of the data standard is that organs are only reported when they are *not* examined, or when they are found to have been either tumorous or autolytic. It follows that an organ can only be discerned to be

primary when it is either tumorous or autolytic in at least one animal, but is not listed as being unexamined in too many animals.

The organs which can be concluded to be primary organs for the purposes of the mouse study are presented in table 1.6.

Table 1.6: Organs presumed to be primary in the mouse study

Female mice		
ADRENAL GLANDS	BRAIN	CECUM
DUODENUM	FEMUR	HARDERIAN GLANDS
JEJUNUM	LIVER	LUNGS
OVARIES	PITUITARY GLAND	SKIN
SPINAL CORD	SPLEEN	STOMACH
SUBMANDIBULAR GLAN	SYSTEMIC TUMORS	THYMUS
THYROID GLAND	URINARY BLADDER	UTERUS
VAGINA		

Male Mice		
ADRENAL GLANDS	BRAIN	CECUM
DUODENUM	EPIDIDYMIDES	FEMUR
HARDERIAN GLANDS	JEJUNUM	KIDNEYS
LIVER	LUNGS	NOSE
PITUITARY GLAND	SEMINAL VESICLES	SKIN
SPINAL CORD	SPLEEN	STOMACH
SUBMANDIBULAR GLAN	SYSTEMIC TUMORS	TESTES
THYMUS	THYROID GLAND	URINARY BLADDER

Organs are presumed not to be primary (i.e., secondary) when they are reported as having been unexamined in at least 60% of animals in each treatment arm. The list of secondary organs in the mouse study is presented in table 1.7.

Table 1.7: Organs presumed to be secondary in the mouse study

Both male and female mice		
BODY CAVITIES	BONE	PERIPHER. NERVE(S)
SKULLCAP	TEETH	

All tumor types reported found in primary organs were tested statistically. The results of the poly-3 tests of incidence and trend (for both sexes) are presented in table 1.9. Table 1.10 is excerpted from table 1.9, and consists only of those tumor types for which at least one test in at least one sex had a p-value below 0.05.

In addition, a number of combination endpoints were analyzed, primarily in response to the sponsor's practice of separating certain tumors depending on whether multiple masses were detected[3]. Note that some of these composites are redundant in the mouse study, but have been included to maximize ease of comparison with the rat study. The list of composite endpoints considered is presented as table 1.8. Table 1.11 displays the results of the analyses of composite endpoints. Note that for several of these endpoints, no mice at all were found to have developed the included tumors. These endpoints are:

[3]For example, the sponsor listed reported "Adenoma bronchiolo-alveolar" and "Adenoma bronchiolo-alveolar, multiple" as two separate endpoints. These endpoints were given different values of TUMORNAM in the dataset `tumor.xpt`, but had the same value of TUMORCOD. They are treated as separate endpoints in table 1.9, but are grouped in table 1.11.

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- Pheochromocytomas
- Keratoacanthomas
- Actrocytomas
- Mesotheliomas of the heart
- Mammary adenocarcinomas
- Mammary fibroadenomas
- Hemangiomas of the mesentheric lymph system
- Pancreatic adenomas
- Carcinoima pars distalis
- Clitoral squamous carcinomas and papilliomas

Table 1.8: Composite endpoints analyzed

Adrenal adenomas	Pheochromocytomas
Bronchiolo-alveolar carcinomas	Lymphomas
Systemic tumors	Dermal fibromas
Keratoacanthomas	Uterine stromal polyps
Hepatocellular tumors	Hemangiomas
Hemangiosarcomas	Astrocytomas
Mesotheliomas of the heart	Mammary adenocarcinomas
Mammary fibroadenomas	Thyroidal adenomas
Uterine adenocarcinomas	Hemangiosarcomas of the mesenteric lymph system
Pancreatic adenomas	Adenoma pars distalis
Carcinoma pars distalis	Clitoral squamous carcinomas and papilliomas
Leydig cell tumors	

Tumors in secondary organs have not been tested statistically, as it is unclear what the mechanism is by which they came to be found. Additionally, the numbers of animals analyzed are too small to make any meaningful statistical inferences. Count data for these tumors are presented in table 1.12.

Among the tests of the uncombined endpoints, the only test to generate a p-value below 0.05 is the test of trend for lymphoma — NOS. In this case the p-value of the test of trend is 0.0433. After making an adjustment for multiplicity, this result is not significant. Furthermore, none of the pairwise tests between the treated groups and the control group are significant, and there is no corresponding signal among the female mice. Additionally, when all lymphomas are grouped together (see table 1.11), there is no evidence of a statistically significant dose related increase in incidence. It follows that the tests for lymphoma — NOS should be considered to have yielded negative results.

Among the analyses of composite endpoints, the only tests which yielded p-values below 0.05 were the tests for hepatocellular tumors in male mice. The p-value of the test of trend was 0.0368, and the tests of comparison between both the mid and high dose groups with control yielded p-values of 0.0110. However, since hepatocellular tumors are common, these p-values do not remain significant after adjusting for multiplicity. It may seem that the fact that three tests yielded p-values below 0.05 provides additional cause for concern, but it must be noted that these tests are not independent of one another, and all could be equally well explained by a single low count in the control group.

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This suggestion that the control count is unusually low is at odd with the fact that only one female control mouse developed a hepatocellular tumor (multiple hepatocellular carcinoma). However, if the female mice are expected to have similar incidence rates to the male mice, it must also be noted that there was no evidence whatsoever of a dose related increase in the incidence of hepatocellular tumors in female mice.

All in all, the evidence is insufficient to confidently conclude a tumorigenic effect for hepatocellular tumors in male mice. Nonetheless, the result is noteworthy, and should be borne in mind when considering other studies included as part of this submission.

Additionally, it is striking that not one mouse was reported as having developed any type of mammary tumors. On the one hand, this is partially explained by the fact that the mammary glands are not mentioned in table 1.1. However, the mammary glands are not included in table 2.1 either, but do seem to have been examined as a matter of routine in the rat study.

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Table 1.9: Reported neoplastic tumors in primary organs in mice

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
ADRENAL GLANDS	Adenoma cortical	Male	p-value of test of trend or comparison	.5223		.5000	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.5%	0.0%
			Poly-3 adjusted number of animals at risk	39.8	36.4	39.8	43.5
	Adenoma subcapsular cell	Male	p-value of test of trend or comparison	.4742	1	.7532	.7769
			Number of animals reported with tumor	1	0	1	1
			Poly-3 adjusted incidence rate	2.5%	0.0%	2.5%	2.3%
			Poly-3 adjusted number of animals at risk	39.8	36.4	39.8	43.5
	Adenoma subcapsular cell, B−ce	Male	p-value of test of trend or comparison	.5223		.5000	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.5%	0.0%
			Poly-3 adjusted number of animals at risk	39.8	36.4	39.9	43.5
BRAIN	Meningioma malignant	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	40.3	40.9	45.2	38.3
CECUM	Adenocarcinoma	Male	p-value of test of trend or comparison	.2102		.5195	.5316
			Number of animals reported with tumor	0	0	1	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.4%	2.3%
			Poly-3 adjusted number of animals at risk	37.2	37.4	40.8	42.9
DUODENUM	Adenocarcinoma	Female	p-value of test of trend or comparison	.4175	1	1	.7468
			Number of animals reported with tumor	1	0	0	1
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	2.6%
			Poly-3 adjusted number of animals at risk	39.6	40.9	44.2	38.3
		Male	p-value of test of trend or comparison	.6556	.5000	.5256	
			Number of animals reported with tumor	0	1	1	0
			Poly-3 adjusted incidence rate	0.0%	2.7%	2.4%	0.0%
			Poly-3 adjusted number of animals at risk	37.2	37.1	41.4	42.9
	Adenoma	Female	p-value of test of trend or comparison	.7578	.5063		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%

Table 1.9: Reported neoplastic tumors in primary organs in mice (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	39.6	40.9	44.2	38.3
EPIDIDYMIDES	Leiomyoma	Male	p-value of test of trend or comparison	.7547	.4868		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.7%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.1	37.4	40.8	43.5
FEMUR	Sarcoma NOS	Female	p-value of test of trend or comparison	.7593	.5063		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	45.2	38.3
HARDERIAN GLANDS	Adenocarcinoma	Female	p-value of test of trend or comparison	.9420	1	.9000	1
			Number of animals reported with tumor	2	0	1	0
			Poly-3 adjusted incidence rate	5.0%	0.0%	2.2%	0.0%
			Poly-3 adjusted number of animals at risk	40.4	40.9	45.2	38.3
	Adenoma	Female	p-value of test of trend or comparison	.6454	.6721	1	.7845
			Number of animals reported with tumor	4	4	0	3
			Poly-3 adjusted incidence rate	10%	9.7%	0.0%	7.6%
			Poly-3 adjusted number of animals at risk	39.9	41.1	45.2	39.6
		Male	p-value of test of trend or comparison	.7519	.9377	.5362	.8971
			Number of animals reported with tumor	5	2	6	3
			Poly-3 adjusted incidence rate	13%	5.3%	15%	6.9%
			Poly-3 adjusted number of animals at risk	39.8	37.8	41.1	43.8
JEJUNUM	Adenoma	Female	p-value of test of trend or comparison	.2360			.4935
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.6%
			Poly-3 adjusted number of animals at risk	39.9	40.9	44.2	38.3
KIDNEYS	Adenoma renal tubule	Male	p-value of test of trend or comparison	.3355	.4868		.5244
			Number of animals reported with tumor	0	1	0	1
			Poly-3 adjusted incidence rate	0.0%	2.7%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	39.8	37.4	40.8	43.5
	Carcinoma renal tubule	Male	p-value of test of trend or comparison	.7547	.4868		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.7%	0.0%	0.0%

Table 1.9: Reported neoplastic tumors in primary organs in mice (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	39.8	37.7	40.8	43.5
LIVER	Adenoma hepatocellular	Male	p-value of test of trend or comparison	.1279	.1105	.0673	.0706
			Number of animals reported with tumor	0	3	4	4
			Poly-3 adjusted incidence rate	0.0%	8.0%	9.4%	9.1%
			Poly-3 adjusted number of animals at risk	39.8	37.4	42.5	43.8
	Carcinoma hepatocellular	Female	p-value of test of trend or comparison	.7593	.5063		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	45.2	38.3
		Male	p-value of test of trend or comparison	.1428	.4625	.0958	.1655
			Number of animals reported with tumor	2	3	7	6
			Poly-3 adjusted incidence rate	5.0%	8.0%	16%	13%
			Poly-3 adjusted number of animals at risk	40.1	37.7	43.7	44.8
	Carcinoma hepatocellular, mult	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	45.2	38.3
		Male	p-value of test of trend or comparison	.3355	.4868		.5244
			Number of animals reported with tumor	0	1	0	1
			Poly-3 adjusted incidence rate	0.0%	2.7%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	39.8	37.5	40.8	43.8
	Hemangiosarcoma	Female	p-value of test of trend or comparison	.5123		.5357	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	45.4	38.3
		Male	p-value of test of trend or comparison	.3799	.4901	1	.5457
			Number of animals reported with tumor	1	2	0	2
			Poly-3 adjusted incidence rate	2.5%	5.3%	0.0%	4.5%
			Poly-3 adjusted number of animals at risk	39.8	38.0	40.8	44.2
LUNGS	Adenoma bronchiolo−alveolar	Female	p-value of test of trend or comparison	.2417	.8891	.5807	.5000
			Number of animals reported with tumor	2	1	3	3
			Poly-3 adjusted incidence rate	5.1%	2.4%	6.6%	7.8%

Table 1.9: Reported neoplastic tumors in primary organs in mice (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	38.9	40.9	45.8	38.3
		Male	p-value of test of trend or comparison	.6465	.7720	.6149	.7705
			Number of animals reported with tumor	7	5	7	6
			Poly-3 adjusted incidence rate	17%	13%	17%	13%
			Poly-3 adjusted number of animals at risk	41.3	37.4	41.4	44.6
	Adenoma bronchiolo−alveolar, m	Male	p-value of test of trend or comparison	.6295	1	1	.8968
			Number of animals reported with tumor	2	0	0	1
			Poly-3 adjusted incidence rate	5.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	39.8	37.4	40.8	43.5
	Carcinoma bronchiolo−alveolar	Female	p-value of test of trend or comparison	.6726	.8844	.5684	.8751
			Number of animals reported with tumor	2	1	3	1
			Poly-3 adjusted incidence rate	5.1%	2.4%	6.6%	2.6%
			Poly-3 adjusted number of animals at risk	39.4	40.9	45.6	38.3
		Male	p-value of test of trend or comparison	.5624	.6376	.8281	.7066
			Number of animals reported with tumor	3	3	2	3
			Poly-3 adjusted incidence rate	7.5%	7.7%	4.8%	6.7%
			Poly-3 adjusted number of animals at risk	40.0	38.9	41.7	44.5
	Carcinoma bronchiolo−alveolar,	Female	p-value of test of trend or comparison	.2360			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.6%
			Poly-3 adjusted number of animals at risk	38.9	40.9	45.2	38.3
		Male	p-value of test of trend or comparison	.7547	.4868		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.7%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.8	37.4	40.8	43.5
NOSE	Adenocarcinoma, glands	Male	p-value of test of trend or comparison	.5250		.5125	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.4%	0.0%
			Poly-3 adjusted number of animals at risk	39.8	37.4	41.4	43.5
OVARIES	Cystadenoma	Female	p-value of test of trend or comparison	.0554		.5244	.2337
			Number of animals reported with tumor	0	0	1	2
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	5.4%

Table 1.9: Reported neoplastic tumors in primary organs in mice (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	39.6	40.9	43.9	37.3
	Luteoma benign	Female	p-value of test of trend or comparison	.1862		.2719	.4868
			Number of animals reported with tumor	0	0	2	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	4.6%	2.7%
			Poly-3 adjusted number of animals at risk	39.6	40.9	43.6	37.3
	Tumor granulosa cell benign	Female	p-value of test of trend or comparison	.4843		.2719	
			Number of animals reported with tumor	0	0	2	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	4.6%	0.0%
			Poly-3 adjusted number of animals at risk	39.6	40.9	43.7	37.3
	Tumor granulosa cell malignant	Female	p-value of test of trend or comparison	.5031		.5244	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	39.6	40.9	43.5	37.3
	Tumor sex cord stromal mixed b	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.6	40.9	43.5	37.3
PITUITARY GLAND	Adenoma pars distalis	Female	p-value of test of trend or comparison	.7467	.2666	.5488	
			Number of animals reported with tumor	0	2	1	0
			Poly-3 adjusted incidence rate	0.0%	4.9%	2.2%	0.0%
			Poly-3 adjusted number of animals at risk	37.3	40.9	45.2	38.2
		Male	p-value of test of trend or comparison	.2107		.5065	.5309
			Number of animals reported with tumor	0	0	1	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.5%	2.3%
			Poly-3 adjusted number of animals at risk	38.6	37.4	39.7	43.9
	Adenoma pars intermedia	Female	p-value of test of trend or comparison	.7687	.5195		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	37.3	40.9	45.2	38.2
SEMINAL VESICLES	Adenoma coagulation gland	Male	p-value of test of trend or comparison	.2704			.5244
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%

Table 1.9: Reported neoplastic tumors in primary organs in mice (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	39.1	37.4	40.8	43.5
	Mesenchymal proliferative lesi	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.6%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.1	37.4	40.8	43.5
SKIN	Carcinoma basal cell	Female	p-value of test of trend or comparison	.2346			.4935
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.6%
			Poly-3 adjusted number of animals at risk	39.9	40.9	45.2	38.3
	Fibroma	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	45.2	38.3
	Hemangioma	Male	p-value of test of trend or comparison	.2704			.5244
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	39.8	37.4	40.8	43.5
	Hemangiosarcoma	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	45.2	38.3
	Malignant fibrous histiocytoma	Male	p-value of test of trend or comparison	.5250		.5125	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.4%	0.0%
			Poly-3 adjusted number of animals at risk	39.8	37.4	41.6	43.5
SPINAL CORD	Hemangioma	Male	p-value of test of trend or comparison	.7547	.4868		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.7%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.1	37.4	40.8	43.5
SPLEEN	Hemangioma	Male	p-value of test of trend or comparison	.5250		.5125	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.4%	0.0%

Table 1.9: Reported neoplastic tumors in primary organs in mice (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	39.8	37.4	41.4	43.5
	Hemangiosarcoma	Female	p-value of test of trend or comparison	.8197	1	.7815	1
			Number of animals reported with tumor	1	0	1	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	2.2%	0.0%
			Poly-3 adjusted number of animals at risk	40.5	40.9	45.2	38.3
		Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.8	37.4	40.8	43.5
STOMACH	Carcinoma squamous cell	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.6%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	38.9	40.9	44.2	38.3
		Male	p-value of test of trend or comparison	.2658			.5185
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	39.6	37.4	40.8	42.7
	Papilloma squamous cell, fores	Female	p-value of test of trend or comparison	.6310	.5190	.5366	
			Number of animals reported with tumor	0	1	1	0
			Poly-3 adjusted incidence rate	0.0%	2.4%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	38.9	41.0	44.2	38.3
SUBMANDIBULAR GLAN	Adenocarcinoma	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	40.6	37.4	40.8	42.5
SYSTEMIC TUMORS	Histiocytic sarcoma	Female	p-value of test of trend or comparison	.1736	.6504	.5526	.3136
			Number of animals reported with tumor	3	3	4	5
			Poly-3 adjusted incidence rate	7.3%	7.3%	8.7%	13%
			Poly-3 adjusted number of animals at risk	41.2	40.9	45.9	38.8
		Male	p-value of test of trend or comparison	.3088	1	1	.7191
			Number of animals reported with tumor	2	0	0	2
			Poly-3 adjusted incidence rate	5.0%	0.0%	0.0%	4.6%

Table 1.9: Reported neoplastic tumors in primary organs in mice (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	40.1	37.4	40.8	43.5
	Lymphoma, NOS	Female	p-value of test of trend or comparison	.1642	.5125	.1537	.2468
			Number of animals reported with tumor	0	1	3	2
			Poly-3 adjusted incidence rate	0.0%	2.4%	6.5%	5.1%
			Poly-3 adjusted number of animals at risk	39.9	41.9	46.4	39.2
		Male	p-value of test of trend or comparison	.0433	.4935		.1441
			Number of animals reported with tumor	0	1	0	3
			Poly-3 adjusted incidence rate	0.0%	2.6%	0.0%	6.7%
			Poly-3 adjusted number of animals at risk	39.8	38.3	40.8	44.7
	Lymphoma, lymphoblastic	Female	p-value of test of trend or comparison	.4130	1	1	.7403
			Number of animals reported with tumor	1	0	0	1
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	2.6%
			Poly-3 adjusted number of animals at risk	40.2	40.9	45.2	38.8
		Male	p-value of test of trend or comparison	.5250		.5125	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.4%	0.0%
			Poly-3 adjusted number of animals at risk	39.8	37.4	41.4	43.5
	Lymphoma, lymphocytic	Female	p-value of test of trend or comparison	.7374	1	.5541	1
			Number of animals reported with tumor	1	0	2	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	4.4%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	45.2	38.3
		Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	40.1	37.4	40.8	43.5
	Lymphoma, plasmacytic	Female	p-value of test of trend or comparison	.7607	.5125		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	41.5	45.2	38.3
	Lymphoma, pleomorphic	Female	p-value of test of trend or comparison	.2101	.6923	.1742	.3254
			Number of animals reported with tumor	2	2	6	4
			Poly-3 adjusted incidence rate	5.0%	4.9%	13%	10%

Table 1.9: Reported neoplastic tumors in primary organs in mice (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	40.4	40.9	45.9	39.9
		Male	p-value of test of trend or comparison	.1529	.6723	1	.3858
			Number of animals reported with tumor	2	2	0	4
			Poly-3 adjusted incidence rate	5.0%	5.3%	0.0%	9.1%
			Poly-3 adjusted number of animals at risk	39.8	37.7	40.8	43.9
	Lymphoma, pleomorphic, cutaneo	Male	p-value of test of trend or comparison	.5220		.5063	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.4%	0.0%
			Poly-3 adjusted number of animals at risk	39.8	37.4	41.0	43.5
	Lymphoma, pleomorphic, leukemi	Male	p-value of test of trend or comparison	.5220		.5063	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.4%	0.0%
			Poly-3 adjusted number of animals at risk	39.8	37.4	40.8	43.5
	Malignant mast cell tumor	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	40.1	37.4	40.8	43.5
	Myeloid leukemia	Female	p-value of test of trend or comparison	.2393			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.5%
			Poly-3 adjusted number of animals at risk	39.9	40.9	45.2	39.3
TESTES	Tumor Leydig cell benign	Male	p-value of test of trend or comparison	.3095	.2337	.1297	.2780
			Number of animals reported with tumor	0	2	3	2
			Poly-3 adjusted incidence rate	0.0%	5.3%	7.3%	4.5%
			Poly-3 adjusted number of animals at risk	39.1	37.5	41.2	44.2
	Tumor Leydig cell benign, mult	Male	p-value of test of trend or comparison	.2704			.5244
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	39.1	37.4	40.8	43.5
	Tumor granulosa cell benign	Male	p-value of test of trend or comparison	.5250		.5125	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.4%	0.0%

Table 1.9: Reported neoplastic tumors in primary organs in mice (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	39.1	37.4	41.4	43.5
THYMUS	Malignant fibrous histiocytoma	Male	p-value of test of trend or comparison	.2715			.5190
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.4%
			Poly-3 adjusted number of animals at risk	38.7	34.3	38.0	41.1
	Thymoma benign	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.6%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	38.8	39.2	42.9	36.5
THYROID GLAND	Adenoma follicular cell	Female	p-value of test of trend or comparison	.8509	.7595	.7823	1
			Number of animals reported with tumor	1	1	1	0
			Poly-3 adjusted incidence rate	2.5%	2.4%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	44.4	38.3
		Male	p-value of test of trend or comparison	.5253		.5063	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.4%	0.0%
			Poly-3 adjusted number of animals at risk	39.7	36.4	40.8	43.5
URINARY BLADDER	Mesenchymal proliferative lesi	Male	p-value of test of trend or comparison	.5190		.5000	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.5%	0.0%
			Poly-3 adjusted number of animals at risk	39.1	37.4	40.0	43.5
UTERUS	Adenocarcinoma	Female	p-value of test of trend or comparison	.7578	.5063		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	44.5	38.3
	Glandular polyp	Female	p-value of test of trend or comparison	.3016	.5125		.4935
			Number of animals reported with tumor	0	1	0	1
			Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	2.6%
			Poly-3 adjusted number of animals at risk	39.9	41.1	44.5	38.6
	Hemangioma	Female	p-value of test of trend or comparison	.9432	1	.9005	1
			Number of animals reported with tumor	2	0	1	0
			Poly-3 adjusted incidence rate	5.0%	0.0%	2.2%	0.0%

Table 1.9: Reported neoplastic tumors in primary organs in mice (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	39.9	40.9	44.9	38.3
	Hemangiosarcoma	Female	p-value of test of trend or comparison	.0577		.5301	.2403
			Number of animals reported with tumor	0	0	1	2
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	5.2%
			Poly-3 adjusted number of animals at risk	39.9	40.9	44.5	38.5
	Leiomyoma	Female	p-value of test of trend or comparison	.8844	.5096	.7823	1
			Number of animals reported with tumor	1	2	1	0
			Poly-3 adjusted incidence rate	2.5%	4.9%	2.2%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	44.5	38.3
	Leiomyosarcoma	Female	p-value of test of trend or comparison	.5093		.5301	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	44.5	38.3
	Mixed Muellerian tumor	Female	p-value of test of trend or comparison	.2360			.4935
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.6%
			Poly-3 adjusted number of animals at risk	39.9	40.9	44.5	38.3
	Stromal polyp	Female	p-value of test of trend or comparison	.8461	.5094	.3449	1
			Number of animals reported with tumor	1	2	3	0
			Poly-3 adjusted incidence rate	2.5%	4.9%	6.7%	0.0%
			Poly-3 adjusted number of animals at risk	40.3	41.2	44.6	38.3
	Stromal polyp, multiple	Female	p-value of test of trend or comparison	.7578	.5063		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	40.9	44.5	38.3
	Tumor granular cell benign	Female	p-value of test of trend or comparison	.1844		.5301	.4935
			Number of animals reported with tumor	0	0	1	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.2%	2.6%
			Poly-3 adjusted number of animals at risk	39.9	40.9	44.5	38.3
VAGINA	Tumor granular cell benign	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.6%	0.0%	0.0%	0.0%

Table 1.9: Reported neoplastic tumors in primary organs in mice (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	39.1	39.8	42.5	37.8

Table 1.10: Tumors for which at least one test was significant (mice)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
SYSTEMIC TUMORS	Lymphoma, NOS	Female	p-value of test of trend or comparison	.1642	.5125	.1537	.2468
			Number of animals reported with tumor	0	1	3	2
			Poly-3 adjusted incidence rate	0.0%	2.4%	6.5%	5.1%
			Poly-3 adjusted number of animals at risk	39.9	41.9	46.4	39.2
		Male	p-value of test of trend or comparison	.0433	.4935		.1441
			Number of animals reported with tumor	0	1	0	3
			Poly-3 adjusted incidence rate	0.0%	2.6%	0.0%	6.7%
			Poly-3 adjusted number of animals at risk	39.8	38.3	40.8	44.7

Table 1.11: Composite endpoint analyses (mice)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
Adenomas pars distalis	Female	p-value of pairwise and trend tests	.7420	.2597	.5422	.
		Observed number of cases	0	2	1	0
		Poly-3 adjusted incidence rate	0%	4.9%	2.2%	0%
		Adjusted number at risk	38.05	40.94	45.87	38.48
	Male	p-value of pairwise and trend tests	.2119	.	.5000	.5301
		Observed number of cases	0	0	1	1
		Poly-3 adjusted incidence rate	0%	0%	2.5%	2.3%
		Adjusted number at risk	39.87	37.35	39.96	44.05
Adrenal adenomas	Male	p-value of pairwise and trend tests	.4776	1	.2984	.7648
		Observed number of cases	1	0	3	1
		Poly-3 adjusted incidence rate	2.4%	0%	7.5%	2.3%
		Adjusted number at risk	41.01	36.35	40.11	43.67

Table 1.11: Composite endpoint analyses in mice (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
Bronchiolo-alveolar carcinomas	Female	p-value of pairwise and trend tests	.4206	.8797	.5668	.6727
		Observed number of cases	2	1	3	2
		Poly-3 adjusted incidence rate	5.0%	2.4%	6.5%	5.2%
		Adjusted number at risk	40.20	40.94	46.25	38.60
	Male	p-value of pairwise and trend tests	.6186	.4568	.8204	.6953
		Observed number of cases	3	4	2	3
		Poly-3 adjusted incidence rate	7.3%	10%	4.8%	6.7%
		Adjusted number at risk	41.25	38.87	41.87	44.69
Dermal fibromas	Female	p-value of pairwise and trend tests	1	1	1	1
		Observed number of cases	1	0	0	0
		Poly-3 adjusted incidence rate	2.5%	0%	0%	0%
		Adjusted number at risk	40.66	40.94	45.87	38.60
Hemangiomas	Female	p-value of pairwise and trend tests	.9431	1	.9035	1
		Observed number of cases	2	0	1	0
		Poly-3 adjusted incidence rate	4.9%	0%	2.2%	0%
		Adjusted number at risk	40.72	40.94	46.26	38.60
	Male	p-value of pairwise and trend tests	.3275	.4805	.5122	.5238
		Observed number of cases	0	1	1	1
		Poly-3 adjusted incidence rate	0%	2.7%	2.4%	2.3%
		Adjusted number at risk	40.98	37.35	42.16	44.14
Hemangiosarcomas	Female	p-value of pairwise and trend tests	.3514	1	.3948	.6630
		Observed number of cases	2	0	4	2
		Poly-3 adjusted incidence rate	4.9%	0%	8.7%	5.2%
		Adjusted number at risk	41.24	40.94	46.11	38.79
	Male	p-value of pairwise and trend tests	.5209	.6630	1	.7183
		Observed number of cases	2	2	0	2

Table 1.11: Composite endpoint analyses in mice (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
		Poly-3 adjusted incidence rate	4.9%	5.3%	0%	4.5%
		Adjusted number at risk	41.01	38.05	41.56	44.85
Hepatocellular tumors	Female	*p*-value of pairwise and trend tests	.9409	.7532	1	1
		Poly-3 adjusted incidence rate	2.5%	2.4%	0%	0%
		Observed number of cases	1	1	0	0
		Adjusted number at risk	40.66	40.94	45.87	38.60
	Male	*p*-value of pairwise and trend tests	.0368	.0557	.0110	.0110
		Poly-3 adjusted incidence rate	4.8%	19%	24%	24%
		Observed number of cases	2	7	11	11
		Adjusted number at risk	41.29	37.79	45.58	45.53
Lymphomas	Female	*p*-value of pairwise and trend tests	.1853	.6574	.0772	.2594
		Observed number of cases	4	4	11	7
		Poly-3 adjusted incidence rate	9.6%	9.4%	23%	17%
		Adjusted number at risk	41.52	42.53	47.86	41.53
	Male	*p*-value of pairwise and trend tests	.0807	.6253	.6737	.1977
		Observed number of cases	3	3	3	7
		Poly-3 adjusted incidence rate	7.3%	7.8%	7.1%	15%
		Adjusted number at risk	41.29	38.62	42.18	45.70
Systemic tumors	Female	*p*-value of pairwise and trend tests	.0563	.6147	.0861	.0998
		Observed number of cases	7	7	15	13
		Poly-3 adjusted incidence rate	16%	16%	31%	30%
		Adjusted number at risk	42.81	42.53	48.60	42.96
	Male	*p*-value of pairwise and trend tests	.1015	.9039	.9278	.3570
		Observed number of cases	6	3	3	9
		Poly-3 adjusted incidence rate	14%	7.8%	7.1%	20%
		Adjusted number at risk	41.98	38.62	42.18	45.70

Table 1.11: Composite endpoint analyses in mice (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
Leydig cell tumors	Male	*p*-value of pairwise and trend tests	.1550	.2276	.1249	.1390
		Observed number of cases	0	2	3	3
		Poly-3 adjusted incidence rate	0%	5.3%	7.2%	6.8%
		Adjusted number at risk	40.34	37.49	41.45	44.35
Thyroidal adenomas	Female	*p*-value of pairwise and trend tests	.8485	.7532	.7815	1
		Observed number of cases	1	1	1	0
		Poly-3 adjusted incidence rate	2.5%	2.4%	2.2%	0%
		Adjusted number at risk	40.66	40.94	45.09	38.60
	Male	*p*-value of pairwise and trend tests	.5250	.	.5062	.
		Observed number of cases	0	0	1	0
		Poly-3 adjusted incidence rate	0%	0%	2.4%	0%
		Adjusted number at risk	40.91	36.35	41.06	43.67
Uterine adenocarcinomas	Female	*p*-value of pairwise and trend tests	.7546	.5000	.	.
		Observed number of cases	0	1	0	0
		Poly-3 adjusted incidence rate	0%	2.4%	0%	0%
		Adjusted number at risk	40.66	40.94	45.15	38.60
Uterine stromal polyps	Female	*p*-value of pairwise and trend tests	.8788	.3078	.3441	1
		Observed number of cases	1	3	3	0
		Poly-3 adjusted incidence rate	2.4%	7.3%	6.6%	0%
		Adjusted number at risk	41.09	41.18	45.34	38.60

Table 1.12: Tumors found in organs presumed to be secondary (mice)

Sex	Organ or Tissue Name	Tumor Name	Quantity	Control	Low dose	Mid dose	High dose
Female	BODY CAVITIES	Fibrosarcoma	Number of tumors found	1	0	0	0
			Number of animals examined	2	2	4	4
		Hemangiosarcoma	Number of tumors found	0	0	1	0
			Number of animals examined	2	2	4	4

Table 1.12: Tumors found in organs presumed to be secondary (mice) (continued)

Sex	Organ or Tissue Name	Tumor Name	Quantity	Control	Low dose	Mid dose	High dose
	SKULLCAP	Osteoma	Number of tumors found	1	0	0	0
			Number of animals examined	2	0	0	1
	TEETH	Odontogenic fibrosarcoma	Number of tumors found	0	0	0	1
			Number of animals examined	0	0	0	3
Male	BONE	Osteosarcoma	Number of tumors found	0	1	0	0
			Number of animals examined	1	1	0	0
	PERIPHER. NERVE(S)	Schwannoma malignant	Number of tumors found	0	0	1	0
			Number of animals examined	1	0	1	0

1.3 Unexamined and autolytic organs

1.3.1 Unexamined animals

Nine animals were reported as having not had any organs examined. The numbers of these animals, broken down by sex and treatment group, are presented in table 1.13.

Table 1.13: Numbers of animals for which no organs were examined

	Treatment group			
Sex	Control	Low Dose	Mid Dose	High Dose
Female	2	0	1	2
Male	2	0	1	1

1.3.2 Autolytic organs

In neither the male nor female mouse study were there any instances reported of organs being autolyzed to the extent that no usable sample could be obtained.

1.3.3 Unexamined organs

A number of organs were reported as unexamined in various animals, as shown in table 1.14. With the exception of the organs designated as secondary (see table 1.7), there is no indication that any other organ types have been unexamined in large numbers, although in both male and female mice, there was a surprising number of animals for which the thymus was not examined.

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Table 1.14: Frequency of organs reported unexamined in mouse study

Organ or tissue name	Female										Male									
	Control		Low Dose		Mid Dose		High Dose		Total		Control		Low Dose		Mid Dose		High Dose		Total	
ADRENAL GLANDS	.	.	.	.	.	.	1	1.7%	1	0.4%	.	.	1	1.7%	2	3.4%	2	3.4%	5	2.1%
BODY CAVITIES	56	97%	58	97%	55	93%	54	93%	223	95%	56	97%	60	100%	59	100%	59	100%	234	99%
BONE	57	98%	59	98%	58	98%	56	97%	230	98%	57	98%	59	98%	59	100%	59	100%	234	99%
BRAIN	.	.	.	.	.	.	.	.			.	.	.	.	1	1.7%	2	3.4%	3	1.3%
CECUM	1	1.7%	.	.	4	6.8%	.	.	5	2.1%	4	6.9%	.	.	1	1.7%	4	6.8%	9	3.8%
DUODENUM	1	1.7%	.	.	3	5.1%	.	.	4	1.7%	4	6.9%	1	1.7%	1	1.7%	4	6.8%	10	4.2%
EPIDIDYMIDES	.	.	.	.	.	.	.	.			1	1.7%	.	.	1	1.7%	2	3.4%	4	1.7%
FEMUR	.	.	.	.	.	.	.	.			1	1.7%	.	.	1	1.7%	2	3.4%	4	1.7%
HARDERIAN GLANDS	.	.	.	.	.	.	.	.			.	.	.	.	1	1.7%	2	3.4%	3	1.3%
JEJUNUM	.	.	.	.	3	5.1%	.	.	3	1.3%	4	6.9%	1	1.7%	1	1.7%	4	6.8%	10	4.2%
KIDNEYS	.	.	.	.	.	.	.	.			.	.	.	.	1	1.7%	2	3.4%	3	1.3%
LIVER	.	.	.	.	.	.	.	.			.	.	.	.	1	1.7%	2	3.4%	3	1.3%
LUNGS	1	1.7%	.	.	.	.	.	.	1	0.4%	.	.	.	.	1	1.7%	2	3.4%	3	1.3%
NOSE	.	.	.	.	.	.	.	.			.	.	.	.	1	1.7%	2	3.4%	3	1.3%
OVARIES	1	1.7%	.	.	2	3.4%	1	1.7%	4	1.7%	.	.	.	.	.	.	.	.		
PERIPHER. NERVE(S)	58	100%	60	100%	59	100%	57	98%	234	100%	57	98%	60	100%	58	98%	59	100%	234	99%
PITUITARY GLAND	4	6.9%	.	.	.	.	1	1.7%	5	2.1%	2	3.4%	.	.	3	5.1%	2	3.4%	7	3.0%
SEMINAL VESICLES	.	.	.	.	.	.	.	.			1	1.7%	.	.	1	1.7%	2	3.4%	4	1.7%
SKIN	.	.	.	.	.	.	.	.			.	.	.	.	1	1.7%	2	3.4%	3	1.3%
SKULLCAP	56	97%	60	100%	59	100%	57	98%	232	99%	57	98%	60	100%	59	100%	58	98%	234	99%
SPINAL CORD	1	1.7%	1	1.7%	.	.	.	.	2	0.9%	1	1.7%	.	.	1	1.7%	2	3.4%	4	1.7%
SPLEEN	.	.	.	.	.	.	.	.			.	.	.	.	1	1.7%	2	3.4%	3	1.3%
STOMACH	1	1.7%	.	.	3	5.1%	.	.	4	1.7%	1	1.7%	.	.	1	1.7%	4	6.8%	6	2.5%
SUBMANDIBULAR GLAN	.	.	.	.	1	1.7%	.	.	1	0.4%	.	.	.	.	1	1.7%	3	5.1%	4	1.7%
SYSTEMIC TUMORS	.	.	.	.	.	.	.	.			.	.	.	.	1	1.7%	2	3.4%	3	1.3%
TEETH	58	100%	60	100%	59	100%	55	95%	232	99%	57	98%	60	100%	58	98%	59	100%	234	99%
TESTES	.	.	.	.	.	.	.	.			1	1.7%	.	.	1	1.7%	2	3.4%	4	1.7%
THYMUS	4	6.9%	2	3.3%	5	8.5%	4	6.9%	15	6.4%	4	6.9%	6	10%	6	10%	7	12%	23	9.7%
THYROID GLAND	.	.	.	.	1	1.7%	.	.	1	0.4%	1	1.7%	1	1.7%	1	1.7%	2	3.4%	5	2.1%
URINARY BLADDER	.	.	1	1.7%	2	3.4%	1	1.7%	4	1.7%	1	1.7%	.	.	2	3.4%	2	3.4%	5	2.1%
UTERUS	.	.	.	.	1	1.7%	.	.	1	0.4%	.	.	.	.	.	.	.	.		
VAGINA	1	1.7%	2	3.3%	3	5.1%	1	1.7%	7	3.0%	.	.	.	.	.	.	.	.		

Chapter 2

Rat study

2.1 Overview

Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Each of these four groups was randomly assigned fifty animals, for a total of two hundred animals of each sex. The animals used were Wistar (Hsd Cpb:WU) rats.

The vehicle for the test was ethanol/Solutol HS 15/tap water in a 10:40:50 ratio. It is not clear from the report whether this was a solution or a mixture. The quantity of vehicle administered was 10 mL/kg per day. The test item was administered as a suspension in the vehicle.

The low, mid, and high dose animals or both sexes were treated with daily dose levels of 10, 20, and 60 mg/kg respectively.

Animals were inspected for morbidity and mortality twice a day (once a day on weekends and public holidays), and detailed clinical observations were performed weekly. Animals that were euthanized *in extremis* or sacrificed at the scheduled end of the study underwent necroscopy, and their organs were subjected to gross pathological examination. Animals found dead were necroscopsied soon as possible. All animals underwent opthalmologic exams at the start of the study, and the control and high dose animals were reexamined after 12, 18, and 24 months.

2.2 Data analysis

2.2.1 Sponsor's analyses

Survival analysis

The sponsor reports the number of rats to have died before week 104. The sponsor claims that these deaths are largely attributable to "massive chronic progressive nephropathy" (male rats) and "a variety of gross lesions of the uterus and mammary gland" (female rats). The sponsor writes that "[b]ecause these lesions did not show dose dependence, an effect on mortality caused by the treatment with BAY 59-7939 is not assumed.". However, it appears that no time-to-event data were considered when assessing the animals' mortality, and that no formal survival analysis has been conducted.

Tumor data analysis

The same statistical analyses of the rat data were conducted as were performed on the the mouse data (see section 1.2.1). However, the sponsor has only included the results from the "conventional Peto test" in the report; the results of the other tests are not not available. The list of organs scheduled for routine examination is presented in table 2.1

The following organs were planned to be examined in all animals:

The list of tumor types for which the sponsor conducted and reported at least one test for which a p-value less than 0.05 is presented in table 2.2. It is important to note that the observed trend

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Table 2.1: Sponsor's list of primary endpoints

Abnormalities	Adrenal glands	Aorta
Brain (cerebrum)	Brain (cerebellum)	Brain (brain stem)
Cecum	Clitoral gland	Colon
Duodenum	Epididymides	Esophagus
Eyes	Exorbital lacrimal glands	Femur (with joint)
Harderian glands	Heart	Ileum
Jejunum	Kidneys	Larynx
Liver	Lungs	Lymph nodes, mandibular
Lymph nodes, mesenteric	Lymph nodes, popliteal	Nasal cavity/nasopharynx
Optic nerves	Ovaries	Oviducts
Pancreas	Pituitary gland	Preputial gland
Prostate	Rectum	Salivary glands (parotid)
Salivary gland (submandibular)	Salivary gland (sublingual)	Sciatic nerve
Seminal vesicles	Skeletal muscle (thigh)	Skin (mammary region)
Spinal chord (cervical)	Spinal chord (thoracic)	Spinal chord (lumbar)
Spleen	Sternum with bone marrow	Stomach
Testes	Thymus	Thyroid glands (with parathyroids)
Tongue	Trachea	Ureters
Urinary bladder	Uterus (with cervix)	Vagina
Zymbal's glands		

for histiocytic sarcomas in female mice was negative, and the reported p-value is therefore relative to the null hypothesis of no protective effect.

Table 2.2: p-values for tumor types reported as significant by the sponsor

Organ/tissue	Tumor	Sex	p-value: Conventional Peto trend test
Single tumor types			
Clitoral Gland	Squamous carcinoma	Female	0.0301
Hemolymphoreticular System	Histiocytic sarcoma	Female	0.0934
		Male	0.0268
Skin	Fibroma	Male	0.0294

The sponsor has made the following comments regarding the tumor findings. Note that these comments do not match up exactly with the tumors listed in table 2.2.

Cortical cell adenomas The sponsor notes that there is an elevated incidence of cortical cell adenomas in the mid and high dose groups, relative to the control. The sponsor also notes that "[h]igher incidences of preneoplastic and neoplastic lesions were seen in the adrenal glands of this present study", without specifying what it is that these incidences are higher than. However, the sponsor concludes "However, without a dose-dependent trend a treatment relationship is not concluded from tumor data in this organ."

Mammary fibromas The sponsor concludes that neither the test of trend nor the pairwise tests (not included in the report) are statistically significant after making a multiplicity adjustment.

Clitoral Squamous carcinoma The sponsor observes that the result for squamous carcinomas of the clitoral gland does not remain significant after adjusting for multiplicity. Thye also write that "induced tumors of the clitoral gland are only described in the context of tumor induction of

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the skin and its adnexes which was clearly not the case in the present study." They thus conclude that incidence of these tumors are not related to the test article.

Histiocytic sarcoma Only two male animals developed histiocytic sarcomas, both in the high dose group. The sponsor concludes that this evidence is insufficient to suspect a tumorigenic effect. Note that the extra conservatism of the exact trend test is most useful in cases where the counts are low, so this result in particular would likely be seen as non-significant if the results of the exact tests had been included.

Dermal fibroma The sponsor makes no comment regarding this finding, which is driven by the fact that only four animals (two in the mid dose group and two in the high dose group) developed dermal fibromas.

2.2.2 Reviewer's analysis

To verify the sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used were provided by the sponsor electronically.

Survival Analysis

Figures 2.1 and 2.2 show the Kaplan-Meier plots for male and female rats respectively. The results of log-rank tests of survival are presented in table 2.3. Intercurrent mortality data are presented in table 2.4. The plots show no sign of any dose related mortality, and the statistical tests indicate no significant results.

Figure 2.1: Survival plot for male rats

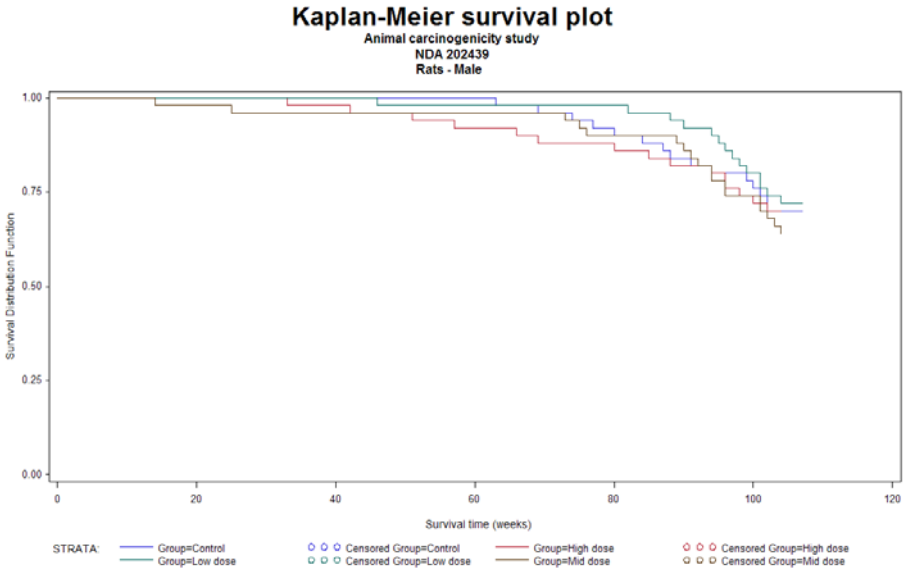

Figure 2.2: Survival plot for female rats

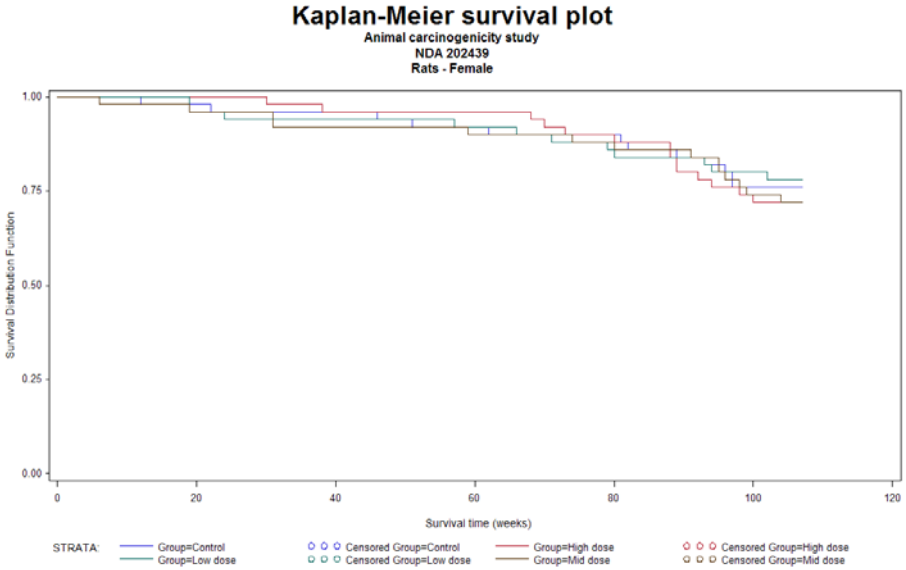

Table 2.3: Results of log-rank tests of survival — Rats

Species and Sex	Number of Groups	Test of homogeneity			Test of trend	
		χ^2 statistic	df	p-value	Two tailed p-value	One tailed p-value
Rats – Female	0.5476	4	3	0.9083	0.7255	0.3627
Rats – Male	1.3163	4	3	0.7253	0.9184	0.4592

Table 2.4: Survival rates at key times — rats

Species and Sex	Dose Group	Dose (mg per kg)	Number and percentage alive								
			Start	52 weeks	(%)	78 weeks	(%)	90 weeks	(%)	Termination	(%)
Rats - Female	Control	0	50	46	92%	45	90%	42	84%	38	76%
	Low dose	10	50	47	94%	44	88%	42	84%	39	78%
	Mid dose	20	50	46	92%	44	88%	43	86%	37	74%
	High dose	60	50	48	96%	45	90%	40	80%	36	72%
Rats - Male	Control	0	50	50	100%	46	92%	42	84%	35	70%
	Low dose	10	50	49	98%	49	98%	47	94%	37	74%
	Mid dose	20	50	48	96%	45	90%	44	88%	33	66%
	High dose	60	50	47	94%	44	88%	41	82%	35	70%

Tumor data analysis

The same poly-3 analyses were conducted for tumors in rats as in mice (see section 1.2.2), with the same adjustment for multiplicity (see table 1.5).

The list of primary organs (see section 1.2.2), as determined from the submitted data, is presented in table 2.5. The list of secondary organs is presented in table 2.6.

Table 2.5: Organs presumed to be primary in the rat study

Female rats		
ADRENAL GLANDS	BRAIN	CLITORAL GLANDS
HARDERIAN GLANDS	HEMOLYMPHORET. SYS	KIDNEYS
LARYNX	LIVER	LUNGS
MAMMARY GLAND	OVARIE	PANCREAS
PITUITARY GLAND	SKIN	SPINAL CORD
THYMUS	THYROID GLAND	TONGUE
URINARY BLADDER	UTERUS	ZYMBAL GLANDS

Male rats		
ADRENAL GLANDS	BRAIN	EYES
FEMUR	HARDERIAN GLANDS	HEART
HEMOLYMPHORET. SYS	KIDNEYS	LARYNX
LIVER	LUNGS	MAMMARY GLAND
MESENT. LYMPH NODE	MESENTERY	NOSE
PANCREAS	PITUITARY GLAND	PREPUTIAL GLANDS
SKIN	SPINAL CORD	SPLEEN
STERNUM	TESTES	THYMUS
THYROID GLAND	TONGUE	URINARY BLADDER
ZYMBAL GLANDS		

Table 2.6: Organs presumed to be secondary in the rat study

Female and male rats		
BODY CAVITIES	BONE	LYMPH NODES

All tumor types reported in the data as being found in primary organs were tested. The results of the poly-3 tests of incidence and trend (for both sexes) are presented in table 2.7. Table 2.8 is excerpted from table 2.7, and consists only of those tumor types for which at least one test in at least one sex had a p-value below 0.05.

In addition, a number of combination endpoints were analyzed, primarily in response to the sponsor's practice of separating certain tumors depending on whether multiple masses were detected. These composite endpoints are the same as those tested in mice, and are listed in table 1.8. Results of these tests are presented in table 2.9. Note that there were no adenomas of the lung reported in any of the rats, so this endpoint is not presented in table 2.9.

Tumors in secondary organs have not been tested statistically, as it is unclear what the mechanism is by which they came to be found. Additionally, the numbers of animals analyzed is too small to draw any meaningful statistical inference. Count data of these tumors are presented in table 2.10.

The tests of two primary endpoints (cortical adenomas of the adrenal gland, fibroadenomas of the mammary gland) have generated p-values below 0.05. In the case of the cortical cell adenomas, the noteworthy p-value is 0.0411, the p-value for the test of trend in female rats. The result is

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generated by counts of four animals in each of the mid and high dose groups, compared with a single case reported in the low dose group, and none at all in the control group. Regardless of whether this tumor is considered common or rare, this p-value does not retain its significance after adjusting for multiplicity. Additionally, there is no indication of a dose related increase in incidence in the male rat study.

In the case of mammary fibroadenomas, the critical p-value is for the test between the high dose group and the control group: 0.0312. However, this endpoint excludes diagnoses of "fibroadenoma, multiple", "fibroadenoma, with superficial inflamation" and "fibroadenoma, one adenomatous type". (Note that the sponsor has given these diagnoses the same tumor code, but different "tumor names".) When these endpoints are combined, we get the results presented in table 2.9. The counts across the control, low dose, mid dose, and high dose groups are 4, 7, 4, and 11 respectively. In this case, the comparison between the control and high dose groups is not significant ($p = 0.0530$). However, the test of trend is significant at the 0.05 level, $p = 0.0307$. However, as in the case of the cortical adenomas, this result loses its significance once the multiplicity of endpoints is taken into account.

The only other composite endpoint for which a p-value below 0.05 is reported is the test of trend for systemic tumors in male rats ($p = 0.0362$). This result is generated by a count of 4 animals in the high dose group and 2 in the control group, with none in the low or mid dose groups. As above this result is no longer statistically significant after adjusting for multiplicity.

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Table 2.7: Reported neoplastic tumors in primary organs in rats

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
ADRENAL GLANDS	Adenoma, cortical	Female	p-value of test of trend or comparison	.0411	.5000	.0553	.0581
			Number of animals reported with tumor	0	1	4	4
			Poly-3 adjusted incidence rate	0.0%	2.3%	9.4%	9.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.2
		Male	p-value of test of trend or comparison	.3062	.5056	.2414	.4884
			Number of animals reported with tumor	0	1	2	1
			Poly-3 adjusted incidence rate	0.0%	2.2%	4.6%	2.4%
			Poly-3 adjusted number of animals at risk	44.4	45.6	43.6	42.5
	Adenoma, cortical, with cysts an	Male	p-value of test of trend or comparison	.7471	.5056		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.2%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	45.6	43.6	42.5
	Pheochromocytoma benign	Female	p-value of test of trend or comparison	.4857	.3080	.1727	.5000
			Number of animals reported with tumor	1	3	4	2
			Poly-3 adjusted incidence rate	2.3%	6.8%	9.4%	4.6%
			Poly-3 adjusted number of animals at risk	43.1	43.9	42.7	43.1
		Male	p-value of test of trend or comparison	.3957	.2129	.9495	.3800
			Number of animals reported with tumor	16	22	10	18
			Poly-3 adjusted incidence rate	36%	47%	23%	41%
			Poly-3 adjusted number of animals at risk	44.9	47.2	44.2	43.7
	Pheochromocytoma benign, multipl	Male	p-value of test of trend or comparison	.9802	1	.9390	1
			Number of animals reported with tumor	3	0	1	0
			Poly-3 adjusted incidence rate	6.7%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	44.7	45.6	43.6	42.5
	Pheochromocytoma benign, mutiple	Male	p-value of test of trend or comparison	.4885		.4943	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	45.6	43.8	42.5
	Pheochromocytoma benign, with he	Female	p-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.5
	Pheochromocytoma benign, with va	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	45.6	43.6	42.5
	Pheochromocytoma malignant	Female	p-value of test of trend or comparison	.4971		.4941	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
		Male	p-value of test of trend or comparison	.5232	.1874	.1730	.4824
			Number of animals reported with tumor	1	4	4	2
			Poly-3 adjusted incidence rate	2.3%	8.8%	9.1%	4.7%
			Poly-3 adjusted number of animals at risk	44.4	45.7	43.9	42.5
BRAIN	Astrocytoma benign	Male	p-value of test of trend or comparison	.2400			.4884
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.9
	Astrocytoma malignant	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Medulloblastoma	Male	p-value of test of trend or comparison	.7486	.5111		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.1%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.7	43.6	42.5
	Tumor granular cell benign, cere	Female	p-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
CLITORAL GLANDS	Adenocarcinoma	Female	p-value of test of trend or comparison	.7397	.4722		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.9%	0.0%	0.0%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	38.9	34.9	35.8	39.6
	Adenoma	Female	p-value of test of trend or comparison	.5068		.4795	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.8%	0.0%
			Poly-3 adjusted number of animals at risk	38.9	34.4	35.8	39.6
	Basal cell carcinoma	Female	p-value of test of trend or comparison	.7420	1	.4696	1
			Number of animals reported with tumor	1	0	2	0
			Poly-3 adjusted incidence rate	2.6%	0.0%	5.5%	0.0%
			Poly-3 adjusted number of animals at risk	39.1	34.4	36.1	39.6
	Basal cell tumor benign	Female	p-value of test of trend or comparison	.5068		.4795	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.8%	0.0%
			Poly-3 adjusted number of animals at risk	38.9	34.4	35.8	39.6
	Squamous cell carcinoma	Female	p-value of test of trend or comparison	.0700			.2532
			Number of animals reported with tumor	0	0	0	2
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	5.0%
			Poly-3 adjusted number of animals at risk	38.9	34.4	35.8	39.6
	Squamous cell papilloma	Female	p-value of test of trend or comparison	.4642	1	1	.7597
			Number of animals reported with tumor	1	0	0	1
			Poly-3 adjusted incidence rate	2.6%	0.0%	0.0%	2.5%
			Poly-3 adjusted number of animals at risk	38.9	34.4	35.8	39.6
EYES	Malignant Schwannoma	Male	p-value of test of trend or comparison	.4828		.4943	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	44.1	46.4	43.6	41.9
HARDERIAN GLANDS	Adenocarcinoma	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
HEART	Benign atriocaval mesothelioma	Male	p-value of test of trend or comparison	.2400			.4884
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.4%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Malignant atriocaval mesotheliom	Male	p-value of test of trend or comparison	.4857		.4943	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
HEMOLYMPHORET. SYS	Lymphoma malignant	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.6	46.4	43.6	42.5
	Lymphoma malignant, pleomorphic	Female	p-value of test of trend or comparison	.4971		.4941	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	43.0	43.1
		Male	p-value of test of trend or comparison	.4234	1	1	.7412
			Number of animals reported with tumor	1	0	0	1
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	2.4%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Malignant fibrous histiocytoma	Male	p-value of test of trend or comparison	.2443			.4943
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	43.4
	Sarcoma histiocytic	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
		Male	p-value of test of trend or comparison	.0566			.2356
			Number of animals reported with tumor	0	0	0	2
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	4.7%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
KIDNEYS	Renal lipoma	Female	p-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Renal liposarcoma	Female	*p*-value of test of trend or comparison	.7485	.5000		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
		Male	*p*-value of test of trend or comparison	.9379	.7638	1	1
			Number of animals reported with tumor	1	1	0	0
			Poly-3 adjusted incidence rate	2.2%	2.2%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.9	46.4	43.6	42.5
	Sarcoma infiltrate/s or metastas	Female	*p*-value of test of trend or comparison	.4971		.4941	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Tumor mesenchymal malignant	Female	*p*-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.8
LARYNX	Basosquamous cell carcinoma	Female	*p*-value of test of trend or comparison	.7485	.5000		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Squamous cell carcinoma, pharynx	Female	*p*-value of test of trend or comparison	.7485	.5000		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
LIVER	Adenoma hepatocellular	Female	*p*-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
		Male	*p*-value of test of trend or comparison	.7486	.5111		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.2%	0.0%	0.0%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Cholangiocarcinoma	Male	p-value of test of trend or comparison	.9379	.7638	1	1
			Number of animals reported with tumor	1	1	0	0
			Poly-3 adjusted incidence rate	2.3%	2.2%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Cholangioma	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	2	0	0	0
			Poly-3 adjusted incidence rate	4.6%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.3	43.1	42.7	43.1
LUNGS	Alveolar/bronchiolar adenoma	Male	p-value of test of trend or comparison	.2400			.4884
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.4%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Bronchiolo−alveolar carcinoma	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Carcinoma squamous cell	Female	p-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.7
MAMMARY GLAND	Adenocarcinoma	Female	p-value of test of trend or comparison	.9803	.9419	.9391	1
			Number of animals reported with tumor	3	1	1	0
			Poly-3 adjusted incidence rate	7.0%	2.3%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.3	42.9	43.1
	Adenocarcinoma, with hemorrhage	Female	p-value of test of trend or comparison	.2558			.5057
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	44.0
	Adenoma	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Adenoma, cystic	Female	p-value of test of trend or comparison	.8107	.2471		
			Number of animals reported with tumor	0	2	0	0
			Poly-3 adjusted incidence rate	0.0%	4.6%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Fibroadenoma	Female	p-value of test of trend or comparison	.0618	.0548	.1727	.0312
			Number of animals reported with tumor	1	6	4	7
			Poly-3 adjusted incidence rate	2.3%	14%	9.4%	16%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	44.3
	Fibroadenoma, multiple	Female	p-value of test of trend or comparison	.1806	.8794	1	.5000
			Number of animals reported with tumor	2	1	0	3
			Poly-3 adjusted incidence rate	4.6%	2.3%	0.0%	6.9%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.3
	Fibroadenoma, multiple, one aden	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Fibroadenoma, with superficial i	Female	p-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.5
	Fibroma, cystic	Female	p-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
MESENT. LYMPH NODE	Hemangioma	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.9	46.4	42.9	42.5
	Hemangiosarcoma	Male	p-value of test of trend or comparison	.4277	1	1	.7471
			Number of animals reported with tumor	1	0	0	1
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	2.4%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	43.7	46.4	42.9	42.5
	Hemangiosarcoma, multiple	Male	p-value of test of trend or comparison	.4855		.4941	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	43.7	46.4	42.9	42.5
MESENTERY	Hemangioma	Male	p-value of test of trend or comparison	.7486	.5111		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.2%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
NOSE	Carcinoma squamous cell, with in	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.5	46.4	43.6	42.5
OVARIES	Adenoma tubulostromal	Female	p-value of test of trend or comparison	.5000		.5000	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	43.3	43.1
	Thecoma benign	Female	p-value of test of trend or comparison	.3136	.5000		.5000
			Number of animals reported with tumor	0	1	0	1
			Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Tumor granulosa cell benign	Female	p-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
PANCREAS	Acinar cell adenocarcinoma	Male	p-value of test of trend or comparison	.7529	.5169		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.2%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.7	46.4	43.6	42.5
	Adenoma acinar	Female	p-value of test of trend or comparison	.3136	.5000		.5000
			Number of animals reported with tumor	0	1	0	1
			Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	2.3%

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Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
		Male	p-value of test of trend or comparison	.4855		.2471	
			Number of animals reported with tumor	0	0	2	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	4.6%	0.0%
			Poly-3 adjusted number of animals at risk	43.7	46.4	43.9	42.5
	Adenoma acinar, multiple	Male	p-value of test of trend or comparison	.2414			.4941
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.4%
			Poly-3 adjusted number of animals at risk	43.7	46.4	43.6	42.5
	Adenoma islet cell	Female	p-value of test of trend or comparison	.4971		.4941	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
		Male	p-value of test of trend or comparison	.3056	.5169		.4941
			Number of animals reported with tumor	0	1	0	1
			Poly-3 adjusted incidence rate	0.0%	2.2%	0.0%	2.4%
			Poly-3 adjusted number of animals at risk	43.7	46.4	43.6	42.5
	Adenoma islet cell, with hemorrh	Male	p-value of test of trend or comparison	.4885		.5000	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	43.7	46.4	43.6	42.5
PITUITARY GLAND	Adenoma pars distalis	Female	p-value of test of trend or comparison	.9788	.8092	.3958	.9926
			Number of animals reported with tumor	8	6	10	2
			Poly-3 adjusted incidence rate	18%	14%	23%	4.6%
			Poly-3 adjusted number of animals at risk	43.4	43.6	43.5	43.5
		Male	p-value of test of trend or comparison	.3955	.1763	.2073	.3305
			Number of animals reported with tumor	3	7	6	5
			Poly-3 adjusted incidence rate	6.8%	15%	14%	12%
			Poly-3 adjusted number of animals at risk	44.4	46.4	41.6	42.5
	Adenoma pars distalis, multiple	Female	p-value of test of trend or comparison	.4406	1	.2991	.7529
			Number of animals reported with tumor	1	0	3	1
			Poly-3 adjusted incidence rate	2.3%	0.0%	7.0%	2.3%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	43.1	43.1	43.0	43.1
	Adenoma pars distalis, with chol	Female	p-value of test of trend or comparison	.7485	.5000		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.3	42.7	43.1
	Carcinoma pars distalis	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Carcinoma pars distalis, invasio	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
PREPUTIAL GLANDS	Adenoma, unilateral	Male	p-value of test of trend or comparison	.2515			.5125
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.4%
			Poly-3 adjusted number of animals at risk	39.8	44.4	39.1	41.5
	Adenoma, unilateral with squamou	Male	p-value of test of trend or comparison	.4908		.5000	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.6%	0.0%
			Poly-3 adjusted number of animals at risk	39.8	44.4	39.1	41.5
	Schwannoma malignant, unilateral	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.8	44.4	39.1	41.5
	Squamous cell carcinoma	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.9	44.4	39.1	41.5
	Squamous cell papilloma, unilate	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.5%	0.0%	0.0%	0.0%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	39.8	44.4	39.1	41.5
SKIN	Carcinoma basal cell, basosquamo	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Carcinoma squamous cell, with ma	Male	p-value of test of trend or comparison	.4857		.4943	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Fibroma	Male	p-value of test of trend or comparison	.1867		.2414	.4884
			Number of animals reported with tumor	0	0	2	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	4.6%	2.3%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.8	42.9
	Fibroma, multiple	Male	p-value of test of trend or comparison	.2443			.4943
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	43.0
	Fibrosarcoma	Male	p-value of test of trend or comparison	.2400			.4884
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.4%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Keratoacanthoma	Male	p-value of test of trend or comparison	.8049	1	.7471	1
			Number of animals reported with tumor	1	0	1	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Keratoacanthoma, with inflammati	Male	p-value of test of trend or comparison	.2400			.4884
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.4%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Liposarcoma	Male	p-value of test of trend or comparison	.4857		.4943	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Papilloma	Male	p-value of test of trend or comparison	.4234	1	1	.7412
			Number of animals reported with tumor	1	0	0	1
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	2.4%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Schwannoma malignant, cystic	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.7	43.1	42.7	43.1
	Tumor hair follicle, benign, tri	Male	p-value of test of trend or comparison	.2400			.4884
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.4%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Tumor hair follicle, trichofolli	Male	p-value of test of trend or comparison	.4857		.4943	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
SPINAL CORD	Sarcoma infiltrate/s or metastas	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.1	43.1	42.7	43.1
SPLEEN	Sarcoma not otherwise specified	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.2%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.5	46.4	43.6	42.5
STERNUM	Hemangioma	Male	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
TESTES	Tumor Leydig cell benign	Male	p-value of test of trend or comparison	.8381	.7645	.9163	.9105
			Number of animals reported with tumor	6	5	3	3
			Poly-3 adjusted incidence rate	14%	11%	6.9%	7.1%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
	Tumor Leydig cell benign, multip	Male	p-value of test of trend or comparison	.7486	.5111		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.2%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	44.4	46.4	43.6	42.5
THYMUS	Thymoma benign	Female	p-value of test of trend or comparison	.9439	.7655	1	1
			Number of animals reported with tumor	1	1	0	0
			Poly-3 adjusted incidence rate	2.5%	2.4%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	39.7	41.1	41.7	42.1
		Male	p-value of test of trend or comparison	.5061		.5309	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	38.6	43.9	43.5	40.7
THYROID GLAND	Adenoma c−cell	Female	p-value of test of trend or comparison	.8389	.8200	.6620	.9419
			Number of animals reported with tumor	3	2	3	1
			Poly-3 adjusted incidence rate	7.0%	4.6%	7.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	43.0	43.1
		Male	p-value of test of trend or comparison	.4235	.6828	1	.6275
			Number of animals reported with tumor	3	3	0	3
			Poly-3 adjusted incidence rate	6.8%	6.5%	0.0%	7.2%
			Poly-3 adjusted number of animals at risk	44.4	46.5	42.6	41.9
	Adenoma c−cell, multiple	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Adenoma follicular cell	Female	p-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
		Male	p-value of test of trend or comparison	.1710	.2584		.2297
			Number of animals reported with tumor	0	2	0	2
			Poly-3 adjusted incidence rate	0.0%	4.3%	0.0%	4.8%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	44.4	46.4	42.6	41.9
	Adenoma follicular cell, cystic	Male	*p*-value of test of trend or comparison	.2370			.4824
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.4%
			Poly-3 adjusted number of animals at risk	44.4	46.3	42.6	41.9
TONGUE	Rhabdomyosarcoma	Female	*p*-value of test of trend or comparison	.4971		.4941	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Squamous cell papilloma	Female	*p*-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
URINARY BLADDER	Transitional cell papilloma	Female	*p*-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
UTERUS	Adenocarcinoma	Female	*p*-value of test of trend or comparison	.1990	1	.4911	.5000
			Number of animals reported with tumor	1	0	2	2
			Poly-3 adjusted incidence rate	2.3%	0.0%	4.7%	4.6%
			Poly-3 adjusted number of animals at risk	43.7	43.1	43.0	43.2
	Adenocarcinoma, arising in polyp	Female	*p*-value of test of trend or comparison	.5000		.5000	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	43.3	43.1
	Adenocarcinoma, arising in strom	Female	*p*-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Adenoma	Female	*p*-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Hemangioma	Female	p-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Polyp glandular	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Polyp stromal	Female	p-value of test of trend or comparison	.6952	.5182	.4814	.7399
			Number of animals reported with tumor	6	7	7	5
			Poly-3 adjusted incidence rate	14%	16%	16%	12%
			Poly-3 adjusted number of animals at risk	43.7	44.2	42.9	43.5
	Polyp stromal, multiple	Female	p-value of test of trend or comparison	.9819	1	.8936	1
			Number of animals reported with tumor	4	0	2	0
			Poly-3 adjusted incidence rate	9.3%	0.0%	4.7%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	43.0	43.1
	Polyp stromal, multiple, with in	Female	p-value of test of trend or comparison	.7485	.5000		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.6	42.7	43.1
	Polyp stromal, with cyst	Female	p-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.3%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Polyp stromal, with cysts	Female	p-value of test of trend or comparison	.2697	.7529	.7471	.5000
			Number of animals reported with tumor	1	1	1	2
			Poly-3 adjusted incidence rate	2.3%	2.3%	2.3%	4.6%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Polyp stromal, with necrosis, in	Female	p-value of test of trend or comparison	.5000		.5000	
			Number of animals reported with tumor	0	0	1	0
			Poly-3 adjusted incidence rate	0.0%	0.0%	2.3%	0.0%

Table 2.7: Reported neoplastic tumors in primary organs in rats (continued)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
			Poly-3 adjusted number of animals at risk	43.1	43.1	43.1	43.1
	Polyp stromal, with pigment	Female	*p*-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
	Sarcoma stromal, arising in poly	Female	*p*-value of test of trend or comparison	.6999	.8794	.8794	.8794
			Number of animals reported with tumor	2	1	1	1
			Poly-3 adjusted incidence rate	4.6%	2.3%	2.3%	2.3%
			Poly-3 adjusted number of animals at risk	43.5	43.1	43.3	43.1
	Schwannoma malignant	Female	*p*-value of test of trend or comparison	.7485	.5000		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.7	42.7	43.1
	Schwannoma malignant, cystic	Female	*p*-value of test of trend or comparison	.2515			.5000
			Number of animals reported with tumor	0	0	0	1
			Poly-3 adjusted incidence rate	0.0%	0.0%	0.0%	2.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.5
	Tumor granular cell benign	Female	*p*-value of test of trend or comparison	.7485	.5000		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.3%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.1
ZYMBAL GLANDS	Sebaceous cell adenoma	Female	*p*-value of test of trend or comparison	1	1	1	1
			Number of animals reported with tumor	1	0	0	0
			Poly-3 adjusted incidence rate	2.4%	0.0%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	42.3	42.1	38.3	40.8
	Squamous cell carcinoma	Female	*p*-value of test of trend or comparison	.7407	.5000		
			Number of animals reported with tumor	0	1	0	0
			Poly-3 adjusted incidence rate	0.0%	2.4%	0.0%	0.0%
			Poly-3 adjusted number of animals at risk	42.3	42.1	38.3	40.8

Table 2.8: Tumors for which at least one test was significant (rats)

Organ	Tumor type	Sex	Quantity	Control	Low dose	Mid dose	High dose
ADRENAL GLANDS	Adenoma, cortical	Female	p-value of test of trend or comparison	.0411	.5000	.0553	.0581
			Number of animals reported with tumor	0	1	4	4
			Poly-3 adjusted incidence rate	0.0%	2.3%	9.4%	9.3%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	43.2
		Male	p-value of test of trend or comparison	.3062	.5056	.2414	.4884
			Number of animals reported with tumor	0	1	2	1
			Poly-3 adjusted incidence rate	0.0%	2.2%	4.6%	2.4%
			Poly-3 adjusted number of animals at risk	44.4	45.6	43.6	42.5
MAMMARY GLAND	Fibroadenoma	Female	p-value of test of trend or comparison	.0618	.0548	.1727	.0312
			Number of animals reported with tumor	1	6	4	7
			Poly-3 adjusted incidence rate	2.3%	14%	9.4%	16%
			Poly-3 adjusted number of animals at risk	43.1	43.1	42.7	44.3

Table 2.9: Composite endpoint analyses (rats)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
Adrenal adenomas	Female	p-value of pairwise and trend tests	.0411	.5000	.0553	.0581
		Observed number of cases	0	1	4	4
		Poly-3 adjusted incidence rate	0%	2.3%	9.4%	9.3%
		Adjusted number at risk	43.14	43.05	42.74	43.24
	Male	p-value of pairwise and trend tests	.4196	.2528	.2414	.4884
		Observed number of cases	0	2	2	1
		Poly-3 adjusted incidence rate	0%	4.4%	4.6%	2.4%
		Adjusted number at risk	44.42	45.59	43.56	42.48
Pheochromocytomas	Female	p-value of pairwise and trend tests	.3181	.3080	.0956	.3080
		Observed number of cases	1	3	5	3
		Poly-3 adjusted incidence rate	2.3%	6.8%	12%	6.9%
		Adjusted number at risk	43.14	43.89	42.74	43.47

Table 2.9: Composite endpoint analyses in mice (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
	Male	p-value of pairwise and trend tests	.5608	.4157	.8852	.5902
		Observed number of cases	21	24	16	20
		Poly-3 adjusted incidence rate	47%	51%	36%	46%
		Adjusted number at risk	45.15	47.23	44.81	43.72
Astrocytomas	Male	p-value of pairwise and trend tests	.4234	1	1	.7412
		Observed number of cases	1	0	0	1
		Poly-3 adjusted incidence rate	2.3%	0%	0%	2.3%
		Adjusted number at risk	44.42	46.40	43.56	42.94
Clitoral squamous tumors	Female	p-value of pairwise and trend tests	.0584	1	1	.3174
		Observed number of cases	1	0	0	3
		Poly-3 adjusted incidence rate	2.6%	0%	0%	7.6%
		Adjusted number at risk	38.92	34.36	35.75	39.61
Dermal fibromas	Male	p-value of pairwise and trend tests	.0668	.	.2414	.2414
		Observed number of cases	0	0	2	2
		Poly-3 adjusted incidence rate	0%	0%	4.6%	4.6%
		Adjusted number at risk	44.42	46.40	43.82	43.51
All hemangiomas	Female	p-value of pairwise and trend tests	.2515	.	.	.5000
		Observed number of cases	0	0	0	1
		Poly-3 adjusted incidence rate	0%	0%	0%	2.3%
		Adjusted number at risk	43.14	43.05	42.74	43.08
	Male	p-value of pairwise and trend tests	.9849	.8873	1	1
		Observed number of cases	2	1	0	0
		Poly-3 adjusted incidence rate	4.5%	2.2%	0%	0%
		Adjusted number at risk	44.55	46.40	43.56	42.52
All hemangiosarcomas	Male	p-value of pairwise and trend tests	.4213	1	.7471	.7412
		Observed number of cases	1	0	1	1

Table 2.9: Composite endpoint analyses in mice (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
		Poly-3 adjusted incidence rate	2.3%	0%	2.3%	2.4%
		Adjusted number at risk	44.42	46.40	43.56	42.52
All hepatocellular tumors	Female	*p*-value of pairwise and trend tests	.2515	.	.	.5000
		Poly-3 adjusted incidence rate	0%	0%	0%	2.3%
		Observed number of cases	0	0	0	1
		Adjusted number at risk	43.14	43.05	42.74	43.08
	Male	*p*-value of pairwise and trend tests	.7486	.5111	.	.
		Poly-3 adjusted incidence rate	0%	2.2%	0%	0%
		Observed number of cases	0	1	0	0
		Adjusted number at risk	44.42	46.40	43.56	42.48
Keratoacanthomas	Male	*p*-value of pairwise and trend tests	.4213	1	.7471	.7412
		Observed number of cases	1	0	1	1
		Poly-3 adjusted incidence rate	2.3%	0%	2.3%	2.4%
		Adjusted number at risk	44.42	46.40	43.56	42.52
Carcinomas of the lung	Female	*p*-value of pairwise and trend tests	.2515	.	.	.5000
		Observed number of cases	0	0	0	1
		Poly-3 adjusted incidence rate	0%	0%	0%	2.3%
		Adjusted number at risk	43.14	43.05	42.74	43.73
All lymphomas	Female	*p*-value of pairwise and trend tests	.4971	.	.4941	.
		Observed number of cases	0	0	1	0
		Poly-3 adjusted incidence rate	0%	0%	2.3%	0%
		Adjusted number at risk	43.14	43.05	42.98	43.08
	Male	*p*-value of pairwise and trend tests	.5775	1	1	.8706
		Observed number of cases	2	0	0	1
		Poly-3 adjusted incidence rate	4.5%	0%	0%	2.4%
		Adjusted number at risk	44.55	46.40	43.56	42.52

Table 2.9: Composite endpoint analyses in mice (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
Mammary adenocarcinomas	Female	*p*-value of pairwise and trend tests	.8211	.9419	.9391	.9446
		Observed number of cases	3	1	1	1
		Poly-3 adjusted incidence rate	7.0%	2.3%	2.3%	2.3%
		Adjusted number at risk	43.14	43.31	42.90	44.03
Mammary fibroadenomas	Female	*p*-value of pairwise and trend tests	.0307	.2601	.6302	.0530
		Observed number of cases	4	7	4	11
		Poly-3 adjusted incidence rate	9.3%	16%	9.4%	24%
		Adjusted number at risk	43.14	43.05	42.74	45.00
Mesentheric hemangiosarcomas	Male	*p*-value of pairwise and trend tests	.4213	1	.7471	.7412
		Observed number of cases	1	0	1	1
		Poly-3 adjusted incidence rate	2.3%	0%	2.3%	2.4%
		Adjusted number at risk	44.42	46.40	43.56	42.52
	Male	*p*-value of pairwise and trend tests	.1752	.	.4943	.4884
		Observed number of cases	0	0	1	1
		Poly-3 adjusted incidence rate	0%	0%	2.3%	2.4%
		Adjusted number at risk	44.42	46.40	43.56	42.54
Pancreatic adenomas	Female	*p*-value of pairwise and trend tests	.2963	.5000	.4941	.5000
		Observed number of cases	0	1	1	1
		Poly-3 adjusted incidence rate	0%	2.3%	2.3%	2.3%
		Adjusted number at risk	43.14	43.05	42.74	43.08
	Male	*p*-value of pairwise and trend tests	.1653	.5169	.1206	.2412
		Observed number of cases	0	1	3	2
		Poly-3 adjusted incidence rate	0%	2.2%	6.8%	4.7%
		Adjusted number at risk	43.75	46.40	43.86	42.48
Pituitary adenomas	Female	*p*-value of pairwise and trend tests	.9708	.7967	.2295	.9870
		Observed number of cases	9	7	13	3
		Poly-3 adjusted incidence rate	21%	16%	30%	6.9%

Table 2.9: Composite endpoint analyses in mice (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
		Adjusted number at risk	43.35	43.88	43.75	43.47
	Male	p-value of pairwise and trend tests	.3955	.1763	.2073	.3305
		Observed number of cases	3	7	6	5
		Poly-3 adjusted incidence rate	6.8%	15%	14%	12%
		Adjusted number at risk	44.42	46.40	41.65	42.48
Pituitary carcinomas	Female	p-value of pairwise and trend tests	1	1	1	1
		Observed number of cases	2	0	0	0
		Poly-3 adjusted incidence rate	4.6%	0%	0%	0%
		Adjusted number at risk	43.14	43.05	42.74	43.08
Systemic tumors	Female	p-value of pairwise and trend tests	.8107	1	.7471	1
		Observed number of cases	1	0	1	0
		Poly-3 adjusted incidence rate	2.3%	0%	2.3%	0%
		Adjusted number at risk	43.14	43.05	42.98	43.08
	Male	p-value of pairwise and trend tests	.0362	1	1	.3271
		Observed number of cases	2	0	0	4
		Poly-3 adjusted incidence rate	4.5%	0%	0%	9.2%
		Adjusted number at risk	44.55	46.40	43.56	43.40
Testicular Leydig cell tumors	Male	p-value of pairwise and trend tests	.8645	.6526	.9163	.9105
		Observed number of cases	6	6	3	3
		Poly-3 adjusted incidence rate	14%	13%	6.9%	7.1%
		Adjusted number at risk	44.42	46.40	43.56	42.48
Thyroidal adenomas	Female	p-value of pairwise and trend tests	.7541	.8990	.7834	.8990
		Observed number of cases	4	2	3	2
		Poly-3 adjusted incidence rate	9.3%	4.6%	7.0%	4.6%
		Adjusted number at risk	43.05	43.11	43.04	43.08
	Male	p-value of pairwise and trend tests	.1105	.3823	1	.2073

Table 2.9: Composite endpoint analyses in mice (continued)

Endpoint	Sex	Quantity	Control	Low dose	Mid dose	High dose
		Observed number of cases	3	5	0	6
		Poly-3 adjusted incidence rate	6.8%	11%	0%	14%
		Adjusted number at risk	44.42	46.54	42.56	41.88
Uterine adenocarcinomas	Female	*p*-value of pairwise and trend tests	.3659	1	.5000	.6920
		Observed number of cases	2	0	3	2
		Poly-3 adjusted incidence rate	4.6%	0%	6.9%	4.6%
		Adjusted number at risk	43.65	43.05	43.50	43.19
Uterine stromal polyps	Female	*p*-value of pairwise and trend tests	.9254	.9223	.8036	.9707
		Observed number of cases	15	10	12	8
		Poly-3 adjusted incidence rate	34%	22%	27%	18%
		Adjusted number at risk	44.05	44.74	43.99	43.47

Table 2.10: Tumors found in organs presumed to be secondary (rats)

Sex	Organ or Tissue Name	Tumor Name	Quantity	Control	Low dose	Mid dose	High dose
Rats - Female	BONE	Osteosarcoma	Number of tumors found	0	0	0	1
			Number of animals examined	0	0	0	1
Rats - Male	BODY CAVITIES	Sarcoma not otherwise specified, mediastinum	Number of tumors found	0	0	1	0
			Number of animals examined	0	0	1	1
	BONE	Fibrosarcoma, with inflammation	Number of tumors found	1	0	0	0
			Number of animals examined	2	0	1	1
		Odontoma, ameloblastic	Number of tumors found	0	0	1	0
			Number of animals examined	2	0	1	1

2.3 Autolytic and unexamined organs

2.3.1 Unexamined animals

There were no rats for which it was reported that not a single organ had been analyzed.

2.3.2 Autolytic organs

Two organs were reported as autolytic to the extent that no usable sample could be obtained. They were the pituitary and thyroid glands of the same rat, animal number 59, a male animal in the low dose group. This autolysis rate is not sufficient to cause any concern about the integrity of the study.

2.3.3 Unexamined organs

A number of organs were reported as unexamined in various animals. These numbers of such organs are reported in table 2.11. While it is not surprising that the organs designated as secondary (see table 2.6) are unexamined in virtually all animals, there is also cause for concern with regards to the clitoral gland (in female rats), the preputial gland and thymus (in male rats) and the Zymbal glands (both male and female rats). Of these, the organ type that cause the greatest concern is the result for the clitoral glands, which were unexamined in at least 10% of animals in each treatment group.

Since that this is a relatively small study, with just 50 animals per arm, the implications of significant numbers of organs being left unexamined are more serious than they would be in a larger study. The case of the clitoral glands is still more worrying given that squamous cell carcinomas of the clitoral gland only narrowly avoided statistical significance (the p-value for the test of trend was 0.07), with two cases being reported in the high dose group, and none in the other treatment groups.

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Table 2.11: Frequency of organs reported unexamined in rat study

Organ or tissue name	Female										Male									
	Control		Low Dose		Mid Dose		High Dose		Total		Control		Low Dose		Mid Dose		High Dose		Total	
ADRENAL GLANDS	.	.	.	.	.	.	.	.			.	.	1	2.0%	.	.	1	2.0%	2	1.0%
BODY CAVITIES	49	98%	50	100%	49	98%	49	98%	197	99%	50	100%	50	100%	49	98%	49	98%	198	99%
BONE	50	100%	50	100%	50	100%	49	98%	199	100%	48	96%	50	100%	49	98%	49	98%	196	98%
BRAIN	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
CLITORAL GLANDS	7	14%	10	20%	8	16%	5	10%	30	15%	.	.	.	.	.	.	.	.	.	.
EYES	.	.	.	.	.	.	.	.	.	.	1	2.0%	.	.	.	.	2	4.0%	3	1.5%
FEMUR	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	4.0%	2	1.0%
HARDERIAN GLANDS	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	4.0%	2	1.0%
HEART	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
KIDNEYS	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
LARYNX	1	2.0%	.	.	.	.	.	.	1	0.5%	1	2.0%	.	.	1	2.0%	2	4.0%	4	2.0%
LIVER	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
LUNGS	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
LYMPH NODES	46	92%	50	100%	49	98%	50	100%	195	98%	49	98%	49	98%	46	92%	48	96%	192	96%
MAMMARY GLAND	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
MESENT. LYMPH NODE	.	.	.	.	.	.	.	.	.	.	1	2.0%	.	.	1	2.0%	1	2.0%	3	1.5%
NOSE	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
PANCREAS	.	.	.	.	.	.	.	.	.	.	1	2.0%	.	.	.	.	1	2.0%	2	1.0%
PITUITARY GLAND	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	4.0%	1	2.0%	3	1.5%
PREPUTIAL GLANDS	.	.	.	.	.	.	.	.	.	.	5	10%	3	6.0%	6	12%	2	4.0%	16	8.0%
SKIN	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
SPINAL CORD	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
SPLEEN	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
STERNUM	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
TESTES	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	0.5%
THYMUS	4	8.0%	2	4.0%	2	4.0%	1	2.0%	9	4.5%	6	12%	3	6.0%	1	2.0%	4	8.0%	14	7.0%
THYROID GLAND	1	2.0%	.	.	1	2.0%	.	.	2	1.0%	.	.	.	.	1	2.0%	2	4.0%	3	1.5%
TONGUE	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	2	4.0%	3	1.5%
URINARY BLADDER	.	.	.	.	.	.	.	.	.	.	.	.	1	2.0%	1	2.0%	1	2.0%	3	1.5%
ZYMBAL GLANDS	2	4.0%	2	4.0%	6	12%	3	6.0%	13	6.5%	1	2.0%	9	18%	2	4.0%	4	8.0%	16	8.0%

Chapter 3

Evaluation of the validity of the study

3.1 Issues of concern when selecting dose levels

The decision 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 [6] 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 [6] 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 [4], 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 [4], the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met:

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

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

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

3.2 Assessing the validity of the mouse study

With the arguable exception of hepatocellular tumors in male mice, this study is considered a negative study. Before accepting these negative findings, it is necessary to consider whether sufficient animals faced a sufficient tumor challenging burden. In both sexes, well over 50% of the animals in each treatment group survived into the ninetieth week. Since each treatment group started with sixty animals, it follows that that Haseman's criterion has been met.

On the question of whether the animals faced an adequate tumor challenge, it is first important to note that there is no evidence (see section 1.2.2) of a dose related effect on mortality. On the question of weight gain, there is no evidence at all of diminished weight gain among the treated animals; on the contrary, the treated animals tended to exhibit greater weight gain that the control animals (see table 3.1).

It follows that in order to conclude that this study posed an adequate tumor challenge to the animals, there must be evidence of clinical signs of severe histopathologic toxic effects attributable to the chemical. It is beyond the scope of this statistical review to make such judgments; such a determination lies with the reviewing pharmacologist. However, in the event that no such clinical signs are found, the interpretability of the negative results must be called into question.

Table 3.1: Weight changes by group

Species and Sex	Δ_C	Δ_L	$\frac{\Delta_L}{\Delta_C} - 1$	Δ_M	$\frac{\Delta_M}{\Delta_C} - 1$	Δ_H	$\frac{\Delta_H}{\Delta_C} - 1$
Mice — Female	6.6	6.4	−3.0%	7.0	+6.1%	6.7	+1.5%
Mice — Male	7.5	8.0	+6.7%	8.1	+8.0%	8.3	+10.7%
Rats — Female	229	229	+0.0%	236	+3.1%	231	+0.9%
Rats — Male	359	359	+0.0%	381	+6.1%	387	+7.8%

3.3 Assessing the validity of the rat study

A similar situation applies to the rat study as to the mouse study. The study is putatively negative, but while the survival rates were high enough to rule out excessive toxicity (table 2.4), there is no evidence of a dose related increase in mortality (table 2.3) or a dose related reduction in weight gain (table 3.1), and so the dose levels can only be concluded to have provided an adequate tumor challenge to the animals if the reviewing pharmacologist finds clinical signs or evidence of histopathologic toxic effects attributable to the chemical. In the absence of such evidence, the negative results of the study must be treated with a greater than usual degree of skepticism, especially in light of the relatively small size of the study.

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Chapter 4

Conclusion

4.1 Mouse Study

Although several tests were significant at the 0.05 level, none remained significant after adjusting for multiplicity, so the study should be viewed as a negative study. The closest exception was the test for hepatocellular tumors in male mice, where the test of trend had a p-value of 0.0368, and the tests of comparison between both the mid and high dose group and the control had p-values of 0.0110. Since the observed incidence rate was 5 times higher in the treatment group than in the control group, further observation seems warranted, despite the nominally non-significant p-value.

It should also be noted that the evidence considered in this review is insufficient to conclude that the high dose level was close enough to the MTD to provide an adequate tumor challenge to the high dose animals. Absent clinical evidence from the pharmacological reviewer, the negative results of this study must be treated somewhat more conservatively than in other studies.

Regardless, this study should not be used to draw conclusions about any tumorigenic effect in the secondary organs (table 1.7); the number of animals for which these organs were analyzed was too small to be useful.

4.2 Rat study

As with the mouse study, several tests were significant at the 0.05 level, but none remained significant after adjusting for multiplicity. The study is thus a negative study. The rat study was also similar to the mouse study in that neither the survival data nor the weight data provides evidence that the maximum dose was close to the MTD. Unless the pharmacological reviewer identifies signs of toxicity or other clinical signs attributable to Rivaroxaban, the negative results of the study should be considered to hold less weight than is normal.

However, regardless of the pharmacological review's determinations, caution should be exercised when making any inference about the tumorigenic effects of Rivaroxaban in the clitoral glands. This is because 15% of female rats (at least 10% in each treatment group) have been reported as having had their clitoral glands unexamined. Since there were only 50 animals in each group to begin with, this means that at most 45 animals in each group had this organ analyzed.

Additionally, no inference should be made concerning the tumorigenic potential of Rivaroxaban in any of the secondary organs (table 2.6).

4.3 Discrepancies in p-values between sponsor's and reviewer's results

It is an interesting feature of this study that the p-values generated by the sponsor seem to be at odds with the independently generated p-values found in this review. The effect is especially

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noteworthy in the case of the mouse study, although this is largely because the sponsor neglected to included tables of p-values in the report of the rat study.

4.3.1 Tests of trend

The sponsor used two different trend tests; a "conventional Peto test" and an "exact Peto test". The trend tests used in this review were exact poly-3 tests. It is not surprising that the p-values generated by the conventional Peto test would be substantially smaller than those generated by other tests; it is well known that asymptotic tests are inappropriately liberal when dealing with rare events and/or small sample sizes. However, it is striking that for the few tests where exact Peto test p-values are presented, there is significant disagreement in reported p-values between the two exact methods.

Tests of trend work by fitting a linear incidence function of the form $I = m\delta + b$, where I is some measure of the tumor incidence rate and δ is a numerical representation of the dose level, and testing the null hypothesis that $m = 0$ against the alternate hypothesis that $m > 0$. There are two standard ways to represent dosage numerically; the values of the predictor δ can take ordinal values $(0, 1, 2, \ldots)$, or can take the actual dose levels $(0, 10, 20, 60)$. The effect of using ordinal values (as the sponsor has chosen to do) compared with actual levels (as has been done in the FDA review) is to build a test that is more sensitive to increases in incidence between the lower dose groups, and less sensitive to increases between the mid and high dose group. In a case where little or no increase in incidence is observed between the mid and high dose groups, a test based on actual values will tend to yield a less significant result.

Table 4.1 shows the p-values (taken from table 1.2) for the sponsor's exact Peto test, which uses ordinal values for dose levels, the p-values for the reviewer's exact poly-3 tests (Taken from tables 1.9 and 1.11), which use actual values, and p-values for analogous poly-3 tests of trend using ordinal values to represent dose levels. Results are only presented for those endpoints for which the sponsor has reported p-values for exact Peto tests (which, since the table of results from the rat study has been omitted, means that only results from the mouse study are included), and for which the estimated trend increasing. As can be seen from the table, the differences in p-values between the exact poly-3 test and the exact Peto test are largely attributable to the coding used for the predictor (dose level). This is not to say that one coding is necessarily better or more valid than another; the selection of a model reflects assumptions about the underlying physiological and pharmacological processes.

Table 4.1: Comparison of p-values of different tests of trend

Endpoint	Sex	p-value		
		Exact Peto (Ordinal)	Exact poly-3 (Ordinal)	Exact poly-3 (Actual)
Hepatocellular adenoma	Male	0.0687	0.0664	0.1279
Hepatocellular carcinoma	Male	0.0562	0.0749	0.1428
All hepatocellular tumors	Male	0.0089	0.0097	0.0368
Lymphoma	Female	0.0711	0.0846	0.1853
	Male	0.1356	0.1378	0.0807
Ovarian cystadenoma	Female	0.0581	0.0554	0.0554

4.3.2 Pairwise tests

The sponsor has tested differences in incidence rates between treated and control groups using Fisher's exact test. This is not a survival adjusted test. The FDA typically uses survival adjusted methods (such as the Poly-3 test) to allow for the comparison of rates between treated groups when different dose groups have different levels of toxicity - if a high dose group experienced significant early mortality then the Fisher's exact test would have a strong bias towards the null when considering late onset tumors. In this case however, there is no evidence of a dose related reduction

of survival. In such a case, Fisher's exact test tends to overcount the effective sample size, with the effect that for tail events, reported p-values are smaller than when using a survival adjusted method. This difference explains the entire difference between the p-values reported for pairwise tests of incidence in table 1.9 and the corresponding p-values presented in table 1.2.

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/s/

MATTHEW T JACKSON
05/11/2011

KARL K LIN
05/11/2011
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202439 **Applicant: Johnson & Johnson** **Stamp Date: 1/5/2011**

Drug Name: Rivaroxaban **NDA/BLA Type: NDA (Standard)**

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

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

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? **Yes**

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

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	√			
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			√	**No safety data reviewed**
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

Reference ID: 2900547

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Phillip Dinh, Ph.D.	02/03/2011
Reviewing Statistician	Date

Reference ID: 2900547

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PHILLIP V DINH
02/03/2011