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

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA211172
Drug Name:	Inotersen (ISIS 420915)
Indication(s):	Treatment of hereditary transthyretin amyloidosis (b) (4)
Applicant:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court, Carlsbad, CA 92010, USA
Laboratory:	Laboratory for mice study: (b) (4) (b) (4)
Date(s):	Received 11/06/2017
Documents Reviewed:	Study 420915-AS12 (transgenic mouse) and the electronic tumor.xpt file were submitted on 11/6/2017 (via S0001).
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Feng Zhou, M.S.
Concurring Reviewers:	Karl Lin, Ph. D., Team Leader
Medical Division:	Division of Neurology Drug Products (DNP)
Nonclinical Team:	David Hawver, Ph.D and Lois Freed, Ph.D
Project Manager:	Fannie (Yuet) Choy
Keywords:	Carcinogenicity, Dose response

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1 Summary

This review evaluates statistically the data of carcinogenicity study of ISIS 420915 when administered daily via subcutaneous to CByB6F1-Tg(HRAS)2Jic hemizygous transgenic mice for at least 26 weeks. The review analyzes the dose-response relationship of tumor incidence and mortality (including tumor-related mortality). The review concludes that there were no ISIS 420915 related effects on animal survival and no statistically significant increases of ISIS 420915- or 401724-related neoplasms in animals treated up to 80 mg/kg/week.

Mouse Study: Mice (25/sex/dose) were dosed by the subcutaneous injection with ISIS 420915 or ISIS 401724 daily for up to 26 weeks. The respective ISIS 420915 doses in the low (LD), mid (MD), and high-dose (HD) groups were 0, 10, 30, or 80 mg/kg/week, respectively, and 30 mg/kg/week of ISIS 401724 for male and female mice. The study had two control groups: vehicle control (VC) and positive control (PC). The positive control (PC) mice (10/sex) were dosed with 75-mg/kg N-methyl-N-nitrosourea (MNU).

The survival analysis showed no statistically significant effects on mortality in either trend analysis or pairwise comparison in ISIS 420915- or 401724 treatment groups in either sex. The pairwise comparisons showed a statistically significant increase in mortality between vehicle control and positive control ($p<0.0001$) for both males and females. The respective survival rates in the VC, LD, MD, HD, ISIS401724, and PC groups at the time they were terminated (Week 27) were 96%, 92%, 96%, 92%, 96%, and 70%, respectively, in male mice; 100%, 100%, 100%, 96%, 96%, and 70%, respectively, in female mice.

The tumor analysis did not show any statistically significant dose-response relationship in incidences in all tumor types tested in male and female mice. The PC group showed statistically significant increases in the incidence of several tumor types in both males and females ($p<0.05$), when compared against the vehicle control. Those tumor types were listed in following table.

Tumor Types with P-Values ≤ 0.05 for Pairwise Comparisons of VC and PC

Animals	Organ Name	Tumor Name	0 mg/kg/week C (N=25)	75 mg/kg PC (N=10)	P-Value C vs. PC
Male Mice	Skin	Papilloma, Squamous Cell	0/25 (25)	7/10 (9)	<0 0001*
	Stomach, Nonglandular	Papilloma, Squamous Cell	0/25/(25)	8/10 (9)	<0 0001*
Female Mice	Skin	Papilloma, Squamous Cell	0/25 (25)	3/10 (9)	0.0140*
	Stomach, Nonglandular	Papilloma, Squamous Cell	0/25 (25)	9/10 (9)	<0 0001*

Note: The p-values marked with an asterisk * indicate statistically significant pairwise comparison at 0 05.

2 Background

Inotersen (ISIS 420915) is a potent integrase strand-transfer inhibitor (INSTI) that is being evaluated for the treatment of hereditary transthyretin amyloidosis to delay disease progression and improve quality of life. The sponsor conducted two carcinogenicity studies in mouse and rat. The sponsor provided the study report 420915-AS12, A 26-weeks Oral Carcinogenicity Study in transgenic mice, on 11/6/2017 via submission NDA211172/eCTD S0001 with the electronic tumor.xpt. A 2-year rat carcinogenicity study (420915-AS13) is still ongoing and the in-life portion of study will be terminated in Q4 2017.

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. Results of this review have been discussed with the reviewing pharmacologist Dr. David Hawver.

3 Mouse Study- 420915-AS12

Study Report: 420915-as12.pdf (statistical report is on page 480);
SAS data: tumor.xpt

This study assessed the carcinogenic potential of ISIS 420915 (human specific TTR mRNA inhibitor) in CByB6F1-Tg(HRAS)2Jic hemizygous transgenic mice after a 26-week dosing period. A mouse specific TTR oligonucleotide (ISIS 401724) was used to evaluate the carcinogenic potential of reduced TTR mRNA. Four groups of 25 animals/sex/group were subcutaneously administered 10, 30, and 80 mg/kg/week ISIS 420915 or 30 mg/kg/week ISIS 401724 weekly (Days 1, 7, 14, 21, 28, etc. up to Day 182). A saline control group of 25 animals/sex received the saline control article in the same manner as the ISIS 420915 and ISIS 401724 groups. One additional group of 10 animals/sex served as a positive control and was dosed via intraperitoneal injection once on Day 1 at 75 mg/kg with the positive control article (N-Nitroso-N-methylurea (NMU); 7.5 mg/mL in citrate buffered saline at pH 4.5). This review refers these dose groups as the vehicle control (VC), low (LD), mid (MD), or high (HD) dose groups, ISIS 401724, and positive control (PC) respectively. Terminal sacrifice occurred on week 27 for animals in all groups. The analyses summarized herein do not include the data from the positive control group.

Assessment of toxicity was based on mortality, clinical observations, body weight, food consumption, clinical and anatomic pathology, and tissue toxicokinetic assessments. The analysis of TTR mRNA expression was also conducted to assess the carcinogenic potential related to exaggerated pharmacology.

3.1 Sponsor's Analyses

3.1.1 Survival Analysis

Intercurrent mortality data were analyzed using the Kaplan-Meier product-limit method.

An overall test comparing all groups was conducted using a log-rank test[7]. Any animal with accidental injury that causes its death or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. If this overall test is statistically significant ($p < 0.05$) and there are more than two groups, then a follow up analysis was done where each treatment group was compared to the control group using a log-rank test.

Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's concluded results: The numbers of study animals surviving to the scheduled terminal necropsy (necropsy count) at Day 184 were as follows (out of 25 animals/sex/group in the saline control and test article groups and 10 animals/sex in the positive control group):

Table E. Survival Rate

The number of animals surviving to the scheduled terminal necropsy (Day 184)*

Dose Level (mg/kg/week)	Male	Female	Overall (M+F)
0 (Saline Control)	24 (96%)	25 (100%)	49 (98%)
10	23 (92%)	25 (100%)	48 (96%)
30	24 (96%)	25 (100%)	49 (98%)
80	23 (92%)	24 (96%)	47 (94%)
30 (ISIS 401724)	24 (96%)	24 (96%)	48 (96%)
75 mg/kg (Positive Control)	7 (70%)	7 (80%)	14 (70%)

*Respective survival percentage calculations are included in parentheses [one female at 75 mg/kg (Positive Control) was found dead on the scheduled day of necropsy (Day 184)].

Thus, the incidence of mortality was slightly higher in the 80 mg/kg/week ISIS 420915 dose groups compared to the control group. The higher level of mortality in the positive control group was an expected outcome. Therefore, there is no test article-related or dose-dependent change in survival.

3.1.2 Tumor Data Analysis

The Poly-3 method[8, 9] was used to assess prevalence of tumors. The survival-adjusted rates based on the risk weights are displayed. The tests of significance are included both an overall trend and pair-wise comparisons of each treatment group with the control. All p-values were reported using upper-tailed test, unless otherwise indicated. Evaluation criteria (p-values of significance) were applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%) The evaluation criteria from the FDA are given in Table D (FDA)[10].

Table D. Evaluation Criteria for Common and Rare Tumors

Test for Positive Trends	Control-High Pair-wise Comparisons
Common and rare tumors were tested at 0.005 and 0.025 significance levels, respectively	Common and rare tumors were tested at 0.01 and 0.05 significance levels, respectively

Electronic data were provided for this study with the final report. The formats of the data sets were prepared following the guidelines of the U.S. Food and Drug Administration, Division of Biometrics[11,12].

Sponsor's findings: There were no statistically significant increases of ISIS 420915- or 401724-related neoplasms in animals treated up to 80 mg/kg/week. Based on the analysis of TTR mRNA expression in liver, ISIS 401724 at 30 mg/kg/week showed a significant reduction (65-70% reduction relative to control) after 26 weeks of treatment.

The sponsor concluded that collectively, the neoplasms that were present did not reach statistical significance after 26 weeks of treatment. Thus, ISIS 420915 did not produce any evidence of a carcinogenic effect in the CByB6F1-Tg(HRAS)2Jic hemizygous transgenic mouse model system.

3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer analyzed the SAS data sets of this study received on 11/6/2017 (via S0001). The dose unit of mg/kg/week hereinafter referred to as mkw.

3.2.1 Survival Analysis

The survival distributions of mice in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female mice, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of deaths that occurred prior to termination of the group were 1 (4%), 2 (8%), 1 (4%), 2 (8%), 1 (4%), and 3 (30%) in male mice and 0 (0%), 0 (0%), 0 (0%), 1 (4%), 1 (4%), and 3 (30%) in female mice in the VC, LD, MD, HD of ISIS 420915, ISIS 401724 30 mkw, and PC groups, respectively. The tests didn't show any statistically significant dose response relationship in mortality across controls and treated groups in both sexes. For both males and females, the positive control group showed significantly increasing mortality over the control group ($p<0.0001$ in all cases).

3.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the papers of Bailer and Portier [2] and Bieler and Williams [3]. In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without developing the tumor before the end

of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k < 1$. The adjusted group size is defined as Σs_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 Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor of the tumor type being tested, 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. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

Multiple testing adjustments currently follow the rules displayed in Table 12.6. [5, 6]

Table 12.6 Recommended decision rules (levels of significance) for controlling the overall false positive rates for various statistical tests performed and submission types

Submission type		Tumor type	Decision rule			
			Trend test alone	Pairwise test alone	Joint test	
					Trend test	Pairwise test
Standard 2 year study with two sexes and two species		Common	0.005	0.01	0.005	0.05
		Rare	0.025	0.05	0.025	0.10
Alternative ICH Studies (One 2-year study in one species and one short- or medium-term alternative study, two sexes)	Two-year study	Common	0.005	0.01	0.005	0.05
		Rare	0.025	0.05	0.025	0.10
	Short- or medium-term alternative study	Common	0.05	0.05	0.05	0.05
		Rare	0.05	0.05	0.05	0.05
Standard 2 year studies with two sexes and one species		Common	0.01	0.025	0.01	0.05
		Rare	0.05	0.10	0.05	0.10

Because of the small group size and short study duration used in transgenic mouse studies, based on the statistical guideline for transgenic mouse studies, the significance level of 0.05 was used in the tests for dose response and pairwise comparisons in tumor incidences of both rare and common tumors.

The tumor rates and the p-values of the tested tumor types are listed in Tables 3A for male mice and 3B for female mice in the appendix.

Reviewer's findings: Based on this recommendation of adjustment for multiple testing discussed above, the tumor data analysis did not show any statistically significant dose-response relationship and pairwise comparison in incidence in all tumor types tested in male and female mice.

The positive control (PC) group showed statistically significant increases in the incidence of several tumors in both males and females ($p<0.05$), when compared to the vehicle control. Those tumor types were listed in the table below.

Tumor Types with P-Values ≤ 0.05 for Pairwise Comparisons of VC and PC

Animals	Organ Name	Tumor Name	0 mg/kg/week C (N=25)	75 mg/kg PC (N=10)	P-Value C vs. PC
Male Mice	Skin	Papilloma, Squamous Cell	0/25 (25)	7/10 (9)	<0.0001
	Stomach, Nonglandular	Papilloma, Squamous Cell	0/25/(25)	8/10 (9)	<0.0001
Female Mice	Skin	Papilloma, Squamous Cell	0/25 (25)	3/10 (9)	0.0140
	Stomach, Nonglandular	Papilloma, Squamous Cell	0/25 (25)	9/10 (9)	<0.0001

Note: The p-values marked with an asterisk * indicate statistically significant pairwise comparison at 0 05.

Feng Zhou
Mathematical Statistician

Concurring Reviewer: Karl Lin, Ph.D., Team Leader, Biometrics-6

cc:
Dr. David Hawver
Dr. Lois Freed
Dr. Yi Tsong
Dr. Karl Lin
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File Name: NDA211172Carcin.doc

4 Appendix

Table 1A: Intercurrent Mortality Rate in Male Mice

	0 mkw Vehicle Control		10 mkw/Low ISIS-420915		30 mkw/Mid ISIS-420915		80 mkw/High ISIS-420915		30 mkw ISIS-401724		75 mg Positive Control	
Week / Type of Death	No of Death	Cum %	No of Death	Cum %	No of Death	Cum %	No of Death	Cum %	No of Death	Cum %	No of Death	Cum %
0 - 13					1	4 00	1	4 00				
14 - 26	1	4 00	2	8 00			1	8 00	1	4 00	3	30 00
Terminal sacrifice	24	96 00	23	92 00	24	96 00	23	92 00	24	96 00	7	70 00
Total	25		25		25		25		25		10	

All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 1B: Intercurrent Mortality Rate in Female Mice

	0 mkw Vehicle Control		10 mkw/Low ISIS-420915		30 mkw/Mid ISIS-420915		80 mkw/High ISIS-420915		30 mkw ISIS-401724		75 mg Positive Control	
Week / Type of Death	No of Death	Cum %	No of Death	Cum %	No of Death	Cum %	No of Death	Cum %	No of Death	Cum %	No of Death	Cum %
14 - 26							1	4 00	1	4 00	3	30 00
Terminal sacrifice	25	100 00	25	100 00	25	100 00	24	96 00	24	96 00	7	70 00
Total	25		25		25		25		25		10	

All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 2A: Intercurrent Mortality Comparison in Male Mice

Test	All ISIS-420915 Dose Groups	Control vs. ISIS-420915 10 mkw	Control vs. ISIS-420915 30 mkw	Control vs. ISIS-420915 80 mkw	Control vs. ISIS-401724 30 mkw	Control vs. Positive Control
Dose-Response (Likelihood Ratio)	0 6518	0 5521	0 9912	0 5362	0 9912	0 0400
Homogeneity (Log-Rank)	0 8190	0 5557	0 9912	0 5396	0 9912	0 0237

#All Cum % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level

Table 2B: Intercurrent Mortality Comparison in Female Mice

Test	All ISIS-420915 Dose Groups	Control vs. ISIS-420915 10 mkw	Control vs. ISIS-420915 30 mkw	Control vs. ISIS-420915 80 mkw	Control vs. ISIS-401724 30 mkw	Control vs. Positive Control
Dose-Response (Likelihood Ratio)	0 2283		0 3678	0 2390	0 3678	0 0047
Homogeneity (Log-Rank)	0 6180		0 4795	0 3173	0 4795	0 0038

#All Cum % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons – Male Mice

Organ name	Tumor name	Vehicle (VC) 0 mkw P - Trend	Low (L) 10 mkw P - VC vs. L	Mid (M) 30 mkw P - VC vs. M	High (H) 80 mkw P - VC vs. H	ISIS 401724 30 mkw P - VC vs. ISIS 401724	Positive (PC) 75 mg P - VC vs. PC
Adipose Tissue, Abdominal	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
Aorta	Lymphoma	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
Bone, Sternum	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
	Lymphoma	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (23)	0/25 (25)	1/10 (9)
		0 4948	NC	0 5000	NC	NC	0 2647
Epididymides	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
	Sarcoma, Stromal [P]	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	1/25 (25)	0/10 (9)
		NC	NC	NC	NC	0 5000	NC
Heart	Lymphoma	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (23)	0/25 (25)	1/10 (9)
		0 4948	NC	0 5000	NC	NC	0 2647
Injection Site, Interscapular	Papilloma, Squamous Cell [P]	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
Injection Site, Proximal To Tail	Papilloma, Squamous Cell [P]	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
Kidneys	Lymphoma	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (23)	0/25 (25)	1/10 (9)
		0 4948	NC	0 5000	NC	NC	0 2647
Liver	Lymphoma	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (23)	0/25 (25)	1/10 (9)
		0 4948	NC	0 5000	NC	NC	0 2647
Lung	Adenoma, Bronchiolar Alveolar [P]	3/25 (25)	2/25 (24)	4/25 (24)	1/25 (23)	3/25 (25)	0/10 (9)
		0 7911	0 8129	0 4762	0 9350	NC	1 0000
	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
	Lymphoma	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (23)	0/25 (25)	1/10 (9)
		0 4948	NC	0 5000	NC	NC	0 2647
Lymph Node, Mandibular	Lymphoma	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
Lymph Node, Mediastinal	Lymphoma	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (23)	0/25 (25)	0/10 (9)
		0 4948	NC	0 5000	NC	NC	NC
Multicentric Neoplasm	Hemangiosarcoma [P]	1/25 (25)	3/25 (24)	0/25 (24)	2/25 (23)	2/25 (25)	1/10 (9)
		0 4304	0 2890	1 0000	0 4681	0 5000	0 4652
	Lymphoma [P]	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (23)	0/25 (25)	1/10 (9)
		0 4948	NC	0 5000	NC	NC	0 2647
Pancreas	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
	Mesothelioma	0/25 (25)	1/25 (25)	0/25 (24)	0/25 (23)	0/25 (25)	0/10 (9)
		0 7423	0 5000	NC	NC	NC	NC
Preputial Glands	Hemangiosarcoma	1/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	1/25 (25)	0/10 (9)
		1 0000	1 0000	1 0000	1 0000	NC	1 0000

Prostate Gland	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
	Hemangiosarcoma	0/25 (25)	0/25 (24)	0/25 (24)	1/25 (23)	0/25 (25)	0/10 (9)
		0 2396	NC	NC	0 4792	NC	NC
Skeletal Muscle, Diaphragm	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
Skin	Carcinoma, Squamous Cell [P]	1/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	0/10 (9)
		1 0000	1 0000	1 0000	1 0000	1 0000	1 0000
	Hemangiosarcoma	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	1/25 (25)	0/10 (9)
		NC	NC	NC	NC	0 5000	NC
	Papilloma, Squamous Cell [P]	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	7/10 (9)
		NC	NC	NC	NC	NC	0 0000 $
Small Intestine, Ileum	Hemangiosarcoma	1/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	0/10 (9)
		1 0000	1 0000	1 0000	1 0000	1 0000	1 0000
Spleen	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
	Hemangiosarcoma	0/25 (25)	2/25 (24)	0/25 (24)	1/25 (23)	1/25 (25)	1/10 (9)
		0 4198	0 2347	NC	0 4792	0 5000	0 2647
	Lymphoma	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (23)	0/25 (25)	0/10 (9)
		0 4948	NC	0 5000	NC	NC	NC
Stomach, Glandular	Carcinoma, Squamous Cell [P]	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
Stomach, Nonglandular	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
	Papilloma, Squamous Cell [P]	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	8/10 (9)
		NC	NC	NC	NC	NC	0 0000 $
Testes	Hemangiosarcoma	0/25 (25)	1/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	0/10 (9)
		0 7396	0 4898	NC	NC	NC	NC
Thymus	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
	Lymphoma	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (23)	0/25 (25)	1/10 (9)
		0 4948	NC	0 5000	NC	NC	0 2647
	Thymoma [P]	0/25 (25)	0/25 (24)	0/25 (24)	1/25 (23)	1/25 (25)	0/10 (9)
		0 2396	NC	NC	0 4792	0 5000	NC
Urinary Bladder	Carcinoma, Squamous Cell	0/25 (25)	0/25 (24)	0/25 (24)	0/25 (23)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
	Mesothelioma [P]	0/25 (25)	1/25 (25)	0/25 (24)	0/25 (23)	0/25 (25)	0/10 (9)
		0 7423	0 5000	NC	NC	NC	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable
Note: In all tumor tables, a tumor marked with "P" is a primary tumor and the tumors without any mark are the secondary or multicentric tumors.

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons – Female Mice

Organ name	Tumor name	Vehicle (VC) 0 mkw P - Trend	Low (L) 10 mkw P - VC vs. L	Mid (M) 30 mkw P - VC vs. M	High (H) 80 mkw P - VC vs. H	ISIS 401724 30 mkw P - VC vs. ISIS 401724	Positive (PC) 75 mg P - VC vs. PC
Adrenal Glands	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756

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Organ name	Tumor name	Vehicle (VC) 0 mkw P - Trend	Low (L) 10 mkw P - VC vs. L	Mid (M) 30 mkw P - VC vs. M	High (H) 80 mkw P - VC vs. H	ISIS 401724 30 mkw P - VC vs. ISIS 401724	Positive (PC) 75 mg P - VC vs. PC
Aorta	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
Bone Marrow, Femur	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
Bone Marrow, Sternum	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (10)
		NC	NC	NC	NC	NC	0 2857
Bone, Sternum	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
Brain	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (10)
		NC	NC	NC	NC	NC	0 2857
Clitoral Glands	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
	Mesothelioma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
	Sarcoma, Stromal [P]	0/25 (25)	0/25 (25)	0/25 (25)	1/25 (24)	0/25 (25)	0/10 (9)
		0 2424	NC	NC	0 4898	NC	NC
Eyes	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (10)
		NC	NC	NC	NC	NC	0 2857
Eyes, Optic Nerves	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (10)
		NC	NC	NC	NC	NC	0 2857
Gallbladder	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
	Mesothelioma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
Harderian Glands	Adenocarcinoma [P]	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	1/25 (25)	0/10 (9)
		NC	NC	NC	NC	0 5000	NC
	Adenoma [P]	0/25 (25)	2/25 (25)	3/25 (25)	0/25 (24)	2/25 (25)	1/10 (9)
		0 7242	0 2449	0 1173	NC	0 2449	0 2647
	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
Heart	Carcinoma, Bronchiolar Alveol	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
	Mesothelioma [P]	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	1/25 (25)	0/10 (9)
		NC	NC	NC	NC	0 5000	NC
Injection Site, Interscapular	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
Injection Site, Proximal To Tail	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (10)
		NC	NC	NC	NC	NC	0 2857
Kidneys	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
Liver	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756

	Mesothelioma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/10 (9) 0 2647
Lung	Adenoma, Bronchiolar Alveolar [P]	2/25 (25) 0 9196	3/25 (25) 0 5000	4/25 (25) 0 3336	0/25 (24) 1 0000	1/25 (25) 0 8827	1/10 (9) 0 6156
	Carcinoma, Bronchiolar Alveol [P]	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/10 (9) 0 2647
	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	2/10 (10) 0 0756
Lymph Node, Mandibular	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	2/10 (10) 0 0756
Lymph Node, Mediastinal	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/10 (9) 0 2647
Lymph Node, Mesenteric	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/10 (10) 0 2857
Mammary Gland	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/10 (10) 0 2857
Multicentric Neoplasm	Hemangioma [P]	0/25 (25) 0 2424	0/25 (25) NC	0/25 (25) NC	1/25 (24) 0 4898	0/25 (25) NC	0/10 (9) NC
	Hemangiosarcoma [P]	0/25 (25) 0 1860	2/25 (25) 0 2449	1/25 (25) 0 5000	2/25 (24) 0 2347	1/25 (25) 0 5000	2/10 (9) 0 0642
	Lymphoma [P]	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	2/10 (10) 0 0756
Nerve, Sciatic	Mesothelioma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/10 (9) 0 2647
Nose, Level A	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	2/10 (10) 0 0756
Nose, Level B	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	2/10 (10) 0 0756
Nose, Level C	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/10 (10) 0 2857
Nose, Level D	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/10 (10) 0 2857
Ovaries	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	2/10 (10) 0 0756
Oviducts	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	2/10 (10) 0 0756
Pituitary Gland	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/10 (10) 0 2857
Skeletal Muscle, Biceps Femoris	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	2/10 (10) 0 0756
Skin	Hemangiosarcoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/10 (9) 0 2647
	Lymphoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/10 (9) 0 2647
	Papilloma, Squamous Cell [P]	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	1/25 (25) 0 5000	3/10 (9) 0 0140 $

Spleen	Hemangiosarcoma	0/25 (25)	2/25 (25)	1/25 (25)	2/25 (24)	1/25 (25)	1/10 (9)
		0 1860	0 2449	0 5000	0 2347	0 5000	0 2647
	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
Stomach, Nonglandular	Papilloma, Squamous Cell [P]	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	9/10 (9)
		NC	NC	NC	NC	NC	0 0000 $
Thymus	Carcinoma, Bronchiolar Alveol	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
	Thymoma [P]	0/25 (25)	2/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	0/10 (9)
		0 8093	0 2449	NC	NC	NC	NC
Thyroid Gland	Adenoma, Follicular Cell [P]	0/25 (25)	0/25 (25)	0/25 (25)	1/25 (24)	0/25 (25)	0/10 (9)
		0 2424	NC	NC	0 4898	NC	NC
Trachea	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647
Ureters	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
Urinary Bladder	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (10)
		NC	NC	NC	NC	NC	0 2857
Uterus With Cervix	Hemangioma	0/25 (25)	0/25 (25)	0/25 (25)	1/25 (24)	0/25 (25)	0/10 (9)
		0 2424	NC	NC	0 4898	NC	NC
	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
Vagina	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	2/10 (10)
		NC	NC	NC	NC	NC	0 0756
Zymbal`s Gland	Lymphoma	0/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)	0/25 (25)	1/10 (9)
		NC	NC	NC	NC	NC	0 2647

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable
Note: In all tumor tables, a tumor marked with "P" is a primary tumor and the tumors without any mark are the secondary or multicentric tumors.

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

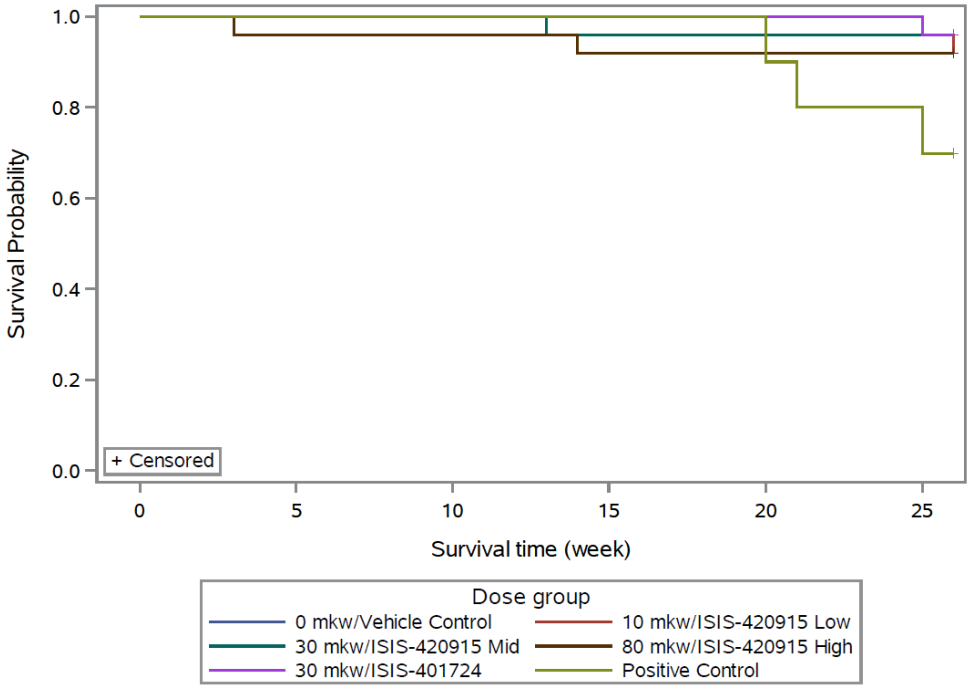
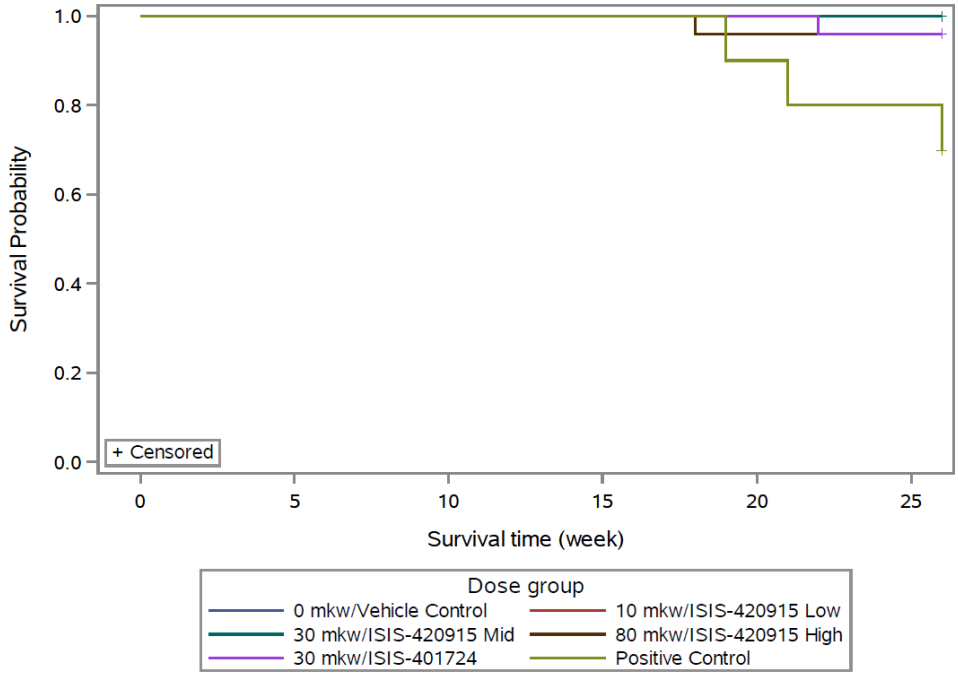


Figure 1B: Kaplan-Meier Survival Functions for Female Mice



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03/08/2018

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Concur with review.