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 #:	NDA 212801
Drug Name:	Osilodrostat film coated tablets for oral use
Indication(s):	Cushing Disease
Applicant:	Novartis
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1 EXECUTIVE SUMMARY

Novartis is seeking approval for osilodrostat (LCI699), an oral inhibitor of 11β-hydroxylase (CYP11B1), for treatment of adults with Cushing's Disease. The sponsor submitted the new drug application (NDA) on March 7, 2019.

1.1 Brief Overview of Clinical Study

This statistical review encompasses one safety and efficacy trial, Study C2301. Study C2301 was a randomized withdrawal (RW) study. The RW period in study C2301 followed a 12-week dose titration period and a 12-week one-arm (OA) period. The RW period consisted of 8 weeks of RW to (1) drug (osilodrostat) or (2) placebo.

1.2 Major Statistical Issues

Some issues with Study C2301 are summarized below.

- The study was not designed to directly evaluate the treatment effect in comparison to placebo in treatment-naïve patients (patients that have not already been exposed to the experimental drug).
- For the same reason, it is difficult to compare safety between the two arms.
- The primary endpoint is assessed at the end of the RW period and includes only 70 (51%) of the 137 patients that were enrolled and treated in the study.
- The key secondary endpoint lacks a comparator arm by design.
- The aggressive dose titration in the study is not likely what would be used in clinical practice. Thus efficacy results and treatment discontinuation due to adverse events may be different from what would be seen in clinical practice.
- Mean urinary free cortisol (mUFC) was not assessed at the timepoint at which the sample was taken. This may delay information needed to make decision on dose adjustment.
- Moreover the samples were collected shortly after each dosing, before the response to the dose had time to stabilize.

Many of the issues outlined above are due to the design. Please refer to Section 3.2.2.2 and Section 5.1 for further details.

1.3 Conclusion and Recommendations

Limitations due to study design are outlined in Sections 1.2 and 5.1. Collective evidence (Section 5.2) lends support to efficacy of the drug, though a more moderate dose titration strategy may result in a decrease in the magnitude of the efficacy (as well as a decrease in the discontinuation rate due to adverse events). Due to limitations of the design of this study and due to the

aggressive dose titration, quantification of the magnitude of the efficacy is difficult. Therefore if the drug is approved, labeling using results from this study should be descriptive in nature.

2 INTRODUCTION

2.1 Overview

The Sponsor is seeking approval for efficacy and safety of osilodrostat for Cushing Disease.

2.1.1 Class and Indication

Osilodrostat (LCI699) is an inhibitor of 11 beta-hydroxylase (CYP11B1). It inhibits synthesis of cortisol at the adrenal glands. The proposed indication is for Cushing disease.

2.1.2 Select Communication History with Sponsor

On May 30, 2013, Novartis submitted IND 117489. The product was at that time referred to as LCI699 hard gelatin capsule. Acknowledgement of orphan designation was on September 2013. The End-of-Phase 2 Type B meeting was held on October 9, 2013.

At this meeting, the Agency recommended a randomized double-blind 8-12 week placebo-controlled study to establish efficacy of LCI699, followed by a controlled extension phase to establish durability of effect and obtain long-term safety. The Agency noted that no drug treatment for Cushing's disease (including LCI699) to date had been shown to increase survival or prevent irreversible morbidity, and that placebo would be added to standard of care blood pressure, glucose electrolyte, and lipid management.

The sponsor agreed to conduct two pivotal studies: the proposed randomized withdrawal study (C2301), and a separate placebo-controlled study (C2302): "A Phase III, multi-center, randomized, double-blind, 48-week study with an initial 12-week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease". Study C2302 is ongoing at the time of this NDA Review submission.

Statistical comments conveyed to the sponsor and documented on September 4, 2018 include the following:

> 1. Please provide the number and percentage of patients with missing mUFC values for the primary and key secondary objectives in Study C2301, and clarify whether they are considered non-responders in these analyses.
>
> 2. In the SAP, it stated "during the randomized withdrawal study period, the patient must be discontinued from the randomized withdrawal period, declared a non- responder, if the

mUFC increases to > 1.5 x ULN, and at least 2 individual urine samples show UFC > 1.5 ULN at a single visit." Clarify what happened to these discontinued patients and whether they are included in the patient disposition table 4-23 from the meeting package.

3. In the future NDA submission, provide a plot showing individual change in mUFC from baseline to Week 24 in the full analysis set (Study C2301).

2.1.3 Specific Studies Reviewed

Study 2301 (Figure 1 and Table 1 below) is the only study submitted that includes randomization. Novartis has provided clinical and safety data from this study. Reports from one-arm studies C1201 and C2201, and safety data from unfinished randomized placebo-controlled study C2302 were submitted. This statistical review focuses on efficacy results from Study C2301.

2.2 Data Sources

The data and final study report for NDA 212801 were submitted electronically as an eCTD submission. The submission is archived at the following link.

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The SDTM and ADaM data sets are located in the proper sections of the submission, and analysis reviewer guides are provided which define variables and their locations.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The study population was comprised of adult male and female patients (18 to 75 years-old) with Cushing's Disease who had confirmed persistent or recurrent hypercortisolism after primary pituitary surgery and/or irradiation, and patients with de novo Cushing's Disease who were not surgical candidates for medical reasons, or refuse to undergo surgery.

The primary and secondary endpoints for Study C2301 are shown in Table 2 below. The primary endpoint was assessed at the end of the RW period (34 weeks), and the secondary endpoint was assessed at the end of the OA period (24 weeks). The primary endpoint was the proportion of

randomized treated patients who were complete responders. In order to be categorized as a complete responder, a patient had to meet all of the following conditions:

- mUFC less than or equal to the "Upper Limit of Normal" (ULN) at the end of the RW period.
- Did not discontinue treatment during RW period.
- Had an mUFC assessment at the end of the RW period (Week 34).
- No dose increase during RW period above the level at Week 26.

In addition, the protocol states, in Section 4.1.3.6, that a patient must be discontinued from the RW period and declared a non-responder if both their mUFC and two of their individual UFC samples are greater than 1.5 times the ULN at a single visit. After being declared a non-responder in this situation, the patient would still receive LCI699 treatment.

The secondary endpoint was the proportion of patients who were complete responders at the end of the OA period. A complete responder for this endpoint was defined as an enrolled patient who had mUFC ≤ ULN at Week 24 and had no dose increase during Study Period 2 above the level established at the end of Study Period 1 (Week 12 – Figure 1). Dose reductions and temporary dose interruptions for safety reasons did not preclude patients from being complete responders for the key secondary endpoint. Enrolled patients who were missing the week 24 mUFC assessment were counted as non-responders for the key secondary endpoint.

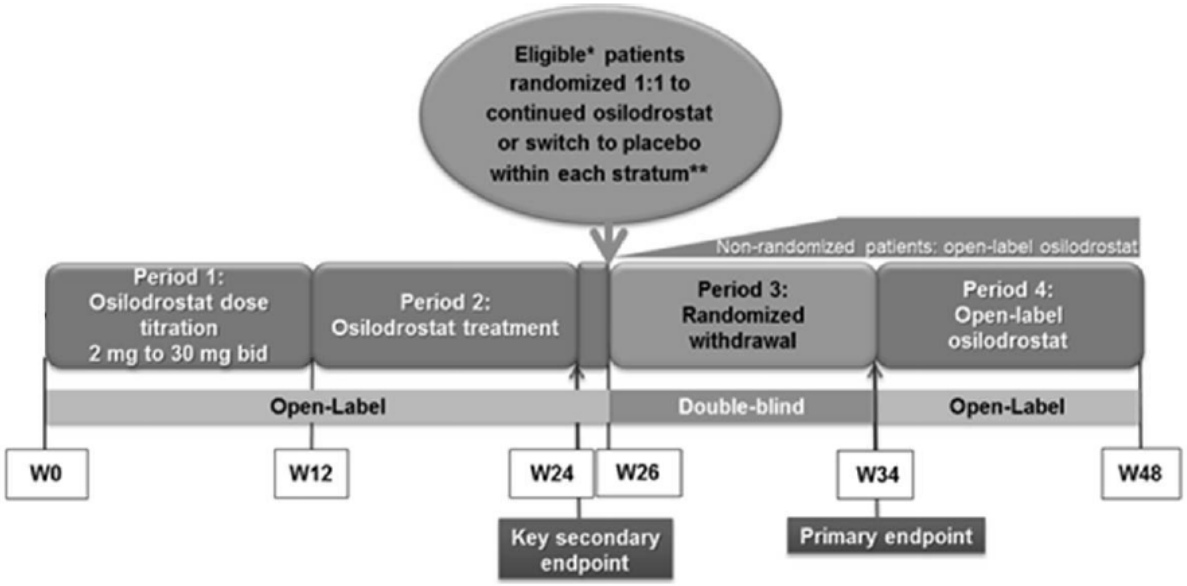

Figure 1: Study Design for Study C2301

Source – Sponsor's protocol, Figure 9-1; Abbreviations: mUFC-mean urinary free cortisol (ng/mL -nanograms per milliliter); ULN – upper limit of normal; BID – twice a day. Period 2 is the one-arm period. The secondary endpoint is assessed at the end of this period; period 3 is the randomized withdrawal period; the primary endpoint is assessed at the end of this period; *To eligible for randomization, the patients had to have mUFC ≤ ULN at week 24, and no further dose increase above the level established at week 12.** Strata were determined by the combination of two stratification factors at randomization: 1) osilodrostat dose at week 24 (≤ 5 mg BID vs. > 5 mg BID) and 2) history of pituitary radiation (yes/no). Note that, according to protocol revision, "…Rescreening is introduced in order to accommodate the long washout periods required" for some cortisol-lowering medical therapies at the time of enrollment.

Table 1 provides more detail for Study C2301, including sample sizes, and study population.

Table 1: Details of Study Design for Study C2301

Trial ID	Study Design*	Treatment/ Sample Size	Endpoint/Analysis	Study Pop.
C2301	MC, DB * RW trial 12 week DT, 24 week (OA) + 8 week RW	Osilodrostat (LCI699)/ 137 patients in OA period; RW Period: N_A=36 Placebo/ N_P=34	Primary: Complete responder at end of RW period (Week 34). Key Secondary: Complete responder at end of OA period (Week 24)	M/F >= 18 Years

RW: Randomized withdrawal, OA: one arm, MC: multi-center, DT- Dose Titration; R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, mUFC -mean urinary free cortisol (ng/mL – nanograms per milliliter);ULN – upper limit of normal for mUFC; Complete Responder: See section 3.2.1, *the OA part of the study was 24 weeks (12 weeks of titration followed by 12 weeks of treatment).

Multiple Testing Procedure

Study C2301 used a hierarchical testing strategy to control Type 1 Error rate at level 0.025, one-sided. The primary endpoint, evaluated at the end of the RW period, was first in the hierarchy, followed by the key secondary endpoint, evaluated at the end of the OA period.

3.2.2 Statistical Methodologies

3.2.2.1 Sponsor Approach

The primary analysis population for the primary endpoint was the randomized analysis set (RAS) consisting of all randomized subjects who received at least one dose of randomized drug (osilodrostat or placebo). The sponsor's defined primary analysis for the primary endpoint (the proportion of these patients who were complete responders at week 34) was a Cochran-Mantel-Haenszel (CMH) exact test. Three different combinations of pituitary irradiation status (PIR) and dose level were included as a stratification factor (see Table 3, Randomization Stratification group, for details).

The primary analysis population for the secondary endpoint was the full analysis set (FAS), defined as all enrolled patients who received at least one dose of osilodrostat. The sponsor's defined primary analysis for the secondary endpoint, the proportion of complete responders at Week 24, was a Clopper-Pearson 95% two-sided confidence interval. In order to be considered statistically significant, the lower bound of the two-sided 95% confidence interval had to be >= 30%.

3.2.2.2 Statistical Reviewer Approach

My preferred analysis is one which estimates the treatment difference between experimental arm and comparator, over the population for which the indication is proposed. The sponsor's analysis of the secondary endpoints included all 137 subjects in the study. The dose titration and one arm periods, from beginning of first week through week 24, come closest to representing this population for which the proposed new drug is intended. However it is difficult to multiply impute missing data for the comparator group, which is missing completely (by design). I know of no established imputation methods for this situation.

The RW analysis, on the other hand, addresses the question of whether it is beneficial to continue on the drug after 26 weeks if there is a response by 26 weeks. The RW analysis may perhaps be used to show that at least some of the effect during the OA or dose titration periods is not due to placebo effect or random changes over time. However it is difficult to quantify this relationship.

For the primary RW endpoint, odds ratios can be difficult to interpret, especially for a non-statistical audience. For example a very high or low odds ratio can be obtained even if both groups have very small response rates. The difference in proportions does not have this drawback and is my preferred approach for this endpoint. This analysis is also provided in Table 4; Miettinen-Nurminen two-sided 95% confidence intervals are provided for each of the three strata. For the secondary endpoint, the use of Clopper-Pearson 95% Confidence Intervals is reasonable to me. The sponsor's non-responder approach for missing data and for patients who discontinued is also acceptable.

Because of the difficulty in interpretation of the primary and secondary endpoints, I also provide, in Figure 2 and Tables 5 and 6, descriptive results for mean mUFC over time for the following groups: 1) the overall population up to beginning of RW period 2) the patients who ended up being randomized 3) the patients who ended up not being randomized, and 4) the LCI699 and placebo groups in the RW period. The mean mUFC trajectories for these groups are provided in Figure 2 over the dose titration period, the OA period, and the RW period. These trajectories may provide additional information on how the drug is working over time. It should be kept in mind that many patients required long washout periods before initiation of treatment. Also the aggressive dose titration used in the study may not reflect what would be used in clinical practice. Therefore the magnitude of changes in mUFC shown in the figures and tables may be larger than what would be seen in clinical practice. Please refer to the clinical review of Dr. Diala El-Maouche for more detail concerning these issues.

3.2.2.3 **Patient Disposition and Characterization of Missing Data**

Characterization of Sponsor's Submitted Data and Variable Definitions

Discontinuation Rates

Table 2 below only shows the number and percent of patient who were permanently discontinued from treatment for each group and period. The seven patients that discontinued treatment by

week 24 (Table 2) are counted as non-responders for the secondary endpoint. There were no other patients that were missing at week 24 (Figure 2 and Table 6). There were six patients (five on placebo and one on LCI699) that were non-responders due to mUFC >1.5xULN and at least two individual UFC values greater than 1.5xULN at a visit. There was one patient on placebo that discontinued treatment during the RW period.

Table 2: Descriptive Statistics, Including Permanent Treatment Discontinuation, for Patients Having Primary or Secondary Efficacy Data, and for Patients Not Randomized

Period	Group	Patients Rand.	N	Disc. Treat. Early	% Disc. Treat.	Imputation Method in Proposed Label
Dose titration	All	NA	137	7*	5.1	Non-Resp.
One Arm**	LCI699.	NA	130	10**	7.2	Non-Resp.
Week 24-Week 26	LCI699	NA	120	2	1.5	NA
RW	LCI699	36	36	0***	0***	Non-Resp.
RW	Placebo	35	34	1***	2.9***	Non-Resp.
RW	Not-Rand.	NA	48	3	6.3	NA

Abbreviations: OA – One-Arm; Non-Resp. -Non-Responder; Not-Rand. Not Randomized; NA – Not Applicable; RW – Randomized Withdrawal; Rand. – Randomized; Disc. Treat. Early– Discontinued Treatment- number of subjects who discontinued treatment during specified period; these patients were discontinued from the study and did not receive open label treatment after discontinuation; % Disc. Treat. – the percentage of patients (out of total of 137) that discontinued during the period (except for RW period- for RW period, this is the percent of RW patients (by group) that discontinued treatment ;NA-Not Applicable;*Discontinued treatment before Week 12;**discontinued >= 12 weeks and < 24 weeks; ***number/percent of patients randomized to LCI699/placebo and receiving at least one dose, who discontinued permanently. (Patients who discontinued from RW period but received open-label LCI699 treatment are not counted as discontinuing treatment early). The "duration of exposure" variable for each patient was used to assess time of treatment discontinuation.

Missing Rates

Non-missing rates for mUFC for dose titration and OA periods are included in Table 5. Non-missing assessments for RW period are included in Table 6. Only one patient had a missing assessment during the RW period. All patients who had missing data for the final assessment for either the primary or secondary endpoint were counted as non-responders for that endpoint. Patients who discontinued from the RW or OA periods, or from the study completely during these periods, were also considered non-responders. However patients could be discontinued from the RW period and counted as non-responders, but still receive open-label LCI699 treatment. Refer to Section 3.2.1 for more detail.

3.2.3 Demographics and Baseline Characteristics

Baseline characteristics (Table 3) seem evenly distributed between treatment and placebo arms. There were only four Black/African Americans (2.9%) included in the study. A total of 120 (88%) of the 137 patients had persistent/recurrent Cushing disease. The other patients had de-novo Cushing disease.

Table 3: Demographics and Baseline Characteristics by Treatment Arm - Study C2301

Treatment Group	**LCI699**	**Placebo***	**Non-Rand.****
N per group	36	35	66
Sex, n (%)			
F	30 (83)	22 (63)	54 (82)
M	6 (17)	13 (37)	12 (18)
Race, n (%)			
Asian	7 (19)	7 (20)	25 (38)
Black / African American	0 (0)	3 (9)	1 (2)
White	27 (75)	23 (66)	39 (59)
Other	2 (6)	2 (6)	1 (2)
Ethnicity, n (%)			
Hispanic Or Latino	5 (14)	2 (6)	5 (8)
Age			
Mean (SD)	44.25 (11.3)	42.0 (13.5)	39.0 (13.4)
Median (min - max)	41 (20 - 69)	40 (19 - 68)	37.5 (19 - 70)
<65, n (%)	34 (94)	34 (97)	62 (94)
>=65, n (%)	2 (6)	1 (3)	4 (6)
Region***			
Asia (%)	7 (19)	7 (20)	25 (38)
Europe (%)	19 (53)	14 (40)	25 (38)
North Am. (%)	8 (22)	14 (40)	14 (21)
South Am. (%)	2 (6)	0 (0)	2 (3)
Rand. Strat., n (%)			
Wk 24 dose**** <= 5mg / PIR	5 (14)	5 (14)	NA
Wk 24 dose <= 5mg/no PIR	21 (58)	21 (60)	NA
Wk 24 dose > 5mg/ no PIR	10 (28)	9 (26)	NA
Status Cushing Disease baseline n (%)			
De novo	4 (11)	2 (6)	11 (17)
Persistent/recurrent	32 (89)	33 (94)	55 (83)
Baseline BMI (kg/m^2)			

Treatment Group	LCI699	Placebo*	Non-Rand.**
Mean (SD)	29.6 (7.4)	30.9 (8.4)	30.4 (7.7)
Median (min - max)	28.5 (18.8 - 47.7)	29.0 (20.8 - 55.1)	28.8 (18.8 - 56.4)

*The placebo group includes one patient who did not receive a dose of randomized drug and therefore did not qualify for evaluation of the primary endpoint; ** The 66 non-randomized patients were the patients in the one-arm period that did not continue or did not otherwise qualify for the randomized withdrawal period of the study. These patients could still continue on the extension part of study;*** Turkey and Russia were considered as part of Europe;**** Week 24 LCI699/placebo dose; all 5mg dose are BID (twice daily); Abbreviations: PIR – Pituitary Irradiation; Rand. Strat. -Randomization Stratification.

3.2.4 Results and Conclusions

3.2.4.1 Primary Endpoint

The primary endpoint of proportion of responders at end of RW period demonstrated superiority using the sponsor's stratified CMH method (Table 4). A sensitivity analysis (not shown) was also conducted excluding six patients who had dose increases in Period 2. The odds ratio was still 13.7 with these patients excluded. The confidence intervals were slightly wider as would be expected.

My preferred analysis using difference of proportions (Table 4, lower half) also demonstrated superiority, with an overall difference in proportions of 57%. The 95% lower and upper confidence limits excluded zero for each of the three strata.

Table 4: Primary and Secondary Endpoint Results -Sponsor's Primary Analysis Method (Study C2301)

Endpoint	Exp	Ctrl	OR	LCL	UCL	P-Val
Responder * (mUFC≤ULN)	31/36 (86.1%)	10/34 (29.4%)	13.7	3.7	53.4	<.001
Responder ** (mUFC≤ULN)	72/137 (52.6%)	NA	NA	43.9%	61.1%	
Responder *** (mUFC≤ULN)	31/36 (86.1%)	10/34 (29.4%)	% Diff. 57	LCL	UCL	
Strat. #1	5/5	1/5	80	18	97	
Strat. #2	17/21	7/21	48	18	69	
Strat. #3	9/10	2/8	65	19	88	

Abbreviations: Exp.-Experimental Arm; Ctr.-Control Arm (Placebo); OR-Odds Ratio; P-Val-P-Value; Strat. – Stratification level according to order shown in Table 3; NA- Not applicable (since the secondary endpoint did not include a control arm) *Primary Endpoint; mUFC-mean urinary free cortisol; ULN-Upper Limit of Normal (138 ng/mL); ** Secondary endpoint.; complete responder: ***Primary endpoint, reviewer approach (difference in proportions, using 95% Miettinen-Nurminen confidence intervals for each stratum).

3.2.4.2 Secondary Endpoints

The key secondary endpoint, proportion of complete responders at week 24, was significant, with 72 of 137 (52.6%) of patients meeting definition for complete responder. The 95% lower confidence limit was also greater than 30%, which met the pre-specified criteria. The overall response rate, defined as the proportion of enrolled patients with mUFC ≤ ULN or at least 50% reduction from baseline, was 82.5% at week 24.

3.2.4.3 Descriptive Statistics – Dose Titration, One Arm, and RW Periods

Figure 2 below shows mean mUFC trajectories for 1) all patients with non-missing assessments at each time point, shown by the wider light gray line 2) the subset (N=71) of these patients that ended up being randomized during the RW period – the solid black line; 3) the subset (N=66) of the 137 patients that were classified as non-responders and were not randomized; represented by the dotted black line; 4) the 36 patients in the RAS randomized to LCI699 dose during RW period (the lower solid line in the RW period); 5) the 34 patients in the RAS randomized to placebo - represented by the dashed line in the RW period. One of the 35 patients randomized to placebo was not exposed to a randomized dose and therefore was not in the RAS.

The 71 patients in the randomized group did not discontinue before the RW period, since discontinuation would have made them ineligible for randomization. However some of the 66 patients in the non-randomized group did discontinue treatment during this period. The missing assessments include patients who discontinued treatment, and these patients' mUFC measurements are probably not missing at random.

For the non-randomized group, the initial average mUFC at the first assessment (1414 ng/mL) is much higher than for the randomized group (Figure 2). The average mUFC for the non-randomized group decreased to 139 mg/mL at week 12, just over the ULN. This is a decrease of 90%. However there were seven (11%) of these 66 patients with missing assessments at week 12. This is also the number of patients that discontinued treatment before week 12 (Table 2). It is likely that the week 12 mUFC measurements for these patients would be on average higher than the mUFC measurements for the other patients in this group, since they were no longer on treatment at week 12.

The decrease in mUFC in the placebo group after week 28 (Table 6 and Figure 2) may be partly attributed to some patients meeting criteria for non-responders and given open-label treatment.

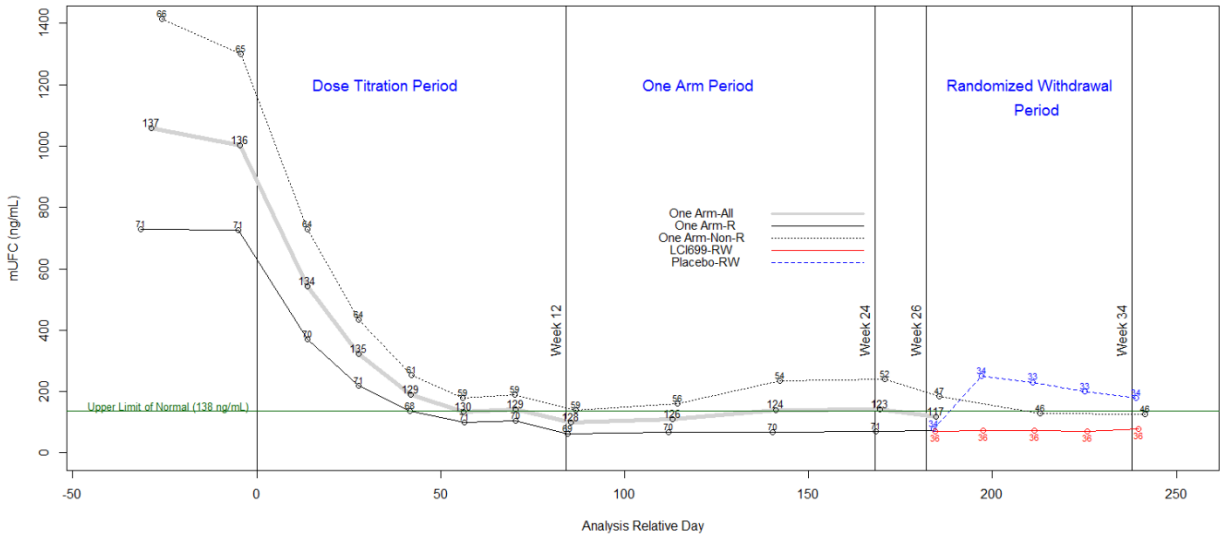

Figure 2: Mean Group mUFC Trajectories during Screening, Dose Titration, One-Arm, and RW Periods
Source- Reviewer. Abbreviations: mUFC – mean urinary free cortisol in ng/mL (nanograms per milliliter); RW-Randomized Withdrawal; One-Arm-All – Group consisting of all 137 patients – trajectory shown from screening and dose titration to time of randomization at Week 26; One-Arm-R – this group was not pre-defined at time 0 - this group consists of all patients that ended up being randomized at week 26 (n=71); the mean trajectory for this group is shown up to time of randomization; only 70 of the 71 patients in this group were included in the RW analysis; one patient was randomized but did not receive at least one dose of randomized treatment; One-Arm-Non-R - Group consisting of all 66 patients that ended up not being randomized; LCI699-RW- patients randomized to drug during RW period; Placebo-RW – patients randomized to placebo during RW period; numbers above trajectory lines are the number of patients assessed at the time point.

Table 5: Descriptive Statistics for mUFC by Visit for Dose Titration and One Arm Period

Week	Day	N	Mean	Std. Dev.	% Not Missing
-4	-29	137	1059	1903	100%
-1	-5	136	1001	1595	99.3%
2	14	134	542	754	97.8%
4	28	135	322	446	98.5%
6	42	129	191	267	94.2%
8	56	130	134	171	94.9%
10	70	129	143	270	94.2%
12	85	128	98	120	93.4%
16	113	126	109	125	92.0%
20	141	124	141	235	90.5%
24	169	123	143	292	89.8%
26	185	117	118	205	85.4%

N – number of patients with assessments for the week; St. Dev. – standard deviation.

Table 6: Descriptive Statistics for mUFC by Visit for Randomized Withdrawal Period

	---------LCI699---------			---------Placebo---------		
Week	N	Mean	Std Dev	N	Mean	Std Dev
26	36	69.6	43.6	34	76.9	58.4
28	36	72.4	51.9	34	253	216
30	36	72.1	62.8	33	231	201
32	36	70.5	50.9	33	201	139
34	36	79.6	99.8	34	178	159

3.3 Evaluation of Safety

Due to study design, it is not possible to make safety comparisons between treated subjects and treatment-naïve subjects. Seven (5.1%) patients discontinued treatment prior to or during dose titration period. Four (2.9%) of these patients discontinued due to adverse events. From beginning of week 12 to end of week 26, 12 subjects discontinued treatment, with eight (5.8% of the 137 patients) discontinuing due to an adverse event. Four patients (2.9% of the 137 patients, and 5.6% of the RW patients) discontinued treatment during the RW phase due to an adverse event. Up to and including the RW period, 14 (10.2%) of patients discontinued treatment due to an adverse event.

There were 39 (28.5%) of the 137 patients that experienced a grade 3 or 4 serious adverse event (SAE) during the study, though only 16 (11.7%) of patients had an SAE that was suspected to be related to the drug. The most common adverse event was adrenal insufficiency, which is a known side effect of this drug.

Please see the clinical review of Dr. Diala El-Maouche for a thorough safety evaluation.

3.4 Benefit-Risk Assessment

Issues outlined in Section 5.1 increase the uncertainty in the benefit-risk assessment. With this in mind, there was a substantial decline in mean mUFC over all the population during the dose titration period, even taking into account patients who were not randomized (Figure 2). The difference in proportions between arms during the RW period may provide some evidence that some of the effect during the dose titration and one arm period is attributable to drug, though, as stated in Section 5.1, this endpoint answers a different question. The aggressive dose titration may also affect the magnitude of the treatment difference.

Treatment discontinuation due to adverse events was only 10.2% up to and including the RW period (week 34). Given the aggressive dose titration, the discontinuation due to adverse events may be less than this in clinical practice. However please refer to the clinical review of Dr. Diala El-Maouche for a thorough benefit-risk assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analysis for sex, race, age, and region is displayed in Table 7. Subgroup analyses are shown both the primary and the secondary endpoints and displayed side by side in the table for each subgroup.

4.1 Gender, Race, Age, and Geographic Region

To assesses the effect of osilodrostat compared to placebo within sex, race, age and region, subgroup analysis was conducted using my preferred analysis for the primary endpoint, defined in Section 3.2.2.2, and the sponsor's analysis method for the secondary endpoint, defined in Section 3.2.2.1. Subgroups such as Black/African Americans and South American region were not included in subgroup analyses due to inadequate sample size. For the primary endpoint, the difference in proportions of responders at end of the RW period was the outcome variable. For the secondary endpoint, the proportion of responders at the end of the OA period was the outcome variable. For the male subgroup, the difference in proportions for the primary endpoint was 17%, much smaller than for the other subgroups. The 95% lower confidence for this subgroup was also less than zero. However the sample size for this subgroup was only 18 for the RW analysis. For the secondary endpoint, the lowest proportion of responders was in the Asian subgroup: 36%. This subgroup had a sample size of only 39 and therefore would also be expected to have high variability in observed outcomes.

Table 7: Treatment and Treatment Differences in Responder Rates by Subgroup

Period	One-Arm				Randomized Withdrawal			
Subgroup	Sample Size	Estimate n (%)	Lower	Upper	Sample Size	Difference in Prop.	Lower 95%	Upper 95%
Overall	137	72 (52.6)	43.9	61.1	70	57	38	76
Female	106	54 (50.9)	41.0	60.8	52	66	45	87
Male	31	18 (58.1)	39.1	75.5	18	17	-31	65
White	89	52 (58.4)	47.5	68.8	49	49	25	73
Asian*	39	14 (35.9)	21.2	52.8	14	57	15	99
Age < 65	130	69 (53.1)	44.1	61.9	67	55	35	75
North Am.	36	20 (55.6)	38.1	72.1	20	42	2	82
Europe	58	35 (60.3)	44.6	73.0	32	59	30	87

Abbreviations: Prop. – proportions; *Asian race group and Asian region group are identical.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The following statistical issues were identified in this application.

- The study was not designed to directly evaluate the treatment effect in comparison to placebo in treatment-naïve patients. Instead it addresses the question of maintenance: whether the drug should continue to be taken by patients who are still using it after 24 weeks, and what the treatment difference will be if the patients stop treatment after 24 weeks.
- Only 70 (51%) of patients qualified to be evaluated for the primary endpoint.
- The secondary endpoint does not have a comparator arm. It is difficult to determine how much of the effect is due to drug, instead of placebo effect and/or random changes over time.
- Since the RW period includes only patients who have been previously treated, there are no treatment-naïve subjects in this group; this makes it more difficult to make safety comparisons between groups
- The aggressive dose titration used in the study is not reflective of what would be used in clinical practice.
- The mUFC measurement was not assessed at the timepoint at which the sample was taken. This may delay information needed to make decision on dose adjustment.
- Moreover the samples were collected shortly after each dosing, before the response to the dose had time to stabilize.

5.2 Collective Evidence

Both primary and secondary endpoints met predefined criteria for statistical significance. There was a very large and significant difference in the proportion of responders vs. non-responders for the primary endpoint (57%). There was also a steep drop in the mean mUFC over all the population during dose titration, including patients who did not meet criteria for being randomized in the RW period (Figure 2). The percent of overall responders at week 24 was also very high: 113 (82.4%) of the 137 treated patients. However due the issues mentioned in Section 5.1, including lack of a comparator arm during dose titration and one-arm periods, and due to the aggressive dose titration used, it is still difficult to quantify the magnitude of effect due to drug (and the magnitude of treatment discontinuation due to adverse events) that is likely to be seen in clinical practice.

5.3 Conclusions and Recommendations

The RW primary endpoint was statistically significant with a large difference in proportions of 57%. Limitations of the RW primary endpoint are outlined in Section 5.1, and it is difficult to interpret on its own since it only includes 51% of treated patients. The collective evidence (Section 5.2) supports effectiveness of the drug, though it is still difficult to quantify the magnitude of benefit.

5.4 Labeling Recommendations

Due to the aggressive dose titration and other issues sited in this review, the magnitude of the treatment effect for both the primary and secondary endpoints for study C2301 may not reflect what would be seen in clinical practice. If the drug is approved, efficacy results for this study should be presented descriptively in text, with appropriate qualifications.

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/s/

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

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 212801
Drug Name:	Osilodrostat, LCI699
Indication(s):	Treatment of patients with Cushing's disease.
Studies	Two Year Oral Gavage Carcinogenicity Study in Rat and Mouse.
Applicant:	Sponsor: Novartis Pharmaceuticals Canada Inc. 385 boul. Bouchard Dorval, Quebec, H9S 1A9, Canada Test facility: (b) (4)
Documents Reviewed:	Electronic submission dated: on March 7, 2019 via SN0001 Electronic data submitted on March 7, 2019 via SN0001.
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Secondary Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products
Reviewing Pharmacologist:	Elena Braithwaite, PhD
Project Manager:	Johnson, Jennifer L.
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in Wistar Hannover rats and one in CD-1 mice. These studies were intended to assess the carcinogenic potential of osilodrostat (LCI699), when administered orally by gavage at appropriate drug levels for about 104 weeks to rats and to mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Braithwaite.

In this review, the phrase "dose response relationship" (trend) 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.

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred Wistar Hannover rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 50 animals, as indicated in Table 1. The dose levels for treated groups were 3, 10, and 30 mg/kg/day for both male and female rats. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group was exposed to Vehicle Item only [ultra pure water] administered orally by gavage for about 104 weeks in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle control	1	0	0	50	50
Low	2	3	3	50	50
Medium	3	10	10	50	50
High	4	30	30	50	50

During the administration period, all animals were checked for morbidity, mortality, injury, twice daily, once in the morning and once in the afternoon on weekdays and weekends. Animals were not removed from cage during observation, unless necessary for identification or confirmation of possible findings. The animals were removed from the cage, and detailed observations were conducted for each animal weekly, beginning during Week 1. The presence of palpable masses was observed during the detailed examination; the site, size and appearance of these masses were recorded when first detected and, following this initial description, the presence or disappearance of these masses were monitored. The observations included, but were not limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling, and unusual behavior, and the palpation of masses. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. All animals were subjected to a complete necropsy examination, which included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues. Histopathological examinations were performed on all animals found dead, killed moribund, or sacrificed at the end of the experiment, all suspected tumors were diagnosed, and the incidences of benign and malignant tumors of different cell types in the various treatment groups were tabulated. Body weights

and food consumption of individual animals were recorded weekly, during weeks 1 to 14, every four weeks from weeks 18 to 78 and every 2 weeks thereafter for the reminder of the study. Terminal body weights were not collected from animals found dead or euthanized moribund

2.1. Sponsor's analyses

2.1.1. Survival analysis

The Kaplan-Meier's curves were presented graphically for male and female rats separately. An overall test for survival was used to compare the homogeneity of survival rates across the groups using a log-rank test at the 0.05 significance level. If the survival rates were significantly different ($p \leq 0.05$), then a follow up analysis was done where the significance of a dose-related trend in mortality across all groups was evaluated using Tarone's method. Using the Multtest procedure (SAS/STAT), Tarone's test was implemented as a Peto two-sided test, with all uncensored deaths coded as 2 and all censored deaths coded as 0. The corresponding arithmetic dose level scores were used to perform this overall trend test. Furthermore, the vehicle control group was compared to each of the other three groups using a Peto two-sided test. The sign of the statistic was used to indicate if either an increase or a decrease of the mortality rate across dose levels is observed for the trend test and each pairwise comparison.

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. Results of trend and pair-wise comparisons were reported at the 0.05, 0.01, and 0.001 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy were 34 (68%), 35 (70%), 38 (76%), and 37 (74%) in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 38 (76%), 43 (86%), 36 (72%) and 35 (70%) in vehicle control, low, medium, and high dose groups, in female rats, respectively. The sponsor's report showed no statistical significance at the 5% level using a log-rank test, for both male and female datasets, with p-value = 0.8049 and p-value = 0.3407 respectively. Therefore, no post-hoc testing was done for these datasets, i.e. neither the trend test nor the pairwise comparisons were performed.

2.1.2. Tumor data analysis

The statistical evaluation of tumor data was done separately for each sex and limited to all non-secondary neoplastic lesions pre-determined in the study plan -required tissues/sites. Furthermore, subcutis and hemolymphoreticular tissue were analyzed using all study animals.

Tumor incidence data were analyzed within each sex, via Peto's method, without continuity correction, incorporating the context (incidental or fatal, or mortality-independent) in which tumors were observed. Neoplastic lesions designated as palpable and found under study plan-required glands were statistically analyzed in a "mortality independent" context according to Peto's onset rate method using all study animals. Whereas, non-palpable neoplastic findings classified as fatal and incidental were statistically analyzed in a "mortality dependent" context according to Peto's death rate method and the prevalence method, respectively.

Neoplastic lesions listed under mammary gland, salivary gland parotid, skin, and subcutis, were statistically analyzed, using all study animals, according to Peto's onset rate method for tumors observed in a "mortality independent" context (Peto *et al*, 1980). These lesions were analyzed using their onset time as given by the first date of their detection during the in-life experimental period.

The incidence of each tumor type was analyzed with a one-sided trend test using the positive dose response relationship in tumor occurrence across vehicle control and treated groups. In addition, one-sided pairwise comparisons of vehicle control and treated groups were conducted. The analysis of tumors was based on the following fixed time intervals: Weeks 1-52, 53-78, 79- 92, 93-104, and terminal sacrifice for male and female rats. The actual dose levels were used as the scores in the analyses.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used and asymptotic tests were used for tumor types with higher incidences.

Adjustment for the multiplicity:

For multiplicity adjustment, the sponsor used significance levels of 0.005 and 0.025 for common (historical incidence of more than 1%) and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons. Site-specific background historical control database was used to determine whether the tumors should be designated as rare or common.

Sponsor's findings:

Following the multiple testing adjustment method described above, the sponsor's analysis showed statistically significant positive trend tests for follicular cell adenoma and the combined follicular cell adenoma and follicular cell carcinoma in gland thyroid in male rats (p-value < 0.0001 and p-value < 0.0001, respectively) regardless if these tumor types were common or rare. Also, in male rats the sponsor's analysis showed a statistically significant positive trend test for hepatocellular adenoma in the liver (p-value = 0.0232), if this tumor is classified as rare. In female rats, the sponsor's analysis showed statistically significant positive trend tests for hepatocellular adenoma, hepatocellular carcinoma, and the combined hepatocellular adenoma and hepatocellular carcinoma in the liver ((p-value < 0.0001, =0.0005, and p-value < 0.0001, respectively), regardless of these tumor types classification (rare or common).

A sequential trend test, excluding group 4, was then performed for the datasets, the sponsor's result showed statistically significant positive trend tests for the combined follicular cell adenoma and follicular cell carcinoma in gland thyroid, and the liver hepatocellular adenoma in male rats (p-value = 0.0038 and p-value = 0.0014, respectively), regardless of these tumor types classification (rare or common).

The pairwise comparisons showed statistically significant increases in the high dose group for the incidences of follicular cell adenoma and the combined follicular cell adenoma and follicular cell carcinoma, in gland thyroid, when compared to the vehicle control group in male rats ((p-value = 0.0021, and p-value = 0.0006, respectively), regardless of these tumor types classification (rare or common). Also, the pairwise comparisons showed a statistically significant increase in the medium dose group for the incidences of liver hepatocellular adenoma when compared to the vehicle control group in male rats ((p-value = 0.0082), regardless of the tumor type classification (rare or common). However, the combined follicular cell, adenoma and follicular cell, carcinoma in male's thyroid gland in medium dose group and the liver hepatocellular adenoma in high dose group were considered to be statistically

significant increases when compared to the vehicle control group, only if these tumors were considered to be rare (p-value = 0.0231, and p-value = 0.0314, respectively). In female rats, the pairwise comparisons showed statistically significant increases in the high dose group for the incidences of hepatocellular adenoma, hepatocellular carcinoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver, when compared to the vehicle control group in male rats ((p-value = 0.0003, p-value = 0.0090, and p-value = 0.0003, respectively), regardless the classification (rare or common) of these tumor types.

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on November 17, 2017 via SN0001.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female rats separately. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, 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 rats, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 34 (68%), 35 (70%), 38 (76%), and 37 (74%) in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 38 (76%), 43 (86%), 36 (72%) and 35 (70%) in vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group in either sex of rats.

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of s_h =1. An animal that dies at Week w_h without development of the given tumor type 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 develops the given tumor 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 comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 105 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (0, 3, 10, and 30 for both male and female rats) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

Following the FDA more recently revised draft guidance for the carcinogenicity study design and data analysis 2015, for the two-year rat study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the vehicle control of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 2.

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons
Treated Groups and Vehicle control Group in Rats

Sex	Organ Name	Tumor Name	0 mg Veh. Cont (N=50) P - Trend	3 mg Low (N=50) P -VC vs. L	10 mg Med (N=50) P -VC vs. M	30 mg High (N=50) P -VC vs. H
Male	Gland, Thyroid	Follicular Cell Adenoma	4/50 (44) <0.0001*	2/50 (44) 0.8988	9/50 (46) 0.1326	16/50 (45) 0.0026*
		Follicular Cell Carcinoma	0/50 (44) 0.1124	0/50 (44) NC	3/50 (46) 0.1292	2/50 (45) 0.2528
		Follicular Cell Adenoma/Carcinoma	4/50 (44) <0.0001*	2/50 (44) 0.8988	12/50 (46) 0.0321[@]	18/50 (45) 0.0007*
	Liver	Hepatocellular Adenoma	0/50 (44) 0.0285[@]	1/50 (44) 0.5000	7/50 (46) 0.0072*	5/50 (45) 0.0294*

Sex	Organ Name	Tumor Name	0 mg Veh. Cont (N=50) P - Trend	3 mg Low (N=50) P -VC vs. L	10 mg Med (N=50) P -VC vs. M	30 mg High (N=50) P -VC vs. H
Female	Liver	Hepatocellular Adenoma	3/50 (46) <0.0001*	0/50 (45) 1.0000	0/50 (44) 1.0000	16/50 (44) 0.0005*
		Hepatocellular Carcinoma	0/50 (46) 0.0006*	1/50 (45) 0.4945	0/50 (44) NC	6/50 (43) 0.0105*
		Hepatocellular Adenoma/Carcinoma	3/50 (46) <0.0001*	1/50 (45) 0.9389	0/50 (44) 1.0000	16/50 (44) 0.0005*

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

@: not statistically significant at 0.025 for rare tumor in dose response relationship (trend) tests nor at 0.01 for common tumors in pairwise comparisons.

Following the multiple testing adjustment method described above, this reviewer's analysis showed statistically significant increasing dose response relationships across the vehicle control and the treated groups of male rats for the incidence of follicular cell adenoma, and the combined follicular cell adenoma and follicular cell carcinoma in the gland thyroid (p <0.0001, and <0.0001, respectively), regardless of these tumor types classification (rare or common). In female rats, this reviewer's analysis showed statistically significant increasing dose response relationships across the vehicle control and the treated groups, for the incidence of hepatocellular adenoma, hepatocellular carcinoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver (p <0.0001, = 0.0006, and < 0.0001, respectively), regardless of these tumor types classification (rare or common).

The pairwise comparisons showed statistically significant increases in the high dose group for the incidences of follicular cell adenoma, and the combined follicular cell adenoma and follicular cell carcinoma in the gland thyroid, when compared to the vehicle control group, in male rats (p-value = 0.0026, and = 0.0007, respectively), regardless of these tumor types classification (rare or common). In the medium dose group of male rats, the pairwise comparisons showed statistically significant increases for the incidences of hepatocellular adenoma in the liver, when compared to the vehicle control group (p-value = 0.0072), regardless of the tumor type classification. Also, in male rats, the pairwise comparisons showed statistically significant increases in high dose group for the incidences of hepatocellular adenoma in the liver when compared to the vehicle control group (p-value = 0.0294), if this tumor was classified as rare.

In female rats, the pairwise comparisons showed statistically significant increases in the high dose group for the incidences of hepatocellular adenoma, and the combined hepatocellular adenoma and hepatocellular carcinoma in the liver when compared to the vehicle control group (p-value=0.0005, and =0.0005, respectively), regardless of these tumor types classification (rare or common). Also, the pairwise comparisons showed statistically significant increases in the high dose group for the incidences of hepatocellular carcinoma in female mice when compared to vehicle control group (p=0.0105), if this tumor is classified as rare.

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. Two hundred eighty CD-1 mice of each sex were assigned randomly to one of the four groups which included three treated groups and one vehicle control group in equal size of 70 animals, as indicated in Table 3. The target dose levels for treated groups were 3, 10, and 30 mg/kg/day for both male and female mice. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The vehicle control group was exposed to vehicle item only [ultra pure water], administered by oral gavage for about 104 weeks in the same manner as the treated groups. However, all female groups were sent to terminal necropsies starting on Day 721 (week 103) due to lowered survival rate of the control group.

Table 3: Experimental Design in Mouse Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle control	1	0	0	70	70
Low	2	3	3	70	70
Medium	3	10	10	70	70
High	4	30	30	70	70

Female mice terminated on Day 721 (week 103).

During the administration period, all animals were checked for morbidity, mortality, injury, twice daily, once in the morning and once in the afternoon on weekdays and weekends. Animals were not removed from cage during observation, unless necessary for identification or confirmation of possible findings. The animals were removed from the cage, and detailed observations were conducted for each animal weekly, beginning during Week 1. The presence of palpable masses was observed during the detailed examination; the site, size and appearance of these masses were recorded when first detected and, following this initial description, the presence or disappearance of these masses were monitored. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Histopathological examinations were performed on all animals found dead, killed moribund, or sacrificed at the end of the experiment, all suspected tumors were diagnosed. Body weights and food consumption of individual animals were recorded weekly, during weeks 1 to 14, every four weeks from weeks 18 to 78 and every 2 weeks thereafter for the reminder of the study. Terminal body weights were not collected from animals found dead or euthanized moribund

3.1. Sponsor's analyses

3.1.1 Survival analysis

The sponsor used similar methodologies to analyze the mouse survival data as those used to analyze the rat survival data.

Sponsor's findings:

Sponsor's analysis showed the numbers of mice surviving to their terminal necropsy were 30 (43%), 25 (36%), 33 (47%), and 17 (24%), in vehicle control, low, medium, and high dose groups in male mice, respectively, and 20 (29%), 30 (43%), 29 (41%), and 22 (31%), in female mice, respectively. The sponsor's report showed statistically significance at the 5% level using a log-rank test, for male datasets, with p-value = 0.0272. Therefore, the overall dose-related trend and the pairwise group comparisons

between the vehicle item group (Group 1) and each of the test item treated groups (Groups 2, 3, and 4) were evaluated via a two-sided Peto's test at the 5% significance level for male mice. However, for female mice, the sponsor's report showed no statistically significance at the 5% level using a log-rank test, with p-value = 0.3649. Therefore, no post-hoc testing was done for female datasets, i.e. neither the trend test nor the pairwise comparisons were performed for female mice.

The sponsor's analysis showed a statistically significant increase in mortality across the vehicle control group and the three treated groups in male mice with p-value = 0.0427. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group in male mice

3.1.2 Tumor data analysis

The sponsor used similar methodologies to analyze the mouse tumor data as those used to analyze the rat tumor data.

The analysis of tumors was based on the following fixed time intervals: Weeks 1-52, 53-78, 79-92, 93- to before sacrifice time (104 for males and 103 for females) and terminal sacrifice. The actual dose levels were used as the scores.

Multiple testing adjustment:

The sponsor used similar test levels of significance as those used for rat study to adjust for multiple testing.

Sponsor's findings:

Following the multiple testing adjustment method described above, the sponsor's analysis showed statistically significant positive trend tests for hepatocellular adenoma, hepatocellular carcinoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver in male mice (p-value = 0.0002, P-value < 0.0001, and p-value < 0.0001, respectively), regardless of these tumor types classification (rare or common).

A sequential trend test, excluding group 4, was then performed for the datasets, the sponsor's result showed statistically significant positive trend test for hepatocellular adenoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver in male mice ((p-value = 0.0018, P-value = 0.0045, respectively), regardless of these tumor types classification (rare or common).

The pairwise comparisons showed statistically significant increases in the medium and high dose group for the incidences of hepatocellular adenoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver, when compared to the vehicle control group in male mice (p-value = 0.0033, p-value = 0.0036, and p-value = 0.0008, p-value < 0.0001, respectively), regardless of these tumor types classification (rare or common). Also, in male mice the pairwise test showed a statistically significant increases in the high dose group for the incidences of hepatocellular carcinoma in the liver, when compared to the vehicle control group (p-value < 0.0001), regardless of the tumor type classification. The incidence of histiocytic sarcoma in hemolymphoreticular tissue in the low dose group in male mice was considered to be statistically significant when compared to the vehicle control group, only if this tumor is classified as rare (p-value = 0.0116).

3.2 Reviewer's analyses

Similar to the rat study, this reviewer independently performed the survival and tumor data analyses of the mouse study. For the analysis of the survival data and the tumor data of the mouse study, this reviewer used similar methodologies that were used for the analyses of the survival and tumor data of the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1 Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 30 (43%), 25 (36%), 33 (47%), and 17 (24%), in vehicle control, low, medium, and high dose groups in male mice, respectively, and 20 (29%), 30 (43%), 29 (41%), and 22 (31%), in female mice, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of mice. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group in either sex of mice.

3.2.2 Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and the pairwise comparisons of vehicle control and treated groups are given in Table 6A and 6B in the appendix for male and female mice, respectively.

Multiple testing adjustment:

For mouse study, this reviewer used similar test levels of significance as those used for rat study to adjust for multiple testing. This reviewer used the number of animals bearing tumors in the vehicle control group to determine the common or rare tumor status.

Reviewer's findings:

The tumor types with p-values less than 0.05 for dose response relationship and/or pairwise comparisons of vehicle control and treated groups are reported in Table 4.

Table 4:Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons **Treated Groups and Vehicle control Group in Mice**

Sex	Organ Name	Tumor Name	0 mg/kg Veh. Cont. (N=65) P - Trend	3 mg/kg Low (N=60) P - VC vs. L	10 mg/kg Med (N=65) P - VC vs. M	30 mg/kg High (N=65) P - VC vs. H
Male	Hemolymphoreticular Tissue	Histiocytic Sarcoma	0/70 (47) 0.7614	6/70 (49) 0.0151*	3/70 (53) 0.1449	1/70 (44) 0.4835
	Liver	Hepatocellular Adenoma	13/70 (50) 0.0023*	15/70 (49) 0.3874	29/70 (57) 0.0072*	27/70 (51) 0.0049*
		Hepatocellular Carcinoma	3/70 (48) 0.0001*	8/70 (49) 0.1060	7/70 (53) 0.2029	18/70 (49) 0.0002*
		Hepatocellular Adenoma/Carcinoma	15/70 (51) 0.0001*	21/70 (51) 0.1501	32/70 (58) 0.0057*	36/70 (55) 0.0002*
Female	Ovary	Luteoma	6/70 (45) 0.0413[@]	2/70 (50) 0.9796	4/70 (44) 0.8334	8/70 (40) 0.2963
	Uterus	Leiomyoma	1/70 (44) 0.0257[@]	1/70 (48) 0.7740	0/70 (44) 1.0000	4/70 (42) 0.1658
		Leiomyoma / Leiomyosarcoma	2/70 (44) 0.0348[@]	3/70 (48) 0.5416	1/70 (44) 0.8793	6/70 (42) 0.1181

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

[@]: not statistically significant at 0.005 for common in dose response relationship (trend) tests.

*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Following the multiple testing adjustment method described above, this reviewer's analyses showed statistically significant increasing dose response relationships across the vehicle control and the treated groups, for the incidence of hepatocellular adenoma, hepatocellular carcinoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver in male mice (p =0.0023, < 0.0001, and <0.0001, respectively), regardless of these tumor types classification (rare or common).

The pairwise comparisons showed statistically significant increases in the high dose group for the incidences of hepatocellular adenoma, hepatocellular carcinoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver, when compared to the vehicle control group in male mice (p =0.0049, = 0.0002, and = 0.0002, respectively), regardless of these tumor types classification (rare or common). Also, in male mice the pairwise test showed a statistically significant increases in the medium dose group for the incidences of hepatocellular adenoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver, when compared to the vehicle control group (p-value =0.0072, and = 0.0057, respectively), regardless of the tumor type classification. The incidence of histiocytic sarcoma in hemolymphoreticular tissue in the low dose group in male mice was considered to be statistically significant when compared to the vehicle control group, only if this tumor is classified as rare (p-value = 0.0151).

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in Wistar

Hannover rats and one in CD-1 mice. These studies were intended to assess the carcinogenic potential of osilodrostat (LCI699), when administered orally by gavage at appropriate drug levels for about 104 weeks.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred Wistar Hannover rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 50 animals, as indicated in Table 1. The dose levels for treated groups were 3, 10, and 30 mg/kg/day for both male and female rats. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group was exposed to Vehicle Item only [ultra pure water] administered orally by gavage for about 104 weeks in the same manner as the treated groups.

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 34 (68%), 35 (70%), 38 (76%), and 37 (74%) in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 38 (76%), 43 (86%), 36 (72%) and 35 (70%) in vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group in either sex of rats.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analyses showed statistically significant increasing dose response relationships across the vehicle control and the treated groups of male rats for the incidence of follicular cell adenoma, and the combined follicular cell adenoma and follicular cell carcinoma in the gland thyroid ($p < 0.0001$, and < 0.0001, respectively), regardless of these tumor types classification (rare or common). In female rats, this reviewer's analysis showed statistically significant increasing dose response relationships across the vehicle control and the treated groups, for the incidence of hepatocellular adenoma, hepatocellular carcinoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver ($p < 0.0001$, $= 0.0006$, and < 0.0001, respectively), regardless of these tumor types classification (rare or common).

The pairwise comparisons showed statistically significant increases in the high dose group for the incidences of follicular cell adenoma, and the combined follicular cell adenoma and follicular cell carcinoma in the gland thyroid, when compared to the vehicle control group, in male rats (p-value = 0.0026, and = 0.0007, respectively), regardless of these tumor types classification (rare or common). In the medium dose group of male rats, the pairwise comparisons showed statistically significant increases for the incidences of hepatocellular adenoma in the liver when compared to the vehicle control group (p-value = 0.0072), regardless of the tumor type classification. Also, in male rats, the pairwise comparisons showed statistically significant increases in high dose group for the incidences of hepatocellular adenoma in the liver when compared to the vehicle control group (p-value = 0.0294), if this tumor was classified as rare.

In female rats, the pairwise comparisons showed statistically significant increases in the high dose group for the incidences of hepatocellular adenoma, and the combined hepatocellular adenoma and hepatocellular carcinoma in the liver when compared to the vehicle control group (p-value=0.0005, and =0.0005, respectively), regardless of these tumor types classification (rare or common). Also, the pairwise comparisons showed statistically significant increases in the high dose group for the incidences of hepatocellular carcinoma in female mice when compared to vehicle control group ($p<0.0105$), if this tumor is classified as rare.

Mouse Study:

Two separate experiments were conducted, one in male mice and one in female mice. Two hundred eighty CD-1 mice of each sex were assigned randomly to one of the four groups which included three treated groups and one vehicle control group in equal size of 70 animals, as indicated in Table 3. The target dose levels for treated groups were 3, 10, and 30 mg/kg/day for both male and female mice. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The vehicle control group was exposed to vehicle item only [ultra pure water], administered by oral gavage for about 104 weeks in the same manner as the treated groups. However, all female groups were sent to terminal necropsies starting on Day 721 (week 103) due to lowered survival rate of the control group.

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 30 (43%), 25 (36%), 33 (47%), and 17 (24%), in vehicle control, low, medium, and high dose groups in male mice, respectively, and 20 (29%), 30 (43%), 29 (41%), and 22 (31%), in female mice, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the vehicle control group and the three treated groups in either sex of mice. The pairwise comparisons showed no statistically significant increase or decrease in mortality between each of the treated groups and the vehicle control group in either sex of mice.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analyses showed statistically significant increasing dose response relationships across the vehicle control and the treated groups, for the incidence of hepatocellular adenoma, hepatocellular carcinoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver in male mice ($p = 0.0023$, < 0.0001, and < 0.0001, respectively), regardless of these tumor types classification (rare or common).

. The pairwise comparisons showed statistically significant increases in the high dose group for the incidences of hepatocellular adenoma, hepatocellular carcinoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver, when compared to the vehicle control group in male mice ($p = 0.0049$, $= 0.0002$, and $= 0.0002$, respectively), regardless of these tumor types classification (rare or common). Also, in male mice the pairwise test showed a statistically significant increases in the medium dose group for the incidences of hepatocellular adenoma, and the combined hepatocellular adenoma and hepatocellular carcinoma, in the liver, when compared to the vehicle control group (p-value $= 0.0072$, and $= 0.0057$, respectively), regardless of the tumor type classification. The incidence of histiocytic sarcoma in hemolymphoreticular tissue in the low dose group in male mice was considered to be statistically significant when compared to the vehicle control group, only if this tumor is classified as rare (p-value = 0.0151).

Malick Mbodj, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI
Hepei Chen, secondary reviewer

cc:
Archival NDA 212801- Osilodrostat, LCI699
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5. Appendix

Table1A: Intercurrent Mortality Rate
Male Rats

	0 mg|kg|day		3 mg|kg|day		10 mg|kg|day		30 mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	.	.	.	.	1	2.00	.	.
53 - 78	4	8.00	4	8.00	.	.	2	4.00
79 - 92	5	18.00	4	16.00	5	12.00	5	14.00
93 - 103	7	32.00	7	30.00	6	24.00	6	26.00
Ter. Sac.	34	68.00	35	70.00	38	76.00	37	74.00
Total	50	100.00	50	100.00	50	100.00	50	100.00

Table1B: Intercurrent Mortality Rate
Female Rats

	0 mg|kg|day		3 mg|kg|day		10 mg|kg|day		30 mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	1	2.00	3	6.00	.	.	3	6.00
53 - 78	1	4.00	2	10.00	7	14.00	3	12.00
79 - 92	3	10.00	.	.	1	16.00	3	18.00
93 - 104	7	24.00	2	14.00	6	28.00	5	28.00
ACCD	.	.	.	.	.	.	1	2.00
Ter. Sac.	38	76.00	43	86.00	36	72.00	35	70.00
Total	50	100.00	50	100.00	50	100.00	50	100.00

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	P-value for Ref. Cont., Low, Med, high	P-value for Ref. Cont. vs Low	P-value for Ref. Cont. vs Med	P-value for Ref. Cont. vs High
Dose-Response (Likelihood Ratio)	0.5644	0.8559	0.3745	0.5693
Homogeneity (Log-Rank)	0.8057	0.8551	0.3716	0.5672

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	P-value for Veh. Cont., Low, Med, high	P-value for Veh. Cont. vs Low	P-value for Veh. Cont. vs Med	P-value for Veh. Cont. vs High
Dose-Response (Likelihood Ratio)	0.2535	0.2514	0.5666	0.5410
Homogeneity (Log-Rank)	0.3421	0.2528	0.5641	0.5400

Table3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Male Rats Poly-3

Organ Name	Tumor Name	0 mg Cont (N=50) P - Trend	3 mg Low (N=50) P - C vs. L	10 mg Med (N=50) P - C vs. M	30 mg High (N=50) P - C vs. H
Body Cavity, Nasal	Chondroma	0/50 (44) 0.2514	0/50 (44) NC	0/50 (46) NC	1/50 (45) 0.5056
	Papilloma	0/50 (44) 0.2514	0/50 (44) NC	0/50 (46) NC	1/50 (45) 0.5056
	Sebaceous Cell Adenoma	1/50 (44) 1.0000	0/50 (44) 1.0000	0/50 (46) 1.0000	0/50 (45) 1.0000
Brain	Astrocytoma, Malignant	1/50 (44) 0.7597	0/50 (44) 1.0000	1/50 (46) 0.7638	0/50 (45) 1.0000
	Granular Cell Tumor, Benign	0/50 (44) 0.7542	1/50 (44) 0.5000	0/50 (46) NC	0/50 (45) NC
	Mixed Glioma, Malignant	1/50 (45) 0.7569	0/50 (44) 1.0000	1/50 (46) 0.7582	0/50 (45) 1.0000
Esophagus	Schwannoma, Malignant	0/50 (44) 0.7542	1/50 (44) 0.5000	0/50 (46) NC	0/50 (45) NC
Gland, Adrenal	Cortical Adenoma	0/50 (44) 0.6952	1/50 (44) 0.5000	3/50 (46) 0.1292	0/50 (45) NC
	Pheochromocytoma, Benign	1/50 (44) 0.1562	0/50 (44) 1.0000	0/50 (46) 1.0000	2/50 (45) 0.5085
Gland, Parathyroid	Adenoma	1/46 (41) 1.0000	0/50 (44) 1.0000	0/45 (41) 1.0000	0/44 (39) 1.0000
Gland, Pituitary	Adenoma	11/48 (45) 0.5384	19/50 (48) 0.0900	18/50 (48) 0.1282	15/50 (49) 0.3317
Gland, Prostate	Carcinoma	0/50 (44) 0.7542	1/50 (45) 0.5056	0/50 (46) NC	0/49 (44) NC
Gland, Thyroid	C-Cell Adenoma	4/50 (44) 0.3472	2/50 (44) 0.8988	2/50 (46) 0.9084	4/50 (45) 0.6559
	C-Cell Carcinoma	0/50 (44) 0.6327	1/50 (44) 0.5000	1/50 (46) 0.5111	0/50 (45) NC
	C-Cell Adenoma/Carcinoma	4/50 (44) 0.4333	3/50 (44) 0.7832	3/50 (46) 0.8010	4/50 (45) 0.6559
	Follicular Cell Adenoma	4/50 (44) <0.0001*	2/50 (44) 0.8988	9/50 (46) 0.1326	16/50 (45) 0.0026*
	Follicular Cell Carcinoma	0/50 (44) 0.1124	0/50 (44) NC	3/50 (46) 0.1292	2/50 (45) 0.2528
	Adenoma/Carcinoma Follicular Cell	4/50 (44) <0.0001*	2/50 (44) 0.8988	12/50 (46) 0.0321	18/50 (45) 0.0007*
Heart	Schwannoma, Benign	1/50 (44) 1.0000	0/50 (44) 1.0000	0/50 (46) 1.0000	0/50 (45) 1.0000
Hemolymphoreticular Tissue	Histiocytic Sarcoma	0/50 (44) 0.7556	1/50 (45) 0.5056	0/50 (46) NC	0/50 (45) NC
	Lymphoma, Malignant	3/50 (45) 0.3375	1/50 (44) 0.9390	2/50 (47) 0.8328	3/50 (46) 0.6721
Liver	Hemangiosarcoma	1/50 (44) 1.0000	0/50 (44) 1.0000	0/50 (46) 1.0000	0/50 (45) 1.0000
	Hepatocellular Adenoma	0/50 (44) 0.0285	1/50 (44) 0.5000	7/50 (46) 0.0072*	5/50 (45) 0.0294*

Male Rats Poly-3

Organ Name	Tumor Name	0 mg Cont (N=50) P - Trend	3 mg Low (N=50) P - C vs. L	10 mg Med (N=50) P - C vs. M	30 mg High (N=50) P - C vs. H
Lung	Bronchioloalveolar Carcinoma	1/50 (44) 1.0000	0/50 (44) 1.0000	0/50 (46) 1.0000	0/50 (45) 1.0000
	Fibrosarcoma	0/50 (44) 0.5084	0/50 (44) NC	1/50 (46) 0.5111	0/50 (45) NC
Lymph Node, Mesenteric	Hemangioma	2/50 (44) 0.8468	4/50 (45) 0.3491	2/50 (46) 0.7084	1/49 (44) 0.8793
	Hemangiosarcoma	0/50 (44) 0.8325	3/50 (44) 0.1207	1/50 (46) 0.5111	0/49 (44) NC
Muscle, Skeletal	Fibroma	0/50 (44) 0.5056	0/50 (44) NC	1/49 (45) 0.5056	0/50 (45) NC
Pancreas	Islet Cell Adenoma	2/50 (44) 0.8807	1/50 (44) 0.8793	3/50 (46) 0.5213	0/50 (45) 1.0000
Skin	Basal Cell Tumor, Benign	1/50 (44) 1.0000	0/48 (42) 1.0000	0/50 (46) 1.0000	0/50 (45) 1.0000
	Fibroma	0/50 (44) 0.5141	0/48 (42) NC	1/50 (46) 0.5111	0/50 (45) NC
	Fibrosarcoma	1/50 (44) 1.0000	0/48 (42) 1.0000	0/50 (46) 1.0000	0/50 (45) 1.0000
	Hair Follicle Tumor, Benign	0/50 (44) 0.2542	0/48 (42) NC	0/50 (46) NC	1/50 (45) 0.5056
	Keratoacanthoma	2/50 (44) 0.3455	0/48 (42) 1.0000	4/50 (46) 0.3599	2/50 (45) 0.7003
	Papilloma	0/50 (44) 0.7459	2/48 (42) 0.2356	1/50 (46) 0.5111	0/50 (45) NC
	Schwannoma, Benign	0/50 (44) 0.5141	0/48 (42) NC	1/50 (46) 0.5111	0/50 (45) NC
	Squamous Cell Carcinoma	1/50 (44) 0.4449	0/48 (42) 1.0000	0/50 (46) 1.0000	1/50 (45) 0.7584
	Squamous Cell Carcinoma/ Keratoacanthoma/ Papilloma	3/50 (44) 0.4388	2/48 (44) 0.8198	4/50 (46) 0.5252	3/50 (45) 0.6725
Small Intestine, Jejunum	Adenocarcinoma	1/50 (44) 1.0000	0/49 (43) 1.0000	0/50 (46) 1.0000	0/50 (45) 1.0000
	Adenoma	1/50 (44) 1.0000	0/49 (43) 1.0000	0/50 (46) 1.0000	0/50 (45) 1.0000
	Leiomyoma	0/50 (44) 0.5112	0/49 (43) NC	1/50 (46) 0.5111	0/50 (45) NC
	Sarcoma	0/50 (44) 0.5112	0/49 (43) NC	1/50 (46) 0.5111	0/50 (45) NC
	Schwannoma, Malignant	0/50 (44) 0.5085	0/49 (43) NC	2/50 (46) 0.2584	0/50 (45) NC
Testis	Interstitial (Leydig) Cell Adenoma	1/50 (44) 0.2653	1/50 (44) 0.7529	1/50 (46) 0.7638	2/50 (45) 0.5085
Thymus	Thymoma, Benign	3/50 (45) 0.7681	1/49 (44) 0.9390	2/50 (46) 0.8263	1/50 (45) 0.9417
	Thymoma, Malignant	0/50 (44) 0.7542	1/49 (44) 0.5000	0/50 (46) NC	0/50 (45) NC
	Thymoma Benign/Malignant	3/50 (45) 0.8305	2/49 (44) 0.8126	2/50 (46) 0.8263	1/50 (45) 0.9417

Male Rats Poly-3

Organ Name	Tumor Name	0 mg Cont (N=50) P - Trend	3 mg Low (N=50) P - C vs. L	10 mg Med (N=50) P - C vs. M	30 mg High (N=50) P - C vs. H
Whole Body	Hemangioma/ Hemangiosarcoma	4/50 (44) 0.9242	7/50 (45) 0.2739	3/50 (46) 0.8010	2/50 (45) 0.9038

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;

NC = Not calculable

*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Female Rats Poly-3

Organ Name	Tumor Name	0 mg Cont (N=50) P - Trend	3 mg Low (N=50) P - C vs. L	10 mg Med (N=50) P - C vs. M	30 mg High (N=50) P - C vs. H
Body Cavity, Nasal	Schwannoma, Malignant	0/50 (46) 0.7430	1/50 (46) 0.5000	0/50 (44) NC	0/50 (43) NC
Brain	Astrocytoma, Malignant	1/50 (46) 0.4258	0/50 (45) 1.0000	0/50 (44) 1.0000	1/50 (43) 0.7357
	Granular Cell Tumor, Benign	0/50 (46) 0.7416	1/50 (45) 0.4945	0/50 (44) NC	0/50 (43) NC
	Granular Cell Tumor, Malignant	0/50 (46) 0.4916	0/50 (45) NC	1/50 (45) 0.4945	0/50 (43) NC
	Granular Cell Tumor Benign/Malignant	0/50 (46) 0.6130	1/50 (45) 0.4945	1/50 (45) 0.4945	0/50 (43) NC
	Oligodendroglioma, Malignant	1/50 (46) 1.0000	0/50 (45) 1.0000	0/50 (44) 1.0000	0/50 (43) 1.0000
Cervix	Granular Cell Tumor, Benign	1/50 (46) 1.0000	0/50 (45) 1.0000	0/50 (44) 1.0000	0/50 (43) 1.0000
Gland, Adrenal	Cortical Adenoma	0/50 (46) 0.0743	2/50 (45) 0.2418	1/50 (44) 0.4889	3/50 (43) 0.1087
	Pheochromocytoma, Benign	0/50 (46) 0.4888	0/50 (45) NC	1/50 (44) 0.4889	0/50 (43) NC
Gland, Mammary	Adenocarcinoma	0/48 (44) 0.3129	1/50 (45) 0.5056	0/49 (43) NC	1/50 (44) 0.5000
	Adenoma	2/48 (44) 0.9191	1/50 (46) 0.8873	1/49 (43) 0.8751	0/50 (43) 1.0000
	Adenoma/Adenocarcinoma	2/50 (46) 0.7365	2/50 (46) 0.6917	1/50 (44) 0.8708	1/50 (44) 0.8708
	Fibroadenoma	5/48 (44) 0.9338	7/50 (46) 0.4112	5/49 (43) 0.6158	2/50 (43) 0.9415
	Mixed Tumor, Benign	0/48 (44) 0.4914	0/50 (45) NC	1/49 (43) 0.4943	0/50 (43) NC
Gland, Parathyroid	Adenoma	0/46 (42) 0.1871	0/49 (44) NC	1/49 (43) 0.5059	1/50 (43) 0.5059
Gland, Pituitary	Adenoma	22/50 (48) 0.3618	13/50 (46) 0.9763	13/50 (48) 0.9834	19/50 (46) 0.7422
	Carcinoma	1/50 (46) 1.0000	0/50 (45) 1.0000	0/50 (44) 1.0000	0/50 (43) 1.0000
	Adenoma/Carcinoma	23/50 (48) 0.4149	13/50 (46) 0.9855	13/50 (48) 0.9901	19/50 (46) 0.8028
Gland, Salivary, Parotid	Mixed Tumor, Benign	0/50 (46) 0.2416	0/50 (45) NC	0/50 (44) NC	1/50 (43) 0.4831
Gland, Thyroid	C-Cell Adenoma	6/50 (46) 0.9433	1/50 (45) 0.9934	1/50 (44) 0.9928	1/50 (43) 0.9922
	C-Cell Carcinoma	1/50 (46) 1.0000	0/50 (45) 1.0000	0/50 (44) 1.0000	0/50 (43) 1.0000
	Adenoma/Carcinoma C-Cell	7/50 (46) 0.9669	1/50 (45) 0.9969	1/50 (44) 0.9966	1/50 (43) 0.9963
	Follicular Cell Adenoma	0/50 (46) 0.1277	1/50 (45) 0.4945	2/50 (44) 0.2362	2/50 (43) 0.2306

Female Rats Poly-3

Organ Name	Tumor Name	0 mg Cont (N=50) P - Trend	3 mg Low (N=50) P - C vs. L	10 mg Med (N=50) P - C vs. M	30 mg High (N=50) P - C vs. H
	Follicular Cell Carcinoma	0/50 (46) 0.7416	1/50 (45) 0.4945	0/50 (44) NC	0/50 (43) NC
	Adenoma/Carcinoma Follicular Cell	0/50 (46) 0.2035	2/50 (45) 0.2418	2/50 (44) 0.2362	2/50 (43) 0.2306
Heart	Schwannoma, Malignant	0/50 (46) 0.4888	0/50 (45) NC	1/50 (44) 0.4889	0/50 (43) NC
Hemolymphoreticular Tissue	Histiocytic Sarcoma	0/50 (46) 0.7416	1/50 (45) 0.4945	0/50 (44) NC	0/50 (43) NC
	Lymphoma, Malignant	0/50 (46) 0.2814	1/50 (45) 0.4945	1/50 (44) 0.4889	1/50 (43) 0.4831
Liver	Hepatocellular Adenoma	3/50 (46) <0.0001*	0/50 (45) 1.0000	0/50 (44) 1.0000	16/50 (44) 0.0005*
	Hepatocellular Carcinoma	0/50 (46) 0.0006*	1/50 (45) 0.4945	0/50 (44) NC	6/50 (43) 0.0105*
	Hepatocellular Adenoma/Carcinoma	3/50 (46) <0.0001*	1/50 (45) 0.9389	0/50 (44) 1.0000	16/50 (44) 0.0005*
	Hepatocholangiocellular Adenoma	0/50 (46) 0.2416	0/50 (45) NC	0/50 (44) NC	1/50 (43) 0.4831
Lung	Bronchioloalveolar Adenoma	0/50 (46) 0.4888	0/50 (45) NC	1/50 (44) 0.4889	0/50 (43) NC
Lymph Node, Mesenteric	Hemangioma	1/50 (46) 0.9343	1/50 (45) 0.7473	0/50 (44) 1.0000	0/49 (43) 1.0000
Muscle, Skeletal	Rhabdomyosarcoma	1/50 (46) 1.0000	0/50 (45) 1.0000	0/50 (44) 1.0000	0/50 (43) 1.0000
Ovary	Cystadenoma	0/50 (46) 0.2416	0/50 (45) NC	0/50 (44) NC	1/49 (43) 0.4831
	Luteoma	1/50 (46) 1.0000	0/50 (45) 1.0000	0/50 (44) 1.0000	0/49 (43) 1.0000
	Tubulostromal Adenoma	2/50 (46) 0.5309	0/50 (45) 1.0000	4/50 (44) 0.3172	1/49 (43) 0.8663
Skin	Basal Cell Tumor, Malignant	0/49 (45) 0.4915	0/50 (45) NC	1/50 (44) 0.4944	0/50 (43) NC
	Granular Cell Tumor, Benign	0/49 (45) 0.7458	1/50 (45) 0.5000	0/50 (44) NC	0/50 (43) NC
	Hair Follicle Tumor, Benign	0/49 (45) 0.2429	0/50 (45) NC	0/50 (44) NC	1/50 (43) 0.4886
Small Intestine, Jejunum	Adenocarcinoma	0/50 (46) 0.7430	1/50 (46) 0.5000	0/50 (44) NC	0/49 (43) NC
	Leiomyoma	0/50 (46) 0.7416	1/50 (45) 0.4945	0/50 (44) NC	0/49 (43) NC
Thymus	Thymoma, Benign	4/50 (46) 0.8306	1/50 (45) 0.9705	2/48 (44) 0.8881	1/50 (43) 0.9670
	Thymoma, Malignant	1/50 (46) 0.3519	0/50 (45) 1.0000	2/48 (44) 0.4831	1/50 (43) 0.7357
	Thymoma Benign/Malignant	5/50 (46) 0.7058	1/50 (45) 0.9859	4/48 (44) 0.7348	2/50 (43) 0.9338
Uterus	Endometrial Adenocarcinoma	2/50 (47) 0.8664	0/50 (45) 1.0000	1/50 (44) 0.8665	0/50 (43) 1.0000

Female Rats Poly-3

Organ Name	Tumor Name	0 mg Cont (N=50) P - Trend	3 mg Low (N=50) P - C vs. L	10 mg Med (N=50) P - C vs. M	30 mg High (N=50) P - C vs. H
	Endometrial Adenoma	1/50 (46) 1.0000	0/50 (45) 1.0000	0/50 (44) 1.0000	0/50 (43) 1.0000
	Endometrial Stromal Polyp	10/50 (46) 0.9843	4/50 (45) 0.9782	3/50 (44) 0.9912	2/50 (43) 0.9974
	Endometrial Adenocarcinoma / Adenoma/ Stromal Polyp	13/50 (47) 0.9959	4/50 (45) 0.9960	4/50 (44) 0.9954	2/50 (43) 0.9997
	Schwannoma, Malignant	1/50 (46) 1.0000	0/50 (45) 1.0000	0/50 (44) 1.0000	0/50 (43) 1.0000
Vagina	Polyp	0/50 (46) 0.7416	1/50 (45) 0.4945	0/50 (44) NC	0/50 (43) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Figure 1A: Kaplan-Meier Survival Curves for
Male Rats

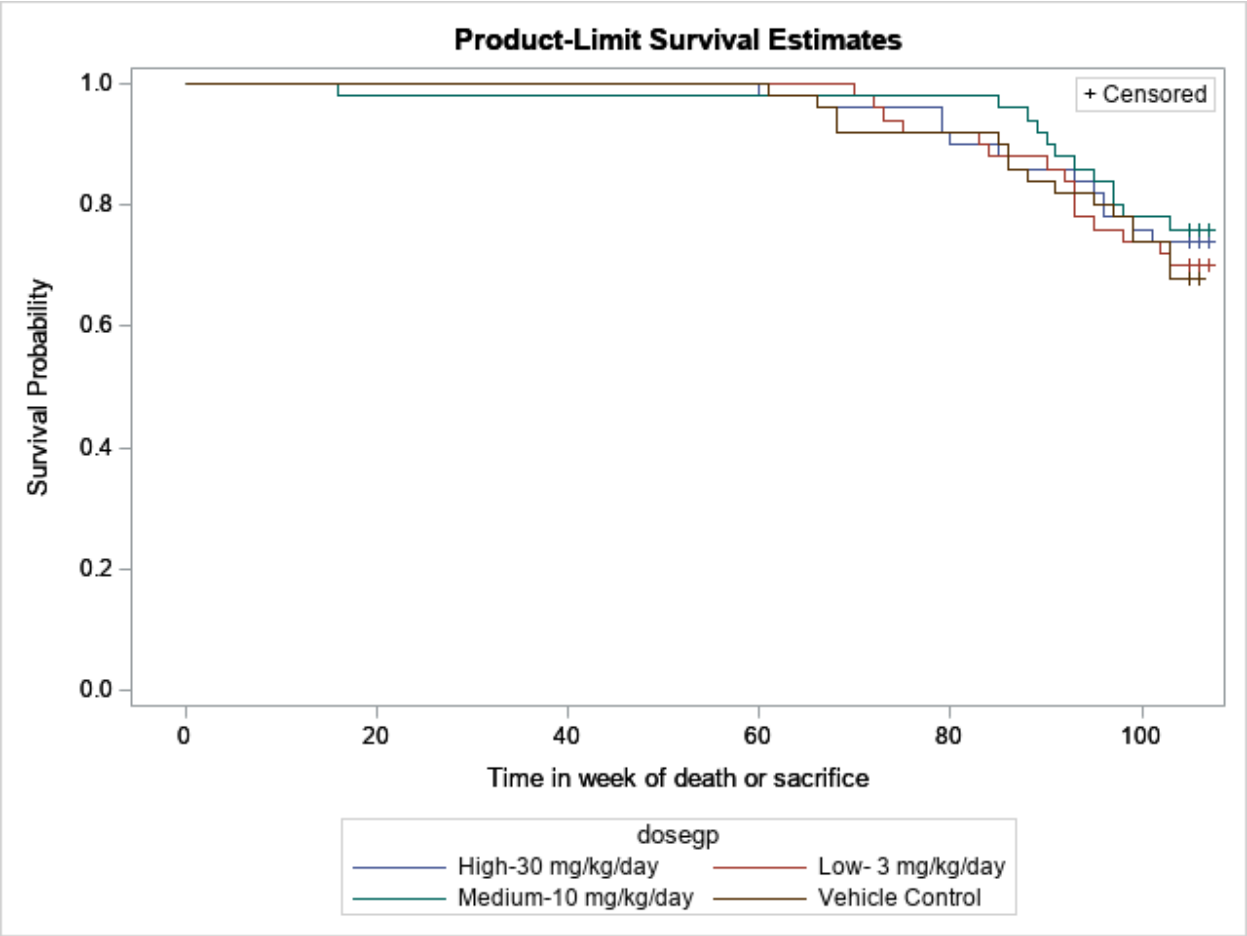


Figure 1B: Kaplan-Meier Survival Curves **for Female Rats**

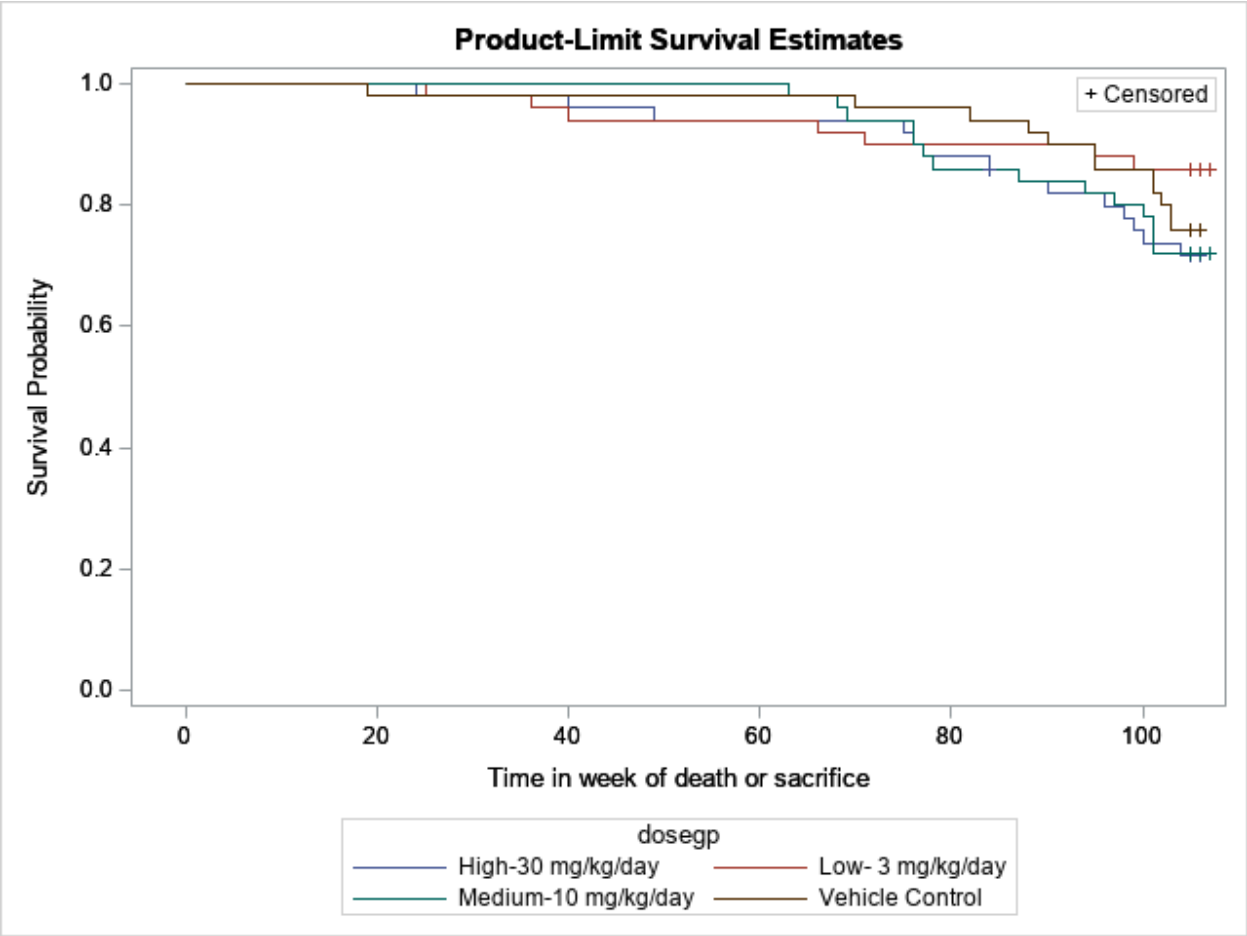


Table4A: Intercurrent Mortality Rate
Male Mice

	0 mg|kg|day		3 mg|kg|day		10 mg|kg|day		30 mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	4	5.71	3	4.29	1	1.43	7	10.00
53 - 78	15	27.14	17	28.57	8	12.86	16	32.86
79 - 92	14	47.14	12	45.71	20	41.43	13	51.43
93 - 104	6	55.71	13	64.29	5	48.57	17	75.71
ACCD	1	1.43	.	.	3	4.29	.	.
Ter. Sac.	30	42.86	25	35.71	33	47.14	17	24.29
Total	70	100.00	70	100.00	70	100.00	70	100.00

Table4B: Intercurrent Mortality Rate
Female Mice

	0 mg|kg|day		3 mg|kg|day		10 mg|kg|day		30 mg|kg|day	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	5	7.14	4	5.71	4	5.71	9	12.86
53 - 78	16	30.00	13	24.29	15	27.14	14	32.86
79 - 92	12	47.14	11	40.00	12	44.29	10	47.14
93 - 103	15	68.57	11	55.71	6	52.86	9	60.00
ACCD.	2	2.86	1	1.43	4	5.71	6	8.57
Ter. Sac.	20	28.57	30	42.86	29	41.43	22	31.43
Total	70	100.00	70	100.00	70	100.00	70	100.00

Table 5A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	**P-value for Veh. Cont., Low, Med, high**	**P-value for Veh. Cont. vs Low**	**P-value for Veh. Cont. vs Med**	**P-value for Veh. Cont. vs High**
Dose-Response (Likelihood Ratio)	0.0502	0.5339	0.2737	0.0614
Homogeneity (Log-Rank)	0.0276*	0.5312	0.2701	0.0591

* = statistically significant at the 0.05 significance level.

Table 5B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	**P-value for Veh. Cont., Low, Med, high**	**P-value for Veh. Cont. vs Low**	**P-value for Veh. Cont. vs Med**	**P-value for Veh. Cont. vs High**
Dose-Response (Likelihood Ratio)	0.6460	0.1258	0.2346	0.8341
Homogeneity (Log-Rank)	0.3694	0.1219	0.2312	0.8327

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and the Pairwise Comparisons

Male Mice Poly-3

Organ Name	Tumor Name	0 mg Cont (N=70) P - Trend	3 mg Low (N=70) P - C vs. L	10 mg Med (N=70) P - C vs. M	30 mg High (N=70) P - C vs. H
Bone Marrow	Hemangiosarcoma	1/70 (47) 0.8282	1/70 (47) 0.7527	1/70 (52) 0.7772	0/70 (43) 1.0000
Bone, Femur	Osteoma	0/70 (47) 0.5026	0/70 (47) NC	1/70 (52) 0.5253	0/70 (43) NC
Brain	Astrocytoma, Malignant	0/70 (47) 0.2316	0/70 (47) NC	0/70 (52) NC	1/70 (44) 0.4835
	Ependymoma, Malignant	0/70 (47) 0.7513	1/70 (47) 0.5000	0/70 (52) NC	0/70 (43) NC
	Meningioma, Malignant	2/70 (48) 1.0000	0/70 (47) 1.0000	0/70 (52) 1.0000	0/70 (43) 1.0000
Gland, Adrenal	Adenoma Subcapsular, Mixed Cells	1/70 (47) 1.0000	0/70 (47) 1.0000	0/70 (52) 1.0000	0/70 (43) 1.0000
	Adenoma Subcapsular, Type A Cell	0/70 (47) 0.1767	0/70 (47) NC	1/70 (52) 0.5253	1/70 (43) 0.4778
	Adenoma Subcapsular, Type B Cell	1/70 (47) 0.3715	0/70 (47) 1.0000	1/70 (52) 0.7772	1/70 (43) 0.7301
	Adenoma Subcapsular Type A/B Cell	1/70 (47) 0.1481	0/70 (47) 1.0000	2/70 (52) 0.5382	2/70 (43) 0.4663
	Carcinoma Subcapsular, Mixed Cells	0/70 (47) 0.5026	0/70 (47) NC	1/70 (52) 0.5253	0/70 (43) NC
	Adenoma/Carcinoma Subcapsular Mixed Cell	1/70 (47) 0.7540	0/70 (47) 1.0000	1/70 (52) 0.7772	0/70 (43) 1.0000
	Carcinoma Subcapsular, Type B Cell	2/70 (47) 0.9854	1/70 (47) 0.8790	0/70 (52) 1.0000	0/70 (43) 1.0000
	Adenoma/Carcinoma Subcapsular Mixed Cell / Type A/B Cell	4/70 (47) 0.6010	1/70 (47) 0.9721	3/70 (52) 0.8216	2/70 (43) 0.8768
	Cortical Adenoma	3/70 (47) 0.8718	3/70 (48) 0.6714	1/70 (52) 0.9526	1/70 (44) 0.9333
	Pheochromocytoma, Benign	0/70 (47) 0.0555	0/70 (47) NC	1/70 (52) 0.5253	2/70 (44) 0.2310
	Pheochromocytoma, Malignant	0/70 (47) 0.7513	1/70 (47) 0.5000	0/70 (52) NC	0/70 (43) NC
	Pheochromocytoma Benign / Malignant	0/70 (47) 0.1071	1/70 (47) 0.5000	1/70 (52) 0.5253	2/70 (44) 0.2310
Gland, Harderian	Adenocarcinoma	0/70 (47) 0.5026	0/70 (47) NC	1/70 (52) 0.5253	0/70 (43) NC
	Adenoma	11/70 (49) 0.1717	7/70 (49) 0.9044	12/70 (54) 0.6048	12/70 (46) 0.4306
	Adenoma/Adenocarcinoma	11/70 (49) 0.1751	7/70 (49) 0.9044	13/70 (54) 0.5161	12/70 (46) 0.4306
	Fibrosarcoma	0/70 (47) 0.7513	1/70 (47) 0.5000	0/70 (52) NC	0/70 (43) NC

Male Mice Poly-3

Organ Name	Tumor Name	0 mg Cont (N=70) P - Trend	3 mg Low (N=70) P - C vs. L	10 mg Med (N=70) P - C vs. M	30 mg High (N=70) P - C vs. H
Gland, Pituitary	Adenoma, Pars Intermedia	0/65 (44) 0.5000	0/70 (47) NC	1/67 (49) 0.5269	0/67 (42) NC
Gland, Preputial	Hemangioma	0/70 (47) 0.5026	0/70 (47) NC	1/70 (52) 0.5253	0/70 (43) NC
Gland, Prostate	Adenoma	0/69 (46) 0.6205	1/70 (47) 0.5054	1/70 (52) 0.5306	0/70 (43) NC
Gland, Seminal Vesicle	Adenoma	0/70 (47) 0.5026	0/70 (47) NC	1/70 (52) 0.5253	0/70 (43) NC
	Hemangiosarcoma	1/70 (47) 1.0000	0/70 (47) 1.0000	0/70 (52) 1.0000	0/70 (43) 1.0000
Gland, Thyroid	Follicular Cell Adenoma	1/68 (45) 0.7822	1/70 (48) 0.7686	2/70 (52) 0.5546	0/70 (43) 1.0000
Heart	Mesothelioma, Malignant	0/70 (47) 0.2316	0/70 (47) NC	0/70 (52) NC	1/70 (44) 0.4835
Hemolymphoreticular Tissue	Histiocytic Sarcoma	0/70 (47) 0.7614	6/70 (49) 0.0151*	3/70 (53) 0.1449	1/70 (44) 0.4835
	Leukemia, Granulocytic	0/70 (47) 0.5026	0/70 (47) NC	1/70 (52) 0.5253	0/70 (43) NC
	Lymphoma, Malignant	8/70 (49) 0.2136	10/70 (52) 0.4527	8/70 (55) 0.7001	11/70 (48) 0.2874
	Mast Cell Tumor, Malignant	0/70 (47) 0.0527	0/70 (47) NC	0/70 (52) NC	2/70 (44) 0.2310
Kidney	Tubular Cell Adenoma	1/70 (47) 0.6737	0/70 (47) 1.0000	2/70 (52) 0.5382	0/70 (43) 1.0000
	Tubular Cell Carcinoma	0/70 (47) 0.7513	1/70 (47) 0.5000	0/70 (52) NC	0/70 (43) NC
	Tubular Cell Benign / Malignant	1/70 (47) 0.7776	1/70 (47) 0.7527	2/70 (52) 0.5382	0/70 (43) 1.0000
Large Intestine, Cecum	Leiomyoma	0/70 (47) 0.7513	1/70 (47) 0.5000	0/70 (52) NC	0/70 (43) NC
Liver	Hemangiosarcoma	4/70 (48) 0.5151	0/70 (47) 1.0000	3/70 (53) 0.8207	2/70 (44) 0.8771
	Hepatocellular Adenoma	13/70 (50) 0.0023*	15/70 (49) 0.3874	29/70 (57) 0.0072*	27/70 (51) 0.0049*
	Hepatocellular Carcinoma	3/70 (48) 0.0001*	8/70 (49) 0.1060	7/70 (53) 0.2029	18/70 (49) 0.0002*
	Hepatocellular Adenoma/Carcinoma	15/70 (51) 0.0001*	21/70 (51) 0.1501	32/70 (58) 0.0057*	36/70 (55) 0.0002*
Lung	Bronchioloalveolar Adenoma	25/70 (54) 0.8587	16/70 (51) 0.9617	23/70 (57) 0.7949	15/70 (48) 0.9610
	Bronchioloalveolar Carcinoma	19/70 (51) 0.7656	19/70 (53) 0.6378	17/70 (55) 0.8145	15/70 (49) 0.8191
	Bronchioloalveolar Adenoma/Carcinoma	40/70 (57) 0.8620	30/70 (55) 0.9718	33/70 (58) 0.9531	29/70 (53) 0.9696

Male Mice Poly-3

Organ Name	Tumor Name	0 mg Cont (N=70) P - Trend	3 mg Low (N=70) P - C vs. L	10 mg Med (N=70) P - C vs. M	30 mg High (N=70) P - C vs. H
	Carcinoma	0/70 (47) 0.5026	0/70 (47) NC	1/70 (52) 0.5253	0/70 (43) NC
	Hemangioma	1/70 (47) 1.0000	0/70 (47) 1.0000	0/70 (52) 1.0000	0/70 (43) 1.0000
	Hemangiosarcoma	1/70 (48) 1.0000	0/70 (47) 1.0000	0/70 (52) 1.0000	0/70 (43) 1.0000
Lymph Node, Mesenteric	Hemangioma	0/70 (47) 0.7513	1/70 (48) 0.5053	0/69 (51) NC	0/70 (43) NC
	Hemangiosarcoma	0/70 (47) 0.5000	0/70 (47) NC	1/69 (51) 0.5204	0/70 (43) NC
Muscle, Skeletal	Hemangiosarcoma	0/70 (47) 0.6175	1/70 (47) 0.5000	2/69 (51) 0.2683	0/70 (43) NC
	Rhabdomyosarcoma	0/70 (47) 0.5000	0/70 (47) NC	1/69 (51) 0.5204	0/70 (43) NC
Skin	Keratoacanthoma	0/70 (47) 0.2316	0/70 (47) NC	0/70 (52) NC	1/69 (44) 0.4835
	Papilloma	0/70 (47) 0.5026	0/70 (47) NC	1/70 (52) 0.5253	0/69 (43) NC
	Squamous Cell Carcinoma	1/70 (48) 0.4023	0/70 (47) 1.0000	0/70 (52) 1.0000	1/69 (43) 0.7245
	Keratoacanthoma/Papilloma /Squamous Cell	1/70 (48) 0.3684	0/70 (47) 1.0000	1/70 (52) 0.7721	1/69 (43) 0.7245
Small Intestine, Duodenum	Adenocarcinoma	0/69 (47) 0.7526	1/70 (48) 0.5053	0/70 (52) NC	0/70 (43) NC
Spinal Cord, Lumbar	Ganglioneuroma	0/70 (47) 0.2328	0/70 (47) NC	0/69 (51) NC	1/70 (44) 0.4835
Spleen	Hemangioma	0/70 (47) 0.0527	0/70 (47) NC	0/70 (52) NC	2/70 (44) 0.2310
	Hemangiosarcoma	2/70 (47) 0.7418	2/70 (47) 0.6916	0/70 (52) 1.0000	1/70 (44) 0.8665
Stomach	Adenocarcinoma	1/70 (48) 1.0000	0/70 (47) 1.0000	0/70 (52) 1.0000	0/70 (43) 1.0000
	Adenoma	1/70 (47) 0.9392	1/70 (47) 0.7527	0/70 (52) 1.0000	0/70 (43) 1.0000
	Adenocarcinoma /Adenoma	2/70 (48) 0.9846	1/70 (47) 0.8750	0/70 (52) 1.0000	0/70 (43) 1.0000
	Squamous Cell Carcinoma	0/70 (47) 0.2946	1/70 (48) 0.5053	0/70 (52) NC	1/70 (44) 0.4835
Testis	Adenoma	0/70 (47) 0.2275	0/70 (47) NC	0/70 (52) NC	1/70 (43) 0.4778
	Interstitial (Leydig) Cell Adenoma	2/70 (47) 0.7313	2/70 (49) 0.7071	0/70 (52) 1.0000	1/70 (43) 0.8620
	Interstitial (Leydig) Cell Carcinoma	0/70 (47) 0.7513	1/70 (47) 0.5000	0/70 (52) NC	0/70 (43) NC

Male Mice Poly-3

Organ Name	Tumor Name	0 mg Cont (N=70) P - Trend	3 mg Low (N=70) P - C vs. L	10 mg Med (N=70) P - C vs. M	30 mg High (N=70) P - C vs. H
	Interstitial (Leydig) Cell Adenoma/Carcinoma	2/70 (47) 0.7990	3/70 (49) 0.5199	0/70 (52) 1.0000	1/70 (43) 0.8620
	Schwannoma, Malignant	0/70 (47) 0.5026	0/70 (47) NC	1/70 (52) 0.5253	0/70 (43) NC
Whole Body	Hemangioma / Hemangiosarcoma	9/70 (49) 0.8768	6/70 (48) 0.8600	7/70 (54) 0.8481	4/70 (45) 0.9502

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and the Pairwise Comparisons

Female Mice Poly-3

Organ Name	Tumor Name	0 mg Cont (N=70) P - Trend	3 mg Low (N=70) P - C vs. L	10 mg Med (N=70) P - C vs. M	30 mg High (N=70) P - C vs. H
Bone Marrow	Hemangioma	1/70 (44) 1.0000	0/70 (48) 1.0000	0/70 (44) 1.0000	0/70 (40) 1.0000
	Hemangiosarcoma	0/70 (44) 0.4655	0/70 (48) NC	2/70 (45) 0.2528	0/70 (40) NC
Bone, Femur	Osteoma	1/69 (44) 1.0000	0/70 (48) 1.0000	0/70 (44) 1.0000	0/69 (39) 1.0000
Brain	Meningioma, Malignant	1/70 (44) 0.7313	0/70 (48) 1.0000	1/70 (45) 0.7584	0/70 (40) 1.0000
Gallbladder	Adenoma	0/68 (43) 0.4826	0/67 (46) NC	1/70 (44) 0.5057	0/67 (39) NC
Gland, Adrenal	Adenoma Subcapsular, Type A Cell	0/70 (44) 0.5385	3/70 (48) 0.1377	0/70 (44) NC	1/70 (40) 0.4762
	Adenoma Subcapsular, Type B Cell	1/70 (44) 1.0000	0/70 (48) 1.0000	0/70 (44) 1.0000	0/70 (40) 1.0000
	Adenoma Subcapsular Type A/B Cell	1/70 (44) 0.6840	3/70 (48) 0.3420	0/70 (44) 1.0000	1/70 (40) 0.7286
	Cortical Adenoma	0/70 (44) 0.2273	0/70 (48) NC	0/70 (44) NC	1/70 (40) 0.4762
	Pheochromocytoma, Benign	1/70 (44) 0.9386	1/70 (48) 0.7740	0/70 (44) 1.0000	0/70 (40) 1.0000
Gland, Harderian	Adenocarcinoma	0/70 (44) 0.7500	1/70 (48) 0.5217	0/70 (44) NC	0/70 (40) NC
	Adenoma	3/70 (44) 0.4416	3/70 (49) 0.7115	7/70 (44) 0.1570	3/70 (41) 0.6275
	Adenoma / Adenocarcinoma	3/70 (44) 0.5089	4/70 (49) 0.5606	7/70 (44) 0.1570	3/70 (41) 0.6275
Gland, Mammary	Adenocarcinoma	2/67 (42) 0.0905	0/70 (48) 1.0000	0/67 (42) 1.0000	3/69 (40) 0.4766
Gland, Pituitary	Adenoma, Pars Distalis	1/67 (43) 0.5764	2/68 (47) 0.5337	4/69 (43) 0.1800	1/68 (40) 0.7346
	Adenoma, Pars Intermedia	0/67 (42) 0.4826	0/68 (47) NC	1/69 (44) 0.5116	0/68 (39) NC
	Adenoma/Carcinoma	1/70 (44) 0.5624	2/70 (49) 0.5407	4/70 (44) 0.1802	1/70 (40) 0.7286
Gland, Thyroid	Follicular Cell Adenoma	1/70 (44) 0.7535	1/70 (49) 0.7789	2/70 (44) 0.5000	0/68 (39) 1.0000
Hemolymphoreticular Tissue	Histiocytic Sarcoma	4/70 (45) 0.7716	4/70 (50) 0.7005	3/70 (44) 0.7737	2/70 (41) 0.8761
	Lymphoma, Malignant	22/70 (51) 0.1977	20/70 (54) 0.7987	25/70 (52) 0.3801	24/70 (50) 0.3857
Liver	Hemangioma	0/70 (44) 0.6066	1/70 (48) 0.5217	2/70 (44) 0.2471	0/70 (40) NC

Female Mice Poly-3

Organ Name	Tumor Name	0 mg Cont (N=70) P - Trend	3 mg Low (N=70) P - C vs. L	10 mg Med (N=70) P - C vs. M	30 mg High (N=70) P - C vs. H
	Hepatocellular Adenoma	2/70 (44) 0.3604	1/70 (48) 0.8945	1/70 (44) 0.8793	2/70 (41) 0.6648
	Hepatocellular Carcinoma	0/70 (44) 0.4773	0/70 (48) NC	1/70 (44) 0.5000	0/70 (40) NC
	Hepatocellular_Adeno/ Carcinoma	2/70 (44) 0.3556	1/70 (48) 0.8945	2/70 (44) 0.6919	2/70 (41) 0.6648
Lung	Bronchioloalveolar Adenoma	11/69 (45) 0.3070	8/70 (51) 0.9085	10/70 (47) 0.7290	10/70 (41) 0.6005
	Bronchioloalveolar Carcinoma	6/69 (45) 0.4037	8/70 (49) 0.4547	7/70 (45) 0.5000	7/70 (43) 0.4642
	Bronchioloalveolar Adenoma/Carcinoma	16/70 (47) 0.3443	16/70 (51) 0.6906	16/70 (48) 0.6141	16/70 (44) 0.4949
Ovary	Choriocarcinoma	0/70 (44) 0.2273	0/70 (48) NC	0/70 (44) NC	1/70 (40) 0.4762
	Cystadenocarcinoma	1/70 (44) 1.0000	0/70 (48) 1.0000	0/70 (44) 1.0000	0/70 (40) 1.0000
	Cystadenoma	2/70 (44) 0.4516	2/70 (48) 0.7239	3/70 (44) 0.5000	2/70 (41) 0.6648
	Granulosa Cell Tumor, Benign	0/70 (44) 0.6042	1/70 (49) 0.5269	2/70 (44) 0.2471	0/70 (40) NC
	Granulosa Cell Tumor, Malignant	0/70 (44) 0.7500	1/70 (48) 0.5217	0/70 (44) NC	0/70 (40) NC
	Granulosa Cell Tumor Benign/Malignant	0/70 (44) 0.7074	2/70 (49) 0.2749	2/70 (44) 0.2471	0/70 (40) NC
	Hemangioma	0/70 (44) 0.4020	2/70 (49) 0.2749	0/70 (44) NC	1/70 (40) 0.4762
	Hemangiosarcoma	1/70 (44) 0.9386	1/70 (48) 0.7740	0/70 (44) 1.0000	0/70 (40) 1.0000
	Leiomyosarcoma, Mesovarian	2/70 (44) 0.5558	0/70 (48) 1.0000	0/70 (44) 1.0000	1/70 (40) 0.8610
	Luteoma	6/70 (45) 0.0413	2/70 (50) 0.9796	4/70 (44) 0.8334	8/70 (40) 0.2963
	Mixed Sex Cord Stromal Tumor, Benign	0/70 (44) 0.7098	2/70 (48) 0.2695	2/70 (44) 0.2471	0/70 (40) NC
	Sertoli Cell Tumor, Benign	0/70 (44) 0.4773	0/70 (48) NC	1/70 (44) 0.5000	0/70 (40) NC
	Tubulostromal Adenoma	0/70 (44) 0.0914	1/70 (48) 0.5217	0/70 (44) NC	2/70 (40) 0.2238
Pancreas	Adenoma, Islet of Langerhans	1/69 (43) 0.3305	0/70 (48) 1.0000	2/70 (45) 0.5172	1/70 (40) 0.7346
Skin	Basal Cell Tumor, Malignant	0/70 (44) 0.7514	1/70 (49) 0.5269	0/70 (44) NC	0/70 (40) NC
	Hemangiosarcoma	1/70 (44) 1.0000	0/70 (48) 1.0000	0/70 (44) 1.0000	0/70 (40) 1.0000

Female Mice Poly-3

Organ Name	Tumor Name	0 mg Cont (N=70) P - Trend	3 mg Low (N=70) P - C vs. L	10 mg Med (N=70) P - C vs. M	30 mg High (N=70) P - C vs. H
	Keratoacanthoma	1/70 (44) 1.0000	0/70 (48) 1.0000	0/70 (44) 1.0000	0/70 (40) 1.0000
	Mast Cell Tumor, Benign	0/70 (44) 0.7514	1/70 (49) 0.5269	0/70 (44) NC	0/70 (40) NC
	Papilloma	0/70 (44) 0.2316	0/70 (48) NC	0/70 (44) NC	1/70 (41) 0.4824
	Squamous Cell Carcinoma	2/70 (44) 0.9854	1/70 (49) 0.8979	0/70 (44) 1.0000	0/70 (40) 1.0000
Small Intestine, Jejunum	Hemangiosarcoma	0/69 (43) 0.4830	0/70 (48) NC	1/70 (45) 0.5114	0/67 (40) NC
Spleen	Hemangiosarcoma	2/70 (44) 1.0000	0/70 (48) 1.0000	0/70 (44) 1.0000	0/70 (40) 1.0000
Stomach	Adenoma	0/70 (44) 0.4773	0/70 (48) NC	1/70 (44) 0.5000	0/70 (40) NC
Tongue	Papilloma	0/70 (44) 0.2273	0/70 (48) NC	0/70 (44) NC	1/70 (40) 0.4762
Uterus	Adenocarcinoma	0/70 (44) 0.7070	2/70 (49) 0.2749	1/70 (44) 0.5000	0/70 (40) NC
	Adenoma	1/70 (44) 0.4106	0/70 (48) 1.0000	0/70 (44) 1.0000	1/70 (41) 0.7350
	Endometrial Stromal Polyp	4/70 (44) 0.8851	4/70 (49) 0.7018	6/70 (44) 0.3694	1/70 (40) 0.9648
	Hemangioma	3/70 (44) 0.6843	4/70 (49) 0.5606	4/70 (44) 0.5000	2/70 (40) 0.7889
	Hemangiosarcoma	0/70 (44) 0.6011	1/70 (49) 0.5269	1/70 (44) 0.5000	0/70 (40) NC
	Leiomyoma	1/70 (44) 0.0257	1/70 (48) 0.7740	0/70 (44) 1.0000	4/70 (42) 0.1658
	Leiomyosarcoma	1/70 (44) 0.3118	2/70 (48) 0.5330	1/70 (44) 0.7529	2/70 (41) 0.4732
	Leiomyoma/Leiomyosarcoma	2/70 (44) 0.0348	3/70 (48) 0.5416	1/70 (44) 0.8793	6/70 (42) 0.1181
	Schwannoma, Malignant	0/70 (44) 0.2896	1/70 (48) 0.5217	0/70 (44) NC	1/70 (40) 0.4762
Whole Body	Hemangioma/Hemangiosarcoma	9/70 (46) 0.9551	9/70 (49) 0.6595	9/70 (47) 0.6228	3/70 (40) 0.9755

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Figure 2A: Kaplan-Meier Survival Curves for
Male Mice

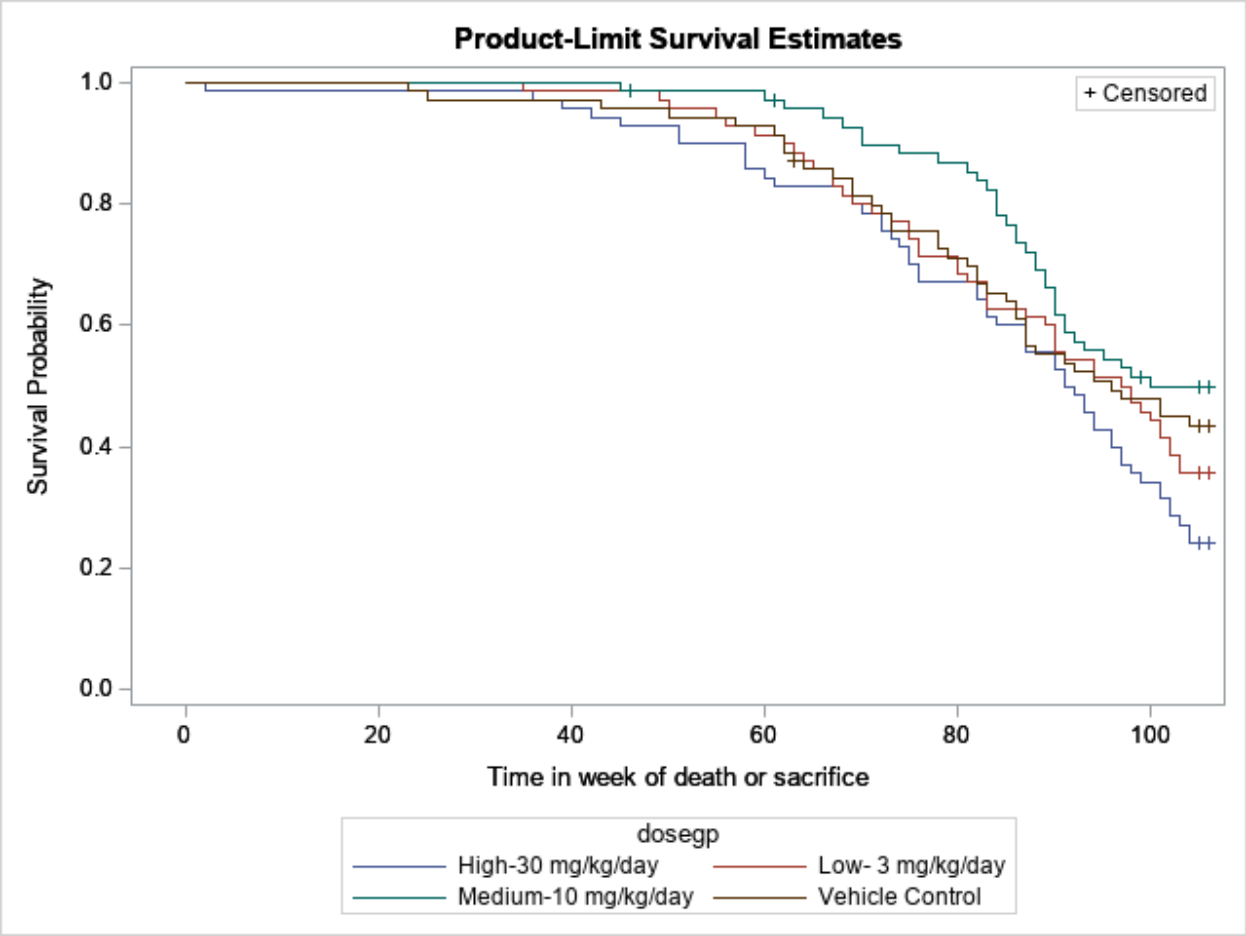
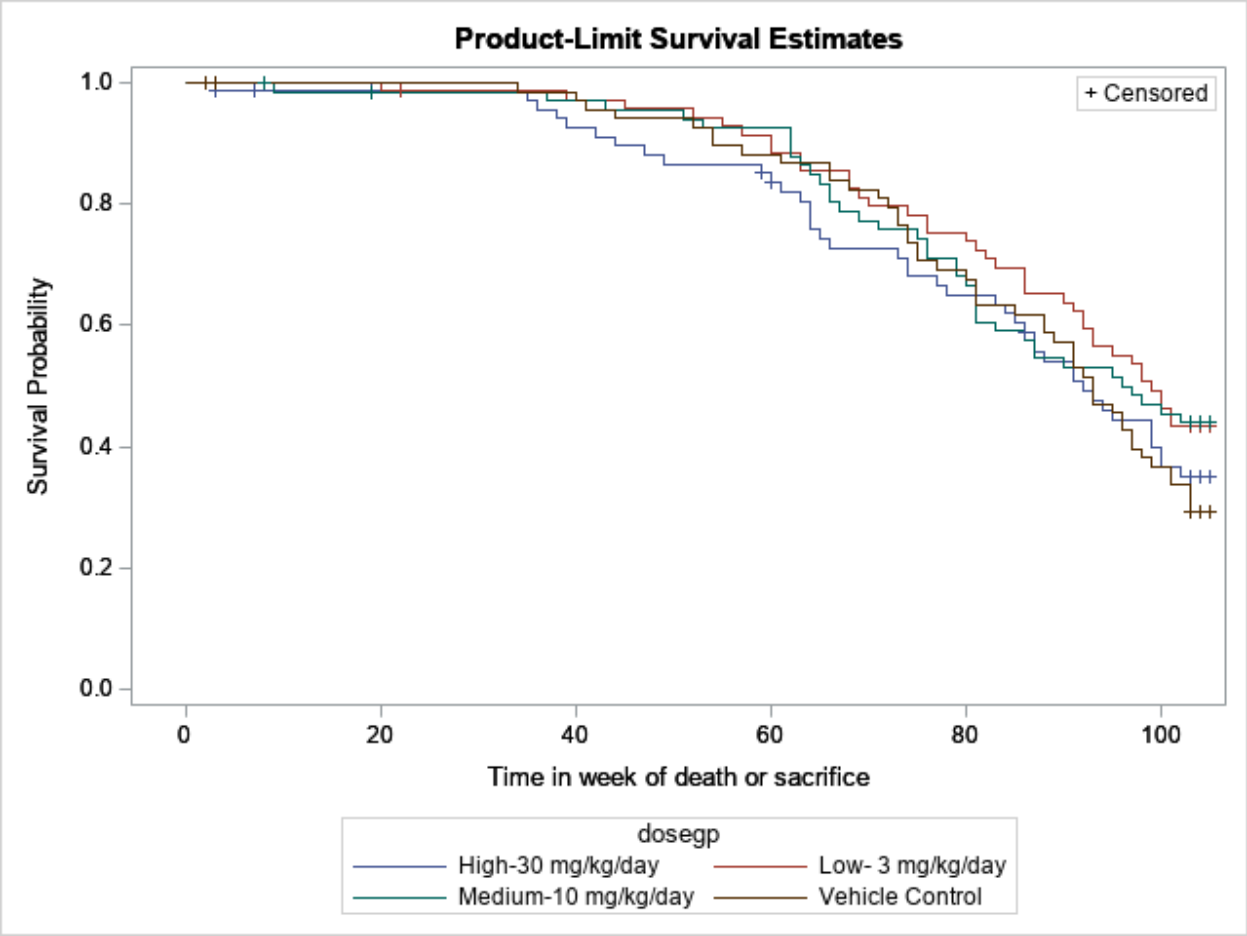


Figure 2B: Kaplan-Meier Survival Curves for
Female Mice



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Concur with review.