

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208325Orig1s000

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

ADDENDUM

NDA/BLA #: NDA 208325

Drug Name: Etelcalcetide

Indication(s): Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis

Applicant: KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen Inc.

Date(s): Primary Review: April 28, 2016
Resubmission Date: December 9, 2016
Addendum to Statistical Review: January 26, 2017

Biometrics Division: II

Statistical Reviewer: Alexander Cambon

Concurring Reviewers: Yun Wang, Team Leader

Medical Division: Division of Metabolism and Endocrinology Products

Clinical Team: Shannon Sullivan/Marina Zemskova

Project Manager: Meghna Jairath

Addendum

The sponsor submitted a Type 1 resubmission for Parsabiv on December 9, 2016. The PDUFA date is February 9, 2017.

This addendum updates the April 28, 2016 statistical review for NDA 208325 (etelcalcetide, trade name Parsabiv). The two updates are described below:

1. The third and sixth columns in Table 7 of the statistical review for this NDA (signed on April 28, 2016 under Supporting Document Number 1) were incorrectly given the heading “(> 30% Red. PTH) Cinacalcet” in the original NDA Review.

The table is shown below, updated with the correct heading for these columns: “(> 30% Red. PTH) Control*”. A footnote is also added to clarify the control arm for each study: “*For studies 229 and 230, the control arm is placebo. For study 360, the control arm is Cinacalcet.”

Table 7: Primary and Secondary Analysis Results - Sponsor

Study	Non-Responder Imputation			Response Rates Excluding Missing data	
	Response Rate	(> 30% Red. PTH) Control*	P-value	Response Rate	(> 30% PTH) Control*
229	74%	8%	<0.0001	-	-
230	75%	10%	<0.0001	-	-
360	68%	58%	0.004	80%	64%
360	Response Rate	(> 50% PTH)			
	52%	40%	0.0015	-	-

*For studies 229 and 230, the control is placebo. For study 360, the control arm is Cinacalcet.

Results using sponsor’s analysis method – FAS, CMH, non-responder imputation. Results using stratified logistic regression are almost identical. Unstratified chi-squared analysis for the active-control study 360: p-value =0.004.

2. In the original NDA review, a multiple imputation method was used for the active control study 360 to impute missing primary endpoint measurements (Achievement of >30% Reduction in iPTH). The table 7a below gives missing data and imputation results for the placebo studies and the active-control study.

Table 7a below shows missing rates for achievement of >30% reduction in iPTH, as well as response and non-response rates using the imputation method described in Section 3.2.4 starting with heading “Treatment Discontinuation and the EAP”.

Table 7a: Response and non-response rates for primary endpoint (>30% Reduction in PTH) including missing rate and using modified retrieved dropout imputation method.

Study	229	229	230	230	360	360
Treatment Group	Etelcalcetide	Placebo	Etelcalcetide	Placebo	Etelcalcetide	Cinacalcet
N per group	254	254	255	260	340	343
Mean percent change in PTH (SE)*	-49.4 (3.4)	14.9 (3.6)	-47.8 (3.7)	18.6 (3.5)	-46.8 (2.7)	-34.8 (2.7)
>30% PTH Red., Including Missing						
N (%)	41 (16)	198 (78)	35 (14)	212 (82)	66 (19)	112 (33)
Y (%)	188 (74)	21 (8)	192 (75)	25 (10)	232 (68)	198 (58)
Missing (%)	25 (10)	35 (14)	28 (11)	23 (9)	42 (12)	33 (10)
>30% PTH Red., Retrieved Dropout Imp*						
N (%)	58 (23)	226 (89)	54 (21)	231 (89)	89 (26)	133 (39)
Y (%)	196 (77)	28 (11)	201 (79)	29 (11)	251 (74)	210 (61)

*Retrieved Dropout method described in Section 3.2.4 starting with “Treatment Discontinuation and the EAP” heading; the change in percent change of iPTH from last assessment before dropout to EAP assessment is imputed for each treatment arm and for early (≤ 8 Weeks) and late (>8 weeks and < 20 weeks) dropouts. This change is then added to the percent change from baseline to the last measurement before dropout (for non-retrieved dropouts). Only retrieved dropouts (those who drop out <20 weeks) are used to impute difference in percent change from dropout in non-retrieved dropouts. For placebo studies, three stratification factors were pre-specified and used: screening PTH (< 600 pg/mL, 600 to 1000 pg/mL, and > 1000 pg/mL), prior cinacalcet use within 8 weeks of randomization (yes/no), and region (North America, non-North America). For the active-control study, prior cinacalcet use was not pre-specified/used as a stratification factor, and screening PTH was categorized as <900 pg/mL and ≥ 900 pg/mL.

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/s/

ALEXANDER CAMBON
01/27/2017

YUN WANG
01/27/2017

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 208325

Applicant: KAI Pharmaceuticals, Inc. a wholly owned subsidiary of Amgen, Inc.

Stamp Date: 08/24/2015

Drug Name: Etelcalcetide

NDA/BLA Type: NDA

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			There are 2 phase 3 double blind efficacy/safety placebo controlled studies, and one active controlled study
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	x			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			ADAM, and define.pdf files were in NDA with appropriate information.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	No interim analysis planned

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

Comments for the 74-day letter:

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Alex Cambon 10/02/2015

Reviewing Statistician Date

Team Leader Date

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/s/

ALEXANDER CAMBON
08/18/2016

MARK D ROTHMANN
08/18/2016
concur



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 208325
Supplement #: Original
Drug Name: Etelcalcetide
Indication(s): Secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis
Applicant: KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen Inc.
Date(s): Submission Date: 08/24/2015.
PDUFA: August 24, 2016; Primary Review Due Date: April 28, 2016
Review Priority: Standard
Biometrics Division: II
Statistical Reviewer: Alexander Cambon
Concurring Reviewers: Mark Rothmann, Team Leader
Medical Division: Division of Metabolism and Endocrinology Products
Clinical Team: William Lubas/Marina Zemskova
Project Manager: Meghna Jairath

Keywords: NDA Review, clinical studies, Cochran-Mantel-Haenszel, sensitivity analysis

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1 EXECUTIVE SUMMARY

Amgen, Inc. is seeking approval for etelcalcetide for secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on hemodialysis (HD). They submitted the new drug application (NDA) on August 24, 2015.

1.1 Conclusions and Recommendations

The primary endpoint is 30% reduction in parathyroid hormone (PTH), which is measured by parathyroid hormone intact (iPTH). In two randomized placebo-controlled trials and one randomized active-controlled trial, the etelcalcetide group had a statistically significant greater proportion of patients that had > 30% reduction in iPTH. This finding was consistent using the sponsor's primary analysis (non-responder imputation) and was also robust across our sensitivity analyses that attempted to address possible shortcomings in the sponsor's primary analysis.

1.2 Brief Overview of Clinical Studies

This submission included two randomized 6 month, placebo-controlled studies (Studies 20120229 and 20120230) and one randomized active-controlled, 6 month study (Study 20120360) comparing AMG 416 (etelcalcetide) with cinacalcet, the only calcimimetic approved for the treatment of secondary HPT.

Primary Endpoint Results

Active-Control Study 20120360

Excluding missing data, response rates for >30% reduction in iPTH are

- 78% in the etelcalcetide arm
- 64% in the cinacalcet arm.

If subjects with missing data are counted as non-responders, the response rate would be

- 68% in the etelcalcetide arm
- 58% in the cinacalcet arm
- p-value =0.004.

Placebo-Controlled Study 20120229

If subjects with missing data are counted as non-responders, the response rate for >30% reduction in iPTH would be

- 74% in etelcalcetide arm
- 8% in placebo arm
- p-value <0.0001.

Placebo-Controlled Study 20120230

If subjects with missing data are counted as non-responders, the response rate for >30% reduction in iPTH would be

- 75% in etelcalcetide arm
- 10% in placebo arm
- p-value<0.0001.

1.3 Statistical Issues and Findings

I found that retrieved dropouts may be different from non-retrieved dropouts with respect to their last % change in iPTH measure before treatment dropout. Therefore I implemented an imputation method that makes use of the change in iPTH measures for a subject between treatment dropout and the EAP. Information from the retrieved dropouts was used to impute this change in the non-retrieved dropouts. This was done separately for each treatment arm.

2 INTRODUCTION

2.1 Overview

Four controlled trials and three uncontrolled trials were a part of this submission. Of these, the three randomized controlled trials listed in Table 1 were selected for full statistical review. These are trials that were used in the sponsor's draft label submitted as part of the NDA. (b) (4) a multi-center single-arm trial to investigate the safety of switching hemodialysis patients with secondary HPT from oral cinacalcet to etelcalcetide. That study is not part of this review because it is a single arm study.

Study 20120360 was a randomized active-controlled, dose titration, parallel-group, double-blind, double-dummy, multi-center, multi-national trial. Patients were randomized 1:1 to either an initial dose of 5 mg etelcalcetide or an initial dose of 30 mg cinacalcet. Studies 20120229 and 20120230 were placebo-controlled, dose titration, parallel-group, double-blind, multi-center, multi-national trials. Patients were randomized in a 1:1 fashion to either an initial dose of 5 mg etelcalcetide or placebo.

Table 1: General Description of All Studies Included in Analysis

Study	Study Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
229	R, PC, DT, PG, DB, MC, MN	26 weeks	4 weeks	etelc. : 254 placebo: 254	M/F ≥ 18 years with CKD and SHPT receiving HD
230	R, PC, DT, PG, DB, MC, MN	26 weeks	4 weeks	etelc.: 255. placebo: 260	M/F ≥ 18 years with CKD and SHPT receiving HD
360	R, AC, DT, PG, DB, DD,MC, MN	26 weeks	4 weeks	etelc. : 340 cinac.: 343	M/F ≥ 18 years with CKD and SHPT receiving HD

Abbreviations: R-Randomized ; PC- Placebo controlled; DT-Dose titration; DB-Double Blind; DD-Double-dummy; PG-Parallel Group; AC-Active controlled; MC-Multi-center; MN-Multi-national; M/F –Male and Female subjects; CKD-chronic kidney disease; SHPT-secondary HPT; HD-hemodialysis; etelc.-Etelcalcetide; cinac.-Cinacalcet

Of the three randomized controlled trials selected for review, primary emphasis is on the active-control study 20120360. Figure 1 below shows timelines for screening, randomization, initiation of treatment, and dose titration. Dose titration is allowed for up to 16 weeks during the treatment period, and then it is maintained for the last 10 weeks.

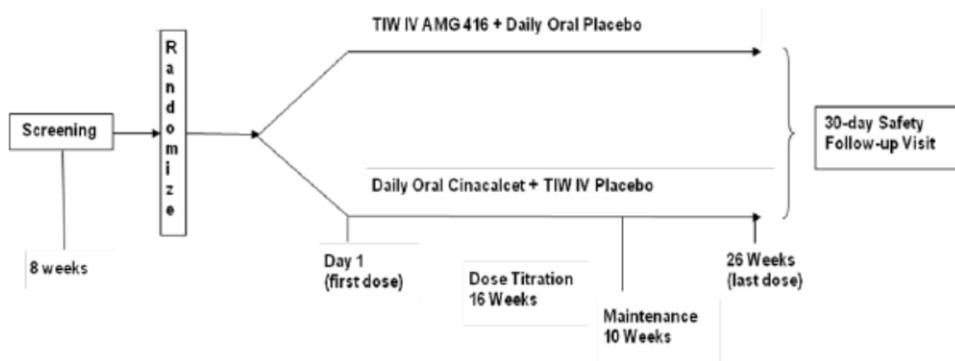


Figure 1: Study Design for Active Control Study

from Sponsor NDA Submission, Section 5.3.5.1, Page 8 of “Protocol and Amendments” for study 360.

Proportion of Patients Enrolled in Domestic Versus Foreign Investigational Centers

From Table 2, the proportion of patients enrolled in US centers was 26% in the randomized active control study, 55% in the second randomized placebo study (230), and close to 50% in the first randomized placebo study (229).

Table 2: Proportion of Subjects Enrolled by Geographic Region and Group

Study	229		230		360	
	Etelcalcetide	Placebo	Etelcalcetide	Placebo	Etelcalcetide	Cinacalcet
Group						
N per group	254	254	255	260	340	343
Geographic Region 1						
Europe N (%)	90 (35)	98 (39)	84 (33)	89 (34)	180 (53)	183 (53)
North America N (%)	132 (52)	129 (51)	146 (57)	150 (58)	103 (30)	105 (31)
Other N (%)	32 (13)	27 (11)	25 (10)	21 (8)	57 (17)	55 (16)
Geographic Region 2						
US N (%)	128 (50)	122 (48)	139 (55)	144 (55)	89 (26)	91 (27)
Other N (%)	126 (50)	132 (52)	116 (45)	116 (45)	251 (74)	252 (73)

2.1.1 Class and Indication

Etelcalcetide is a synthetic peptide and calcimimetic that targets the calcium-sensing receptor (CaSR) in parathyroid tissue. It is defined as a small molecule. It acts by decreasing circulating PTH levels. It is being investigated for treatment of secondary HPT in patients with CKD on hemodialysis. The recommended initial dosage is 5 mg administered three times a week as an IV bolus dose at the end of the hemodialysis treatment during rinseback or during IV administration after rinseback. In the three trials, dose levels of AMG 416 were adjusted individually every 4 weeks based on PTH and serum calcium levels. The maximum allowable dose was 15 mg.

2.1.2 History of Drug Development

KAI Pharmaceuticals, Inc. submitted IND 109773 for the indication of secondary HPT in end-stage renal disease (ESRD) subjects on August 19, 2010.

The protocol submitted to Global Submit and dated 01/28/2013 is located at

<\\cdsesub1\evsprod\ind109773\0087\m5\53-clin-stud-rep\shpt\5351-stud-rep-contr\20120360\protocol-20120360.pdf>

contains the same primary and secondary endpoints, and the same method of averaging iPTH measurements over the EAP (Efficacy Assessment Phase), defined as Weeks 20 to 27 inclusive. It is contained in Sequence 0087 which is dated 03/19/2013 (per the link above). Per a KAI briefing document to the FDA dated 6/04/2012 and found here:

<\\cdsesub4\NONECTD\IND109773\5086003>

in Question 2, Section 10.2, the sponsor asked for FDA confirmation/agreement with the responder analysis.

Based on feedback from the FDA on February 14, 2012, KAI proposed using a responder analysis for the primary endpoint, with a responder defined as a subject whose iPTH is reduced more than 30% from baseline during the EAP:

KAI would like to confirm with the FDA that this proposed primary endpoint, as detailed in the proposed Phase 3 SHPT clinical trials, is appropriate to demonstrate efficacy to support an NDA for KAI-4169 for the treatment of SHPT?

The response from the FDA was:

The proposed primary endpoint is adequate to demonstrate the efficacy of KAI-4169 for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on hemodialysis.

Also in Sequence number 0095, dated 3/26/2013, the cover letter from Amgen (on behalf of KAI) states that the protocol was amended to (among other things)

Allow adjustment of vitamin D for hypocalcemia during the study.

<\\cdsesub1\evsprod\ind109773\0095\m1\us\cover-letter.pdf>

2.2 Data Sources

The data and final study report were submitted electronically as an eCTD submission. The submission, organized as an .enx file, was archived at the following link:

<\\CDSESUB1\evsprod\NDA208325\208325.enx>

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 defined variables and their locations.

To reproduce randomized treatment assignments, sponsor code would be needed, including seeds for randomized treatment assignments. This was requested on January 8, 2016, and the following response from Amgen was received February 17, 2016:

Randomization for Studies 20120229, 20120230, and 20120360 was performed using a fixed stratified permuted block randomization list generated by Amgen's Global Randomization and Blinding organization using Amgen's randomization system. Amgen utilizes a fully validated randomization system with a randomization engine leased from (b) (4). The underlying programs are owned by (b) (4) and are not immediately available to Amgen. This response includes the completed randomization requests documenting the specifications utilized in the creation of the randomization lists. The final seed numbers for the subject randomization lists generated for these studies are listed below:

- Study 20120229: (b) (4)
- Study 20120230: (b) (4)
- Study 20120360: (b) (4)

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The primary, secondary and safety endpoints for the two placebo studies and the active-control study are shown in Table 3 below.

Table 3: Primary and Secondary Endpoints

Study	Endpoint Type	Description
360	Primary	Achievement of a > 30% reduction from baseline in mean pre-dialysis serum PTH level during the efficacy assessment phase (EAP) (non-inferiority)
360	Key Secondary	Achievement of a > 50% reduction from baseline in mean pre-dialysis serum PTH during the EAP (superiority)
360	Key Secondary	Achievement of a > 30% reduction from baseline in mean pre-dialysis serum PTH during the EAP (superiority)
360	Key Secondary	Reduction in mean number of days of vomiting or nausea per week in the first 8 weeks.
360	Other Secondary	Percent change from baseline in mean pre-dialysis serum cCa during the EAP
360	Other Secondary	Achievement of mean pre-dialysis serum P ≤ 4.5 mg/dL during the EAP
360	Other Secondary	Mean severity of nausea in the first 8 weeks
360	Other Secondary	Mean number of episodes of vomiting per week in the first 8 weeks
360	Safety	Incidence of cCa < 8.3 mg/dL at any time during the study
360	Safety	Incidence of cCa < 8.0 mg/dL at any time during the study
360	Safety	Incidence of cCa < 7.5 mg/dL at any time during the study
360	Safety	Incidence of hyperphosphatemia, defined as serum P > 5.5 mg/dL at any time during the study
360	Safety	Incidence of symptomatic hypocalcemia at any time during the study
360	Safety	Nature, frequency, severity, and relationship to treatment-emergent adverse events
230, 229	Primary	Achievement of a > 30% reduction from baseline in mean pre-dialysis serum PTH level during the efficacy assessment phase (EAP)
230, 229	Secondary	Achievement of predialysis iPTH ≤ 300 pg/mL during the EAP
230, 229	Secondary	Percent change from baseline in predialysis iPTH during the EAP
230, 229	Secondary	Percent change from baseline in predialysis serum cCa during the EAP
230, 229	Secondary	Percent change from baseline in predialysis cCa x P during the EAP
230, 229	Secondary	Percent change from baseline in predialysis serum phosphorus during the EAP
230, 229	Safety	Nature, frequency, severity, and relationship to treatment of all adverse events reported throughout the study
230, 229	Safety	Vital signs and changes in ECG and laboratory parameters, including clinical chemistry
230, 229	Safety	Evaluation of antibody formation to AMG 416

The endpoints are listed in the order they are tested according to the hierarchical testing procedure for each study. The endpoint highlighted in yellow for the active control study (360) was the first endpoint in the hierarchy not to achieve statistical significance. Therefore the endpoints following it (below it in this table for study 360) in the hierarchical testing order were not formally tested.

3.2.1.1 Multiple Testing Procedure

For the active control study (360), the sponsor's pre-specified multiple testing procedure was to test each primary and key secondary endpoint in the order listed in Table 3 above at the specified significance level (0.025 one-sided). All endpoints down to but not including reduction in mean number of days of vomiting or nausea per week in the first 8 weeks achieved statistical significance. The row which includes this endpoint is highlighted in yellow. The label claims seem to be consistent in that, (b) (4), (b) (4)

3.2.1.2 Non-Inferiority Margin

Both non-inferiority and superiority were pre-specified and achieved on the primary endpoint (>30% reduction in PTH during the EAP). Since superiority was achieved, the non-inferiority margin is not an issue here. However justification for the non-inferiority margin is given in Section 10.2 of the protocol, and we are satisfied that this meets applicable standards and guidances including Draft Guidance for Industry, Non-Inferiority Trials, dated March 2010. The pertinent paragraph from the sponsor's protocol is below:

A non-inferiority margin was determined based on data collected in the Amgen EVOLVE trial (Study 20050182). This was a randomized, placebo-controlled trial and using a similar patient population as intended to be recruited in this study, rates of 25% and 60% in the placebo and cinacalcet arms, respectively, were derived and the two-sided 95% confidence interval for the treatment difference based on the large sample normal approximation is (31%, 39%). Half of the lower limit of the confidence interval for the treatment difference (compared to placebo) is 15.5%. Based on short term variation in serum PTH values, a difference of 12% in the proportion of achieving PTH reduction between treatment groups would not be considered a clinically meaningful difference. Twelve percent, which is smaller than the above margin and the loss of effect that would be clinically acceptable, was selected as the non-inferiority margin for this study.

3.2.2 Statistical Methodologies

3.2.2.1 Sponsor Statistical Methodology

The sponsor's efficacy analysis was based on the Full Analysis Set (FAS), which the sponsor defined as all randomized subjects. Subjects were analyzed according to randomized treatment group. The sponsor pre-specified primary analysis was the Cochran-Mantel-Haenszel (CMH) test. Pre-specified stratification factors were region (North America/Other), and screening iPTH level: (<900 pg/ml vs \geq 900 pg/ml for the active-control study and <600 pg/ml, 600-1000 pg/ml, and > 1000 pg/ml for the two placebo-controlled studies). In my opinion this is an appropriate statistical method for these studies.

Number of Measurements Required During the Efficacy Evaluation Phase

The sponsor's pre-specified analysis involved averaging available measurements for each subject over the EAP to evaluate the primary endpoint. Using written communication, the sponsor sought input regarding "averaging over the EAP" during the IND phase of drug development (February 14, 2012). The agency replied affirmatively regarding the sponsor's method in response to this request. The sponsor uses any available iPTH measurement for a subject during the EAP, which is from week 20 to 27 of the treatment period. Using this method, it is possible for a subject to have one EAP measurement at week 20, and to be counted as a responder or non-responder, and then discontinue treatment at this point (or just prior) due to an adverse event. This is the case for subject 36025012001 in the active control study. From the adlbep and adlb data sets, the subject stayed on treatment until just before week 19, at which time they had an

adverse event, and treatment was discontinued. They then had an EAP measurement at week 20. Since they had a reduction in PTH >30% at week 20, they were counted as a responder. They are also counted as completing the study (according to the “Completed Study” Flag in the data set), although they are not counted as completing treatment according to the “Completing IP” (Investigational Product) Flag. From the adlb and adlbp data sets, the week 20 iPTH measurement (-57%) was used to assess the primary endpoint (>30% reduction in iPTH) as being achieved.

Table 4 shows the frequency of subjects in the active control study with zero to six iPTH measurements during the EAP; 75 of the 683 subjects (11%) had missing data for the primary endpoint because they had no iPTH measurements during the EAP. Therefore they were counted as non-responders for the primary analysis. For the 608 out of the 683 subjects with at least one available measurement during the EAP, 99% had at least two iPTH measurements during the EAP, and 97% had at least three EAP measurements.

Table 4: Number of EAP Measurements Per Subject - Active Control Study

Number of EAP Measurements N	Subjects with this # of EAP Measurements N	Percent of subjects with this # of EAP Measurements (of subjects having at least 1 EAP measurement) %	Percent of All Subjects
0 (ie – missing)	75	N/A	11 (% missing)
1	7	1	1
2	10	2	1
3	21	3	3
4	77	13	11
5	492	81	72
6	1	0	0
Total	608+75=683		

At least one EAP measurement is required in order to have non-missing endpoint data; 75 of the 683 subjects in the active-control study had no EAP measurements (first row) and were counted as non-responders in the sponsor’s primary analysis. Subjects with at least one EAP measurement have their EAP measurements averaged in order to calculate the value of the endpoint.

Sensitivity Analysis

The sponsor used non-responder imputation for subjects with missing endpoint measurements. That is, any subject that had no available iPTH measurements during the EAP was counted as a non-responder. To evaluate robustness of the non-responder imputation analysis, I used the following sensitivity analyses:

- 1) An un-stratified tipping point analysis (Campbell, Pennello, & Yue, 2011).
- 2) Retrieved dropout methods, including methods which account for differences between retrieved dropouts and non-retrieved dropouts.

Retrieved Dropouts – Active Control Study

The method of averaging over any available measurement(s) during the EAP to assess the primary endpoint has implications for a retrieved dropout analysis. Since the EAP is from week 20 to week 27, it is possible to discontinue treatment during that time, but still have a non-missing primary endpoint measurement. If a subject discontinues treatment on or after week 20, the measurements used for the endpoint can be taken before the discontinuation. If this is the case, the dropout cannot really be said to be “retrieved”. However, those who discontinue treatment before week 20 must be followed up and have a measurement during the EAP in order to have a non-missing primary endpoint. Therefore it may make sense to separate treatment discontinuation by week of discontinuation. Table 5 separates treatment duration for each treatment arm into three categories:

- 1) Treatment duration ≥ 20 weeks
- 2) Treatment duration > 8 weeks and < 20 weeks
- 3) Treatment duration ≤ 8 weeks.

Table 5 also displays descriptive statistics for the last % change in iPTH from baseline measurement before treatment dropout for each dropout category. This information is used to further refine treatment dropout analysis to take into account differences between retrieved and non-retrieved dropouts.

Table 5: Comparison of Early and Late Treatment Dropouts Using Cut-offs of 8 and 20 Weeks (Active-Control Study)

Treatment Group	Etelcalcetide	Etelcalcetide	Etelcalcetide	Cinacalcet	Cinacalcet	Cinacalcet
Treatment Dropout Group	<=Week 8	>8 to< 20	>= Week 20	<=Week 8	>8 to< 20	>= Week 20
N per group	26	30	284	25	20	298
Last % iPTH Change from Baseline Measurement before Treatment Dropout – Non-Retrieved Dropouts Only						
N	16	18	-	10	13	-
Mean (95%CI)	-30.9 (-45.9 - -15.9)	-39.0 (-57.9 - -20.1)	-	-30.8 (-49.9 - -11.7)	-44.0 (-64.6 - -23.5)	-
Median (min - max)	-39.3 (-91.4 - 56.4)	-47.6 (-89.8 - 68.0)	-	-10.4 (-91.9 - 17.5)	-44.3 (-94.0 - 7.9)	-
Missing	8	0	-	10	0	-
Last % iPTH Change from Baseline Measurement before Treatment Dropout – Retrieved Dropouts Only						
N	2	12	-	4	7	-
Mean (95%CI)	-50.6 (-89.0 - -12.2)	-40.7 (-59.5 - -21.9)	-	8.4 (-24.1 - 40.8)	-1.3 (-19.3 - 16.6)	-
Median (min - max)	-50.6 (-70.2 - -31.0)	-42.3 (-90.1 - 19.4)	-	23.3 (-46.7 - 33.6)	6.3 (-33.5 - 33.7)	-
Missing	0	0	-	1	0	-
% iPTH Change from BL to EAP						
N	2	12	284	5	7	298
Mean (95%CI)	-58.9 (-72.1 - -45.6)	-41.2 (-53.8 - -28.6)	-51.2 (-55.1 - -47.2)	20.4 (7.7 - 33.0)	-1.0 (-25.7 - 23.8)	-39.7 (-43.9 - -35.5)
Median (min - max)	-58.9 (-82.3 - -35.4)	-43.8 (-91.6 - 24.6)	-60.0 (-95.9 - 89.4)	20.0 (-29.4 - 50.5)	12.9 (-73.5 - 76.7)	-46.6 (-94.6 - 125.9)
Missing	24	18	0	20	13	0
Treatment Duration (Weeks)						
N	24	30	284	23	20	298
Mean (95%CI)	4.3 (3.4 - 5.2)	13.5 (12.2 - 14.7)	25.7 (25.6 - 25.8)	3.7 (2.5 - 4.8)	13.7 (12.3 - 15.1)	25.7 (25.6 - 25.8)
Median (min - max)	4.4 (0.1 - 7.9)	13.3 (8.1 - 18.9)	25.9 (20.0 - 27.1)	2.9 (0.4 - 8.0)	13.4 (8.1 - 19.7)	25.9 (20.3 - 28.1)
Missing	2	0	0	2	0	0

Table 5: Comparison of Early and Late Treatment Dropouts Using Cut-offs of 8 and 20 Weeks (Active-Control Study) – cont.

Treatment Group	Etelcalcetide		Cinacalcet		Cinacalcet	
Treatment Dropout Group	<=Week 8	>8 to< 20	>= Week 20	<=Week 8	>8 to< 20	>= Week 20
N per group	26	30	284	25	20	298
Baseline iPTH (pg/mL)						
Mean (95%CI)	1119 (746 - 1491)	988 (859 - 1117)	1101 (1030 - 1171)	1409 (1075 - 1742)	1229 (876 - 1582)	1110 (1032 - 1188)
Median (min - max)	774 (445 - 4380)	900 (469 - 1861)	921 (298 - 3722)	1129 (591 - 4065)	862 (548 - 3143)	923 (323 - 4840)
> 30% Red. PTH, NR Imp.						
N (%)	24 (92)	22 (73)	62 (22)	25 (100)	17 (85)	103 (35)
Y (%)	2 (8)	8 (27)	222 (78)	0 (0)	3 (15)	195 (65)
>30% Red PTH, No Imp.						
N (%)	0 (0)	4 (33)	62 (22)	5 (100)	4 (57)	103 (35)
Y (%)	2 (100)	8 (67)	222 (78)	0 (0)	3 (43)	195 (65)
Missing	24	18	0	20	13	0
Sex						
Female N (%)	11 (42)	12 (40)	125 (44)	8 (32)	6 (30)	137 (46)
Male N (%)	15 (58)	18 (60)	159 (56)	17 (68)	14 (70)	161 (54)
Age >= 65 Years Flag						
N (%)	20 (77)	25 (83)	217 (76)	17 (68)	16 (80)	210 (70)
Y (%)	6 (23)	5 (17)	67 (24)	8 (32)	4 (20)	88 (30)
Race						
Asian N (%)	1 (4)	0 (0)	8 (3)	0 (0)	0 (0)	7 (2)
Black Or African American N (%)	2 (8)	7 (23)	45 (16)	2 (8)	2 (10)	48 (16)
White N (%)	23 (88)	18 (60)	220 (77)	23 (92)	18 (90)	236 (79)
Other N (%)	0 (0.0)	5 (17)	5 (2)	0 (0)	0 (0)	4 (1)
Ethnicity						
Hisp. Or Latino N (%)	3 (12)	3 (10)	32 (11)	3 (12)	1 (5)	37 (12)
Other N (%)	23 (88)	27 (90)	252 (89)	22 (88)	19 (95)	261 (88)

Abbreviations: NR- non-responder

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Demographics

The distribution of baseline demographic characteristics, which are shown in Table 6, are similar between treatment groups within each of the three studies.

Table 6: Demographics and Baseline Characteristics by Treatment Arm and Study

Study	229		230		360	
Group	Etelcalcetide	Placebo	Etelcalcetide	Placebo	Etelcalcetide	Cinacalcet
N per group	254	254	255	260	340	343
Sex						
Females N (%)	103 (41)	114 (45)	93 (36)	95 (37)	148 (44)	151 (44)
Males N (%)	151 (59)	140 (55)	162 (64)	165 (63)	192 (56)	192 (56)
Age						
Mean (95%CI)	58 (57 - 60)	57 (55 - 59)	58 (57 - 60)	59 (57 - 61)	54 (53 - 55)	55 (54 - 57)
Median (min - max)	59 (21 - 93)	58 (22 - 90)	59 (23 - 91)	59 (22 - 90)	55 (18 - 87)	56 (21 - 86)
>= 65 Years N (%)	90 (35)	86 (34)	90 (35)	91 (35)	78 (23)	100 (29)
>= 75 Years N (%)	35 (14)	27 (11)	39 (15)	37 (14)	23 (7)	33 (10)
Race						
Asian N (%)	5 (2)	3 (1)	13 (5)	6 (2)	9 (3)	7 (2)
Black Or African American N (%)	72 (28)	69 (27)	64 (25)	80 (31)	54 (16)	52 (15)
White N (%)	173 (68)	175 (69)	163 (64)	169 (65)	261 (77)	277 (81)
Other N (%)	4 (2)	4 (2)	6 (2)	2 (1)	10 (3)	4 (1)
Ethnicity						
Hisp. / Latino N (%)	33 (13)	33 (13)	32 (13)	33 (13)	38 (11)	41 (12)
Not Hisp. Lat. N (%)	221 (87)	220 (87)	221 (87)	227 (87)	302 (89)	302 (88)
Missing N	0	1	2	0	0	0
Baseline BMI (kg/m)						
Mean (95%CI)	28.7 (27.7 - 29.7)	28.3 (27.5 - 29.2)	28.9 (28.0 - 29.8)	28.8 (28.0 - 29.6)	28.0 (27.3 - 28.8)	27.6 (27.0 - 28.3)
Median (min - max)	26.9 (15.2 - 79.1)	27.2 (15.0 - 57.4)	27.6 (15.0 - 59.7)	27.9 (15.4 - 58.2)	26.9 (16.2 - 57.2)	26.9 (15.6 - 58.1)
Missing	1	2	0	0	3	2
Geographic Region 1						
Europe N (%)	90 (35)	98 (39)	84 (33)	89 (34)	180 (53)	183 (53)
N America N (%)	132 (52)	129 (51)	146 (57)	150 (58)	103 (30)	105 (31)
Other N (%)	32 (13)	27 (11)	25 (10)	21 (8)	57 (17)	55 (16)
Baseline PTH (pg/ml)						
<600 N (%)	87 (34)	84 (33)	84 (33)	84 (32)		
600-1000 N (%)	115 (45)	114 (45)	118 (46)	121 (47)		
>1000 N (%)	52 (20)	56 (22)	53 (21)	55 (21)		
<900 N (%)					169 (50)	171 (50)
>=900 N (%)					171 (50)	172 (50)

Table 6: Demographics and Baseline Characteristics by Treatment Arm and Study (cont.)

Study	229		230		360	
	Etelcalcetide	Placebo	Etelcalcetide	Placebo	Etelcalcetide	Cinacalcet
Group						
N per group	254	254	255	260	340	343
Baseline PTH (pg/ml)						
Mean (95%CI)	849 (785 - 913)	820 (772 - 867)	845 (788 - 902)	852 (785 - 919)	1092 (1026 - 1158)	1139 (1064 - 1214)
Median (min - max)	706 (337 - 4614)	706 (298 - 2850)	740 (359 - 4669)	726 (378 - 6477)	900 (298 - 4380)	930 (323 - 4840)
Baseline Ca. Suppl.						
Yes (%)	18 (7)	9 (4)	22 (9)	6 (2)	160 (47)	161 (47)
Missing	236	245	233	254	180	182
Baseline Ca Cont Ph Binder or Ca Supp						
No (%)	155 (61)	161 (63)	167 (65)	153 (59)	168 (49)	175 (51)
Yes (%)	99 (39)	93 (37)	88 (35)	107 (41)	172 (51)	168 (49)
Baseline Phosphate Binder Use						
Yes (%)	216 (85)	213 (84)	202 (79)	220 (85)	172 (51)	165 (48)
Missing	38	41	53	40	168	178
Baseline Vitamin D (Nutritional) Use						
Yes (%)	55 (22)	63 (25)	81 (32)	86 (33)	73 (21)	69 (20)
Missing	199	191	174	174	267	274
Baseline Vitamin D (Sterol) Use						
No (%)	63 (25)	69 (27)	95 (37)	100 (38)	140 (41)	137 (40)
Yes (%)	191 (75)	185 (73)	160 (63)	160 (62)	200 (59)	206 (60)
BL Corrected Calcium (mg/dL)						
Mean (95%CI)	9.65 (9.57 - 9.73)	9.61 (9.54 - 9.69)	9.63 (9.55 - 9.71)	9.70 (9.61 - 9.78)	9.67 (9.59 - 9.75)	9.58 (9.50 - 9.65)
Median (min - max)	9.60 (8.47 - 11.73)	9.57 (8.17 - 12.10)	9.53 (8.20 - 11.87)	9.60 (8.37 - 11.83)	9.60 (7.70 - 12.30)	9.55 (8.10 - 12.75)
Recent Cinacalcet Use						
No (%)	210 (83)	204 (80)	205 (80)	206 (79)	340 (100)	343 (100)
Yes (%)	44 (17)	50 (20)	50 (20)	54 (21)	0 (0)	0 (0)
Hist. Cinacalcet Use						
No (%)	151 (59)	145 (57)	118 (46)	134 (52)	260 (76)	251 (73)
Yes (%)	103 (41)	109 (43)	137 (54)	126 (48)	80 (24)	92 (27)

3.2.4 Results and Conclusions

Table 7 below shows primary and secondary analysis results using the sponsor’s pre-specified non-responder imputation. (Also see section 1.2). Superiority is achieved both for >30% reduction in iPTH (p=0.004 for the active-control study), and for 50% reduction in iPTH (p=0.0015). Results are not shown for secondary endpoint nausea or vomiting which were found not to be significant. Appropriately, the sponsor did not formally test any secondary endpoints which were included after nausea and vomiting in the multiple testing hierarchy. (b) (4)

Table 7: Primary and Secondary Analysis Results - Sponsor

Study	Non-Responder Imputation			Response Rates Excluding Missing data	
	Response Rate	(> 30% Red. PTH)	P-value	Response Rate	(> 30% PTH)
	Etelcalcetide	Cinacalcet		Etelcalcetide	Cinacalcet
229	74%	8%	<0.0001	-	-
230	75%	10%	<0.0001	-	-
360	68%	58%	0.004	80%	64%
360	Response Rate	(> 50% PTH)		-	-
	52%	40%	0.0015		

Results using sponsor’s analysis method – FAS, CMH, non-responder imputation. Results using stratified logistic regression are almost identical. Unstratified chi-squared analysis for the active-control study 360: p-value =0.004.

Tipping Point Analysis

To test robustness of the sponsor’s primary analysis, which incorporates non-responder imputation, an un-stratified tipping point analysis was performed (Campbell et al., 2011). Using this approach, overturning the significance of the results would require imputing 12 out of the 33 subjects with missing primary endpoint data on the cinacalcet arm as responders instead of non-responders, while at the same time still imputing all 42 subjects with missing data on the etelcalcetide arm as non-responders. This seems an unlikely scenario. Figure 2 shows tipping point analysis for this primary endpoint for a wide range of scenarios. It can be seen that all scenarios which fail to conclude superiority of the primary analysis require at least 12 more subjects on the cinacalcet arm to be switched to responder status compared to the etelcalcetide arm.

		Number Missing Subjects on Etelcalcetide Arm Switched to Responder Status												
		0	1	2	3	4	5	6	7	8	9	10	11	12
Missing Subjects on Cinac. Arm Switched to Responder Status	11	0.046	0.038	0.031	0.025	0.020	0.016	0.013	0.010	0.008	0.006	0.005	0.004	0.003
	12	0.055	0.046	0.037	0.030	0.025	0.020	0.016	0.013	0.010	0.008	0.006	0.005	0.004
	13	0.066	0.055	0.045	0.037	0.030	0.024	0.019	0.016	0.012	0.010	0.008	0.006	0.005
	14	0.078	0.065	0.054	0.045	0.036	0.030	0.024	0.019	0.015	0.012	0.010	0.007	0.006
	15	0.092	0.078	0.065	0.054	0.044	0.036	0.029	0.024	0.019	0.015	0.012	0.009	0.007
	16	0.109	0.092	0.077	0.064	0.053	0.044	0.036	0.029	0.023	0.019	0.015	0.012	0.009
	17	0.127	0.108	0.091	0.076	0.063	0.052	0.043	0.035	0.028	0.023	0.018	0.015	0.011
	18	0.148	0.126	0.107	0.090	0.075	0.063	0.052	0.043	0.035	0.028	0.023	0.018	0.014
	19	0.171	0.147	0.125	0.106	0.089	0.075	0.062	0.051	0.042	0.034	0.028	0.022	0.018
	20	0.197	0.170	0.146	0.124	0.105	0.088	0.074	0.061	0.051	0.041	0.034	0.027	0.022
	21	0.226	0.196	0.169	0.145	0.123	0.104	0.088	0.073	0.061	0.050	0.041	0.033	0.027
	22	0.258	0.225	0.195	0.168	0.144	0.122	0.103	0.087	0.072	0.060	0.049	0.040	0.033
	23	0.293	0.257	0.224	0.194	0.167	0.143	0.121	0.102	0.086	0.072	0.059	0.049	0.040
	24	0.331	0.292	0.255	0.222	0.192	0.165	0.141	0.120	0.101	0.085	0.071	0.059	0.048

Figure 2: Tipping Point Scenarios for Primary Endpoint (>30% Reduction in iPTH). Scenarios in yellow are those which overturn the primary analysis from significant to not significant. Values inside each cell are p-values for that scenario (chi-squared test).

Treatment Discontinuation and the EAP

The non-responder imputation method imputes non-response for all subjects that have no iPTH measurements during the EAP. However those who discontinue treatment early are counted as responders if they are followed up and have iPTH measurements during the EAP demonstrating >30% reduction from baseline. Therefore, using information from these subjects (the retrieved dropouts) may provide useful information for those who are not followed up (non-retrieved dropouts). In addition, as pointed out in Section 3.2.3, it may be more realistic to represent treatment completers by those who continued treatment for at least 20 weeks (since all subjects who continued treatment for at least 20 week have a non-missing endpoint measurement), and treatment dropouts by those who discontinued treatment before 20 weeks. Retrieved dropouts would then be represented by those subjects who discontinued treatment before week 20, but had at least one iPTH measurement during the EAP.

Early and Late Retrieved Dropouts

There may also be differences between subjects who drop out early vs. those who drop out closer to 20 weeks. For example early dropouts have less exposure to treatment. As well, Table 5 shows there is a smaller proportion of retrieved dropouts among those who drop out earlier. The cut-off of 8 weeks in this table was chosen to allow approximately equal sample sizes for the two

groups. However the proportion and number of retrieved dropouts in the early treatment dropout group is small: 2 out of 26 subjects (8%) on the etelcalcetide arm, and 5 out of 25 (25%) on the cinacalcet arm. This is in contrast to the larger proportion for the later retrieved dropouts: 12 of 30 (40%) on the etelcalcetide arm and 13 of 20 (65%) on the cinacalcet arm.

In addition, there may be differences in response rates between treatment arms for both the earlier and later retrieved dropouts. The two retrieved dropouts in the early dropout group on the etelcalcetide arm both responded (>30% reduction in iPTH during the EAP), while the 5 early dropouts that were retrieved on the cinacalcet arm were all non-responders. The response rates for the retrieved dropouts who dropped out later (between weeks 8 and 20) is 8 of 12 (67%) on the etelcalcetide group and 3 out of 7 (43%) on the cinacalcet arm.

Differences between Retrieved Dropouts and Non-Retrieved Dropouts

However it may also be that the retrieved dropouts are different in some respects from the non-retrieved dropouts. One way to compare the retrieved and non-retrieved dropouts is by comparing the last % change in iPTH measurement before treatment dropout (LPBTD). This is also shown in Table 5. The LPBTD means of the early and later non-retrieved dropouts on the etelcalcetide arm are similar to those on the cinacalcet arm (means of -30.9% and -39.0% respectively on the etelcalcetide arm vs. -30.8% and -44.0% on the cinacalcet arm). However the early and late retrieved dropout pattern for LPBTD is different for each arm (means of -50.6% and -40.7% respectively on the etelcalcetide arm vs. 8.4% and -1.3% on the cinacalcet arm). So while the non-retrieved dropout pattern appears to be similar between arms, the non-retrieved dropout pattern does not appear similar to the retrieved dropout pattern using the LPBTD information. This information leads me to believe that the retrieved dropout pattern may not be an adequate representation for the non-retrieved dropout pattern.

Therefore, it may be more reasonable to use the change in % iPTH from LPBTD to the EAP from the retrieved dropouts to represent the % iPTH change over the same period for the non-retrieved dropouts. This can be done for each treatment dropout category and for each treatment arm. It can be seen from Table 5 that, for the etelcalcetide arm, the early and late retrieved dropouts maintain their decrease in % iPTH (on average) during this period. For the cinacalcet arm, the early retrieved dropouts do not seem to maintain their % iPTH, though the sample size is small. The later dropouts (>8 and < 20 weeks) on the cinacalcet arm maintain their % iPTH during this period, though they are starting from a higher % iPTH level. Using this information from the retrieved dropouts, a multiple imputation method can be used to impute change in % iPTH from dropout to the EAP for the non-retrieved dropouts. The method allows for differences in this change between treatment arms. From this imputation, the % change in iPTH from baseline to EAP can be calculated, and the primary endpoint (>30% reduction in iPTH from baseline to EAP), can also be derived. The results from this multiple imputation approach are consistent with results from the primary analysis (p=0.0035).

3.3 Evaluation of Safety

Please see the clinical review of Dr. William Lubas for the evaluation of safety.

The sponsor’s safety endpoint, reduction in nausea or vomiting, did not achieve significance for the active control study 360, (b) (4)

Table 8 shows adverse frequency and percentage of events by treatment arm pooled over the placebo studies. Table 9 shows frequency and percentage of events by treatment for the active control study. The difference in “Blood calcium decreased” between treatment arms is 9%: 69% in the etelcalcetide arm vs. 60% in the cinacalcet arm.

Table 8: Adverse Reactions - (b) (4)

Adverse Reaction	Placebo	Etelcalcetide
	(N = 513) (b) (4)	(N = 503) (b) (4)
Blood calcium decreased	(b) (4) (10)	(b) (4) (64)
Muscle spasms	(7)	12
Diarrhea	(9)	11
Nausea	(6)	11
Vomiting	(5)	(9)
Headache	(6)	(8)
Hypocalcemia	0.2	(7)
Paresthesia ^a	(1)	(6)

Taken from Table 1 of sponsor draft label: Adverse Reactions with Frequency \geq 5% of Patients on Hemodialysis in the etelcalcetide group in Combined Placebo-Controlled Studies



(b) (4)

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroups relevant to this application include sex, age, race, ethnicity, and geographic region which are shown in Table 10.

4.1 Sex, Race, Age, and Geographic Region

Response frequencies and percentages for the primary endpoint are displayed in Table 10 below for subgroups race, sex, age, ethnicity and region. Treatment effects are consistent in direction across subgroups, though magnitude of effects vary somewhat. Subgroup by treatment interaction p-values are given in Table 11 below. There are seven subgroup-treatment interactions tested for each of the three studies. Out of the 15 interaction p-values, only two are less than 0.05 (Study 230, Region subgroup: $p=0.018$, race subgroup: $p=0.019$). This is slightly more than what would be expected due to chance alone, and significance would not stand up under multiple testing approaches. Moreover, for the three lowest p-values (sex, race and region, all in study 230), from Table 11, the interaction p-values for the same subgroup in other two studies are not close to significant, and the response rates for etelcalcetide for one of these subgroups (for example male vs. female) are never consistently higher or lower across the three studies. There is a very large difference in response rates in region for Study 230 (82.6% for non-North America versus 69.9% for North America) and for the Black/African American and Hispanic subgroups (71.9% and 65.6% respectively compared to 79.1% for White), but similar large differences in response rates are not seen in the other placebo study or in the active-control study for these same subgroups.

Figure 3, Figure 4, Figure 5, and Figure 6 display boxplots of % reduction in iPTH (the continuous measure from which the primary endpoint is derived) by study, treatment and subgroup, for sex, region, race, and age respectively. These boxplots, including the one for region, are consistent with response rates in Table 10 in that they do not show any large visually obvious treatment subgroup interactions.

Table 10: Results by Subgroup - Attainment of >30% Decrease in iPTH from Baseline to EAP Using NR Imputation

Study	229		230		360	
Group	Etelcalcetide	Placebo	Etelcalcetide	Placebo	Etelcalcetide	Cinacalcet
N per group	254	254	255	260	340	343
Overall						
N (%)	66 (26)	233 (92)	63 (25)	235 (90)	108 (32)	145 (42)
Y (%)	188 (74)	21 (8)	192 (75)	25 (10)	232 (68)	198 (58)
Male						
N (%)	35 (23)	127 (91)	34 (21)	151 (92)	67 (35)	86 (45)
Y (%)	116 (77)	13 (9)	128 (79)	14 (8)	125 (65)	106 (55)
Female						
N (%)	31 (30)	106 (93)	29 (31)	84 (88)	41 (28)	59 (39)
Y (%)	72 (70)	8 (7)	64 (69)	11 (12)	107 (72)	92 (61)
North Am.						
N (%)	34 (26)	115 (89)	44 (30)	133 (89)	36 (35)	51 (49)
Y (%)	98 (74)	14 (11)	102 (70)	17 (11)	67 (65)	54 (51)
Other Region						
N (%)	32 (26)	118 (94)	19 (17)	102 (93)	72 (30)	94 (39)
Y (%)	90 (74)	7 (6)	90 (83)	8 (7)	165 (70)	144 (61)
Age>=65						
N (%)	21 (23)	75 (87)	22 (24)	85 (93)	22 (28)	32 (32)
Y (%)	69 (77)	11 (13)	68 (76)	6 (7)	56 (72)	68 (68)
Age<65						
N (%)	45 (27)	158 (94)	41 (25)	150 (89)	86 (33)	113 (47)
Y (%)	119 (73)	10 (6)	124 (75)	19 (11)	176 (67)	130 (53)
White						
N (%)	43 (25)	162 (93)	34 (21)	159 (94)	84 (32)	118 (43)
Y (%)	130 (75)	13 (7)	129 (79)	10 (6)	177 (68)	159 (57)
Black/AA						
N (%)	20 (28)	63 (91)	18 (28)	68 (85)	16 (30)	24 (46)
Y (%)	52 (72)	6 (9)	46 (72)	12 (15)	38 (70)	28 (54)
Hispanic/Latino						
N (%)	9 (27)	31 (94)	11 (34)	30 (91)	13 (34)	21 (51)
Y (%)	24 (73)	2 (6)	21 (66)	3 (9)	25 (66)	20 (49)

Abbreviations: NR- non-responder

Table 10: Results by Subgroup - Attainment of >30% Decrease in iPTH from Baseline to EAP Using NR Imputation (cont.)

Study	229		230		360	
Group	Etelcalcetide	Placebo	Etelcalcetide	Placebo	Etelcalcetide	Cinacalcet
N per group	254	254	255	260	340	343
Asian						
N (%)	2 (40)	2 (67)	6 (46)	4 (67)	1 (11)	3 (43)
Y (%)	3 (60)	1 (33)	7 (54)	2 (33)	8 (89)	4 (57)

Abbreviations: NR-non-responder

Table 11a: Subgroup-Treatment Interaction P-Values

Study	Sex	Age	Race (overall)	Ethnicity	Region
229	0.688	0.375	0.390	0.885	0.132
230	0.061	0.382	0.019	0.512	0.018
360	0.813	0.369	0.840	0.604	0.642

Baseline iPTH level has possible main effect – p=0.002 – for study 360

Table 11b: Race Subgroup-Treatment Interaction P-values by Race Groups

Study	Asian	Black/AA	Native Hawaiian	Other
229	0.090	0.554	-	0.992
230	0.004	0.016	0.196	0.990
360	0.333	0.455	0.985	0.981

White used as reference

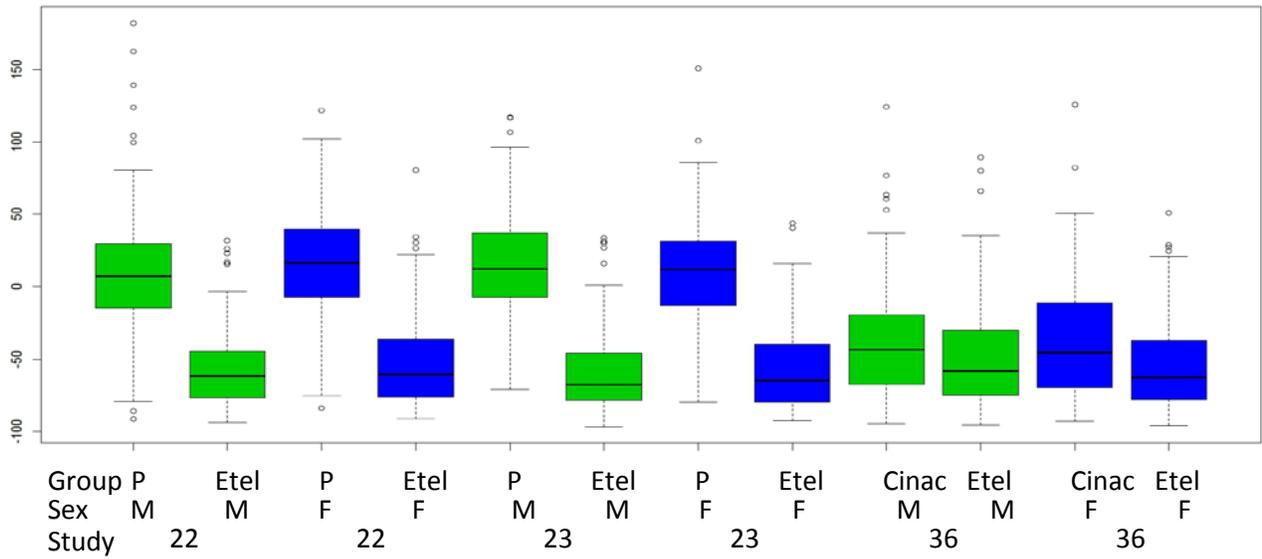


Figure 3: Boxplots of % Change in iPTH By Sex and Study

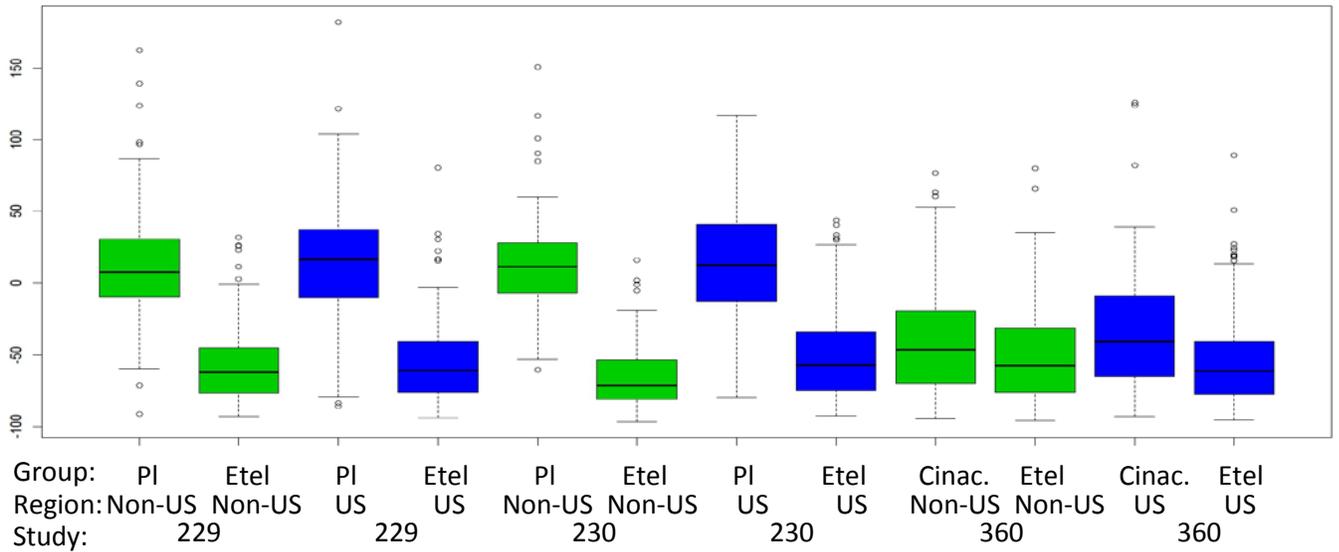
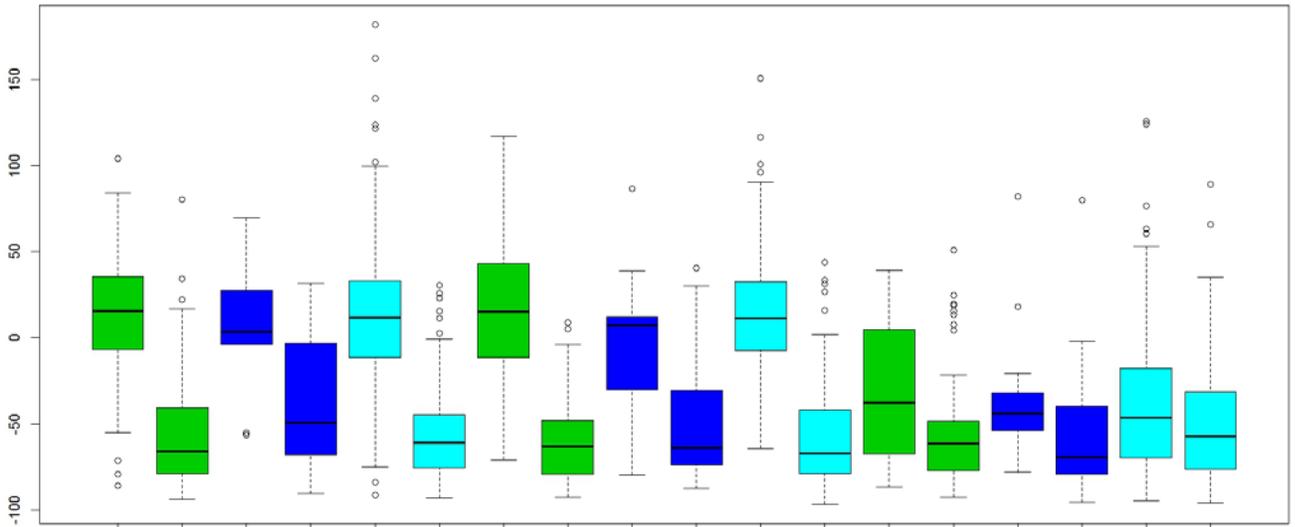
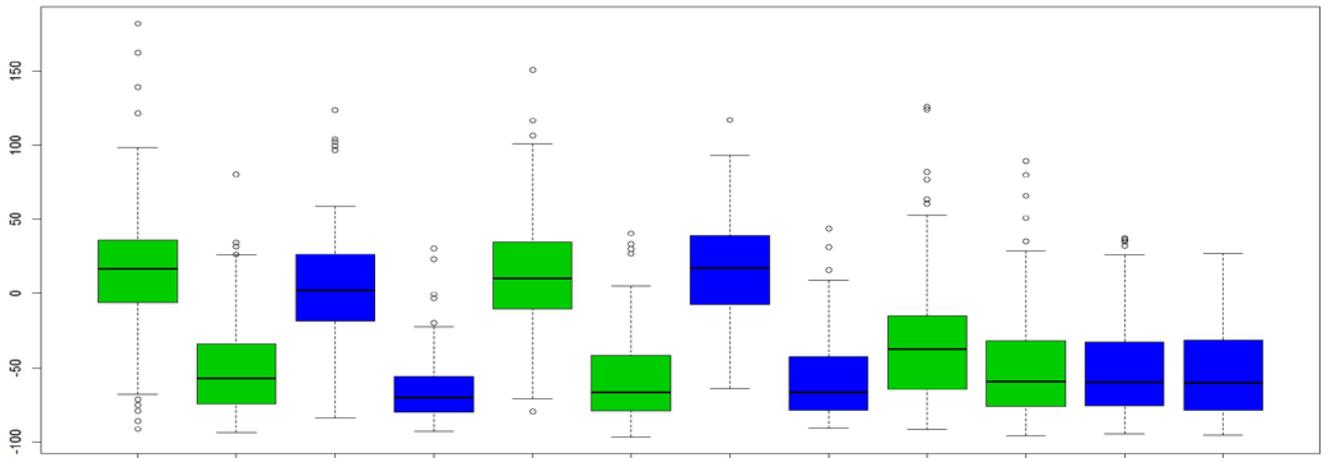


Figure 4: Boxplots of % Change in iPTH at EAP by Region and Study



Group: PI Etel.
 Race: Black/AA Other White Black/AA Other White Black/AA Other White Black/AA Other White
 Study: 229 230 360

Figure 5: Boxplots of % Change in iPTH by Race and Study



Group: PI Etel.
 Age: <65 <65 >=65 >=65 <65 <65 >=65 >=65 <65 <65 >=65 >=65
 Study: 229 229 230 230 230 360 360

Figure 6: Boxplots of % Change in iPTH by Age and Study

5 SUMMARY AND CONCLUSIONS

5.1 Conclusions

The primary endpoint is 30% reduction in parathyroid hormone (PTH), which is measured by parathyroid hormone intact (iPTH). In two randomized placebo-controlled trials and one randomized active-controlled trial, the etelcalcetide group had a statistically significant greater proportion of patients that had >30% reduction in iPTH. This finding was consistent using the sponsor's primary analysis (non-responder imputation) and also using our sensitivity analyses that attempted to address possible shortcomings in the sponsor's primary analysis.

5.2 Labeling Recommendations

For Table 3 of the draft label "Effects of [TRADENAME] on PTH, Corrected Serum Calcium...", the columns under heading (b) (4)

place of (b) (4). Also for all tables, the term "main outcome measure" should be used in place of (b) (4). The terms (b) (4) and (b) (4) should not be used.

References

- Agresti, A. (2002). *Categorical Data Analysis*: Wiley.
- Campbell, G., Pennello, G., & Yue, L. (2011). Missing Data in the Regulation of Medical Devices. *Journal of Biopharmaceutical Statistics*, 21(2), 180-195. doi: 10.1080/10543406.2011.550094

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/s/

ALEXANDER CAMBON
04/28/2016

MARK D ROTHMANN
04/28/2016
I concur



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

STATISTICAL REVIEW AND EVALUATION CARCINOGENICITY STUDIES

NDA/BLA #: NDA 208325/S-0000

Drug Name: AMG 416 (Parsabiv (Elelcalcetide)) Tablets

Indication(s): Treatment of secondary hyperparathyroidism (sHPT) in patients with chronic kidney disease (CKD) on hemodialysis

Applicant: Amgen Inc.
One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA
Laboratory for transgenic mice study: (b) (4)
(b) (4)
Laboratory for rats study: (b) (4)
(b) (4)
Bioanalytical Site: (b) (4)
(b) (4)

Date(s): Received on 1/6/2016; Exec CAC scheduled on early March 2016

Documents Reviewed: Study 116846 (transgenic mice) and Study 116848 (rats) reports and electronic datasets submitted with the electronic submission on 8/24/2015

Review Priority: Regular

Biometrics Division: Division of Biometrics VI

Statistical Reviewer: Feng Zhou, M.S.

Concurring Reviewers: Karl Lin, Ph.D., Team Leader

Medical Division: Division of Metabolism and Endocrinology Products

Pharmacology Team: Miyun Tsai-Turton, Ph.D; Calvin (Lee) Elmore, Ph.D

Project Manager: Meghna Jairath, Project Manager

Keywords: Carcinogenicity, Dose response

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1 Summary

This review evaluates statistically the tumorigenicity data of carcinogenicity studies of AMG416 in NDA208325. The studies were a 2-year study in the Sprague Dawley rats and a 26 week study in the Tg.rasH2 mice. The review analyzes the dose-response relationship of tumor incidence and mortality (including tumor-related mortality). The analyses of tumor data consisted of trend analyses for dose-response relationship in tumor incidence and pairwise comparisons in tumor incidence between individual treated groups, the vehicle control, and the saline control; and between the positive control (in the 26 week transgenic mouse study only) and two control groups. From the statistical point of view, the review concludes that AMG416 at higher doses (0.8 and 1.6 mg/kg/day) decreased survival in female rats and showed a statistically significant dose response relationship in mortality across saline control and treated groups in female rats. The tumor analysis did not show any statistically significant dose-response relationship in tumor incidence for either sex of two species.

Rat Study: Rats (65/sex/dose) were dosed by the subcutaneous (SC) route with AMG416 daily for up to 104 weeks. The AMG416 doses were 0.2, 0.4, 0.8, or 1.6-mg/kg/day in the low (LD), mid (MD), Mid-high (MH), and high-dose (HD) groups in both sexes, respectively. The study had two control groups: saline (C1) and vehicle (C2). Two higher (MH and HD) dose groups were terminated at Week 89 because their group numbers falls below 15.

Survival analysis did show statistically significant dose-response relationships in mortality in females. Statistical significance was achieved when compared to C1 ($p = 0.021$). The test did not reach the statistical significant level of 0.05 when compared to C2 ($p=0.0627$). The pairwise comparisons results did show statistically significant increased mortality in the higher doses treated groups (MH and HD) when compared to C1 ($p=0.008$ and 0.0179). The test did not reach the statistical significant level of 0.05 when compared to C2 ($p=0.0530$ and $p=0.0912$). The pairwise comparisons didn't show a statistically significant mortality between two controls. No statistically significant dose-response relationship was observed in males. The respective survival rate in the C1, C2, LD, MD, MH, and HD groups at the termination (week 105 or week 89) were 38%, 40%, 38%, 25%, 35%, and 29% in males and 37%, 40%, 32%, 28%, 23%, and 23% in females.

There was no statistically significant dose-response relationship in tumor incidence in either sex.

Mouse Study: Mice (25/sex/dose) were dosed by the subcutaneous (SC) route with AMG416 daily for up to 26 weeks. The respective AMG416 dose in the low (LD), mid (MD), and high-dose (HD) groups was 0.3, 1, and 3 mg/kg for females; and 0.375, 0.75 and 1.5 mg/kg for males. The study had three control groups: saline (C1), vehicle (C2), and urethane (positive control or PC). The PC mice (10/sex) were dosed with 1000-mg/kg urethane.

Survival analysis did not show a statistically significant dose response relationship or pairwise comparison in mortality in either sex. The respective survival rates in the C1, C2, LD, MD, HD, PC groups at the termination (Week 26) were 96%, 96%, 96%, 96%, 92%, and 0% in males; 92%, 100%, 100%, 100%, 96%, and 0% in females.

The tumor analysis did not show any statistically significant dose-response relationship in tumor incidence in male and female mice. The PC group showed statistically significant increases in the

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incidence of a number of tumors in both males and females ($p < 0.05$), when compared to the individual controls. Those tumor types included Carcinoma in harderian gland, adenoma in liver, alveolar-bronchioal (adenoma and carcinoma) in lungs; lymphangioma in salivary glands, hemangiosarcoma in spleen, and thymoma in thymus.

2 Background

The sponsor conducted two studies under a Special Protocol Assessment (SPA) agreement: a 26-week subcutaneous carcinogenicity study in transgenic Tg.rasH2 mice (116846); a 24-month subcutaneous carcinogenicity study in the Sprague Dawley rats (116848). This review analyzed the SAS data sets of these studies received from the sponsor on 8/24/2015 via submission NDA208325/S0000.

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases. Results of this review have been discussed with the reviewing pharmacologist Dr. Miyun Tsai-Turton.

3 Rat Study

Study Report: 116848.pdf; [REDACTED] (b) (4)

This study assessed the carcinogenic potential of AMG416 in male and female Sprague Dawley rats. The test material was administered daily by the subcutaneous (SC) route at doses of 0.2, 0.4, 0.8, and 1.6 mg for at least 104 weeks. This review refers these dose groups as the low (LD), mid (MD), Mid-high (MH), and high (HD) dose groups, respectively. There were two controls (pertinent saline control (C1) and vehicle control (C2)). All dosing formulations, including the saline and vehicle control, were [REDACTED] (b) (4) and aliquoted for sufficient volumes for 28 daily doses following each preparation. There were 65 rats/sex/dose. Assessment of oncogenic potential was based on mortality, clinical observations, body weight, food consumption, and anatomic pathology.

3.1 Sponsor's Analyses

3.1.1 Survival Analysis

Intercurrent mortality data were analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test⁹. If this overall test was significant ($p < 0.05$) and there were more than two groups, then a follow up analysis was done where each treatment group was compared to the control group using a log-rank test.

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

The sponsor terminated the animals in the treated groups during week 88 to week 92 based on survival as recommended by the Food and Drug Administration, Center for Drug Evaluation and Research.

Termination of animals resulted when the following survival numbers were reached:

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- 1) Terminated a test article-treated sex group when surviving animals in that sex group declined to 15. If week 100 had been reached, then all groups (Groups 1-6) of that sex were terminated.
- 2) If survival in a control group (saline or vehicle) declined to 20 then all groups of that sex (Groups 1-6) were terminated.
- 3) If survival in a high dose sex group declined to 20, before other dose groups of that sex, then dosing of that high dose sex group only was stopped. The surviving high dose sex group animals remained on study until that sex group declined to 15 or the other termination end points mentioned above were reached.
- 4) Terminated all groups of a given sex when the number of animals in all test article treated groups of that sex reached n=15.

Sponsor's concluded: There were no AMG 416-related changes in survival or causes of death/moribundity occurred in either sex. The most common causes of death/moribundity in males across all groups were pituitary tumors or could not be determined. In females, the most common causes of death/moribundity across all groups were pituitary tumors and mammary tumors.

3.1.2 Tumor Data Analysis

Tumor incidence data were analyzed using both survival-adjusted and survival-unadjusted tests. The unadjusted tests were based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage trend test¹⁰ was performed, and Fisher's exact test¹¹ was used to compare each treatment group with the control groups (separately for both control groups; see the statistical comparisons table the sponsor's report). The survival adjusted test was conducted according to the prevalence/mortality methods described by Peto et al.¹² Evaluation criteria (p-values of significance) were applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%).¹³

Adjustment for multiple testing: In order to control the overall false positive error, the sponsor tested the common and the rare tumors at 0.005 and 0.025 significance levels, respectively (Lin, 2000) for positive dose response relationships in individual tumor types, and at 0.01 and 0.05 for pairwise comparisons in individual tumor types. Tumors are considered by the sponsors as common with a background rate of $\geq 1\%$ and as rare with a background incidence of $< 1\%$.

Sponsor's concluded: Daily SC injections of AMG 416 for up to 652 days to male and female CD® [CrI:CD®(SD)] rats at dose levels of 0.2, 0.4, 0.8, and 1.6 mg/kg/day did not produce evidence of an oncogenic effect. There was no test article-related statistically significant increase in the incidence of any tumor type in any tissue for either sex.

3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer performed survival and tumor data analyses using data submitted electronically in NDA 208325 on 8/24/2015. There were two controls (saline control and vehicle control), this reviewer performed survival and tumor data analyses compared with two controls separately.

3.2.1 *Survival Analysis*

The survival distributions of rats in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, mid-high, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 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 3A and 3B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death were 40 (62%), 45 (60%), 40 (62%), 49 (75%), 42 (65%), and 46 (71%) in male rats and 41 (63%), 45 (60%), 44 (68%), 47 (72%), 50 (77%), and 50 (77%) in female rats in the C1, C2, LD, MD, MH, and HD groups, respectively. The tests did show a statistically significant dose response relationship in mortality across saline control (C1) and treated groups in female rats ($p=0.021$). The test did not reach the statistical significant level of 0.05 when compared to vehicle control (C2) ($p=0.0627$). The pairwise comparisons results did show statistically significant increased mortality in the higher doses treated groups (MH and HD) when compared to C1 ($p=0.008$ and 0.0179). The test did not reach the statistical significant level of 0.05 when compared to C2 ($p=0.0530$ and $p=0.0912$). The pairwise comparisons didn't show a statistically significant mortality between two controls. The tests didn't show a statistically significant dose response relationship in mortality across control and treated groups in male rats.

3.2.2 *Tumor Data Analysis*

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the 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 but develops the tumor type being tested gets a score of $s_h=1$. An animal that dies at week w_h without developing the tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k < 1$. The adjusted group size is defined as $\sum s_h$. As an interpretation, an animal with score $s_h=1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of $k=3$ is suggested in the literature. Hence, this reviewer used $k=3$ for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 5A, 5B, 5C, and 5D in the appendix for male and female rats, respectively.

Multiple testing adjustment: For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of test levels $\alpha=0.005$ for common tumors and $\alpha=0.025$ for rare tumors for a submission with two species,

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

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: Following two tables display the tumor types showed p-values less than or equal to 0.05 either for dose response relationships or pairwise comparisons between treated groups and two controls separately in female rats.

Comparisons of Treated Groups and Saline Control in Female Rats

Organ Name	Tumor Name	0 mg SalineCont N=65	2 mg LD N=65	4 mg MD N=65	8 mg MHD N=65	16 mg HD N=65	P_Value Dose Resp	P_Value C1vs.L	P_Value C1vs.M	P_Value C1vs.MH	P_Value C1vs.HD
mammary gland	F BROADENOMA	19	10	13	19	20	0.0404	0.0198	0.0665	0.3517	0.2619

Comparisons of Treated Groups and Vehicle Control in Female Rats

Organ Name	Tumor Name	0 mg Veh Cont N=65	2 mg LD N=65	4 mg MD N=65	8 mg MHD N=65	16 mg HD N=65	P_Value Dose Resp	P_Value C2vs L	P_Value C2vs M	P_Value C2vs.MH	P_Value C2vs.HD
mammary gland	FIBROADENOMA	28	10	13	19	20	0.2881	0.0198	0.0665	0.3517	0.6882

Based on the criteria of adjustment for multiple testing discussed above, none of the observed tumors was considered to have a statistically significant positive dose response relationship in either sex. The pairwise comparisons didn't show a statistically significant for tumor incidence of fibroadenoma in mammary gland between two controls ($p=0.0784$).

4 Mouse Study

Study Report: 116846.pdf; **SAS data:** (b) (4)

This study assessed the carcinogenic potential of AMG416 in male and female hemizygous Tg.rasH2 mice. The test material was administered daily by the subcutaneous (SC) route at doses of 0.3, 1, and 3 mg/kg to female mice, and 0.375, 0.75 and 1.5 mg/kg to male mice for approximately 26 weeks. This review refers these dose groups as the low (LD), mid (MD), and high (HD) dose groups, respectively. There were two controls (pertinent saline control (C1) and vehicle control (C2)). All treatments were administered at a dose volume of 10 mL/kg body weight. There were 25 mice /sex/dose. There were 10 male mice and 10 female mice treated with 1000 mg/kg of Urethane as positive control (PC).

On Days 183 or 184, surviving animals from the main cohort were sacrificed by CO2 overdose and necropsied. Animals in the TK cohort were sacrificed by CO2 overdose after completion of blood collection during Weeks 1 or 26. Antemortem evaluations included mortality, clinical

signs, body weights and body weight changes, and food consumption. Postmortem macroscopic (gross necropsy) and microscopic (histology) evaluations were performed.

4.1 Sponsor's Analyses

4.1.1 *Survival Analysis*

Kaplan-Meier estimates of group survival rates were calculated, by sex, and shown graphically. The generalized Wilcoxon test for survival was used to compare the homogeneity of survival rates across the vehicle control and AMG 416 groups, by sex, at the 0.05 significance level. Additionally, the positive control group and the saline control group were compared separately to the vehicle control group using the generalized Wilcoxon test. Survival times in which the status of the animal's death was classified as an accidental death, planned interim sacrifice or terminal sacrifice were considered censored values for the purpose of the Kaplan-Meier estimates and survival rate analyses.

Sponsor's findings: Among males and females, there was a statistically significant difference in survival rates when comparing the positive control to the vehicle control and to the saline control groups separately. There were no statistically significant differences in survival rates of the AMG 416 treated groups when compared to the saline and vehicle control groups.

4.1.2 *Tumor Data Analysis*

The incidences of tumors were analyzed by Peto's mortality-prevalence method, without continuity correction, incorporating the context (incidental, fatal, or mortality-independent) in which tumors were observed. Because of the sparse number of deaths during the study, the following fixed intervals were used for incidental tumor analyses: Days 1 through 120 and Days 121 through and including terminal sacrifice. A minimum exposure of 121 days was considered sufficient to be included with animals surviving through scheduled termination. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis. Tumors classified as mortality-independent were analyzed with Peto's mortality independent method incorporating the day of detection. Each diagnosed tumor type was analyzed separately and, at the discretion of the study director, analysis of combined tumor types and/or organs was performed. All metastases and invasive tumors were considered secondary and not included in the analyses.

A 1-sided comparison of each AMG 416 group with the vehicle control was performed. An exact permutation test was conducted for all analyses. Findings were evaluated for statistical significance at both the 0.01 and 0.05 levels and all p values were reported.

Sponsor's findings:

There were no statistically significant tumor findings in the AMG 416 treatment groups when compared to the saline and vehicle control groups. There was a statistically significant increase in the following tumors when comparing the positive control with the vehicle control group:

Sex	Organ	Tumor
M	LUNGS WITH BRONCHI	ALVEOLAR-BRONCHIOLAR ADENOMA (B)
		CARCINOMA/ADENOMA
	SPLEEN	HEMANGIOSARCOMA (M)
F	LUNGS WITH BRONCHI	ALVEOLAR-BRONCHIOLAR ADENOMA (B)
		ALVEOLAR-BRONCHIOLAR CARCINOMA (M)
		CARCINOMA/ADENOMA
	SPLEEN	HEMANGIOSARCOMA (M)
(B)- Benign; (M)- Malignant		

4.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer performed survival and tumor data analyses using data submitted electronically in NDA 208325 on 8/24/2015.

4.2.1 Survival Analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 2A and 2B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively.

Reviewer's findings: The animals in the positive control group were terminated on week 13. The rest of animals were terminated on week 26. This reviewer's analysis showed 1 (4%), 1 (4%), 1 (4%), 1 (4%), 2 (8%), and 10 (100%) number (percent) of deaths in male mice, and 2 (8%), 0, 0, 0, 1 (4%), and 10 (100%) number (percent) of deaths in female mice the C1, C2, LD, MD, HD, PC groups, respectively. The tests did not show any statistically significant dose response relationship in mortality across control and treated groups in either sex. The pairwise comparisons did not show statistically significant increased mortality in the treated groups compared to each of the controls in either male or female mice. The pairwise comparisons didn't show a statistically significant mortality between two controls ($p=0.0935$).

4.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups using the same method that was used for the rats study. The tumor rates and the p-values of the tested tumor types are listed in Tables 6A, 6B, 6C, and 6D in the appendix for male and female mice, respectively.

Reviewer's findings: Because of the small group size and short study duration used in transgenic mouse studies, based on the statistical guideline for transgenic mouse studies, the significance level of 0.05 was used in the tests for dose response and pairwise comparisons in tumor incidences of both rare and common tumors. Based on this recommendation of adjustment for multiple testing discussed above, the tumor analysis did not show any statistically significant dose-response relationship in tumor incidence in male and female mice. The PC group showed statistically significant increases in the incidence of a number of tumors in both males and females ($p<0.05$), when compared to the two controls individually. Those tumor types included Carcinoma in harderian gland, adenoma in liver, alveolar-bronchiloar (adenoma and carcinoma) in lungs; lymphangioma in salvary glands, hemangiosarcoma in spleen, and thymoma in thymus.

Tumor Types with P-Values ≤ 0.05 for Pairwise Comparisons of Saline Control in Female Mice

Organ Name	Tumor Name	0 mkd Saline C N=25	30 mkd LD N=25	1 mkd MD N=25	3 mkd HD N=25	P-Value			
						Dose Response	C1 vs. LD	C1 vs. MD	C1 vs. HD
lungs with bron	alveolar-bronchiolar adenoma	0	3	1	4	0.0634	0.1248	0.5102	0.0597

Tumor Types with P-Values ≤ 0.05 for Pairwise Comparisons of Vehicle Control in Female Mice

Organ Name	Tumor Name	0 mkd Vehicle C N=25	30 mkd LD N=25	1 mkd MD N=25	3 mkd HD N=25	P-Value			
						Dose Response	C2 vs. LD	C2 vs. MD	C2 vs. HD
lungs with bron	alveolar-bronchiolar adenoma	1	3	1	4	0.1185	0.3046	0.7551	0.1743

Tumor Types with P-Values ≤ 0.05 for Pairwise Comparisons of Saline, Vehicle, and Positive Controls in Male Mice

Organ Name	Tumor Name	0 mg/kg/day Saline C (N=25)	0 mg/kg/day Vehicle C (N=25)	1000 mg/kg of Urethane PC (N=10)	P-Value Saline C vs. PC	P-Value Vehicle C vs. PC
harderian gland	carcinoma	0	1	0	.	0.0385
liver	adenoma	1	0	0	0.0400	.
lungs with bron	alveolar-bronchiolar carcinoma	1	0	0	0.0400	.
	alveolar-bronchiolar adenoma	2	1	10	<0.001*	<0.001*
salivary glands	lymphangioma	1	0	0	0.0400	.
spleen	hemangiosarcoma	1	2	9	<0.001*	<0.001*

*Indicted the significant at 0.001 alpha levels.

Tumor Types with P-Values ≤ 0.05 for Pairwise Comparisons of Saline, Vehicle, and Positive Controls in Female Mice

Organ Name	Tumor Name	0 mg/kg/day Saline C (N=25)	0 mg/kg/day Vehicle C (N=25)	1000 mg/kg of Urethane PC (N=10)	P-Value Saline C vs. PC	P-Value Vehicle C vs. PC
harderian gland	adenoma	0	1	0	.	0.0385
liver	adenoma	2	1	0	0.0800	0.0385
lungs with bron	alveolar-bronchiolar carcinoma	0	0	4	0.0400	<0.001*
	alveolar-bronchiolar adenoma	0	1	10	<0.001*	<0.001*
spleen	hemangiosarcoma	1	1	9	<0.001*	<0.001*
thymus	thymoma	0	1	0	.	0.0385

*Indicted the significant at 0.001 alpha levels.

5 Conclusion

This review evaluates statistically the tumorigenicity data of carcinogenicity studies of AMG416 in NDA208325. The studies were a 2-year study in the Sprague Dawley rats and a 26 week study in the Tg.rasH2 mice. The review analyzes the dose-response relationship of tumor incidence and mortality (including tumor-related mortality). The analyses of tumor data consisted of trend analyses for dose-response relationship in tumor incidence and pairwise comparisons in tumor incidence between individual treated groups, the vehicle, and the saline control; and between the positive control (in the 26 week transgenic mouse study only) and the vehicle control groups. From the statistical point of view, the review concludes that AMG416 at higher doses (0.8 and 1.6 mg/kg/day)

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decreased survival in female rats and showed a statistically significant dose response relationship in mortality across saline control and treated groups in female rats. The tumor analysis did not show any statistically significant dose-response relationship in tumor incidence for either sex of two species. The PC group showed statistically significant increases in the incidence of a number of tumors in both males and females ($p < 0.05$), when compared to the two controls individually. Those tumor types included Carcinoma in harderian gland, adenoma in liver, alveolar-bronchioal (adenoma and carcinoma) in lungs; lymphangioma in salivary glands, hemangiosarcoma in spleen, and thymoma in thymus.

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6 Appendix

Table 1A: Intercurrent Mortality – Male Rats

Week	0 mg/kg/day Saline control (n=65)		0 mg/kg/day Vehicle control (n=65)		0.2 mg/kg/day LD (n=65)		0.4 mg/kg/day MD (n=65)		0.8 mg/kg/day MHD (n=65)		1.6 mg/kg/day HD (n=65)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 26	2	3.08	1	1.54	2	3.08	0	0	3	4.62	1	1.54
26 - 52	4	9.23	6	10.77	2	6.15	4	6.15	3	9.23	11	18.46
53 - 78	14	30.77	27	52.31	20	36.92	29	50.77	18	36.92	21	50.77
79 - 91	17	56.92	8	64.62	15	60.00	14	72.31	17	63.08	10	66.15
92 - 104	3	61.54	3	69.23	1	61.54	2	75.38	1	64.62	3	70.77
Ter. Sac.	25	38.46	20	30.77	25	38.46	16	24.62	23	35.38	19	29.23

* Cum. %: Cumulative percentage except for Ter. Sac.

Table 1B: Intercurrent Mortality - Female Rats

Week	0 mg/kg/day Saline control (n=65)		0 mg/kg/day Vehicle control (n=65)		0.2 mg/kg/day LD (n=65)		0.4 mg/kg/day MD (n=65)		0.8 mg/kg/day MHD (n=65)		1.6 mg/kg/day HD (n=65)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 26	1	1.54	0	0	0	0	0	0	0	0	1	1.54
26 - 52	4	7.69	3	4.62	6	9.23	4	6.15	6	9.23	9	15.38
53 - 78	16	32.31	22	38.46	29	53.85	28	49.23	29	53.85	26	55.38
79 - 91	18	60.00	17	64.62	9	67.69	15	72.31	15	76.92	14	76.92
91 - 104	2	63.08	3	69.23	0	0	0	0	0	0	0	0
Ter. Sac.	24	36.92	20	30.77	21	32.31	18	27.69	15	23.08	15	23.08

* Cum. %: Cumulative percentage except for Ter. Sac.

Table 2A: Intercurrent Mortality - Male Mice

Week	0 mg/kg/day Saline control (n=25)		0 mg/kg/day Vehicle control (n=25)		0.375 mg/kg/day LD (n=25)		0.75 mg/kg/day MD (n=25)		1.5 mg/kg/day HD (n=25)		1000 mg/kg of Urethane Positive Control (n=10)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 26	1	4.00	1	4.00	1	4.00	1	4.00	2	8.00	10	100.00
Ter. Sac.	24	96.00	24	96.00	24	96.00	24	96.00	23	92.00	.	.

* Cum. %: Cumulative percentage except for Ter. Sac.

Table 2B: Intercurrent Mortality – Female Mice

Week	0 mg/kg/day Saline control (n=25)		0 mg/kg/day Vehicle control (n=25)		0.3 mg/kg/day LD (n=25)		1.0 mg/kg/day MD (n=25)		3.0 mg/kg/day HD (n=25)		1000 mg/kg of Urethane Positive Control (n=10)	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 26	2	8.00	0	0	0	0	0	0	1	4.00	10	100.00
Ter. Sac.	23	92.00	25	100.00	25	100.00	25	100.00	24	96.00	.	.

* Cum. %: Cumulative percentage except for Ter. Sac.

Table 3A: Intercurrent Mortality Comparison – Male Rats

Test	Statistic	Compared with Combined Controls P-Value	Compared with Saline Control P-Value	Compared with Vehicle Control P-Value
Dose-Response	Likelihood Ratio	0.3063	0.1676	0.6111
Homogeneity	Log-Rank	0.4693	0.2968	0.5347

Table 3B: Intercurrent Mortality Comparison – Female Rats

Test	Statistic	Compared with Combined Controls P-Value	Compared with Saline Control P-Value	Compared with Vehicle Control P-Value
Dose-Response	Likelihood Ratio	0.0090	0.0206	0.0627
Homogeneity	Log-Rank	0.0728	0.1272	0.3934
High Dose (1.6 mg/kg/day)	Likelihood Ratio	0.0079	0.0082	0.0530
Homogeneity	Log-Rank	0.0053	0.0069	0.0480
Mid-High Dose (0.8 mg/kg/day)	Likelihood Ratio	0.0196	0.0179	0.0912
Homogeneity	Log-Rank	0.0148	0.0157	0.0841

Table 4A: Intercurrent Mortality Comparison – Male Mice

Test	Statistic	Compared with Combined Controls P-Value	Compared with Saline Control P-Value	Compared with Vehicle Control P-Value
Dose-Response	Likelihood Ratio	0.7533	0.8829	0.4987
Homogeneity	Log-Rank	0.9165	0.8792	0.8941
Compared with positive control				
Dose-Response	Likelihood Ratio	0.0967	0.0742	0.0285
Homogeneity	Log-Rank	0.0003	<0.001	<0.001

Table 4B: Intercurrent Mortality Comparison – Female Mice

Test	Statistic	Compared with Combined Controls P-Value	Compared with Saline Control P-Value	Compared with Vehicle Control P-Value
Dose-Response	Likelihood Ratio	0.8294	0.9139	0.0959
Homogeneity	Log-Rank	0.5664	0.2912	0.3916
Compared with positive control				
Dose-Response	Likelihood Ratio	0.6140	0.0127	0.0009
Homogeneity	Log-Rank	0.0009	0.0007	0.0009

Table 5A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Saline Control – Male Rats

Organ Name	Tumor Name	0 mg Saline Cont N=65	0.2 mkd LD N=65	0.4 mkd MD N=65	0.8 mkd MHD N=65	1.6 mkd HD N=65	P-value				
							Dos-Resp	C1 vs. LD	C1 vs. MD	C1 vs. MHD	C1 vs. HD
adrenal glands	PHEOCHROMOCYTOMA	10	5	13	4	4	0.9370	0.8392	0.2348	0.8998	0.8626
bone	OSTEOSARCOMA	0	0	1	0	0	0.3853	.	0.4719	.	.
bone marrow, fe	HEMANGIOMA	0	0	1	0	0	0.3853	.	0.4719	.	.
	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6096	.	0.1050	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659

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Organ Name	Tumor Name	0 mg Saline Cont N=65	0.2 mkd LD N=65	0.4 mkd MD N=65	0.8 mkd MHD N=65	1.6 mkd HD N=65	P-value				
							Dos- Resp	C1 vs. LD	C1 vs. MD	C1 vs. MHD	C1 vs. HD
bone marrow, st	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6096	.	0.1050	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
brain	ASTROCYTOMA	1	1	1	3	1	0.3604	0.7473	0.7240	0.2837	0.7176
	GRANULAR CELL TUMOR	1	1	2	1	0	0.7678	0.7418	0.4663	0.7360	0.4598
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	OLIGODENDROGLIOMA	0	1	1	0	0	0.6572	0.4946	0.4719	.	.
	RETICULOSIS	1	0	0	0	1	0.3797	0.4891	0.4719	0.4835	0.7176
cavity, abdomin	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
	LYMPHOMA	1	0	0	0	0	0.7844	0.4891	0.4719	0.4835	0.4598
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
cavity, thoraci	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
coagulating gla	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
epididymides	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	MESOTHELIOMA	1	0	0	0	0	0.7844	0.4891	0.4719	0.4835	0.4598
eyes	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6096	.	0.1050	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
galt	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
harderian gland	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
heart	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.
	MESOTHELIOMA, ATRIOC	0	0	0	0	1	0.1835	.	.	.	0.4598
	SCHWANNOMA, ENDOCARD	0	0	0	1	0	0.3853	.	.	0.4835	.
injection site,	FIBROMA	1	0	0	0	0	0.7844	0.4891	0.4719	0.4835	0.4598
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	PAPILLOMA, FIBROUS	0	0	1	0	0	0.3853	.	0.4719	.	.
kidneys	ADENOMA, RENAL TUBUL	0	0	0	1	0	0.3853	.	.	0.4835	.
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.
	L POMA	1	0	0	0	0	0.7808	0.4839	0.4667	0.4783	0.4545
	L POSARCOMA	1	0	0	0	0	0.7844	0.4891	0.4719	0.4835	0.4598
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
lacrimial glands	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6096	.	0.1050	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
large intestine	LEIOMYOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
			1	0	0	0	0.5780	0.4891	.	.	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
larynx	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6096	.	0.1050	.	.
liver	ADENOMA, HEPATOCELLU	1	2	2	2	1	0.5027	0.4835	0.4574	0.4750	0.7110
	CARCINOMA, HEPATOCEL	1	2	1	1	1	0.5126	0.4918	0.7240	0.7360	0.7110
	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6096	.	0.1050	.	.
	LYMPHOMA	1	0	0	1	0	0.5381	0.4891	0.4719	0.7418	0.4598
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
lung	ADENOMA, BRONCHIOLAR	0	0	0	1	0	0.3853	.	.	0.4835	.
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.

Organ Name	Tumor Name	0 mg Saline Cont N=65	0.2 mkd LD N=65	0.4 mkd MD N=65	0.8 mkd MHD N=65	1.6 mkd HD N=65	P-value				
							Dos- Resp	C1 vs. LD	C1 vs. MD	C1 vs. MHD	C1 vs. HD
lymph node, iii	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
	LYMPHOMA	0	0	0	0	1	0.1872	.	.	.	0.4659
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
lymph node, man	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6096	.	0.1050	.	.
	LYMPHOMA	1	0	0	1	0	0.5381	0.4891	0.4719	0.7418	0.4598
lymph node, mes	HEMANGIOSARCOMA	0	0	0	0	1	0.1835	.	.	.	0.4598
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.
	LYMPHOMA	1	0	0	1	0	0.5381	0.4891	0.4719	0.7418	0.4598
lymph node, ren	SARCOMA, HISTIOCYTIC	0	0	1	0	0	0.3853	.	0.4719	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
	ADENOCARC NOMA	1	0	1	1	0	0.6106	0.4891	0.7240	0.7360	0.4598
	ADENOLIPOMA	0	0	0	0	1	0.1872	.	.	.	0.4659
mammary gland	FIBROADENOMA	3	1	1	0	0	0.9798	0.6750	0.6480	0.8665	0.8470
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6096	.	0.1050	.	.
multicentric ne	LYMPHOMA	1	0	1	1	1	0.3459	0.4891	0.7240	0.7418	0.7176
	SARCOMA, HISTIOCYTIC	0	0	1	0	1	0.1821	.	0.4719	.	0.4659
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.
nerve, sciatic	ADENOMA, ACINAR CELL	2	2	1	2	0	0.8467	0.6834	0.4574	0.6663	0.7110
	ADENOMA, ISLET CELL	4	4	2	10	2	0.4772	0.6307	0.6064	0.0668	0.5817
pancreas	CARCINOMA, ISLET CEL	5	1	0	0	1	0.9354	0.8881	0.9630	0.9670	0.8572
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
parathyroid gla	ADENOMA	2	0	1	0	0	0.9079	0.7418	0.4574	0.7360	0.7110
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
pharynx	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.
pituitary gland	ADENOMA, PARS DISTAL	37	35	39	40	29	0.7967	0.4760	0.1747	0.3447	0.6578
	CRANIOPHARYNGIOMA	0	1	0	0	0	0.5753	0.4946	.	.	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
preputial gland	CARCINOMA, SQUAMOUS	2	0	0	1	0	0.7713	0.7418	0.7240	0.4750	0.7110
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
prostate gland	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	ADENOCARC NOMA	0	0	1	0	0	0.3853	.	0.4719	.	.
	ADENOMA	0	0	1	0	0	0.3853	.	0.4719	.	.
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
salivary gland,	ADENOMA	1	0	0	0	0	0.7844	0.4891	0.4719	0.4835	0.4598
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
				2	0	0	0.5345	.	0.2255	.	.
seminal vesicle	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	SCHWANNOMA	0	0	1	0	0	0.3853	.	0.4719	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
skeletal muscle	HEMANGIOSARCOMA	0	0	0	1	0	0.3853	.	.	0.4835	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
skin	ADENOMA, BASAL CELL	0	0	1	0	0	0.3853	.	0.4719	.	.

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Organ Name	Tumor Name	0 mg Saline Cont N=65	0.2 mkd LD N=65	0.4 mkd MD N=65	0.8 mkd MHD N=65	1.6 mkd HD N=65	P-value				
							Dos- Resp	C1 vs. LD	C1 vs. MD	C1 vs. MHD	C1 vs. HD
skin, subcutis	ADENOMA, SEBACEOUS C	1	1	0	0	0	0.8641	0.7473	0.4719	0.4835	0.4598
	CARCINOMA, BASAL CEL	0	0	1	0	0	0.3853	.	0.4719	.	.
	CARCINOMA, SEBACEOUS	0	0	0	0	1	0.1835	.	.	.	0.4598
	FIBROSARCOMA	0	0	1	0	0	0.3853	.	0.4719	.	.
	KERATOACANTHOMA	0	1	0	1	1	0.1995	0.4891	.	0.4835	0.4598
	PAPILLOMA, FIBROUS	0	1	0	0	0	0.5780	0.4891	.	.	.
	PAPILLOMA, SQUAMOUS	1	2	2	0	0	0.9000	0.4835	0.4574	0.4835	0.4598
	FIBROMA	2	1	2	3	0	0.7446	0.4835	0.6573	0.4684	0.7110
	FIBROSARCOMA	2	1	1	2	1	0.5028	0.4755	0.4584	0.6580	0.4312
	FIBROUS HISTIOCYTOMA	1	0	0	0	0	0.7844	0.4891	0.4719	0.4835	0.4598
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
	L POMA	0	0	1	0	0	0.3853	.	0.4719	.	.
	L POSARCOMA	1	0	0	0	0	0.7808	0.4839	0.4667	0.4783	0.4545
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
	OSTEOSARCOMA	0	1	0	0	0	0.5753	0.4946	.	.	.
	SCHWANNOMA	0	1	2	1	0	0.6131	0.4946	0.2199	0.4835	.
small intestine	ADENOMA	0	0	0	0	1	0.1835	.	.	.	0.4598
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
spinal cord, ce	RETICULOSIS	0	0	0	0	1	0.1872	.	.	.	0.4659
spinal cord, lu	RETICULOSIS	0	0	0	0	1	0.1872	.	.	.	0.4659
spinal cord, th	RETICULOSIS	0	0	0	0	1	0.1872	.	.	.	0.4659
spleen	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6096	.	0.1050	.	.
	LYMPHOMA	1	0	0	1	0	0.5381	0.4891	0.4719	0.7418	0.4598
stomach, glandu	ADENOCARC NOMA	0	0	0	0	1	0.1835	.	.	.	0.4598
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
stomach, nongla	CARCINOMA, SQUAMOUS	1	0	0	0	0	0.7844	0.4891	0.4719	0.4835	0.4598
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
testes	ADENOMA, INTERSTITIA	1	0	0	1	0	0.5358	0.4891	0.4719	0.7360	0.4598
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
thymus	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6096	.	0.1050	.	.
	LYMPHOMA	0	0	1	1	0	0.4533	.	0.4719	0.4891	.
	THYMOMA	0	0	0	1	0	0.3853	.	.	0.4835	.
thyroid gland	ADENOMA, C-CELL	12	3	2	2	2	0.9946	0.9878	0.9933	0.9954	0.9914
	ADENOMA, FOLLICULAR	1	1	1	4	0	0.5094	0.7418	0.7240	0.1606	0.4598
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
tongue	CARCINOMA, SQUAMOUS	0	0	1	0	0	0.3853	.	0.4719	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
trachea	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5345	.	0.2255	.	.
	LYMPHOMA	0	0	0	1	0	0.3881	.	.	0.4891	.
urinary bladder	ADENOCARC NOMA	0	0	1	0	0	0.3853	.	0.4719	.	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3853	.	0.4719	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1872	.	.	.	0.4659
zymbal s gland	ADENOMA, ZYMBALS GLA	0	0	1	0	0	0.3853	.	0.4719	.	.
	CARCINOMA, SEBACEOUS	0	0	1	0	1	0.1821	.	0.4719	.	0.4659

Table 5B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control – Male Rats

Organ Name	Tumor Name	0 mkd	0.2	0.4	0.8	1.6	P-value
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		Vehicle Control N=65	mkd LD N=65	mkd MD N=65	mkd MHD N=65	mkd HD N=65	Dos Response	C2 vs. LD	C2 vs. MD	C2 vs. MHD	C2 vs. HD
adrenal glands	ADENOMA, CORTICAL	1	0	0	0	0	0.8066	0.5233	0.5060	0.5176	0.4938
	PHEOCHROMOCYTOMA	7	5	13	4	4	0.8783	0.6700	0.1232	0.7663	0.7113
bone	OSTEOSARCOMA	0	0	1	0	0	0.3962	.	0.5060	.	.
bone marrow, fe	HEMANGIOMA	0	0	1	0	0	0.3962	.	0.5060	.	.
	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6298	.	0.1295	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6298	.	0.1295	.	.
bone marrow, st	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6298	.	0.1295	.	.
brain	ASTROCYTOMA	2	1	1	3	1	0.4860	0.5345	0.5000	0.5223	0.4909
	GRANULAR CELL TUMOR	1	1	2	1	0	0.7890	0.2709	0.5181	0.2650	0.4938
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	OLIGODENDROGLIOMA	0	1	1	0	0	0.6725	0.5287	0.5060	.	.
	RETICULOSIS	0	0	0	0	1	0.1925	.	.	.	0.5000
cavity, abdomin	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
cavity, thoraci	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
coagulating gla	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
epididymides	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
eyes	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6298	.	0.1295	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
galt	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
harderian gland	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
heart	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
	MESOTHELIOMA, ATRIOC	0	0	0	0	1	0.1887	.	.	.	0.4938
	SCHWANNOMA, ENDOCARD	0	0	0	1	0	0.3962	.	.	0.5176	.
injection site,	FIBROMA	1	0	0	0	0	0.8066	0.5233	0.5060	0.5176	0.4938
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	PAP LLOMA, F BROUS	0	0	1	0	0	0.3962	.	0.5060	.	.
kidneys	ADENOMA, RENAL TUBUL	0	0	0	1	0	0.3962	.	.	0.5176	.
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
	LIPOSARCOMA	2	0	0	0	0	0.9633	0.7756	0.7590	0.7703	0.7469
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
lacrimal glands	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6298	.	0.1295	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
large intestine	LEIOMYOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
			1	0	0	0	0.5943	0.5233	.	.	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
larynx	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6298	.	0.1295	.	.
liver	ADENOMA, HEPATOCELLU	4	2	2	2	1	0.8607	0.6944	0.6621	0.6840	0.8047
	CARC NOMA, HEPATOCEL	0	2	1	1	1	0.4230	0.2767	0.5060	0.5176	0.4938

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	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6298	.	0.1295	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
lung	ADENOMA, BRONCHIOLAR	0	0	0	1	0	0.3962	.	.	0.5176	.
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
lymph node, ili	LYMPHOMA	0	0	0	0	1	0.1925	.	.	.	0.5000
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
lymph node, man	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6298	.	0.1295	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
lymph node, mes	HEMANGIOSARCOMA	0	0	0	0	1	0.1887	.	.	.	0.4938
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	SARCOMA, HISTIOCYTIC	0	0	1	0	0	0.3962	.	0.5060	.	.
lymph node, ren	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
mammary gland	ADENOCARCINOMA	0	0	1	1	0	0.4674	.	0.5060	0.5176	.
	ADENOLIPOMA	0	0	0	0	1	0.1925	.	.	.	0.5000
	FIBROADENOMA	0	1	1	0	0	0.6751	0.5233	0.5060	.	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
multicentric ne	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6298	.	0.1295	.	.
	LYMPHOMA	0	0	1	1	1	0.1680	.	0.5060	0.5233	0.5000
	SARCOMA, HISTIOCYTIC	0	0	1	0	1	0.1925	.	0.5060	.	0.5000
nerve, sciatic	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
pancreas	ADENOMA, AC NAR CELL	0	2	1	2	0	0.6151	0.2767	0.5060	0.2650	.
	ADENOMA, ISLET CELL	6	4	2	10	2	0.6614	0.6732	0.8598	0.2492	0.8431
	CARC NOMA, ISLET CEL	4	1	0	0	1	0.8866	0.8407	0.9420	0.9473	0.8047
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
parathyroid gla	ADENOMA	2	0	1	0	0	0.9217	0.7756	0.5091	0.7703	0.7469
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
pharynx	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
pituitary gland	ADENOMA, PARS DISTAL	35	35	39	40	29	0.7990	0.4740	0.1762	0.3445	0.6500
	CRANIOPHARYNGIOMA	0	1	0	0	0	0.5915	0.5287	.	.	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
	SCHWANNOMA	1	0	0	0	0	0.8028	0.5172	0.5000	0.5116	0.4878
preputial gland	CARC NOMA, SQUAMOUS	0	0	0	1	0	0.3962	.	.	0.5176	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
prostate gland	ADENOCARCINOMA	0	0	1	0	0	0.3962	.	0.5060	.	.
	ADENOMA	0	0	1	0	0	0.3962	.	0.5060	.	.
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
salivary gland,	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
				2	0	0	0.5544	.	0.2590	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	SCHWANNOMA	0	0	1	0	0	0.3962	.	0.5060	.	.
seminal vesicle	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000

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skeletal muscle	HEMANGIOSARCOMA	0	0	0	1	0	0.3962	.	.	0.5176	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
skin	ADENOMA, BASAL CELL	0	0	1	0	0	0.3962	.	0.5060	.	.
	ADENOMA, SEBACEOUS C	0	1	0	0	0	0.5915	0.5287	.	.	.
	CARC NOMA, BASAL CEL	0	0	1	0	0	0.3962	.	0.5060	.	.
	CARC NOMA, SEBACEOUS	0	0	0	0	1	0.1887	.	.	.	0.4938
	FIBROSARCOMA	0	0	1	0	0	0.3962	.	0.5060	.	.
	KERATOACANTHOMA	2	1	0	1	1	0.5552	0.5353	0.7590	0.5268	0.4906
	PAP LLOMA, F BROUS	0	1	0	0	0	0.5943	0.5233	.	.	.
	PAP LLOMA, SQUAMOUS	2	2	2	0	0	0.9652	0.3441	0.3170	0.7703	0.7469
	P LOMATRICOMA	1	0	0	0	0	0.8028	0.5172	0.5000	0.5116	0.4878
skin, subcutis	FIBROMA	0	1	2	3	0	0.4869	0.5233	0.2590	0.1341	.
	FIBROSARCOMA	2	1	1	2	1	0.5336	0.5262	0.5089	0.3259	0.4815
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
	LIPOMA	0	0	1	0	0	0.3962	.	0.5060	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
	OSTEOSARCOMA	0	1	0	0	0	0.5915	0.5287	.	.	.
	SCHWANNOMA	0	1	2	1	0	0.6356	0.5287	0.2530	0.5176	.
small intestine	ADENOCARCINOMA	1	0	0	0	0	0.8028	0.5172	0.5000	0.5116	0.4878
	ADENOMA	0	0	0	0	1	0.1887	.	.	.	0.4938
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
spinal cord, ce	RETICULOSIS	0	0	0	0	1	0.1925	.	.	.	0.5000
spinal cord, lu	RETICULOSIS	0	0	0	0	1	0.1925	.	.	.	0.5000
spinal cord, th	RETICULOSIS	0	0	0	0	1	0.1925	.	.	.	0.5000
spleen	FIBROSARCOMA	1	0	0	0	0	0.8066	0.5233	0.5060	0.5176	0.4938
	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6298	.	0.1295	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
stomach, glandu	ADENOCARCINOMA	0	0	0	0	1	0.1887	.	.	.	0.4938
	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
stomach, nongla	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
testes	ADENOMA, INTERSTITIA	1	0	0	1	0	0.5559	0.5233	0.5060	0.2650	0.4938
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
thymus	LEUKEMIA, GRANULOCYT	0	0	3	0	0	0.6298	.	0.1295	.	.
	LYMPHOMA	0	0	1	1	0	0.4686	.	0.5060	0.5233	.
	THYMOMA	0	0	0	1	0	0.3962	.	.	0.5176	.
thyroid gland	ADENOMA, C-CELL	2	3	2	2	2	0.5230	0.5550	0.3170	0.3441	0.6828
	ADENOMA, FOLLICULAR	1	1	1	4	0	0.5407	0.2709	0.2530	0.2028	0.4938
	CARC NOMA, FOLLICULA	2	0	0	0	0	0.9633	0.7756	0.7590	0.7703	0.7469
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
tongue	CARC NOMA, SQUAMOUS	0	0	1	0	0	0.3962	.	0.5060	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
trachea	LEUKEMIA, GRANULOCYT	0	0	2	0	0	0.5544	.	0.2590	.	.
	LYMPHOMA	0	0	0	1	0	0.3991	.	.	0.5233	.
urinary bladder	ADENOCARCINOMA	0	0	1	0	0	0.3962	.	0.5060	.	.
	LEUKEMIA, GRANULOCYT	0	0	1	0	0	0.3962	.	0.5060	.	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1925	.	.	.	0.5000
zymbal s gland	ADENOMA, ZYMBALS GLA	0	0	1	0	0	0.3962	.	0.5060	.	.
	CARC NOMA, SEBACEOUS	0	0	1	0	1	0.1925	.	0.5060	.	0.5000

Table 5C: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Saline Control – Female Rats

Organ Name	Tumor Name	0 mkd Saline Control N=65	0.2 mkd LD N=65	0.4 mkd MD N=65	0.8 mkd MHD N=65	1.6 mkd HD N=65	P-value				
							Dos Response	C1 vs. LD	C1 vs. MD	C1 vs. MHD	C1 vs. HD
adrenal glands	ADENOMA, CORTICAL	1	1	1	1	1	0.4369	0.7233	0.7168	0.7101	0.6883
	PHEOCHROMOCYTOMA	3	0	2	1	0	0.8903	0.8522	0.4348	0.6182	0.8235
bone marrow, fe	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1791	.	.	.	0.4390
bone marrow, st	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1791	.	.	.	0.4390
brain	ASTROCYTOMA	1	2	0	0	1	0.5174	0.4564	0.4651	0.4524	0.6883
	CARC NOMA, PARS DIST	2	2	0	1	0	0.8854	0.6384	0.7110	0.4296	0.6823
cavity, abdomin	FIBROSARCOMA	0	1	0	0	0	0.5672	0.4713	.	.	.
	MESOTHELIOMA	0	0	0	0	1	0.1791	.	.	.	0.4390
	SARCOMA, HISTIOCYTIC	1	0	0	0	0	0.7673	0.4659	0.4598	0.4471	0.4337
cavity, thoraci	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1791	.	.	.	0.4390
clitoral glands	CARC NOMA, SQUAMOUS	0	1	0	0	0	0.5672	0.4713	.	.	.
eyes	CARC NOMA, SQUAMOUS	1	0	0	0	0	0.7673	0.4659	0.4598	0.4471	0.4337
galt	LYMPHOMA	0	1	0	0	0	0.5672	0.4713	.	.	.
injection site,	SARCOMA, HISTIOCYTIC	1	0	0	0	0	0.7673	0.4659	0.4598	0.4471	0.4337
kidneys	SARCOMA, HISTIOCYTIC	1	0	0	0	0	0.7673	0.4659	0.4598	0.4471	0.4337
liver	SARCOMA, HISTIOCYTIC	1	0	0	0	1	0.3600	0.4659	0.4598	0.4471	0.6823
lung	ADENOCARCINOMA	0	0	0	1	1	0.1002	.	.	0.4588	0.4390
	LYMPHOMA	0	0	0	0	1	0.1791	.	.	.	0.4390
	PHEOCHROMOCYTOMA	0	0	0	1	0	0.3713	.	.	0.4588	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	1	0.3600	0.4659	0.4598	0.4471	0.6823
lymph node, hep	SARCOMA, HISTIOCYTIC	1	0	0	0	0	0.7673	0.4659	0.4598	0.4471	0.4337
lymph node, ili	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1791	.	.	.	0.4390
lymph node, man	LYMPHOMA	0	0	0	0	1	0.1791	.	.	.	0.4390
lymph node, mes	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1791	.	.	.	0.4390
lymph node, tra	LYMPHOMA	0	0	0	0	1	0.1791	.	.	.	0.4390
mammary gland	ADENOCARCINOMA	28	18	17	21	21	0.4823	0.8204	0.8064	0.5271	0.6060
	ADENOMA	0	1	1	1	1	0.2535	0.4713	0.4651	0.4588	0.4390
	FIBROADENOMA	19	10	13	19	20	0.0404	0.9040	0.7629	0.4831	0.2619
multicentric ne	LYMPHOMA	1	1	0	0	2	0.1715	0.7176	0.4598	0.4471	0.4000
	SARCOMA, HISTIOCYTIC	1	0	0	0	1	0.3600	0.4659	0.4598	0.4471	0.6823
ovaries	SEX-CORD/STROMAL TUM	0	2	1	2	1	0.3300	0.2192	0.4651	0.2076	0.4390
pancreas	ADENOMA, AC NAR CELL	0	0	1	0	0	0.3682	.	0.4651	.	.
	CARC NOMA, ISLET CEL	1	1	0	0	0	0.8518	0.7176	0.4598	0.4471	0.4337
parathyroid gla	ADENOMA	0	1	0	0	0	0.5672	0.4713	.	.	.
pituitary gland	ADENOMA, PARS DISTAL	49	56	56	57	46	0.8230	0.2519	0.2519	0.1136	0.6106
	CARC NOMA, PARS DIST	2	1	0	1	0	0.8336	0.4483	0.7110	0.4296	0.6823
skeletal muscle	SARCOMA, HISTIOCYTIC	1	0	0	0	0	0.7673	0.4659	0.4598	0.4471	0.4337
skin	KERATOACANTHOMA	0	0	0	0	1	0.1832	.	.	.	0.4458
	LYMPHOMA	0	0	0	0	1	0.1791	.	.	.	0.4390
skin, subcutis	HEMANGIOPERICYTOMA	0	0	0	1	0	0.3713	.	.	0.4588	.
	SARCOMA, HISTIOCYTIC	1	0	0	0	0	0.7673	0.4659	0.4598	0.4471	0.4337
	SCHWANNOMA	0	0	0	1	0	0.3713	.	.	0.4588	.
spleen	HEMANGIOSARCOMA	0	0	0	0	1	0.1791	.	.	.	0.4390
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1791	.	.	.	0.4390
thymus	LYMPHOMA	1	0	0	0	0	0.7673	0.4659	0.4598	0.4471	0.4337
thyroid gland	ADENOMA, C-CELL	3	4	4	4	1	0.7662	0.4231	0.4231	0.3954	0.5853
	ADENOMA, FOLLICULAR	1	0	3	0	0	0.7718	0.4713	0.2658	0.4524	0.4390
	CARC NOMA, C-CELL	2	0	0	0	0	0.9468	0.7176	0.7110	0.6972	0.6823

Organ Name	Tumor Name	0 mkd Saline Control N=65	0.2 mkd LD N=65	0.4 mkd MD N=65	0.8 mkd MHD N=65	1.6 mkd HD N=65	P-value				
							Dos Response	C1 vs. LD	C1 vs. MD	C1 vs. MHD	C1 vs. HD
urinary bladder	CARC NOMA, FOLLICULA	1	0	0	1	0	0.5175	0.4713	0.4651	0.7101	0.4390
	SARCOMA, HISTIOCYTIC	1	0	0	0	0	0.7673	0.4659	0.4598	0.4471	0.4337
uterus with cer	ADENOCARCINOMA	1	0	0	0	0	0.7711	0.4713	0.4651	0.4524	0.4390
	GRANULAR CELL TUMOR	3	0	2	1	1	0.6376	0.8522	0.4231	0.6182	0.5853
	LEIOMYOMA	0	0	0	0	1	0.1791	.	.	.	0.4390
	POLYP, GLANDULAR	1	0	0	0	0	0.7673	0.4659	0.4598	0.4471	0.4337
	POLYP, STROMAL	5	3	5	4	2	0.7298	0.5636	0.5719	0.3970	0.6590
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1791	.	.	.	0.4390
	SARCOMA, STROMAL	0	1	0	0	1	0.2445	0.4713	.	.	0.4390
Vagina	CARC NOMA, SQUAMOUS	1	0	0	0	0	0.7711	0.4713	0.4651	0.4524	0.4390
	GRANULAR CELL TUMOR	0	0	0	3	1	0.0839	.	.	0.0925	0.4390
	SARCOMA, STROMAL	0	1	0	0	0	0.5672	0.4713	.	.	.
zymbal s gland	CARC NOMA, ZYMBALS G	1	0	0	0	0	0.7673	0.4659	0.4598	0.4471	0.4337

Table 5D: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control – Female Rats

Organ Name	Tumor Name	0 mkd Vehicle Control N=65	0.2 mkd LD N=65	0.4 mkd MD N=65	0.8 mkd MHD N=65	1.6 mkd HD N=65	P-value				
							Dos Response	C2 vs. LD	C2 vs. MD	C2 vs. MHD	C2 vs. HD
adrenal glands	ADENOMA, CORTICAL	0	1	1	1	1	0.2565	0.4767	0.4706	0.4643	0.4444
	PHEOCHROMOCYTOMA	3	0	2	1	0	0.8958	0.8613	0.4554	0.6360	0.8337
bone marrow, fe	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1800	.	.	.	0.4444
bone marrow, st	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1800	.	.	.	0.4444
brain	ASTROCYTOMA	0	2	0	0	1	0.4006	0.2244	.	.	0.4444
	CARC NOMA, PARS DIST	2	2	0	1	0	0.8882	0.6471	0.7168	0.4376	0.6883
	RETICULOSIS	1	0	0	0	0	0.7750	0.4767	0.4706	0.4578	0.4444
cavity, abdomin	FIBROSARCOMA	0	1	0	0	0	0.5700	0.4767	.	.	.
	MESOTHELIOMA	0	0	0	0	1	0.1800	.	.	.	0.4444
cavity, thoraci	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1800	.	.	.	0.4444
clitoral glands	CARC NOMA, SQUAMOUS	1	1	0	0	0	0.8575	0.7291	0.4706	0.4578	0.4444
galt	LYMPHOMA	0	1	0	0	0	0.5700	0.4767	.	.	.
injection site,	FIBROMA	1	0	0	0	0	0.7750	0.4767	0.4706	0.4578	0.4444
	LYMPHOMA	1	0	0	0	0	0.7711	0.4713	0.4651	0.4524	0.4390
liver	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1800	.	.	.	0.4444
lung	ADENOCARCINOMA	0	0	0	1	1	0.1012	.	.	0.4643	0.4444
	LYMPHOMA	0	0	0	0	1	0.1800	.	.	.	0.4444
	PHEOCHROMOCYTOMA	0	0	0	1	0	0.3731	.	.	0.4643	.
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1800	.	.	.	0.4444
lymph node, ili	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1800	.	.	.	0.4444
lymph node, man	LYMPHOMA	0	0	0	0	1	0.1800	.	.	.	0.4444
lymph node, mes	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1800	.	.	.	0.4444
lymph node, tra	LYMPHOMA	0	0	0	0	1	0.1800	.	.	.	0.4444
mammary gland	ADENOCARCINOMA	22	18	17	21	21	0.3056	0.6123	0.5968	0.4485	0.5224
	ADENOMA	0	1	1	1	1	0.2565	0.4767	0.4706	0.4643	0.4444
	FIBROADENOMA	28	10	13	19	20	0.2881	0.9978	0.9891	0.8718	0.6882
multicentric ne	LYMPHOMA	1	1	0	0	2	0.1737	0.7233	0.4651	0.4524	0.4079
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1800	.	.	.	0.4444
ovaries	SEX-CORD/STROMAL TUM	0	2	1	2	1	0.3343	0.2244	0.4706	0.2126	0.4444
pancreas	ADENOMA, AC NAR CELL	0	0	1	0	0	0.3700	.	0.4706	.	.

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Organ Name	Tumor Name	0 mkd Vehicle Control N=65	0.2 mkd LD N=65	0.4 mkd MD N=65	0.8 mkd MHD N=65	1.6 mkd HD N=65	P-value				
							Dos Response	C2 vs. LD	C2 vs. MD	C2 vs. MHD	C2 vs. HD
parathyroid gla	ADENOMA, ISLET CELL	2	0	0	0	0	0.9503	0.7291	0.7227	0.7091	0.6944
	CARC NOMA, ISLET CEL	2	1	0	0	0	0.9583	0.4647	0.7227	0.7091	0.6944
pituitary gland	ADENOMA	0	1	0	0	0	0.5700	0.4767	.	.	.
skin	ADENOMA, PARS DISTAL	49	56	56	57	46	0.8617	0.3275	0.3275	0.1621	0.6848
	CARC NOMA, PARS DIST	2	1	0	1	0	0.8368	0.4564	0.7168	0.4376	0.6883
skin, subcutis	KERATOACANTHOMA	0	0	0	0	1	0.1841	.	.	.	0.4512
	LYMPHOMA	1	0	0	0	1	0.3618	0.4713	0.4651	0.4524	0.6883
spleen	FIBROSARCOMA	1	0	0	0	0	0.7711	0.4713	0.4651	0.4524	0.4390
	HEMANGIOPERICYTOMA	0	0	0	1	0	0.3731	.	.	0.4643	.
	SCHWANNOMA	0	0	0	1	0	0.3731	.	.	0.4643	.
thyroid gland	HEMANGIOSARCOMA	0	0	0	0	1	0.1800	.	.	.	0.4444
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1800	.	.	.	0.4444
	ADENOMA, C-CELL	7	4	4	4	1	0.9532	0.6542	0.6542	0.6208	0.9346
uterus with cer	ADENOMA, FOLLICULAR	0	0	3	0	0	0.5932	.	0.1042	.	.
	CARC NOMA, C-CELL	1	0	0	0	0	0.7750	0.4767	0.4706	0.4578	0.4444
	CARC NOMA, FOLLICULA	0	0	0	1	0	0.3731	.	.	0.4643	.
	GRANULAR CELL TUMOR	0	0	2	1	1	0.2216	.	0.2185	0.4643	0.4444
	LEIOMYOMA	0	0	0	0	1	0.1800	.	.	.	0.4444
Vagina	POLYP, STROMAL	3	3	5	4	2	0.5495	0.5943	0.3078	0.4094	0.3742
	SARCOMA, HISTIOCYTIC	0	0	0	0	1	0.1800	.	.	.	0.4444
	SARCOMA, STROMAL	0	1	0	0	1	0.2469	0.4767	.	.	0.4444
	GRANULAR CELL TUMOR	0	0	0	3	1	0.0852	.	.	0.0959	0.4444
	SARCOMA, STROMAL	0	1	0	0	0	0.5700	0.4767	.	.	.

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Saline Control – Male Mice

Organ Name	Tumor Name	0 mg/kg/day Saline C N=25	0.375 mg/kg/day LD N=25	0.75 mg/kg/day MD N=25	1.5 mg/kg/day HD N=25	P-Value			
						Dos Response	C1 vs. LD	C1 vs. MD	C1 vs. HD
harderian gland	adenoma	0	1	0	2	0.1069	0.5000	.	0.2447
	carcinoma	0	1	0	0	0.5000	0.5000	.	.
liver	adenoma	1	0	0	0	0.7500	0.5000	0.5000	0.5000
lungs with bron	alveolar-bronchiolar	1	0	0	0	0.7500	0.5000	0.5000	0.5000
muscle		2	1	3	2	0.4002	0.5000	0.5000	0.6957
	hemangiosarcoma	0	0	1	0	0.5000	.	0.5000	.
salivary glands	lymphangioma	1	0	0	1	0.5000	0.5000	0.5000	0.7553
skin	papilloma	0	0	0	1	0.2500	.	.	0.5000
skin - soi (wit	papilloma	0	0	1	0	0.5000	.	0.5000	.
spleen	hemangiosarcoma	1	2	1	2	0.3784	0.5000	0.7553	0.5000
stomach	squamous cell carcin	0	1	0	0	0.5000	0.5000	.	.

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control – Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle C N=25	0.375 mg/kg/day LD N=25	0.75 mg/kg/day MD N=25	1.5 mg/kg/day HD N=25	P-Value			
						Dos Response	C2 vs. LD	C2 vs. MD	C2 vs. HD
harderian	adenoma	0	1	0	2	0.1036	0.4898	.	0.2347

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Organ Name	Tumor Name	0 mg/kg/day Vehicle C N=25	0.375 mg/kg/day LD N=25	0.75 mg/kg/day MD N=25	1.5 mg/kg/day HD N=25	P-Value			
						Dos Response	C2 vs. LD	C2 vs. MD	C2 vs. HD
gland	carcinoma	1	1	0	0	0.8067	0.7449	0.4898	0.4898
lungs with bron	alveolar-bronchiolar	1	1	3	2	0.2444	0.7449	0.2890	0.4844
muscle	hemangiosarcoma	0	0	1	0	0.4948	.	0.4898	.
salivary glands	lymphangioma	0	0	0	1	0.2474	.	.	0.4898
skin	papilloma	0	0	0	1	0.2474	.	.	0.4898
skin - soi (wit	papilloma	0	0	1	0	0.4948	.	0.4898	.
spleen	hemangiosarcoma	2	2	1	2	0.4731	0.6798	0.4844	0.6798
stomach	squamous cell carcin	0	1	0	0	0.4948	0.4898	.	.

Table 6C: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Saline Control – Female Mice

Organ Name	Tumor Name	0 mg/kg/day Saline C N=25	0.3 mg/kg/day LD N=25	1.0 mg/kg/day MD N=25	3.0 mg/kg/day HD N=25	P-Value Dos Response	P-Value		
							C1 vs. LD	C1 vs. MD	C1 vs. HD
Forelimb	hemangiosarcoma	0	1	0	0	0.5000	0.5102	.	.
harderian gland	adenoma	0	1	1	0	0.4948	0.5102	0.5102	.
	carcinoma	0	1	2	0	0.5889	0.5102	0.2551	.
Liver	adenoma	2	0	0	0	0.9419	0.7653	0.7653	0.7553
lungs with bron	alveolar-bronchiolar	0	1	0	0	0.5000	0.5102	.	.
			3	1	4	0.0634	0.1248	0.5102	0.0597
Spleen	hemangiosarcoma	1	4	2	0	0.9263	0.1871	0.5156	0.5000
Thymus	thymoma	0	0	0	1	0.2449	.	.	0.5000
uterus	hemangiosarcoma	0	0	2	0	0.4317	.	0.2551	.

Table 6D: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control – Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle C N=25	0.3 mg/kg/day LD N=25	1.0 mg/kg/day MD N=25	3.0 mg/kg/day HD N=25	P-Value Dos Response	P-Value		
							C2 vs. LD	C2 vs. MD	C2 vs. HD
forelimb	hemangiosarcoma	0	1	0	0	0.4949	0.5000	.	.
harderian gland	adenoma	1	1	1	0	0.7276	0.7551	0.7551	0.4898
	carcinoma	0	1	2	0	0.5842	0.5000	0.2449	.
liver	adenoma	1	0	0	0	0.7475	0.5000	0.5000	0.4898
lungs with bron	alveolar-bronchiolar	0	1	0	0	0.4949	0.5000	.	.
			3	1	4	0.1185	0.3046	0.7551	0.1743
Spleen	hemangiosarcoma	1	4	2	0	0.9227	0.1743	0.5000	0.4898
Thymus	thymoma	1	0	0	1	0.4280	0.5000	0.5000	0.7449
Uterus	hemangiosarcoma	0	0	2	0	0.4280	.	0.2449	.

Table 7A: Tumor Rates and P-Values for Comparisons between Controls and PC– Male Mice

Organ Name	Tumor Name	0 mg/kg/day Saline C (N=25)	0 mg/kg/day Vehicle C (N=25)	1000 mg/kg of Urethane PC (N=10)	P-Value Saline C vs. PC	P-Value Vehicle C vs. PC	P-Value Saline Vs. Vehicle
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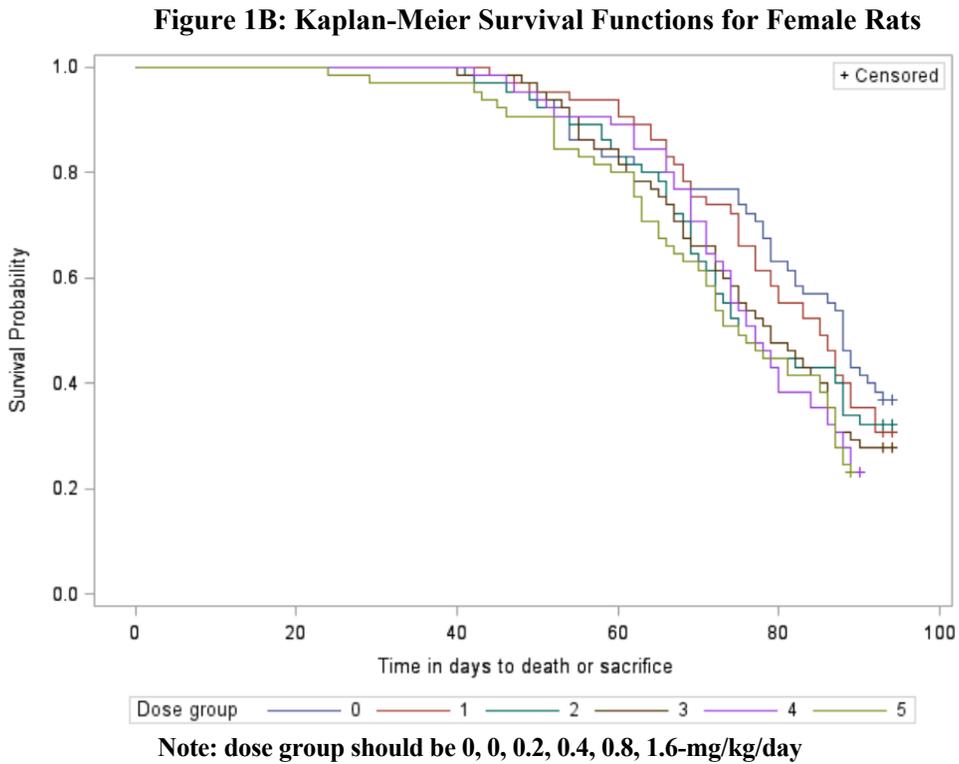
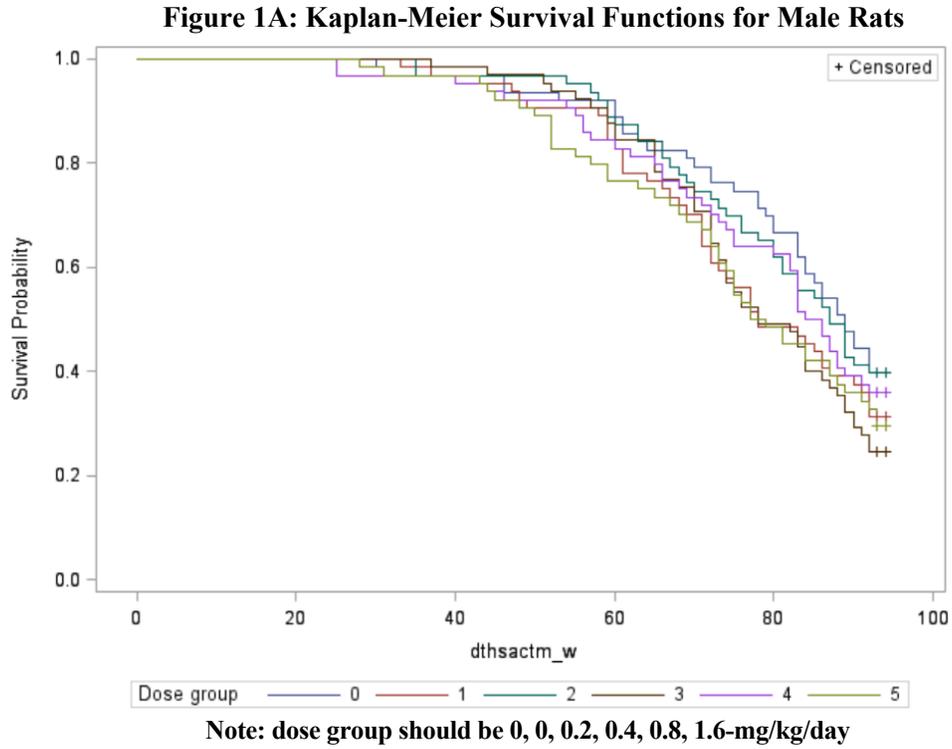
Organ Name	Tumor Name	0 mg/kg/day Saline C (N=25)	0 mg/kg/day Vehicle C (N=25)	1000 mg/kg of Urethane PC (N=10)	P-Value Saline C vs. PC	P-Value Vehicle C vs. PC	P-Value Saline Vs. Vehicle
harderian gland	Adenoma	0	0	0	.	.	.
	Carcinoma	0	1	0	.	0.0385	0.5102
liver	Adenoma	1	0	0	0.0400	.	0.5102
	alveolar-bronchiolar carcinoma	1	0	0	0.0400	.	0.5102
lungs with bron	alveolar-bronchiolar adenoma	2	1	10	<0.001*	<0.001*	0.5102
	hemangiosarcoma	0	0	0	.	.	.
muscle	hemangiosarcoma	0	0	0	.	.	.
salivary glands	Lymphangioma	1	0	0	0.0400	.	0.5102
skin	Papilloma	0	0	0	.	.	.
skin - soi (wit	Papilloma	0	0	0	.	.	.
spleen	hemangiosarcoma	1	2	9	<0.001*	<0.001*	0.5102

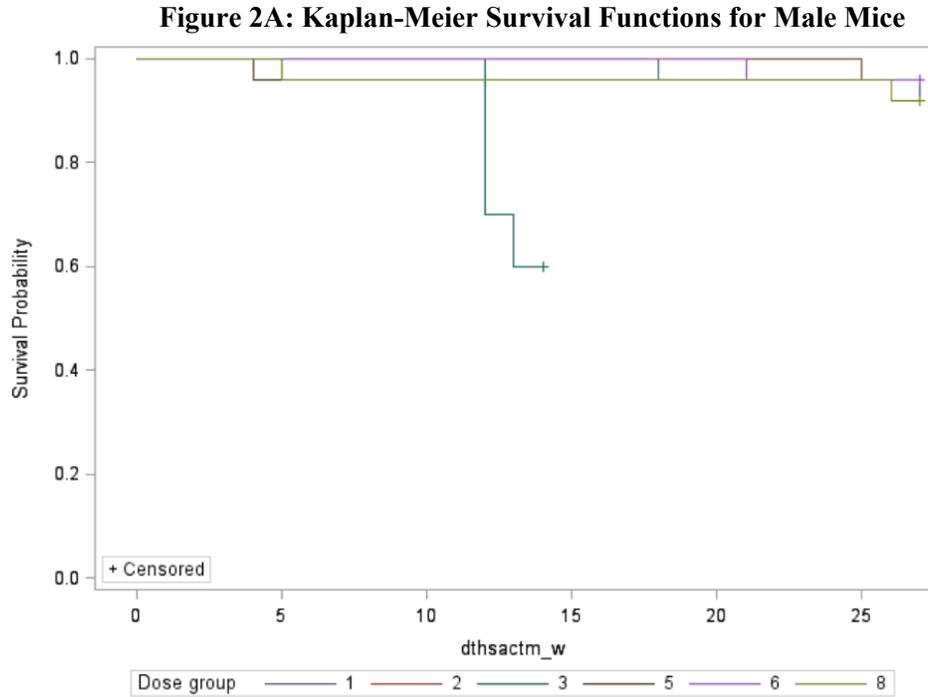
*Indicted the significant at 0.001 alpha levels. PC=1000 mg/kg of Urethane.

Table 7B: Tumor Rates and P-Values for Comparisons between Combined VC and PC– Female Mice

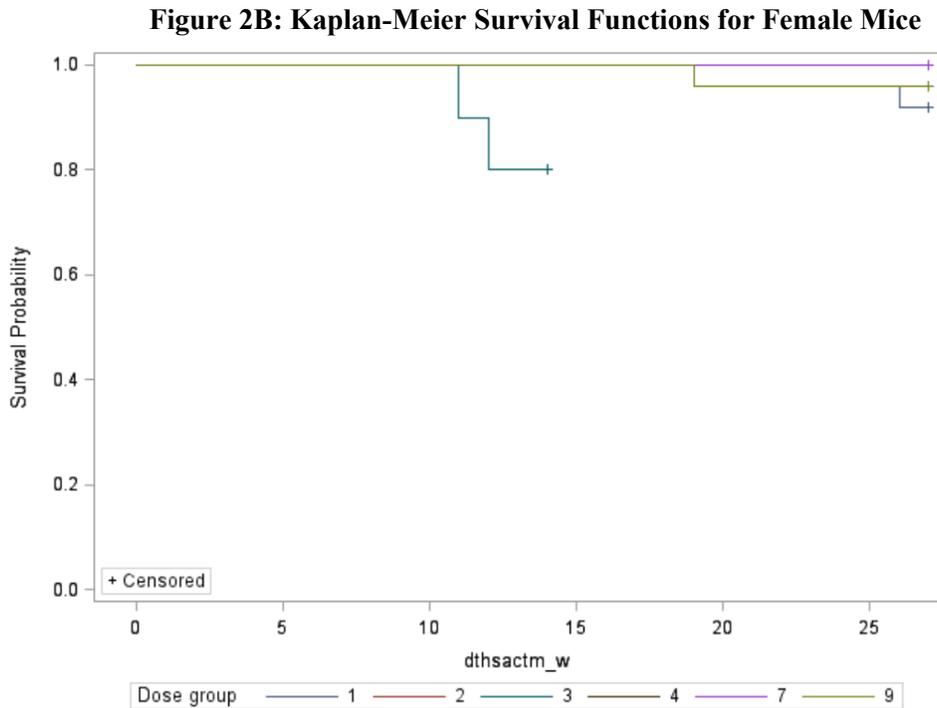
Organ Name	Tumor Name	0 mg/kg/day Saline C (N=25)	0 mg/kg/day Vehicle C (N=25)	1000 mg/kg of Urethane PC (N=10)	P-Value Saline C vs. PC	P-Value Vehicle C vs. PC	P-Value Saline vs. Vehicle
harderian gland	adenoma	0	1	0	.	0.0385	.
	carcinoma	0	0	0	.	.	0.5102
liver	adenoma	2	1	0	0.0800	0.0385	0.5102
	alveolar-bronchiolar carcinoma	0	0	4	0.0400	<0.001*	.
lungs with bron	alveolar-bronchiolar adenoma	0	1	10	<0.001*	<0.001*	0.5102
	hemangiosarcoma	0	0	1	0.0769	0.0741	.
spleen	hemangiosarcoma	1	1	9	<0.001*	<0.001*	0.2551
thymus	thymoma	0	1	0	.	0.0385	0.5102
uterus	hemangiosarcoma	0	0	0	.	.	.

*Indicted the significant at 0.001 alpha levels. PC=1000 mg/kg of Urethane.





Note: dose group should be 0, 0, 0.375, 0.75, or 1.5-mg/kg/day and 3=1000 mg/kg of Urethane, positive control



Note: dose group should be 0, 0, 0.3, 1.0, or 3.0-mg/kg/day and 3=1000 mg/kg of Urethane, positive control

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