

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211996Orig1s000 212161Orig1s000

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 212-161

Drug Name: Tafamidis capsules (61 mg)

Indication(s): To reduce (b) (4) cardiovascular-related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM)

Applicant: Pfizer

Date(s): Submission Date: November 2, 2018
PDUFA Date: July 2, 2018

Review Priority: Priority

Biometrics Division: Division of Biometrics I, HFD-710

Statistical Reviewer: Jialu Zhang, Ph.D.

Concurring Reviewers: James H. M. Hung, Ph.D.

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Keywords:

Link to keywords:

http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

Reference is made to NDA 212161 submitted simultaneously with NDA 211996 on November 2, 2018. Study B3461028 in NDA 211996 showed that tafamidis meglumine 20 mg and 80 mg had statistically significant treatment effect compared with placebo.

NDA 212161 included a new formulation of tafamidis, 61mg mg soft gelatin capsules using the free acid form of the drug substance. The proposed indication was the same as in NDA 211996, which was to reduce the combination of [REDACTED]^{(b) (4)} cardiovascular-related hospitalization in the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) due to wild-type or variant TTR. This NDA did not contain any new efficacy data. Please refer to the statistical review for NDA 211996 for efficacy information.

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/s/

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04/08/2019 02:31:49 PM

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04/08/2019 02:58:35 PM



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: NDA 211-996

Drug Name: VYNDAQEL (tafamidis meglumine)

Indication(s): To reduce (b) (4) cardiovascular-related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM)

Applicant: Pfizer

Date(s): Submission Date: November 2, 2018
PDUFA Date: July 2, 2018

Review Priority: Priority

Biometrics Division: Division of Biometrics I, HFD-710

Statistical Reviewer: Jialu Zhang, Ph.D.

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1 EXECUTIVE SUMMARY

In this submission, the sponsor seeks the approval for tafamidis in reduction of (b) (4) cardiovascular-related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM). The development program included a single phase 3, multicenter, three-arm, placebo-controlled, randomized study B3461028 to determine efficacy, safety and tolerability of tafamidis.

The study B3461028 randomized 441 subjects in a ratio of 2:1:2 to placebo, tafamidis 20 mg and tafamidis 80 mg. Randomization were stratified by NYHA classification (Class I or II, versus Class III) and TTR genotype (wild-type and variant).

The primary efficacy endpoint for this study was a hierarchical combination of all-cause mortality and frequency of cardiovascular-related hospitalizations over the duration of the trial. The proposed primary analysis, Finkelstein-Schoenfeld (FS) analysis, is a score test based on the sum of scores for the treatment group. The FS analysis of all-cause mortality and frequency of cardiovascular-related hospitalizations showed a statistically significant favorable treatment effect in tafamidis group ($p < 0.001$).

Analyses on individual components of the primary endpoint (all-cause mortality, and CV hospitalization) also showed significant treatment benefits. The estimate of hazard ratio on all-cause mortality from Cox-proportional hazard model was 0.70 (95% CI 0.51, 0.96), which showed a 30% risk reduction in pooled tafamidis group compared to placebo. The estimated relative risk ratio for CV hospitalization between pooled tafamidis and placebo groups was 0.68 (95% CI 0.59, 0.81) based on Poisson regression model, indicating that the estimated frequency of cardiovascular (CV) hospitalization based on Poisson model in pooled tafamidis group was 32% less than placebo group.

Tafamidis demonstrated significant treatment effect in 6-Minute Walk Test (6MWT) and in the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score. Pooled tafamidis group showed a least-square (LS) mean difference of 75.7 meters in the change from baseline in 6-Minute Walk Distance (6MWD) and a LS mean difference of 13.7 in the change from baseline in KCCQ-OS score when compared with placebo.

The treatment effect appeared to be relatively constant across different subgroups. The dose of 80 mg and 20 mg tafamidis appeared to be equally effective based on the primary and key secondary analyses in Study B3461028.

Missing data was a main concern during the discussions on study design. To address the concern of informative censoring, the sponsor proposed sensitivity analyses using multiple imputations and pattern mixture model. The sensitivity analyses on the primary and key secondary endpoints showed consistent results as the main analyses.

Tafamidis demonstrated statistically significant treatment effect in subjects with either transthyretin genetic variants or wild-type transthyretin resulting in amyloid cardiomyopathy.

INTRODUCTION

1.1 Overview

This development program included a single Phase 3, multicenter, three-arm, placebo-controlled, randomized study with a 30-month double-blind treatment phase, to determine efficacy, safety and tolerability of tafamidis on clinical outcomes in subjects with either transthyretin genetic variants or wild-type transthyretin resulting in amyloid cardiomyopathy (TTR-CM).

Table 1: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
B3461028	Phase 3	30 months	4-week safety follow up if subject did not enroll into extension study	88 for tafamidis 20 mg 176 for tafamidis 80 mg 177 for placebo	Subjects Diagnosed With Transthyretin Cardiomyopathy (TTR-CM)

Tafamidis or placebo was administered once daily, in addition to standard of care, for 30 months in subjects diagnosed with variant or wild-type TTR-CM. For any subject who discontinued prior to 30 months, the subject's vital status and whether the subject had a heart and/or liver transplant or implantation of a cardiac mechanical assist device were determined by Month 30 follow-up contact.

Upon completion of the study at the Month 30 visit, subjects were eligible for treatment with tafamidis in a separate extension study (B3461045).

1.2 Data Sources

The sponsor's electronic data were submitted on September 20, 2018 and in the directory <\\CDSESUB1\evsprod\NDA211996\0002\m5\datasets\b3461028>.

Additional datasets were submitted on November 14, 2018 in response to the Division's request. The data can be found under directory <\\CDSESUB1\evsprod\NDA211996\0006\m5\datasets\b3461028\analysis\legacy\datasets>.

2 STATISTICAL EVALUATION

2.1 Data and Analysis Quality

The reviewer was able to reproduce all the key results in the primary and secondary analyses in Study B3461028. The reviewer was able to trace how the endpoint was derived from the original data source.

The reviewer performed Finkelstein-Schoenfeld (FS) analysis by excluding individual centers. This was done by re-generating all the pairwise ranking score for the remaining subjects. No single site had significant impact on the overall primary efficacy results in Study B3461028.

2.2 Evaluation of Efficacy

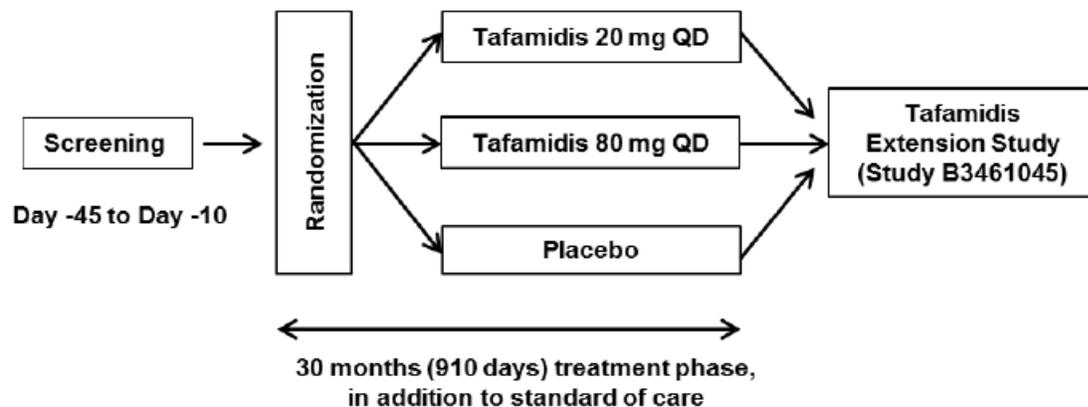
2.2.1 Study B3461028

2.2.1.1 Study Design and Endpoints

This is a Phase 3, multicenter, three-arm, placebo-controlled, randomized study with a 30-month double-blind treatment phase, to determine efficacy, safety and tolerability of tafamidis on clinical outcomes in subjects with either variant or wild-type TTR-CM.

441 subjects were randomized in a ratio of 2:1:2 to placebo, tafamidis 20 mg and tafamidis 80 mg. Randomization was also stratified based on NYHA classification (Class I or II, versus Class III) and TTR genotype (wild-type and variant). Subjects were to be treated for 30 months (defined as 910 days in this study). Subjects who discontinued prior to 30 months, sponsor performed follow-up contact to determine the subjects' vital status. Figure 1 is the study design diagram. Subjects were eligible for the extension study B3461045 upon completion of the study. In the extension study, subjects in tafamidis groups continued on their assigned dose and subjects in placebo group were randomized to either tafamidis 80 mg or 20 mg.

Figure 1: Study Diagram



[Source: Figure 1 in the sponsor's CSR]

The primary efficacy endpoint for this study was a hierarchical combination of all-cause mortality and frequency of cardiovascular-related hospitalizations over the duration of the trial.

The key secondary endpoints were

- Change from Baseline to Month 30 in 6MWD
- Change from Baseline to Month 30 in the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS)

Other secondary endpoints include

- Cardiovascular-related mortality
- Frequency of cardiovascular-related hospitalization
- All-cause mortality
- TTR stabilization at Month 1

2.2.1.2 Statistical Methodologies

Finkelstein-Schoenfeld analysis

The proposed primary analysis, Finkelstein-Schoenfeld (FS) analysis, is a score test based on the sum of scores for the treatment group. The method combined all-cause mortality and CV hospitalization frequency. The test score was computed using a pairwise ranking procedure. The test statistic was based on the sum of these scores and was stratified by TTR genotype (variant and wild-type) and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III).

Within each stratum, each subject was compared to every other subject in a pair-wise manner. The pair-wise comparison assigned a +1 to the “better” subject and a -1 to the “worse” subject. All-cause mortality was given higher priority in the calculation and only when two given subjects tied on all-cause mortality then CV hospitalization frequency would be used in the comparison. Comparisons of cardiovascular related hospitalization frequency for subjects who completed all 30 months study duration were based on the earlier of the two actual study durations. Subjects, who discontinued for transplantation or for implantation of a cardiac mechanical assist device, were handled in the primary analysis in the same manner as death.

- If both subjects were dead, then the subject with a longer survival time was assigned +1.
- If one subject was alive and the other was not, the live subject received a +1 and the deceased one a -1.
- If both subjects were alive, the comparison used cardiovascular-related hospitalization to assign scores. The subject with the fewer cardiovascular related hospitalization (frequency) received a +1 while the other received -1.
- In the case where one subject was censored before a second subject died, and where the vital status of the first subject at Month 30 was missing, the frequency of cardiovascular-related hospitalizations at the shorter of their follow-up times was used to assign +1 or -1.

The proposed test is a score test based on the sum of the scores for the treated group. The test statistic can be written as

$$T = \sum_k \sum_{i \in A_k} D_i U_i$$

A_k is the set of the subjects in the k th strata and U_i is the score calculated within each stratum. $D_i=1$ for subjects in tafamidis group and $D_i=0$ for subjects in placebo group. $K=1,2,3,4$ for four strata. The variance is written as

$$V = \sum_k \frac{m_k(n_k - m_k)}{n_k(n_k - 1)} \left(\sum_{i \in A_k} U_i^2 \right)$$

m_k is the total number of tafamidis subjects in the k th stratum. N_k is the total number of subjects in the k th stratum.

The hypothesis was tested by comparing T/\sqrt{V} to a normal distribution.

Multiple Imputations

To address the concern of informative censoring, the sponsor proposed to perform a multiple imputation analysis using Rubin’s method for missing cardiovascular-related hospitalization data.

The study duration of 30 months was partitioned into 3 intervals of 10 months each (so-called period 1, period 2 and period 3). Within each short time interval (10 months), a Poisson regression model with a constant rate was assumed for hospitalization counts and was fitted

separately for placebo and treatment group. The model was based on subjects who have data in that period.

The probability function is $f(y) = \frac{\lambda^y e^{-\lambda}}{y!}$, where $y = 0, 1, 2, \dots$

A generalized linear model with log link function is written as

$$\log(\lambda) = b_0 + b_1 \text{NYHAclass} + b_2 \text{TTRgenotype} \text{ (this is for period 1)}$$

b_0, b_1, b_2 and its variance-covariance matrix can be computed from the maximum likelihood estimates. Once b_0, b_1, b_2 et al were estimated, coefficients $\widehat{b}_0, \widehat{b}_1, \widehat{b}_2$ can be randomly generated from a multivariate normal distribution based on b_0, b_1, b_2 MLE and variance-covariance matrix computed from the above generalized linear model. λ was calculated by $\lambda = \exp(b_0 + b_1 \text{NYHAclass} + b_2 \text{TTRgenotype})$. 1000 λ were generated using 1000 coefficients $\widehat{b}_0, \widehat{b}_1$ and \widehat{b}_2 . A random hospitalization count was generated for each λ . For subjects with partial data during the interval, the actual observed frequency was added to the hospitalization frequency imputed for the portion of the interval the subject did not participate.

Missing data were imputed in a similar way in Period 2 and Period 3 except that Period 2 also included the hospitalization count from Period 1 as follows

$$\log(\lambda) = b_0 + b_1 \text{NYHAclass} + b_2 \text{TTRgenotype} + b_3 \text{hospCountPeriod1}$$

Period 3 included the hospitalization count from both Period 1 and Period 2.

1000 independent sets of the Poisson model parameter were generated for each subject in each interval. The hospitalization counts were paired for all three intervals to generate 1000 complete 30-month data.

The null hypothesis was tested based on the 1000 imputed data sets by computing the components of the complete-data Finkelstein-Schoenfeld statistic. The results of 1000 imputed datasets were combined following Rubin's method (1987).

Pattern Mixture Analysis

To support the robustness of the conclusion on the two key secondary endpoints, the sponsor proposed sensitivity analyses using pattern-mixture model. The pattern-mixture analyses grouped the subjects based on missing-data patterns. Patterns were defined under the following two cases:

Case 1:

Pattern 1A – all subjects who have provided the key secondary endpoint data for month 30

Pattern 1B – all subjects who have not provided the key secondary endpoint data for month 30

Case 2:

Pattern 2A – all subjects who have the key secondary endpoint data for month 15 or beyond
Pattern 2B – all subjects who do not have key secondary endpoint data beyond month 15

The pattern mixture analysis used a MMRM that included center and subject within center as random effects, and treatment, visit, TTR genotype (variant and wild-type), pattern, visit by treatment interaction, and treatment by pattern interaction as fixed effects and baseline score as covariate with an unstructured covariance matrix.

Win Ratio and Confidence Interval

The win ratio method allocated all tafamidis and placebo pairs (tafamidis subject compared to a placebo subject) to the categories listed below in a hierarchical fashion and within each stratum. Categories (a) and (c) represent tafamidis wins based on all-cause mortality and frequency of CV-related hospitalization respectively. Similarly, categories (b) and (d) represent placebo wins based on all-cause mortality and frequency of CV-related hospitalization respectively. Category (e) represents ties, pairs where subjects were not able to be differentiated based on all-cause mortality and frequency of CV-related hospitalization.

- (a) Death on Placebo first
- (b) Death on Tafamidis first
- (c) More Cardiovascular-related Hospitalizations Frequency on Placebo
- (d) More Cardiovascular-related Hospitalizations Frequency on Tafamidis
- (e) Tied

The overall win ratio was calculated by adding (a)+(c) for all 4 strata and dividing it by the sum of (b)+(d) across all 4 strata.

The standard error of log (Win Ratio) can be calculated as

$SE(\text{Log Win Ratio}) = \log(\text{Win Ratio}) / Z \text{ score from FS method}$

The confidence interval can be computed as follows

$95\% \text{ CI for Win Ratio} = \exp(\log(\text{Win Ratio}) \pm 1.96 * SE(\text{Log Win Ratio}))$.

2.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A summary of patient disposition was summarized in Table 2. Placebo group had a higher discontinuation rate. Both the death rate and the rate of subjects unwilling to participate were higher in the placebo group.

Table 2: Patient Disposition

		tafamidis 20 mg	tafamidis 80 mg	Pooled tafamidis	Placebo
N		88	176	264	177
Completed (%)		60 (68)	113 (64)	173 (66)	85 (48)
Discontinued	Total (%)	28 (32)	63 (36)	91 (34)	92 (52)
	death (%)	14 (16)	25 (14)	39 (15)	38 (22)
	AE (%)	5 (6)	12 (7)	17 (6)	11 (6)
	subject no longer willing to participate (%)	8 (9)	17 (10)	25	37 (21)
	protocol violation	0	1	1	1
	loss to follow-up	0	1	1	0
	cardiac device implantation	0	2	2	0
	organ transplantation	1	3	4	4
	other	0	2	2	1

[Source: Reviewer's Table]

Table 3 provided a summary of patient demographics and some baseline characteristics. Overall, there were more male subjects than female subjects in the study. Majority of subjects were white. Over 60% subjects were from US. 24% subjects had variant TTR-CM. About one third (32%) subjects belonged to NYHA class III at baseline.

Table 3: Patient Demographic and Baseline Characteristics

		tafamidis 20 mg	tafamidis 80 mg	Pooled tafamidis	Placebo
N		88	176	264	177
Age	Mean (STD)	73.3 (7.1)	75.2 (7.2)	74.5 (7.2)	74.1 (6.7)
Gender	Male (%)	83 (94)	158 (90)	241 (91)	157 (89)
	Female (%)	5 (6)	18 (10)	23 (9)	20 (11)
Race	White (%)	75 (85)	136 (77)	211 (80)	146 (83)
	Black (%)	11 (13)	26 (15)	37 (14)	26 (15)
	Asian (%)	2 (2)	11 (6)	13 (5)	5 (3)
	Other (%)	0	3 (2)	3 (1)	0
Country	US (%)	63 (72)	108 (61)	171 (65)	108 (61)
	non US (%)	25 (28)	68 (39)	93 (35)	69 (39)
baseline NYHA class	Class I or II (%)	65 (74)	121 (69)	186 (70)	114 (64)
	Class III (%)	23 (26)	55 (31)	78 (30)	63 (36)
TTR Genotype	Wild (%)	67 (76)	134 (76)	201 (76)	134 (76)
	Variant (%)	21 (24)	42 (24)	63 (24)	43 (24)

[Source: Reviewer's Table]

2.2.1.4 Results and Conclusions

Primary Endpoint

The Finkelstein-Schoenfeld analysis of all-cause mortality and frequency of CV-related hospitalization showed a significant treatment effect in tafamidis group (Table 4). The reviewer performed additional FS analyses on combination of CV death and CV-related hospitalization, as well as combination of all-cause mortality and all-cause hospitalization, both analyses also showed significant and consistent treatment effect in tafamidis group (Table 4).

Table 4: Finkelstein-Schoenfeld Analysis of Composite Endpoints

	test statistic	p-value
all-cause death + cv hospitalization (primary endpoint)	3.44	0.0006
CV death + CV hospitalization	3.89	<0.001
all-cause death + all cause hospitalization	2.62	0.009

[Source: Reviewer's table]

Sensitivity analysis using multiple imputations was performed to handle the missing CV hospitalization data. 1000 imputed data sets were generated and analyzed using FS analysis. FS test statistics were combined by Rubin's method. The p-value from the sensitivity analysis was 0.008. Result from the sensitivity analysis was consistent with the primary analysis.

Table 5 provided a summary of mortality and hospitalization events for all subjects.

Table 5: Summary of Mortality and Hospitalization

	Tafamidis 20 mg (N=88)	Tafamidis 80 mg (N=176)	Pooled Tafamidis (N=264)	Placebo (N=177)
	n (%)	n (%)	n (%)	n (%)
All Subjects:				
Total Deaths ^a	23 (26.1)	49 (27.8)	72 (27.3)	72 (40.7)
CV-related	17 (19.3)	36 (20.5)	53 (20.1)	50 (28.2)
Indeterminate	1 (1.1)	4 (2.3)	5 (1.9)	9 (5.1)
Non-CV-related	5 (5.7)	9 (5.1)	14 (5.3)	13 (7.3)
Total Hospitalized ^b	65 (73.9)	125 (71.0)	190 (72.0)	136 (76.8)
CV-related	42 (47.7)	96 (54.5)	138 (52.3)	107 (60.5)
Indeterminate	1 (1.1)	2 (1.1)	3 (1.1)	0
Non-CV-related	44 (50.0)	81 (46.0)	125 (47.3)	80 (45.2)
Heart Transplants ^c	1 (1.1)	6 (3.4)	7 (2.7)	4 (2.3)
Cardiac Mechanical Assist Device Implantation	0	2 (1.1)	2 (0.8)	0

Note: A subject may be counted for each category of hospitalization that applies.

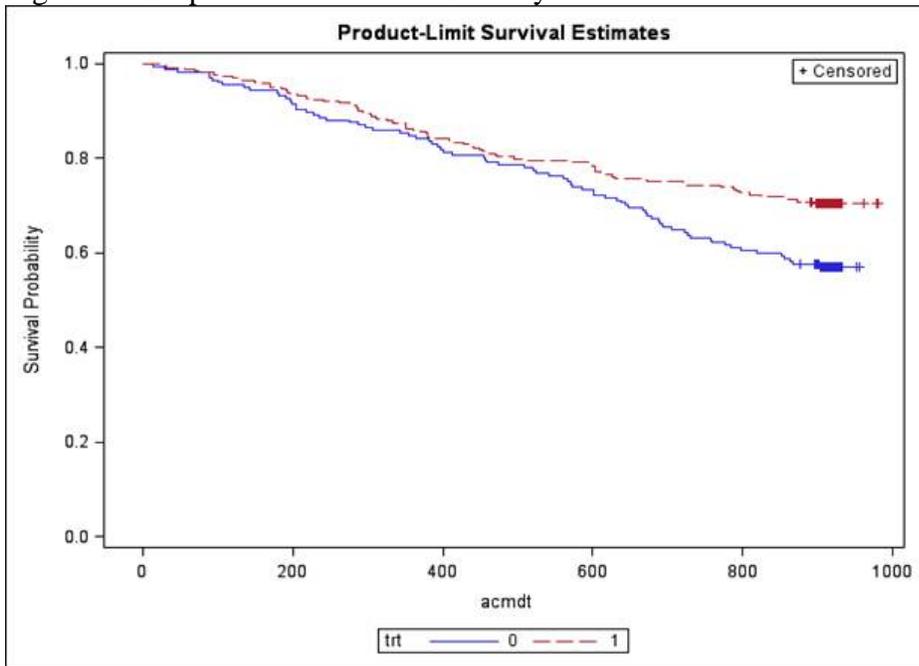
[Source: Sponsor's CSR Table 9, verified by the reviewer]

All-cause Mortality

In the primary analysis, heart transplants and cardiac mechanical assist device implantation were also considered as all-cause mortality events. Pooled tafamidis group and placebo group had 78

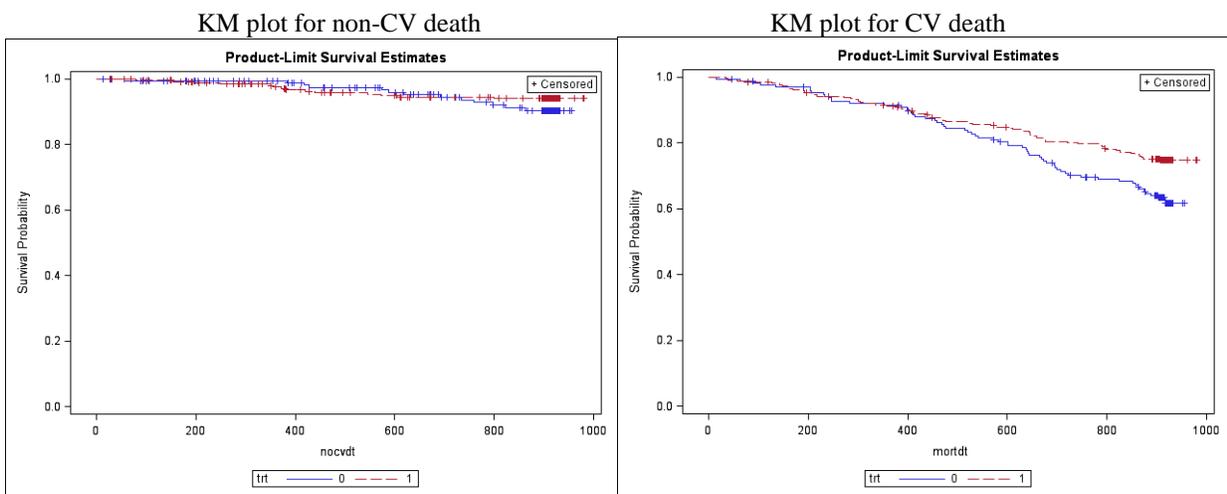
and 76 all-cause mortality events respectively. The estimated hazard ratio on all-cause mortality was 0.70 with 95% CI (0.51, 0.96) and a p-value of 0.0259, indicating a significant reduction in mortality risk in pooled tafamidis group. Kaplan Meier curve on all-cause mortality showed clear separation after 18 months of treatment (Figure 2). Further dissection on the mortality events into CV death and non-CV death showed that the treatment effect on mortality was driven by CV death (Figure 3).

Figure 2: KM plot for All-Cause Mortality



[Source: Reviewer’s figure]

Figure 3: KM Plots for Non-CV Death and CV Death



[Source: reviewer’s figure]

CV Hospitalization

The comparison of CV hospitalization in two treatment groups can be difficult to interpret in the presence of death events, especially when the drug has a substantial survival benefit. Death is a competing risk for CV hospitalization. The treatment group with fewer death events tends to have a larger number of CV hospitalization. Results would often be difficult to interpret when mortality and CV hospitalizations are not in the same direction. However, pooled tafamidis group showed treatment effect on both mortality and CV hospitalization in this study.

138 subjects in pooled tafamidis group and 107 subjects in placebo group had at least one CV-related hospitalization. The relative risk ratio in CV hospitalization estimated using Poisson Regression model was 0.676, indicating that the estimated frequency of CV hospitalization in pooled tafamidis group was 32% less than the placebo group (Table 6).

Pooled tafamidis group also had a much lower frequency of CV hospitalization per year than placebo group among those who were alive at Month 30. The mean frequency of CV hospitalization per year, on the other hand, appeared to be higher in pooled tafamidis group than in placebo. One possible explanation is that the result was driven by a few NYHA class III subjects in pooled tafamidis group. These subjects died within a few months after randomization. Their short durations in the study led to higher frequency of CV hospitalization in the estimation than the rest of the population and therefore drove up the overall mean frequency of CV hospitalization in tafamidis group.

Table 6: Analyses on CV hospitalization

	Pooled Tafamidis	Placebo
Total N	264	177
Total Number of Subjects with CV hospitalization	138	107
Average CV hospitalizations during 30 months (per year) among those alive at Month 30	0.297	0.455
Frequency of CV hospitalization per year		
Mean	0.999	0.884
Median	0.395	0.403
Mix, Max	0, 21.49	0, 7.23
Frequency of CV hospitalization per year based on Poisson regression analysis (95% CI)	0.475 (0.418, 0.540)	0.703 (0.617, 0.800)
Relative Risk Ratio based on Poisson regression analysis (95% CI)	0.676 (0.564, 0.811)	

[Source: reviewer's table]

6MWD

The change from baseline to Month 30 in 6MWD in pooled tafamidis arm was significantly better than the change from baseline to Month 30 in placebo arm (Table 7). The LS mean (SE) difference on the change from baseline between pooled tafamidis and placebo was 75.68 meters (95% CI 57.6, 93.8) and the difference was statistically significant (p <0.0001).

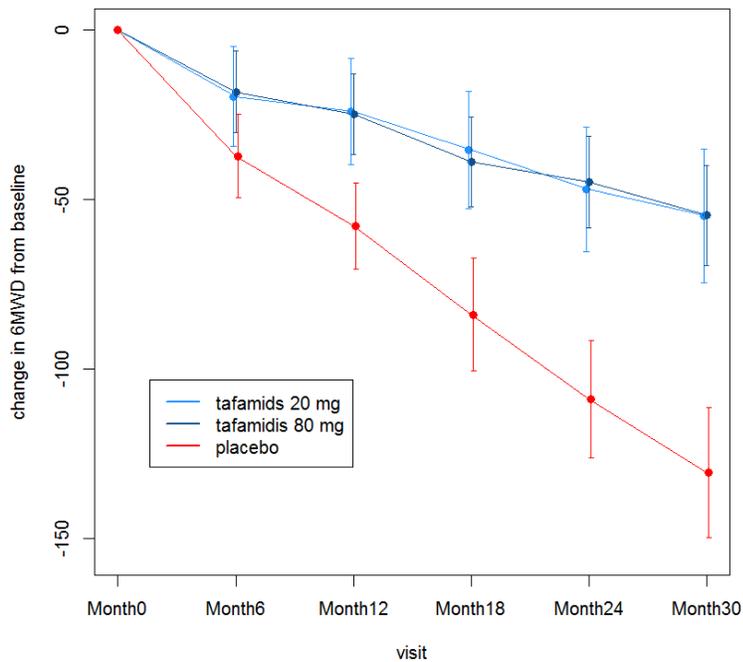
Table 7: Summary Statistics on 6MWD at Baseline and Month 30

		Pooled Tafamidis	Placebo
Baseline	N	264	177
	Mean	350.6	353.3
	STD	121	126
Month 30	N	155	70
	Mean	370.4	333.8
	STD	119	117
Treatment Difference in Change from Baseline	LS Mean	75.68	
	95% CI	(57.6, 93.8)	
	P-value	<0.0001	

[Source: Reviewer’s Table]

Figure 4 showed that the changes in 6MWD in pooled tafamidis group and placebo group had clear separation even at Month 6. The trend consistently continued to Month 30. In addition, tafamidis 20 mg group and 80 mg group showed very similar treatment effect in 6MWD.

Figure 4: LS Mean Change from Baseline in 6MWD

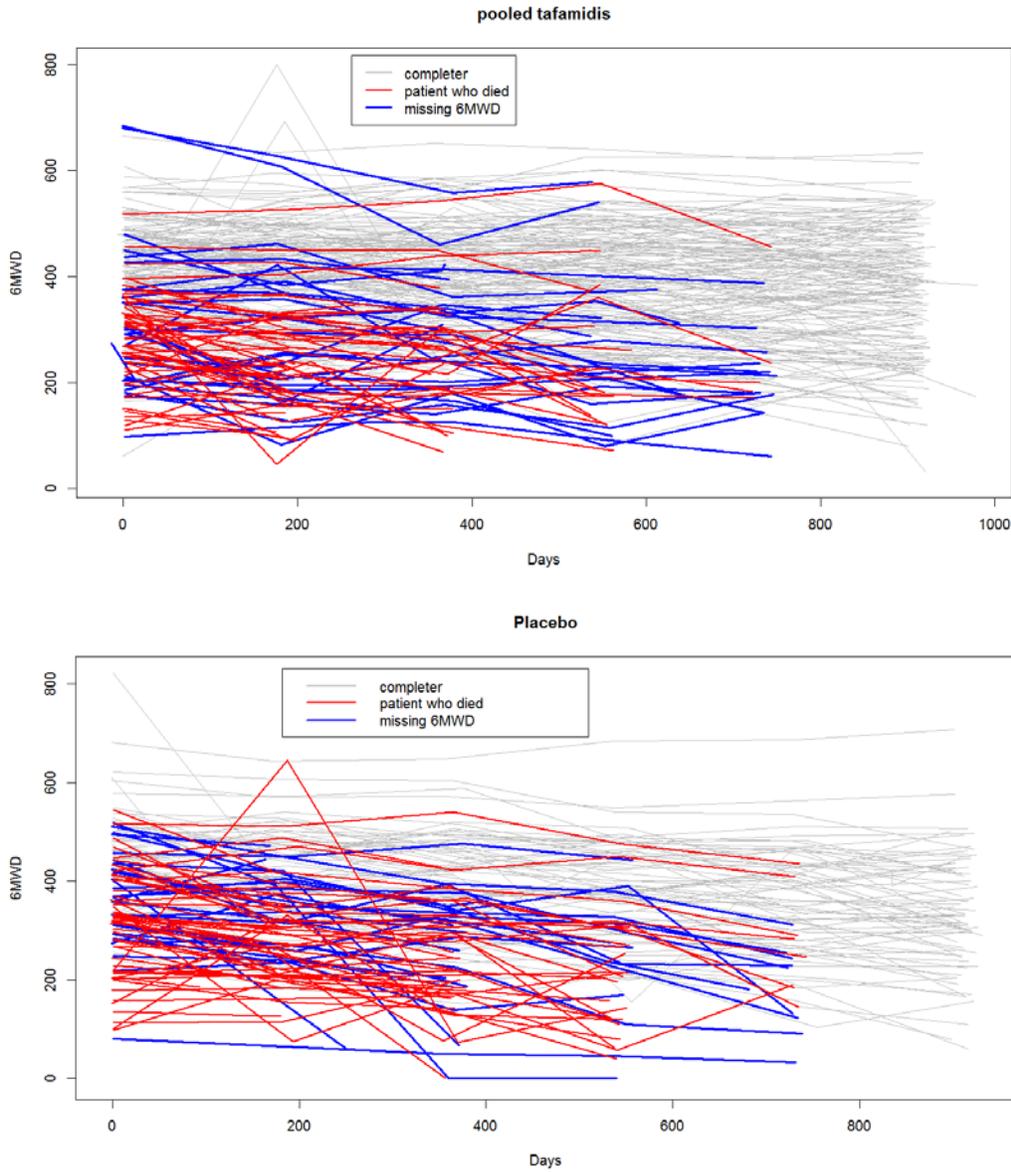


[Source: Reviewer’s figure]

Figure 5 is a spaghetti plot to show the missing pattern of 6MWD. More subjects who died and discontinued early appeared to have lower 6MWD in their last visit. This suggested that missing at random assumption may not be valid in this case. The sponsor proposed pattern mixture analysis to group the subjects based on missing-data pattern, which can be used to handle data not missing at random. Sensitivity analysis on 6MWD using pattern mixture model had a more

conservative estimate compared to the main analysis using MMRM (Table 8). However, the treatment effect on 6MWD was still very significant and conclusion remained the same.

Figure 5: 6MWD Missing Patterns



[Source: Reviewer’s figure]

Table 8: Comparison of Main Analysis and Sensitivity Analysis Results on 6MWD (ITT)

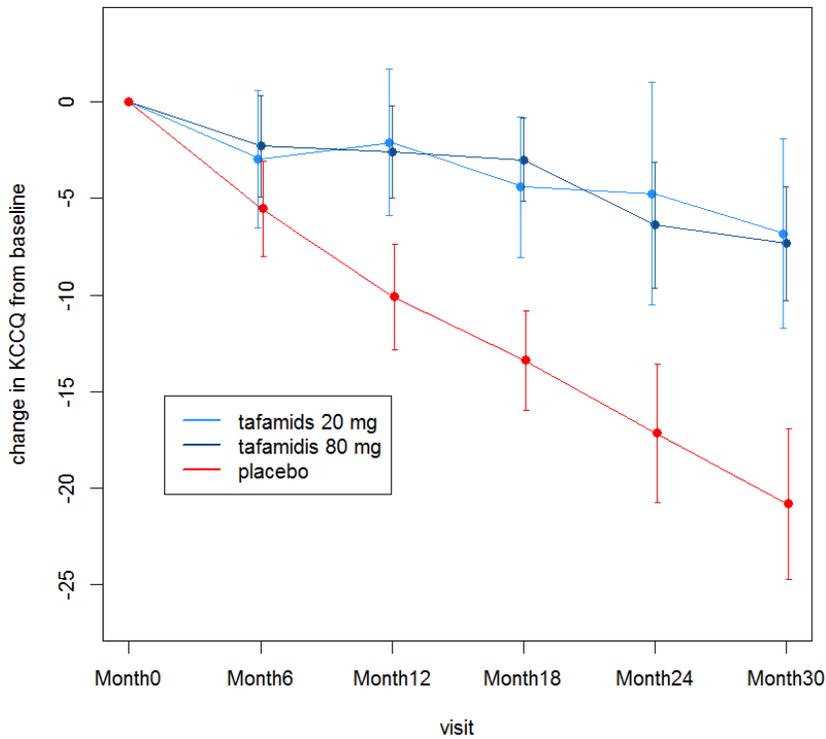
	LS means	95% CI
Main analysis	75.7	(57.6, 93.8)
Pattern mixture analysis	61.5	(44.4, 78.5)

[Source: Reviewer’s table]

KCCQ

Tafamidis 20 mg group and 80 mg group also showed very similar treatment effect on KCCQ-OS score (Figure 6). At Month 30, the difference in LS mean (SE) change from baseline between pooled tafamidis and placebo was 13.65 ($p < 0.0001$, Table 9).

Figure 6: LS Mean Change from Baseline in KCCQ



[Source: Reviewer's figure]

Table 9: Summary Statistics on KCCQ at Baseline and Month 30

		Pooled Tafamidis	Placebo
Baseline	N	264	177
	Mean	67.3	65.9
	STD	21.4	21.7
Month 30	N	170	84
	Mean	68.2	53.8
	STD	21.9	24.4
Treatment Difference in Change from Baseline	LS Mean	13.65	
	95% CI	(9.5, 17.8)	
	P-value	<0.0001	

[Source: Reviewer's table]

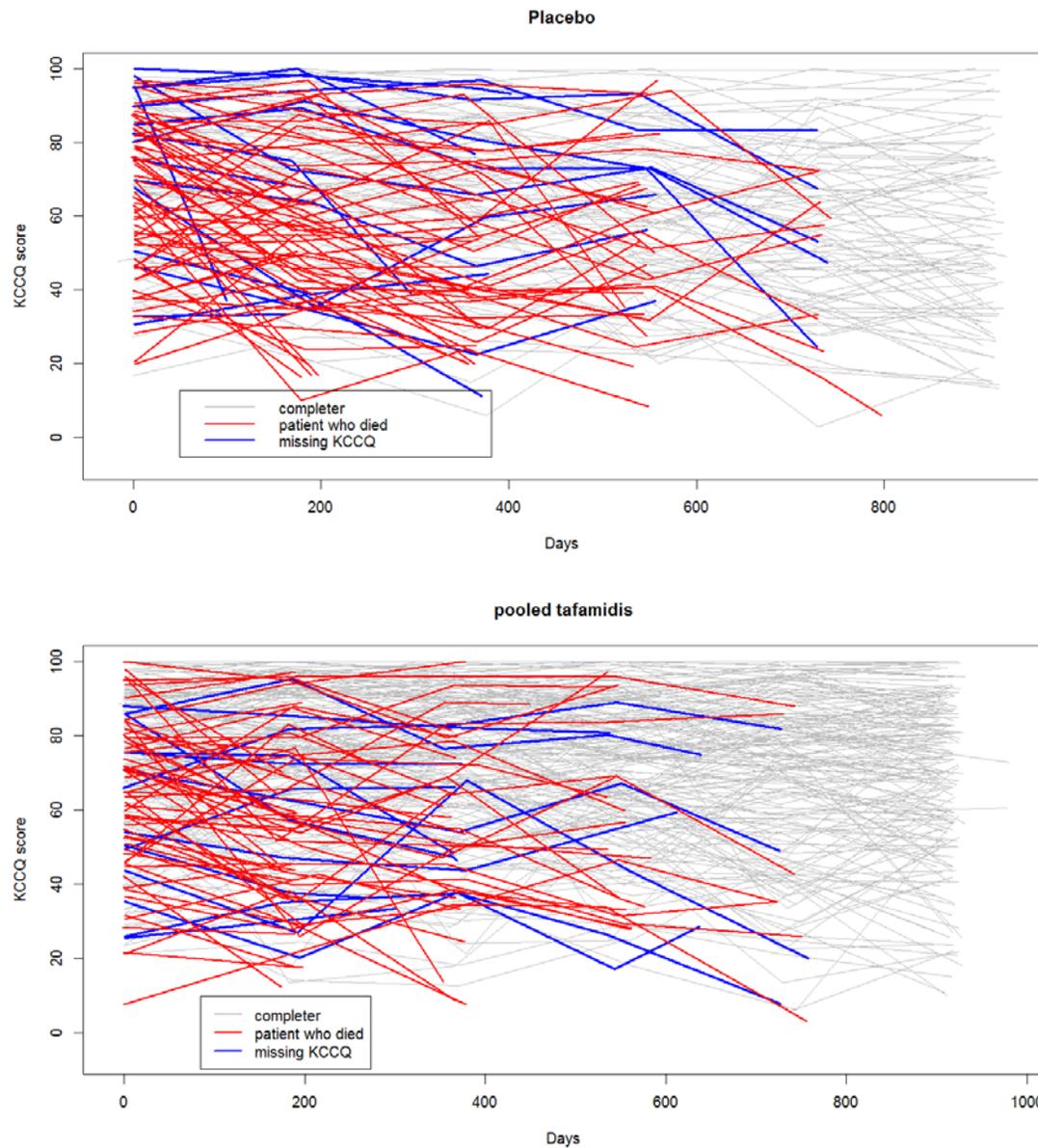
The spaghetti plot (Figure 7) showed KCCQ missing patterns. Same pattern mixture model was also used as sensitivity analysis for KCCQ. The results from the sensitivity analysis were consistent with the main analysis (Table 10).

Table 10: Comparison of Main Analysis and Sensitivity Analysis Results on KCCQ (ITT)

	LS means	95% CI
Main analysis	13.7	(9.5, 7.8)
Pattern mixture analysis	11.6	(7.5, 15.8)

[Source: Reviewer's table]

Figure 7: KCCQ Missing Patterns



[Source: Reviewer's figure]

Mortality in the Extension Study

B3461045 is the on-going extension study to B3461028. Eligible subjects were required to complete 30 months of blinded treatment in study B3461028 prior to enrollment. Subjects on active treatment in the parent study continued on their same dose; however, placebo subjects were randomized to either a 20 mg or 80 mg dose of tafamidis. Upon the cut-off date of February 15, 2018, there were additional 23 deaths occurred in the extension study B3461045 (Table 11).

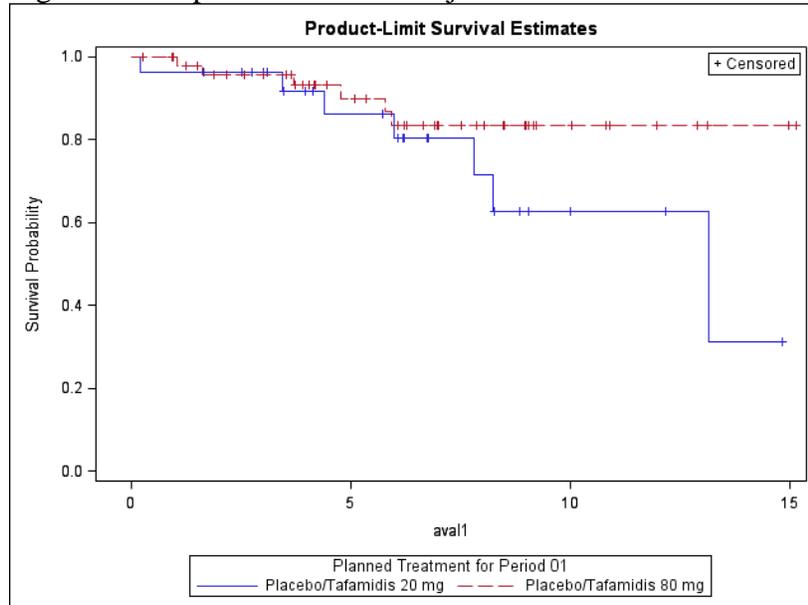
Table 11: Summary of All Mortality Events (Including Extension Study)

Orig treatment / extension treatment	Death (%)*	N
Placebo / NA	76 (77%)	99
Placebo / tafamidis 20 mg	7 (26%)	27
Placebo / tafamidis 80 mg	6 (12%)	51
Tafamidis 20 mg / NA	24 (83%)	29
Tafamidis 20 mg / tafamidis 20 mg	4 (7%)	59
Tafamidis 80 mg / NA	54 (76%)	71
Tafamidis 80 mg / tafamidis 80 mg	6 (6%)	106
Total	177 (40%)	441

* subjects who had transplantation or implantation of a cardiac mechanical assist device were treated as death events
[Source: reviewer's table]

It was noted that the placebo subjects who enrolled into the extension study and randomized to tafamidis 80 mg had fewer mortality events than the placebo subjects randomized to tafamidis 20 mg (Figure 8).

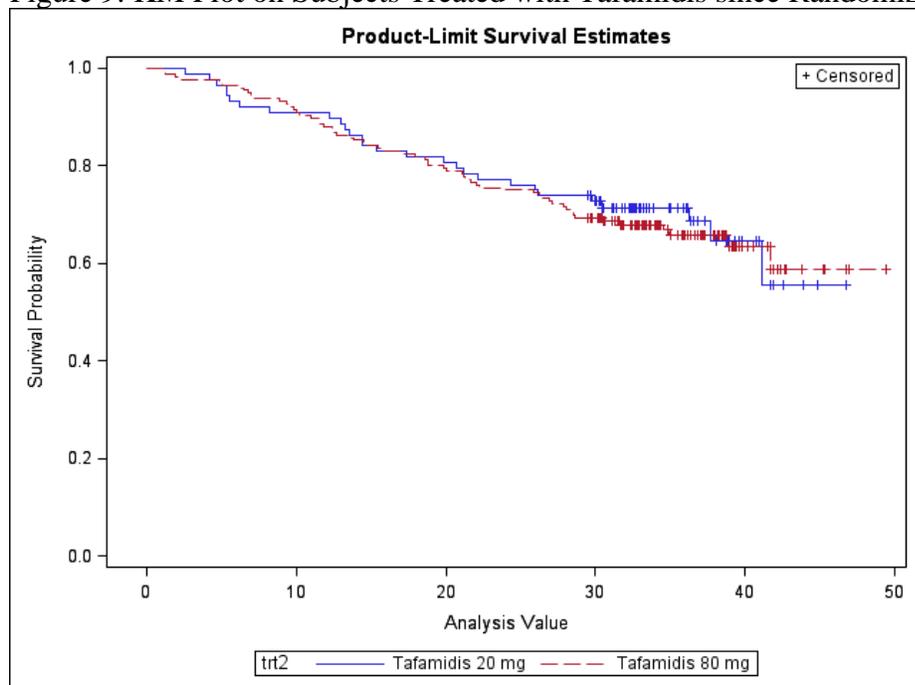
Figure 8: KM plot on Placebo Subjects Enrolled into Extension Study



* the start point for the KM plot was the start date for tafamidis treatment in these placebo subjects
[Source: Reviewer's figure]

However, if we look at the subjects who had been treated with tafamidis since randomization in study B3461028, KM plot did not show any difference between the two dose groups in terms of mortality (Figure 9). This comparison included more subjects and had longer duration.

Figure 9: KM Plot on Subjects Treated with Tafamidis since Randomization



[Source: Reviewer's figure]

Given the small number of mortality events in the placebo subjects treated with tafamidis in the extension study and the short duration (within 15 months) of the study, it is possible that the difference observed between 20 mg and 80 mg in the extension study was due to chance.

2.3 Evaluation of Safety

Please refer to the clinical safety review.

3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

3.1 Gender, Race, Age, and Geographic Region

The treatment effect appeared to be relatively constant across different subgroups. Tafamidis 20 mg and 80 mg showed similar treatment effect in the primary analysis. Subjects in US and outside US showed similar treatment effect in the primary analysis as well (Table 12). Various subgroups were also analyzed for 6MWD and KCCQ and the treatment effect were also consistent across subgroups (Table 13).

Table 12: Subgroup Analyses on the Primary Endpoint Components

	N	All-cause mortality HR	95% CI	CV hospitalization relative risk ratio*	95% CI
US	279	0.69	(0.45, 1.07)	0.60	(0.48, 0.76)
OUS	162	0.54	(0.27, 1.07)	0.83	(0.62, 1.13)
20 mg versus placebo	265	0.60	(0.36, 1.01)	0.66	(0.51, 0.86)
80 mg versus placebo	353	0.68	(0.46, 1.02)	0.70	(0.57, 0.85)

* based on Poisson Regression model

[Source: Reviewer's table]

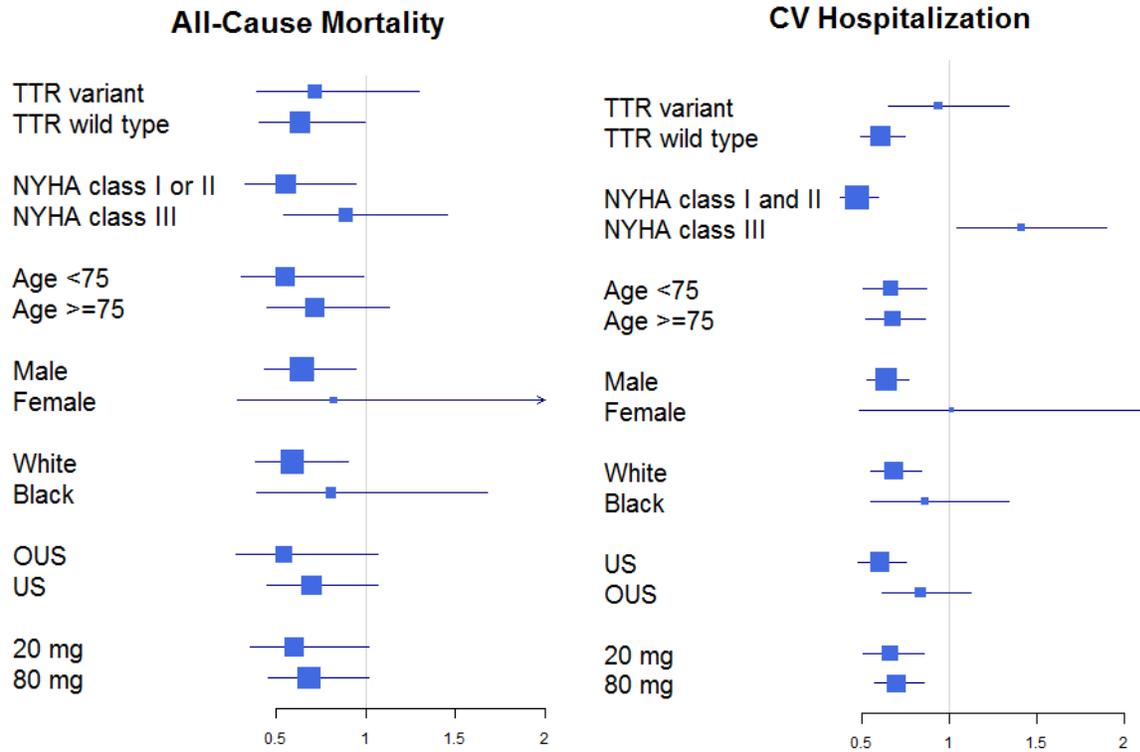
Table 13: Subgroup Analyses on Key Secondary Endpoints

	Subgroup	tafamidis pooled			placebo			LS	
		N	Mean	STD	N	Mean	STD	means	95% CI
6MWD	NYHA class I or II	132	-27.1	86.3	57	-93.5	110	85.4	(64.1, 106.7)
	NYHA class III	23	-50	96.1	13	-72.9	82.1	31.6	(-11.7, 74.8)
	TTR wild type	131	-24.4	89.5	62	-89.1	107.2	77.1	(56.0, 98.3)
	TTR variant	24	-63.8	71.3	8	-93.9	93.7	79.6	(21.1, 138.1)
	80 mg vs placebo	101	-31.2	85.3	70	-89.7	105	75.8	(56.0, 95.6)
	20 mg vs placebo	54	-29.1	93.3	70	-89.7	105	75.6	(48.7, 102.5)
KCCQ	NYHA class I or II	141	-4.3	18	64	-15.1	22.4	13.6	(9.2, 18.0)
	NYHA class III	29	-1.7	24.8	20	-13.3	18.2	13.1	(3.3, 22.8)
	TTR wild type	140	-4	18.4	74	-13.8	20.7	12.7	(8.6, 16.8)
	TTR variant	30	-3.1	23.6	10	-21	26.4	18.2	(3.0, 33.4)
	80 mg vs placebo	110	-3.9	19.3	84	-14.6	21.4	13.5	(9.2, 17.8)
	20 mg vs placebo	60	-3.8	19.5	84	-14.6	21.4	14	(8.2, 19.8)

[Source: Reviewer's table]

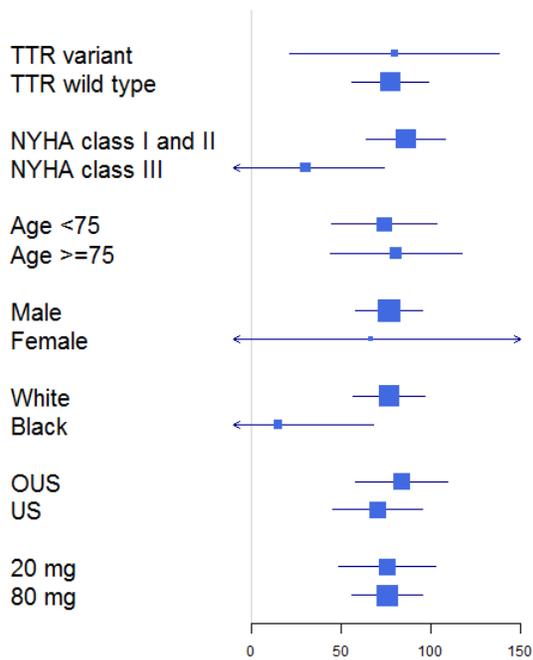
Figure 10, Figure 11, and Figure 12 are forest plots showing the treatment difference between tafamidis and placebo in various subgroups. The subjects in NYHA Class III showed very different treatment effect in CV hospitalization compared with subjects in NYHA Class I and Class II. With death as a confounding factor, i.e., the treatment has a large mortality effect, caution needs to be taken in interpreting this finding.

Figure 10: Subgroup Analyses on All-cause Mortality and CV Hospitalization



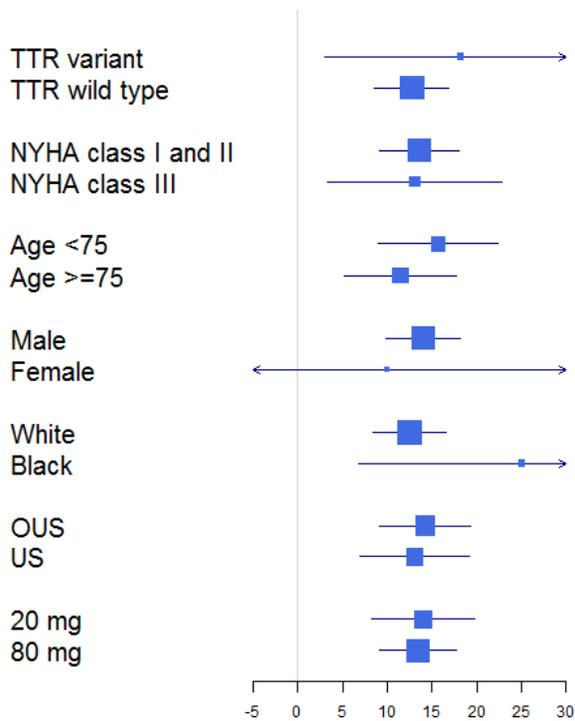
[Source: Reviewer's figure]

Figure 11: Subgroup Analyses on 6MWD



[Source: Reviewer's figure]

Figure 12: Subgroup Analyses on KCCQ Overall Summary Score



[Source: Reviewer's figure]

3.2 Other Special/Subgroup Populations

No other subgroups were analyzed. Please refer to Section 4.1 for more details.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

Informative censoring was a main concern during the discussions on study design. If a subject discontinues early, the primary analysis using FS method only compares the frequency of CV hospitalizations within the shorter duration for both subjects. If subjects had informative censoring (e.g., a subject discontinued early but could have much more CV hospitalizations after discontinuation), the results of FS analysis can potentially be misleading. To address this concern, the sponsor proposed sensitivity analyses using multiple imputations or pattern mixture model. The sensitivity analyses on the primary and key secondary endpoints showed consistent results as the main analyses.

4.2 Collective Evidence

The primary analysis (FS analysis) of all-cause mortality and frequency of CV-related hospitalization showed a significant treatment effect in tafamidis group ($p < 0.001$).

Analyses on individual components of the primary endpoint (all-cause mortality, and CV hospitalization) also showed significant treatment benefit. The estimate of hazard ratio on all-cause mortality from Cox-proportional hazard model was 0.70 (95% CI 0.51, 0.96). The estimated relative risk ratio for CV hospitalization between pooled tafamidis and placebo groups was 0.68 (95% CI 0.59, 0.81) based on Poisson regression model.

Tafamidis demonstrated significant treatment effect in 6MWD and in the KCCQ-OS score. Pooled tafamidis group showed a LS mean difference of 75.7 meters in the change from baseline in 6MWD and a LS mean difference of 13.7 in the change from baseline in KCCQ-OS score when compared with placebo.

4.3 Conclusions and Recommendations

Tafamidis demonstrated statistically significant treatment effect in subjects with either transthyretin genetic variants or wild-type transthyretin resulting in amyloid cardiomyopathy. Sensitivity analyses showed that the results were robust and consistent. 80 mg tafamidis and 20 mg tafamidis appeared to be equally effective based on the primary and key secondary analyses in Study B3461028.

4.4 Labeling Recommendations



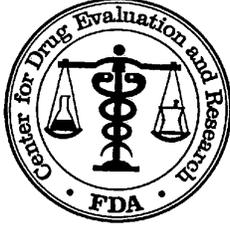
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JIALU ZHANG
03/27/2019 05:17:43 PM

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03/28/2019 10:18:38 AM



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

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number: NDA 211996

Drug Name: VYNDAQEL[®] (Tafamidis meglumine) capsule 20mg

Indication: Reduction of ^{(b) (4)} cardiovascular-related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM).

Applicant: Pfizer Inc.
445 Eastern Point Road, MS 8260-1157
Groton, CT 06340
Test Facility for Rats Study: ^{(b) (4)}
^{(b) (4)}

Documents Reviewed: Study (Sprague-Dawley Rats) report and Electronic data submitted on August 30, 2018 via NDA211996/SN-0001;

Review Priority: Priority

Biometrics Division: Division of Biometrics -6

Statistical Reviewer: Zhuang Miao, Ph.D.
Concurring Reviewer: Feng Zhou
Karl Lin, Ph.D.

Medical Division: Division of Cardiovascular and Renal Products
Reviewing Pharmacologist: Link, William, Ph.D.
Project Manager: Kord Bacheh Changi, Maryam

Keywords: Carcinogenicity, Dose response

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1. Summary

In this submission the sponsor included the report of one animal carcinogenicity study in Sprague-dawley rats. The study was intended to assess the carcinogenic potential of PF-06291826, a novel specific stabilizer of the tetrameric form of transthyretin (TTR), when administered orally by gavage at appropriate drug levels for 104 weeks in male rats and 103 weeks in female rats.

Rat Study: In each of these two experiments there were three treated groups, one vehicle control group and one water control group. Three hundred and thirty Sprague Dawley rats of each sex were randomly assigned to the treated, vehicle control group and water control group. The low dose group and middle dose group have the equal size of 60 rats per group. The vehicle control group, water control group and high dose group have the equal size of 70 rats per group. The dose levels for treated groups were 3, 10, and 30 mg/kg/day for both male and female rats. There were two control groups, vehicle control and water control. The rats in the vehicle control group received the vehicle, Vitamin E TPGS, NF Grade (Vit E TPGS). The rats in the water control group received the ultra pure water (UPW). The study for male rats was designed to continue for up to 104 weeks, however in accordance with study termination criteria, all surviving male rats were sacrificed during Week 105. The study for female rats was designed to continue for up to 103 weeks, however in accordance with study termination criteria, all surviving female rats were sacrificed during Week 103.

The survival analyses did not show a statistically significant dose response relationship in mortality across vehicle control and treated groups, or across water control and treated groups for both males and females.

In the tumor analysis, no tumor types had statistically significant dose response relationships in male or female rats. The pairwise comparisons did not show statistically significant increases in incidence in any observed tumor type in any treated groups in male or female rats.

2. Background

In this submission the sponsor included the report of one animal carcinogenicity study in Sprague-dawley rats. The study was intended to assess the carcinogenic potential of PF-06291826, a novel specific stabilizer of the tetrameric form of transthyretin (TTR), when administered orally by gavage at appropriate drug levels for 104 weeks in male rats and 103 weeks in female rats. Results of this review have been discussed with the reviewing pharmacologist Dr. William Link. This review analyzed the SAS data sets of these studies received from the sponsor on August 30, 2018 via NDA211996/SN-0001.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as the dose increases.

3. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group and one water control group. Three hundred and thirty Sprague Dawley rats of each sex were randomly assigned to the treated, vehicle control group and water control group. The low dose group and middle dose group have the equal size of 60 rats per group. The vehicle control group, water control group and high dose group have the equal size of 70 rats per group. The dose levels for treated groups were 3, 10, and 30 mg/kg/day. There were two control groups, vehicle control and water control. The rats in the vehicle control group received the vehicle, Vitamin E

TPGS, NF Grade (Vit E TPGS). The rats in the water control group received the ultra pure water (UPW). The study for male rats was designed to continue for up to 104 weeks, however in accordance with study termination criteria, all surviving male rats were sacrificed during Week 105. The study for female rats was designed to continue for up to 103 weeks, however in accordance with study termination criteria, all surviving female rats were sacrificed during Week 103.

Group 5 female reached 20 animals left on Day 711 and dosing of that group was stopped on Day 713. Group 2 female (control) reached 20 animals on study Day 714 and terminal necropsies of the entire female portion of the study was initiated on study Day 716.

Table 1: Study Design in Rat Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Ultra Pure Water	70	70
2	0	Vitamin E TPGS	70	70
3	3	PF-06291826	60	60
4	10	PF-06291826	60	60
5	30	PF-06291826	70	70

3.1. Sponsor's analyses

3.1.1. Survival analysis

Kaplan-Meier estimates of group survival rates were calculated, by sex, and shown graphically. Groups were compared using a log-rank test. A two-sided trend test using Groups 2-5 (using ordinal coefficients) and two-sided pairwise tests of Groups 1, 3, 4, and 5 versus Group 2 were all performed at the 0.05 level of significance. In all of these methods, accidental deaths and scheduled sacrifices were treated as censored observations.

Sponsor's findings: Sponsor's analysis showed the numbers (percents) of death were 48 (70%), 49 (69%), 40 (67%), 43 (72%) and 47 (67%) in water control, vehicle control, low, medium, and high dose groups, respectively in males and 45 (64%), 50 (71%), 43 (72%), 44 (73%) and 50 (71%), respectively in females. The sponsor made the following conclusions:

Males

The trend test was not statistically significant when all groups were included in the analysis. None of the pairwise comparisons were statistically significant.

Females

The trend test was not statistically significant when all groups were included in the analysis. None of the pairwise comparisons were statistically significant.

3.1.2. Tumor data analysis

Only tissues in the study protocol were statistically analyzed. When examined, the incidences of tumors in tissues not in the study protocol were summarized but not subject to statistical analysis.

Group incidences of each observed neoplastic lesion or combinations were analyzed using a one-sided Peto's trend test (Groups 2-5) and one-sided pairwise tests (Groups 3-5 vs. Group 2) to test for evidence of a

positive relationship between neoplasm incidence and dose. In addition, one-sided pairwise tests for Group 2 vs. Group 1 were performed to test for evidence of a positive difference between neoplasm incidence and vehicle control.

An exact permutation test was conducted for analyses of data of tumors with low tumor incidence. The asymptotic Peto, exact Peto, and survival/mortality adjusted trend tests were calculated using ordinal coefficients.

Tumors observed in mortality-independent (palpable) sites (e.g. skin/subcutis, mammary gland, etc.) were analyzed using the onset-rate method. Any tumors of this type that were not detected prior to necropsy were assigned an onset time equal to the time of death/sacrifice. For the analysis of these tumor types, the final sacrifice period for each sex was regarded as just a single time point. Fatal tumors were analyzed using the death-rate method. Fatal and palpable tumors that were found during the terminal sacrifice period were treated as incidental for the statistical analysis, as the animals lived past the last in-life study day (last day of dosing), thus no tumor at that point of the study was analyzed as fatal. Animals with incidental tumors were regarded as censored observations in the corresponding fatal-tumor analysis.

Incidental tumors, including all tumors observed in sites that were not mortality-independent in either terminal sacrifice animals or animals deemed to have died accidentally, were analyzed using the prevalence method. Animals with fatal tumors were omitted from the corresponding incidental tumor analysis. For the analysis of these lesions, the following approximate time intervals, expressed in Study Weeks, were used: Weeks 0-50, 51-80, 81-end of study (up to but not including the initiation of group terminal sacrifices), and terminal sacrifice (defined as all necropsies occurring after the initiation of terminal sacrifices for any group). The actual intervals used for analysis may have differed (separately for males and females) due to early or interim sacrifices, accidental deaths, survival rates, and/or the final sacrifice period. The actual intervals used for each sex are described in the Statistics Report.

For tumors that were a mix of fatal and incidental, the results from the different methods were combined to yield an overall Peto test result. Peto test p-values were assessed using FDA Guidance for statistical decision rules controlling the overall false positive rates of alternative ICH rodent carcinogenicity studies. Common and rare tumors were tested at 0.01 and 0.05 significance levels, respectively. All p-values of less than 0.05 are summarized in the Results section of the Statistics Report, even when considered not statistically significant due to “common” tumor historical control background rates. The determination of whether a tumor was common (greater than 1% rate in historical controls) or rare was made by the Study and Peer Review Pathologists using data from the Test Facility, and/or alternative relevant sources when there was insufficient or inconclusive data.

In the event of a negative study (no statistically significant tumor findings), an assessment of the validity of the study design was made through an evaluation of the group survival rates.

Sponsor’s findings: There were no statistically significant differences between the vehicle control and treated groups in male rats or female rats.

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically via NDA211996/SN-0001.

3.2.1. Survival analysis

The survival distributions of animals in all five groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested for vehicle control, water control, low, medium and high dose groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 2 and 3 in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1 and 2 in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 4, 5, 6 and 7 in the appendix for males and females, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percents) of death were 48 (68.6%), 49 (70%), 40 (66.7%), 43 (71.7%) and 47 (67.1%) in male rats and 45 (64.3%), 50 (71.4%), 43 (71.7%), 44 (73.3%) and 50 (71.4) in female rats in the water control, vehicle control, low, median and high dose groups, respectively.

The survival analyses did not show a statistically significant dose response relationship in mortality across vehicle control and treated groups, or across water control and treated groups for both males and females.

3.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pairwise comparison of each of the treated groups with control group. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (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 a 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 for the positive dose response relationship tests and pairwise comparisons are listed in Tables 8, 9, 10 and 11 in the appendix for male and female rats, respectively.

Adjustment for multiple testing: For the adjustment of multiple testing of dose response relationship for a submission with one chronic rat study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for the chronic rat study. For pairwise comparisons for the chronic rat study in the above type of submission with one chronic rat study, the same guidance document suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for the chronic rat study.

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: no tumor types had statistically significant dose response relationships in male or female rats. The pairwise comparisons did not show statistically significant increases in incidence in any observed tumor type in any treated groups in male or female rats.

4. Conclusion

In this submission the sponsor included the report of one animal carcinogenicity study in Sprague-dawley rats. The study was intended to assess the carcinogenic potential of PF-06291826, a novel specific stabilizer of the tetrameric form of transthyretin (TTR), when administered orally by gavage at appropriate drug levels for 104 weeks in male rats, and 103 weeks in female rats.

Rat Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one vehicle control group and one water control group. Three hundred and thirty Sprague Dawley rats of each sex were randomly assigned to the treated, vehicle control group and water control group. The low dose group and middle dose group have the equal size of 60 rats per group. The vehicle control group, water control group and high dose group have the equal size of 70 rats per group. The dose levels for treated groups were 3, 10, and 30 mg/kg/day. There were two control groups, vehicle control and water control. The rats in the vehicle control group received the vehicle, Vitamin E TPGS, NF Grade (Vit E TPGS). The rats in the water control group received the ultra pure water (UPW). The study for male rats was designed to continue for up to 104 weeks, however in accordance with study termination criteria, all surviving male rats were sacrificed during Week 105. The study for female rats was designed to continue for up to 103 weeks, however in accordance with study termination criteria, all surviving female rats were sacrificed during Week 103.

The survival analyses did not show a statistically significant dose response relationship in mortality across vehicle control and treated groups, or between water control and treated groups for both males and females.

In the tumor analysis, no tumor types have statistically significant dose response relationships in male or female rats. The pairwise comparisons do not show statistically significant increases in incidence in any observed tumor type in any treated groups in male or female rats.

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Archival NDA 211996

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Jean Wu, Ph.D.

William Link, Ph.D.

5. Appendix

Table 2: Intercurrent Mortality Rate -Male Rats

Week	Water (N=70) 0 mg/kg/day		Vehicle(Vitamin E) (N=70) 0 mg/kg/day		Low (N=60) 3 mg/kg/day		Medium (N=60) 10 mg/kg/day		High (N=70) 30 mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	4	5.71	3	4.29	4	6.67	1	1.67	1	1.43
53 - 78	18	31.43	18	30.00	19	38.33	16	28.33	21	31.43
79 - 91	10	45.71	14	50.00	8	51.67	16	55.00	17	55.71
92 - 104	16	68.57	14	70.00	9	66.67	10	71.67	8	67.14
Ter. Sac.	22	31.43	21	30.00	20	33.33	17	28.33	23	32.86

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

Table 3: Intercurrent Mortality Rate -Female Rats

Week	Water (N=70) 0 mg/kg/day		Vehicle(Vitamin E) (N=70) 0 mg/kg/day		Low (N=60) 3 mg/kg/day		Medium (N=60) 10 mg/kg/day		High (N=70) 30 mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	1	1.43	3	4.29	1	1.67	3	5.00	4	5.71
53 - 78	18	27.14	14	24.29	17	30.00	17	33.33	22	37.14
79 - 91	17	51.43	17	48.57	16	56.67	11	51.67	20	65.71
92 - 103	9	64.29	16	71.43	9	71.67	13	73.33	4	71.43
Ter. Sac.	25	35.71	20	28.57	17	28.33	16	26.67	20	28.57

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

Table 4: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Male Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.9693	0.8520	0.7254	0.9498
Homogeneity	Log-Rank	0.9878	0.8504	0.7222	0.9493

Table 5: Intercurrent Mortality Comparison between Treated Groups and Water Control -Male Rats

Test	Statistic	P_Value Dose Response	P_Value Water vs. Low	P_Value Water vs. Medium	P_Value Water vs. High
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Test	Statistic	P_Value Dose Response	P_Value Water vs. Low	P_Value Water vs. Medium	P_Value Water vs. High
Dose-Response	Likelihood Ratio	0.9495	0.8446	0.7306	0.9763
Homogeneity	Log-Rank	0.9880	0.8431	0.7277	0.9760

Table 6: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control -Female Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.3837	0.6867	0.5240	0.3637
Homogeneity	Log-Rank	0.8179	0.6821	0.5161	0.3557

Table 7: Intercurrent Mortality Comparison between Treated Groups and Water Control -Female Rats

Test	Statistic	P_Value Dose Response	P_Value Water vs. Low	P_Value Water vs. Med	P_Value Water vs. High
Dose-Response	Likelihood Ratio	0.2172	0.3432	0.2640	0.1550
Homogeneity	Log-Rank	0.4947	0.3360	0.2572	0.1490

Table 8: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Treated Groups and Vehicle Control -Male Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Vehicle vs. Low	10 mg/kg/day Med (N=60) P-Value - Vehicle vs. Medium	30 mg/kg/day High (N=70) P-Value - Vehicle vs. High
BONE	CHONDROSARCOMA	0/5 (3) 0.5000	0/1 (0) NC	0/2 (1) NC	1/5 (4) 0.5714
	OSTEOSARCOMA	0/5 (3) 0.0286	0/1 (0) NC	1/2 (1) 0.2500	3/5 (3) 0.0500
Bone	C_Chondromas+Osteosarcomas	0/5(3) 0.0179	0/1 (0) NC	1/2 (1) 0.2500	4/5 (4) 0.0286
BRAIN	ASTROCYTOMA, MALIGNANT	0/69 (47) 0.4254	2/60 (38) 0.1969	1/60 (40) 0.4598	1/70 (45) 0.4891
	GRANULAR CELL TUMOR, MALIGNANT	2/69 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
	OLIGODENDROGLIOMA, MALIGNANT	1/69 (47) 0.8217	1/60 (38) 0.6972	1/60 (39) 0.7042	0/70 (45) 1.0000
Brain	C_astrocytoma+oligodendrogloma	1/69 (48) 0.7003	3/60 (39) 0.2410	2/60 (40) 0.4391	1/70 (45) 0.7418
GLAND, ADRENAL	CORTICAL ADENOMA	2/70 (47) 0.9190	1/60 (38) 0.8358	1/60 (39) 0.8416	0/70 (45) 1.0000
	PHEOCHROMOCYTOMA, BENIGN	4/70 (48) 0.6635	6/60 (37) 0.2174	7/60 (41) 0.1774	4/70 (45) 0.6059
	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (47) 0.3144	1/60 (37) 0.4405	0/60 (39) NC	1/70 (45) 0.4891
Gland Adrenal	C_cort aden+cort carc	2/70 (47) 0.9190	1/60 (38) 0.8358	1/60 (39) 0.8416	0/70 (45) 1.0000
	C_pheochromacytoma B+M	4/70 (48) 0.7138	7/60 (37) 0.1326	7/60 (41) 0.1774	4/70 (45) 0.6059
GLAND, MAMMARY	ADENOMA	0/61 (40) 0.7241	1/50 (30) 0.4286	0/56 (36) NC	0/62 (39) NC
	FIBROADENOMA	1/61 (40) 0.4060	0/50 (30) 1.0000	2/56 (36) 0.4600	1/62 (39) 0.7468
Gland Mammary	C_Adeno+Fibroadeno	1/61 (40) 0.5321	1/50 (30) 0.6770	2/56 (36) 0.4600	1/62 (39) 0.7468
GLAND, PARATHYROID	ADENOMA	3/67 (45) 1.0000	0/50 (32) 1.0000	0/57 (37) 1.0000	0/63 (42) 1.0000
GLAND, PITUITARY	ADENOMA	33/70 (55) 0.0987	34/60 (51) 0.3055	34/60 (51) 0.3055	45/70 (62) 0.1067
	ADENOMA, PARS INTERMEDIA	1/70 (47) 0.0334	0/60 (37) 1.0000	2/60 (40) 0.4391	4/70 (46) 0.1740

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Vehicle vs. Low	10 mg/kg/day Med (N=60) P-Value - Vehicle vs. Medium	30 mg/kg/day High (N=70) P-Value - Vehicle vs. High
	CARCINOMA	1/70 (47) 0.9239	1/60 (38) 0.6972	0/60 (39) 1.0000	0/70 (45) 1.0000
GLAND, PREPUTIAL	CARCINOMA, ACINAR	0/4 (3) 0.2500	0/4 (1) NC	0/6 (5) NC	1/4 (3) 0.5000
GLAND, SALIVARY, M	CARCINOMA, NOS	0/70 (47) 0.4970	0/60 (37) NC	1/59 (38) 0.4471	0/70 (45) NC
GLAND, THYROID	C-CELL ADENOMA	7/70 (47) 0.3543	8/60 (38) 0.3234	3/60 (39) 0.9177	9/70 (47) 0.3923
	C-CELL CARCINOMA	0/70 (47) 0.3144	1/60 (37) 0.4405	0/60 (39) NC	1/70 (45) 0.4891
	FOLLICULAR CELL ADENOMA	3/70 (47) 0.3763	1/60 (37) 0.9076	3/60 (39) 0.5688	3/70 (46) 0.6512
	FOLLICULAR CELL CARCINOMA	1/70 (47) 0.5475	1/60 (37) 0.6899	0/60 (39) 1.0000	1/70 (45) 0.7418
Gland Thyroid	C_C Cell Adeno+Carcino	7/70 (47) 0.2943	9/60 (38) 0.2257	3/60 (39) 0.9177	10/70 (47) 0.2965
	C_follicular cell Adeno+Carcino	4/70 (48) 0.3817	2/60 (38) 0.8355	3/60 (39) 0.6884	4/70 (46) 0.6186
HEART	MESOTHELIOMA, BENIGN	1/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
HEMOLYMPHORE TICULA	HISTIOCYTIC SARCOMA	0/70 (47) 0.3074	1/60 (37) 0.4405	1/60 (39) 0.4535	1/70 (46) 0.4946
	LEUKEMIA, GRANULOCYTIC	1/70 (47) 0.8217	1/60 (38) 0.6972	1/60 (39) 0.7042	0/70 (45) 1.0000
	LYMPHOMA, MALIGNANT	2/70 (48) 0.9400	2/60 (38) 0.5989	1/60 (40) 0.8424	0/70 (45) 1.0000
KIDNEY	LIPOMA	1/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
	LIPOSARCOMA	0/70 (47) 0.5000	0/60 (37) NC	1/60 (39) 0.4535	0/70 (45) NC
	TUBULAR CELL CARCINOMA	1/70 (47) 0.5226	1/60 (38) 0.6972	2/60 (39) 0.4296	1/70 (46) 0.7473
LIVER	FIBROSARCOMA	1/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
	HEPATOCELLULAR ADENOMA	4/70 (47) 0.6788	1/60 (37) 0.9503	1/60 (39) 0.9560	2/70 (45) 0.8881
LYMPH NODE, MESENT	HEMANGIOSARCOMA	0/67 (45) 0.5060	0/60 (37) NC	1/60 (39) 0.4643	0/70 (45) NC
	SARCOMA	1/67 (45) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Vehicle vs. Low	10 mg/kg/day Med (N=60) P-Value - Vehicle vs. Medium	30 mg/kg/day High (N=70) P-Value - Vehicle vs. High
Multiple Organs	C_Lipomas+Liposarcomas	5/70 (47) 0.6921	0/60 (37) 1.0000	2/60 (39) 0.9104	2/70 (45) 0.9377
	C_hemangiosar+heman	3/70 (48) 0.7968	1/60 (37) 0.9039	1/60 (39) 0.9126	1/70 (45) 0.9334
	C_mesotheliomas	2/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
Oral cavity+Tongue	C_papillo+carcinomas	2/70 (48) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
PANCREAS	ADENOMA	17/70 (49) 0.9093	5/60 (38) 0.9955	3/60 (39) 0.9997	8/70 (48) 0.9888
	ADENOMA, ACINAR	3/70 (48) 0.9217	1/60 (37) 0.9039	4/60 (39) 0.3840	0/70 (45) 1.0000
	CARCINOMA	1/70 (47) 0.8521	2/60 (37) 0.4101	4/60 (40) 0.1341	0/70 (45) 1.0000
	CARCINOMA, ACINAR	1/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
Pancreas	C_acinar adenoma+carcinoma	4/70 (48) 0.9532	1/60 (37) 0.9478	4/60 (39) 0.5210	0/70 (45) 1.0000
	C_adenoma+carcinoma	18/70 (49) 0.9480	6/60 (38) 0.9930	7/60 (40) 0.9887	8/70 (48) 0.9935
	C_adenomas+acinar adenomas	19/70 (49) 0.9530	5/60 (38) 0.9986	7/60 (39) 0.9918	8/70 (48) 0.9964
	C_carcinomas+acinar carcinomas	2/70 (47) 0.9113	2/60 (37) 0.5966	4/60 (40) 0.2645	0/70 (45) 1.0000
SKIN	BASAL CELL TUMOR, BENIGN	0/70 (47) 0.7202	1/60 (37) 0.4405	0/60 (39) NC	0/70 (45) NC
	HAIR FOLLICLE TUMOR, BENIGN	4/70 (49) 0.7947	3/60 (38) 0.6649	2/60 (39) 0.8370	2/70 (46) 0.8830
	PAPILLOMA	0/70 (47) 0.0680	0/60 (37) NC	1/60 (39) 0.4535	2/70 (45) 0.2365
	POLYP	0/70 (47) 0.5000	0/60 (37) NC	1/60 (39) 0.4535	0/70 (45) NC
	SEBACEOUS CELL ADENOMA	0/70 (47) 0.2679	0/60 (37) NC	0/60 (39) NC	1/70 (45) 0.4891
	SEBACEOUS CELL CARCINOMA	0/70 (47) 0.8841	3/60 (39) 0.0893	0/60 (39) NC	0/70 (45) NC
	SQUAMOUS CELL CARCINOMA	1/70 (47) 0.4141	0/60 (37) 1.0000	1/60 (39) 0.7042	1/70 (46) 0.7473
Skin	C_carcinomas	1/70 (47) 0.7127	3/60 (39) 0.2410	1/60 (39) 0.7042	1/70 (46) 0.7473

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Vehicle vs. Low	10 mg/kg/day Med (N=60) P-Value - Vehicle vs. Medium	30 mg/kg/day High (N=70) P-Value - Vehicle vs. High
	C_carcinomas+Papill+Keratoac	1/70 (47) 0.2898	3/60 (39) 0.2410	2/60 (39) 0.4296	3/70 (46) 0.3002
SMALL INTESTINE, D	ADENOCARCINOMA	0/69 (46) 0.5030	0/60 (37) NC	1/60 (39) 0.4588	0/70 (45) NC
SMALL INTESTINE, J	LEIOMYOMA	1/64 (45) 1.0000	0/58 (36) 1.0000	0/57 (38) 1.0000	0/67 (44) 1.0000
SPINAL CORD, THORA	ASTROCYTOMA, MALIGNANT	0/70 (47) 0.2679	0/60 (37) NC	0/60 (39) NC	1/70 (45) 0.4891
SPLEEN	HEMANGIOSARCOMA	1/70 (47) 0.4651	0/60 (37) 1.0000	0/60 (39) 1.0000	1/70 (45) 0.7418
	LIPOSARCOMA	0/70 (47) 0.2679	0/60 (37) NC	0/60 (39) NC	1/70 (45) 0.4891
STOMACH	ADENOCARCINOMA	1/70 (47) 0.4715	0/60 (37) 1.0000	0/60 (39) 1.0000	1/70 (46) 0.7473
	CARCINOMA	0/70 (47) 0.2679	0/60 (37) NC	0/60 (39) NC	1/70 (45) 0.4891
Stomach	C_carci+adenocarci	1/70 (47) 0.1803	0/60 (37) 1.0000	0/60 (39) 1.0000	2/70 (46) 0.4918
SUBCUTIS	FIBROLIPOMA	0/18 (12) 0.6923	1/11 (9) 0.4286	0/15 (12) NC	0/7 (6) NC
	FIBROMA	5/18 (13) 0.5812	3/11 (9) 0.7545	4/15 (12) 0.7519	2/7 (6) 0.7616
	FIBROSARCOMA	1/18 (12) 0.1093	1/11 (8) 0.6526	1/15 (13) 0.7800	2/7 (6) 0.2451
	HEMANGIOSARCOMA	2/18 (13) 1.0000	0/11 (8) 1.0000	0/15 (12) 1.0000	0/7 (6) 1.0000
	LIPOMA	4/18 (12) 0.6801	0/11 (8) 1.0000	1/15 (12) 0.9814	1/7 (6) 0.9076
	MELANOMA, BENIGN	0/18 (12) 0.4737	0/11 (8) NC	1/15 (12) 0.5000	0/7 (6) NC
	MYXOMA	2/18 (13) 1.0000	0/11 (8) 1.0000	0/15 (12) 1.0000	0/7 (6) 1.0000
	SARCOMA, NOS	2/18 (13) 0.7332	0/11 (8) 1.0000	2/15 (12) 0.6722	0/7 (6) 1.0000
Subcutis	C_fibroma+fibrosarcoma	6/18 (14) 0.2961	4/11 (9) 0.6369	5/15 (13) 0.7329	4/7 (7) 0.4381
	C_sarcomas+fibroma	7/18 (14) 0.6785	3/11 (9) 0.8889	6/15 (12) NC	2/7 (6) 0.8808
TESTIS	INTERSTITIAL (LEYDIG) CELL ADENOMA	1/70 (47) 0.9229	1/60 (37) 0.6899	0/60 (39) 1.0000	0/70 (45) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Vehicle vs. Low	10 mg/kg/day Med (N=60) P-Value - Vehicle vs. Medium	30 mg/kg/day High (N=70) P-Value - Vehicle vs. High
	MESOTHELIOMA, MALIGNANT	1/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
TONGUE	CARCINOMA	1/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
URINARY BLADDER	LIPOMA	1/69 (46) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/67 (43) 1.0000
	POLYP	0/69 (46) 0.4970	0/60 (37) NC	1/60 (39) 0.4588	0/67 (43) NC

Table 9: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Treated Groups and Water Control -Male Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=60) P-value - Water vs. Low	10 mg/kg/day Med (N=60) P-value - Water vs. Medium	30 mg/kg/day High (N=70) P-value - Water vs. High
BONE	CHONDROSARCOMA	0/1 (0) 0.8000	0/1 (0) NC	0/2 (1) NC	1/5 (4) NC
	OSTEOSARCOMA	1/1 (1)	0/1 (0) NC	1/2 (1) NC	3/5 (3) NC
Bone	C_Chondromas+Osteosarcomas	1/1 (1) NC	0/1 (0) NC	1/2 (1) NC	4/5 (4) NC
BRAIN	ASTROCYTOMA, MALIGNANT	0/70 (46) 0.4305	2/60 (38) 0.2017	1/60 (40) 0.4651	1/70 (45) 0.4945
	MIXED GLIOMA, MALIGNANT	1/70 (46) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
	OLIGODENDROGLIOMA, MALIGNANT	0/70 (46) 0.6236	1/60 (38) 0.4524	1/60 (39) 0.4588	0/70 (45) NC
Brain	C_astrocytoma+oligodendrogloma	0/70 (46) 0.5776	3/60 (39) 0.0925	2/60 (40) 0.2134	1/70 (45) 0.4945
GLAND, ADRENAL	CORTICAL ADENOMA	0/70 (46) 0.6236	1/60 (38) 0.4524	1/60 (39) 0.4588	0/70 (45) NC
	CORTICAL CARCINOMA	1/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
	PHEOCHROMOCYTOMA, BENIGN	5/70 (46) 0.7524	6/60 (37) 0.3468	7/60 (41) 0.2990	4/70 (45) 0.7464
	PHEOCHROMOCYTOMA, COMPLEX, MALIGNANT	1/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
	PHEOCHROMOCYTOMA, MALIGNANT	1/70 (46) 0.5516	1/60 (37) 0.6959	0/60 (39) 1.0000	1/70 (45) 0.7473
Gland Adrenal	C_cort aden+cort carc	1/70 (47) 0.8217	1/60 (38) 0.6972	1/60 (39) 0.7042	0/70 (45) 1.0000
	C_pheochromacytoma B+M	6/70 (47) 0.8388	7/60 (37) 0.3174	7/60 (41) 0.3935	4/70 (45) 0.8238
GLAND, MAMMARY	ADENOMA	1/59 (38) 0.9308	1/50 (30) 0.6914	0/56 (36) 1.0000	0/62 (39) 1.0000
	FIBROADENOMA	2/59 (39) 0.5770	0/50 (30) 1.0000	2/56 (36) 0.6616	1/62 (39) 0.8799
Gland Mammary	C_Adeno+Fibroadeno	3/70 (47) 0.7841	1/60 (37) 0.9076	2/60 (39) 0.7562	1/70 (46) 0.9389
GLAND, PARATHYROID	ADENOMA	1/64 (43) 1.0000	0/50 (32) 1.0000	0/57 (37) 1.0000	0/63 (42) 1.0000
GLAND, PITUITARY	ADENOMA	39/68 (58) 0.2255	34/60 (51) 0.6060	34/60 (51) 0.6060	45/70 (62) 0.3304

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=60) P-value - Water vs. Low	10 mg/kg/day Med (N=60) P-value - Water vs. Medium	30 mg/kg/day High (N=70) P-value - Water vs. High
	ADENOMA, PARS INTERMEDIA	3/68 (47) 0.1391	0/60 (37) 1.0000	2/60 (40) 0.7654	4/70 (46) 0.4878
	CARCINOMA	1/68 (46) 0.9262	1/60 (38) 0.7031	0/60 (39) 1.0000	0/70 (45) 1.0000
GLAND, PREPUTIAL	CARCINOMA, ACINAR	0/7 (5) 0.2143	0/4 (1) NC	0/6 (5) NC	1/4 (3) 0.3750
GLAND, SALIVARY, M	CARCINOMA, NOS	0/70 (46) 0.5000	0/60 (37) NC	1/59 (38) 0.4524	0/70 (45) NC
GLAND, THYROID	C-CELL ADENOMA	12/70 (47) 0.7103	8/60 (38) 0.7697	3/60 (39) 0.9946	9/70 (47) 0.8390
	C-CELL CARCINOMA	2/70 (47) 0.7068	1/60 (37) 0.8298	0/60 (39) 1.0000	1/70 (45) 0.8709
	FOLLICULAR CELL ADENOMA	2/70 (46) 0.2736	1/60 (37) 0.8348	3/60 (39) 0.4213	3/70 (46) 0.5000
	FOLLICULAR CELL CARCINOMA	1/70 (46) 0.5516	1/60 (37) 0.6959	0/60 (39) 1.0000	1/70 (45) 0.7473
Gland Thyroid	C_C Cellll Adeno+Carcino	14/70 (48) 0.7509	9/60 (38) 0.7920	3/60 (39) 0.9982	10/70 (47) 0.8690
	C_follicular cell Adeno+Carcino	3/70 (46) 0.2972	2/60 (38) 0.7547	3/60 (39) 0.5799	4/70 (46) 0.5000
HEMOLYMPHORET ICULA	HISTIOCYTIC SARCOMA	0/70 (46) 0.3117	1/60 (37) 0.4458	1/60 (39) 0.4588	1/70 (46) 0.5000
	LEUKEMIA, GRANULOCYTIC	0/70 (46) 0.6236	1/60 (38) 0.4524	1/60 (39) 0.4588	0/70 (45) NC
	LYMPHOMA, MALIGNANT	2/70 (47) 0.9421	2/60 (38) 0.6076	1/60 (40) 0.8470	0/70 (45) 1.0000
KIDNEY	LIPOSARCOMA	0/70 (46) 0.5030	0/60 (37) NC	1/60 (39) 0.4588	0/70 (45) NC
	TUBULAR CELL CARCINOMA	1/70 (46) 0.5278	1/60 (38) 0.7031	2/60 (39) 0.4376	1/70 (46) 0.7527
LARGE INTESTINE, C	LEIOMYOMA	1/64 (44) 1.0000	0/58 (36) 1.0000	0/54 (37) 1.0000	0/68 (44) 1.0000
	LIPOMA	1/64 (44) 1.0000	0/58 (36) 1.0000	0/54 (37) 1.0000	0/68 (44) 1.0000
LIVER	HEPATOCELLULAR ADENOMA	2/70 (46) 0.4325	1/60 (37) 0.8348	1/60 (39) 0.8463	2/70 (45) 0.6834
LUNG	SQUAMOUS CELL CARCINOMA	1/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
LYMPH NODE, MESENT	HEMANGIOSARCOMA	1/70 (46) 0.7545	0/60 (37) 1.0000	1/60 (39) 0.7101	0/70 (45) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=60) P-value - Water vs. Low	10 mg/kg/day Med (N=60) P-value - Water vs. Medium	30 mg/kg/day High (N=70) P-value - Water vs. High
Multiple Organs	C_Lipomas+Liposarcomas	3/70 (46) 0.4568	0/60 (37) 1.0000	2/60 (39) 0.7642	2/70 (45) 0.8126
	C_hemangiosar+heman	3/70 (47) 0.8008	1/60 (37) 0.9076	1/60 (39) 0.9160	1/70 (45) 0.9362
Oral cavity+Tongue	C_papillo+carcinomas	1/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
PANCREAS	ADENOMA	10/70 (48) 0.5481	5/60 (38) 0.8893	3/60 (39) 0.9808	8/70 (48) 0.7833
	ADENOMA, ACINAR	2/70 (46) 0.8786	1/60 (37) 0.8348	4/60 (39) 0.2627	0/70 (45) 1.0000
	CARCINOMA	0/70 (46) 0.7637	2/60 (37) 0.1957	4/60 (40) 0.0430	0/70 (45) NC
Pancreas	C_acinar adenoma+carcinoma	2/70 (46) 0.8786	1/60 (37) 0.8348	4/60 (39) 0.2627	0/70 (45) 1.0000
	C_adenoma+carcinoma	10/70 (48) 0.6268	6/60 (38) 0.8087	7/60 (40) 0.7457	8/70 (48) 0.7833
	C_adenomas+acinar adenomas	12/70 (48) 0.7069	5/60 (38) 0.9518	7/60 (39) 0.8538	8/70 (48) 0.8958
	C_carcinomas+acinar carcinomas	0/70 (46) 0.7637	2/60 (37) 0.1957	4/60 (40) 0.0430	0/70 (45) NC
SKIN	BASAL CELL TUMOR, BENIGN	3/70 (46) 0.9948	1/60 (37) 0.9112	0/60 (39) 1.0000	0/70 (45) 1.0000
	HAIR FOLLICLE TUMOR, BENIGN	3/70 (47) 0.7210	3/60 (38) 0.5555	2/60 (39) 0.7562	2/70 (46) 0.8126
	HAIR FOLLICLE TUMOR, MALIGNANT	1/70 (46) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
	KERATOACANTHOMA	1/70 (46) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
	PAPILLOMA	1/70 (46) 0.1861	0/60 (37) 1.0000	1/60 (39) 0.7101	2/70 (45) 0.4917
	POLYP	0/70 (46) 0.5030	0/60 (37) NC	1/60 (39) 0.4588	0/70 (45) NC
	SEBACEOUS CELL ADENOMA	0/70 (46) 0.2695	0/60 (37) NC	0/60 (39) NC	1/70 (45) 0.4945
	SEBACEOUS CELL CARCINOMA	1/70 (46) 0.9536	3/60 (39) 0.2482	0/60 (39) 1.0000	0/70 (45) 1.0000
	SQUAMOUS CELL CARCINOMA	0/70 (46) 0.2017	0/60 (37) NC	1/60 (39) 0.4588	1/70 (46) 0.5000
Skin	C_carcinomas	1/70 (46) 0.7178	3/60 (39) 0.2482	1/60 (39) 0.7101	1/70 (46) 0.7527

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	3 mg/kg/day Low (N=60) P-value - Water vs. Low	10 mg/kg/day Med (N=60) P-value - Water vs. Medium	30 mg/kg/day High (N=70) P-value - Water vs. High
	C_carcinomas+Papill+Keratoac	2/70 (46) 0.4145	3/60 (39) 0.4213	2/60 (39) 0.6270	3/70 (46) 0.5000
SMALL INTESTINE, D	ADENOCARCINOMA	0/69 (46) 0.5030	0/60 (37) NC	1/60 (39) 0.4588	0/70 (45) NC
SMALL INTESTINE, J	ADENOCARCINOMA	1/69 (46) 1.0000	0/58 (36) 1.0000	0/57 (38) 1.0000	0/67 (44) 1.0000
SPINAL CORD, THORA	ASTROCYTOMA, MALIGNANT	0/70 (46) 0.2695	0/60 (37) NC	0/60 (39) NC	1/70 (45) 0.4945
SPLEEN	HEMANGIOSARCOMA	2/70 (47) 0.6219	0/60 (37) 1.0000	0/60 (39) 1.0000	1/70 (45) 0.8709
	LIPOSARCOMA	0/70 (46) 0.2695	0/60 (37) NC	0/60 (39) NC	1/70 (45) 0.4945
STOMACH	ADENOCARCINOMA	0/70 (46) 0.2738	0/60 (37) NC	0/60 (39) NC	1/70 (46) 0.5000
	CARCINOMA	0/70 (46) 0.2695	0/60 (37) NC	0/60 (39) NC	1/70 (45) 0.4945
Stomach	C_carci+adenocarci	0/70 (46) 0.0738	0/60 (37) NC	0/60 (39) NC	2/70 (46) 0.2473
SUBCUTIS	FIBROLIPOMA	0/14 (11) 0.7105	1/11 (9) 0.4500	0/15 (12) NC	0/7 (6) NC
	FIBROMA	6/14 (13) 0.6787	3/11 (9) 0.8511	4/15 (12) 0.8558	2/7 (6) 0.8467
	FIBROSARCOMA	2/14 (11) 0.2166	1/11 (8) 0.8297	1/15 (13) 0.9185	2/7 (6) 0.4454
	LIPOMA	2/14 (11) 0.4430	0/11 (8) 1.0000	1/15 (12) 0.9068	1/7 (6) 0.7574
	MELANOMA, BENIGN	0/14 (11) 0.4865	0/11 (8) NC	1/15 (12) 0.5217	0/7 (6) NC
	SARCOMA, NOS	0/14 (11) 0.4009	0/11 (8) NC	2/15 (12) 0.2609	0/7 (6) NC
Subcutis	C_fibroma+fibrosarcoma	7/14 (13) 0.4328	4/11 (9) 0.8065	5/15 (13) 0.8811	4/7 (7) 0.6300
	C_sarcomas+fibroma	6/14 (13) 0.6290	3/11 (9) 0.8511	6/15 (12) 0.5821	2/7 (6) 0.8467
TESTIS	INTERSTITIAL (LEYDIG) CELL ADENOMA	3/70 (46) 0.9948	1/60 (37) 0.9112	0/60 (39) 1.0000	0/70 (45) 1.0000
TONGUE	CARCINOMA	1/70 (47) 1.0000	0/60 (37) 1.0000	0/60 (39) 1.0000	0/70 (45) 1.0000
URINARY BLADDER	POLYP	0/70 (46) 0.4970	0/60 (37) NC	1/60 (39) 0.4588	0/67 (43) NC

Table 10: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Treated Groups and Vehicle Control -Female Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Vehicle vs. Low	10 mg/kg/day Med (N=60) P-Value - Vehicle vs. Medium	30 mg/kg/day High (N=70) P-Value - Vehicle vs. High
BODY CAVITY, ABDOM	MESOTHELIOMA, MALIGNANT	0/1 (1) 0.5000	0/1 (1) NC	1/2 (2) 0.6667	0/1 (0) NC
	RHABDOMYOSARCOMA	0/1 (1) 0.3333	0/1 (1) NC	1/2 (1) 0.5000	0/1 (0) NC
BRAIN	ASTROCYTOMA, MALIGNANT	0/69 (45) 0.4845	0/60 (38) NC	1/60 (38) 0.4578	0/69 (40) NC
CERVIX	ENDOMETRIAL STROMAL SARCOMA	1/70 (46) 1.0000	0/60 (38) 1.0000	0/60 (37) 1.0000	0/70 (41) 1.0000
	FIBROMA	1/70 (46) 1.0000	0/60 (38) 1.0000	0/60 (37) 1.0000	0/70 (41) 1.0000
EYE	MELANOMA, BENIGN	0/70 (46) 0.7160	1/60 (38) 0.4524	0/60 (37) NC	0/70 (41) NC
GLAND, ADRENAL	CORTICAL ADENOMA	1/70 (46) 0.9216	1/60 (39) 0.7101	0/60 (37) 1.0000	0/70 (41) 1.0000
	PHEOCHROMOCYTOMA, BENIGN	0/70 (46) 0.2531	0/60 (38) NC	0/60 (37) NC	1/70 (41) 0.4713
GLAND, CLITORAL	ADENOCARCINOMA	1/3 (3) 0.7857	0/1 (1) 1.0000	1/3 (3) 0.8000	0/1 (1) 1.0000
	ADENOMA	0/3 (3) 0.5714	1/1 (1) 0.2500	0/3 (2) NC	0/1 (1) NC
GLAND, MAMMARY	ADENOCARCINOMA	20/70 (53) 0.4375	16/60 (44) 0.6363	10/59 (40) 0.9373	18/70 (47) 0.5586
	ADENOMA	3/70 (47) 0.0086	4/60 (39) 0.3954	2/59 (37) 0.7365	10/70 (45) 0.0287
	FIBROADENOMA	30/70 (53) 0.9990	26/60 (46) 0.5839	21/59 (43) 0.8324	13/70 (45) 0.9986
	LIPOMA	1/70 (46) 1.0000	0/60 (38) 1.0000	0/59 (36) 1.0000	0/70 (41) 1.0000
Gland mammary	C_ adeno+adenocarci	22/70 (53) 0.1175	17/60 (44) 0.6893	10/60 (41) 0.9758	25/70 (50) 0.2526
	C_ adeno+adenocarci+fibroaden	41/70 (58) 0.7762	32/60 (48) 0.7444	28/60 (46) 0.8963	34/70 (54) 0.8576
	C_ adeno+fibroaden	31/70 (53) 0.9319	27/60 (47) 0.6213	21/60 (44) 0.8967	22/70 (49) 0.9421
GLAND, PARATHYROID	ADENOMA	1/68 (45) 0.9126	1/56 (36) 0.6944	0/55 (33) 1.0000	0/64 (37) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Vehicle vs. Low	10 mg/kg/day Med (N=60) P-Value - Vehicle vs. Medium	30 mg/kg/day High (N=70) P-Value - Vehicle vs. High
GLAND, PITUITARY	ADENOMA	47/70 (62) 0.0469	45/60 (55) 0.2867	45/60 (55) 0.2867	59/70 (67) 0.0560
	CARCINOMA	0/70 (46) 0.2531	0/60 (38) NC	0/60 (37) NC	1/70 (41) 0.4713
	CRANIOPHARYNGIOMA, MALIGNANT	0/70 (46) 0.2531	0/60 (38) NC	0/60 (37) NC	1/70 (41) 0.4713
GLAND, THYROID	C-CELL ADENOMA	4/70 (47) 0.6789	2/60 (38) 0.8422	9/60 (38) 0.0517	2/70 (41) 0.8641
	C-CELL CARCINOMA	3/70 (47) 0.8383	3/60 (38) 0.5555	4/60 (37) 0.3669	1/70 (41) 0.9235
Gland thyroid	C_cell ade+carc	7/70 (48) 0.8577	5/60 (38) 0.6892	12/60 (39) 0.0600	3/70 (42) 0.9297
HEART	SCHWANNOMA, BENIGN	0/70 (46) 0.2987	1/60 (38) 0.4524	0/60 (37) NC	1/70 (41) 0.4713
HEMOLYMPHORETICULA	HISTIOCYTIC SARCOMA	2/70 (47) 0.9721	2/60 (39) 0.6182	0/60 (37) 1.0000	0/70 (41) 1.0000
	LEUKEMIA, GRANULOCYTIC	0/70 (46) 0.2531	0/60 (38) NC	0/60 (37) NC	1/70 (41) 0.4713
	LYMPHOMA, MALIGNANT	0/70 (46) 0.4847	0/60 (38) NC	1/60 (38) 0.4524	0/70 (41) NC
KIDNEY	LIPOMA	0/70 (46) 0.4847	0/60 (38) NC	1/60 (38) 0.4524	0/70 (41) NC
	TUBULAR CELL CARCINOMA	2/70 (48) 0.1350	0/60 (38) 1.0000	1/60 (37) 0.8249	3/70 (43) 0.4474
LARGE INTESTINE, R	PAPILLOMA	0/6 (4) 0.3333	0/1 (1) NC	0/2 (1) NC	1/3 (3) 0.4286
LIVER	CHOLANGIOCARCINOMA	0/70 (46) 0.2531	0/60 (38) NC	0/60 (37) NC	1/70 (41) 0.4713
	CHOLANGIOMA	1/70 (47) 1.0000	0/60 (38) 1.0000	0/60 (37) 1.0000	0/70 (41) 1.0000
	HEMANGIOSARCOMA	0/70 (46) 0.0629	0/60 (38) NC	0/60 (37) NC	2/70 (41) 0.2192
	HEPATOCELLULAR ADENOMA	1/70 (46) 0.0530	0/60 (38) 1.0000	0/60 (37) 1.0000	3/70 (42) 0.2745
	HEPATOCELLULAR CARCINOMA	0/70 (46) 0.2531	0/60 (38) NC	0/60 (37) NC	1/70 (41) 0.4713
Multiple Organs	C_Lipomas+Liposarcomas	1/70 (46) 0.7785	1/60 (38) 0.7031	2/60 (38) 0.4279	0/70 (41) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Vehicle vs. Low	10 mg/kg/day Med (N=60) P-Value - Vehicle vs. Medium	30 mg/kg/day High (N=70) P-Value - Vehicle vs. High
	C_hemangiosar+heman	1/70 (47) 0.0521	0/60 (38) 1.0000	0/60 (37) 1.0000	3/70 (42) 0.2668
	C_mesotheliomas	0/70 (46) 0.4847	0/60 (38) NC	1/60 (38) 0.4524	0/70 (41) NC
OVARY	HISTIOCYTIC SARCOMA	0/69 (45) 0.7187	1/60 (38) 0.4578	0/60 (37) NC	0/69 (40) NC
	LUTEOMA	0/69 (45) 0.4813	0/60 (38) NC	1/60 (37) 0.4512	0/69 (40) NC
	MIXED SEX CORD STROMAL TUMOR, BENIGN	0/69 (45) 0.7187	1/60 (38) 0.4578	0/60 (37) NC	0/69 (40) NC
	MIXED SEX CORD STROMAL TUMOR, MALIGNANT	0/69 (45) 0.2500	0/60 (38) NC	0/60 (37) NC	1/69 (40) 0.4706
	TUBULOSTROMAL CARCINOMA	0/69 (45) 0.2547	0/60 (38) NC	0/60 (37) NC	1/69 (41) 0.4767
Oral cavity+Tongue	C_papillo+carcinomas	2/70 (47) 0.5121	0/60 (38) 1.0000	2/60 (37) 0.5966	1/70 (41) 0.8522
PANCREAS	ADENOMA	3/70 (47) 0.9568	1/60 (38) 0.9119	1/60 (37) 0.9076	0/70 (41) 1.0000
	ADENOMA, ACINAR	0/70 (46) 0.2987	1/60 (38) 0.4524	0/60 (37) NC	1/70 (41) 0.4713
	CARCINOMA	1/70 (46) 0.4433	0/60 (38) 1.0000	0/60 (37) 1.0000	1/70 (41) 0.7233
SKIN	BASAL CELL TUMOR, MALIGNANT	0/70 (46) 0.2783	1/60 (39) 0.4588	1/60 (37) 0.4458	1/70 (41) 0.4713
	POLYP	0/70 (46) 0.6036	1/60 (38) 0.4524	1/60 (38) 0.4524	0/70 (41) NC
	SQUAMOUS CELL CARCINOMA	0/70 (46) 0.1792	0/60 (38) NC	1/60 (37) 0.4458	1/70 (41) 0.4713
SMALL INTESTINE, J	ADENOCARCINOMA	1/68 (46) 1.0000	0/59 (38) 1.0000	0/59 (37) 1.0000	0/70 (41) 1.0000
SPLEEN	HEMANGIOSARCOMA	1/70 (47) 0.4433	0/59 (37) 1.0000	0/60 (37) 1.0000	1/70 (41) 0.7176
SUBCUTIS	FIBROLIPOMA	1/8 (6) 1.0000	0/3 (2) 1.0000	0/3 (1) 1.0000	0/1 (0) NC
	FIBROMA	3/8 (6) 0.6667	0/3 (2) 1.0000	1/3 (2) 0.7857	0/1 (0) NC
	FIBROSARCOMA	1/8 (6) 0.3778	0/3 (2) 1.0000	1/3 (2) 0.4643	0/1 (0) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Vehicle vs. Low	10 mg/kg/day Med (N=60) P-Value - Vehicle vs. Medium	30 mg/kg/day High (N=70) P-Value - Vehicle vs. High
	LIPOMA	0/8 (6) 0.1111	1/3 (2) 0.2500	1/3 (2) 0.2500	0/1 (0) NC
	MELANOMA, MALIGNANT	0/8 (6) 0.1000	0/3 (2) NC	0/3 (1) NC	1/1 (1) 0.1429
THYMUS	THYMOMA, MALIGNANT	0/70 (46) 0.7160	1/60 (38) 0.4524	0/60 (37) NC	0/70 (41) NC
TONGUE	CARCINOMA	1/70 (47) 1.0000	0/60 (38) 1.0000	0/60 (37) 1.0000	0/70 (41) 1.0000
UTERUS	ENDOMETRIAL ADENOMA	0/70 (46) 0.7160	1/60 (38) 0.4524	0/60 (37) NC	0/70 (41) NC
	ENDOMETRIAL STROMAL SARCOMA	1/70 (46) 1.0000	0/60 (38) 1.0000	0/60 (37) 1.0000	0/70 (41) 1.0000
	GRANULAR CELL TUMOR, BENIGN	1/70 (46) 1.0000	0/60 (38) 1.0000	0/60 (37) 1.0000	0/70 (41) 1.0000
	GRANULAR CELL TUMOR, MALIGNANT	0/70 (46) 0.4815	0/60 (38) NC	1/60 (37) 0.4458	0/70 (41) NC
	HISTIOCYTIC SARCOMA	0/70 (46) 0.7160	1/60 (38) 0.4524	0/60 (37) NC	0/70 (41) NC
	LEIOMYOSARCOMA	0/70 (46) 0.2981	1/60 (39) 0.4588	0/60 (37) NC	1/70 (41) 0.4713
	POLYP	5/70 (48) 0.3966	4/60 (38) 0.6275	3/60 (38) 0.7776	5/70 (42) 0.5419
VAGINA	GRANULAR CELL TUMOR, BENIGN	0/70 (46) 0.7848	2/59 (37) 0.1957	0/59 (36) NC	0/70 (41) NC
	GRANULAR CELL TUMOR, MALIGNANT	0/70 (46) 0.4845	0/59 (37) NC	1/59 (37) 0.4458	0/70 (41) NC
	POLYP	0/70 (46) 0.2562	0/59 (37) NC	0/59 (36) NC	1/70 (41) 0.4713
	SQUAMOUS CELL CARCINOMA	0/70 (46) 0.7125	1/59 (37) 0.4458	0/59 (36) NC	0/70 (41) NC

Table 11: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Treated Groups and Water Control -Female Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Water vs. Low	10 mg/kg/day Med (N=60) P-Value - Water vs. Medium	30 mg/kg/day High (N=70) P-Value - Water vs. High
BRAIN	ASTROCYTOMA, MALIGNANT	0/70 (48) 0.4756	0/60 (38) NC	1/60 (38) 0.4419	0/69 (40) NC
CERVIX	SQUAMOUS CELL CARCINOMA	1/70 (48) 1.0000	0/60 (38) 1.0000	0/60 (37) 1.0000	0/70 (41) 1.0000
EYE	MELANOMA, BENIGN	0/70 (48) 0.7073	1/60 (38) 0.4419	0/60 (37) NC	0/70 (41) NC
GLAND, ADRENAL	CORTICAL ADENOMA	3/70 (48) 0.9935	1/60 (39) 0.9126	0/60 (37) 1.0000	0/70 (41) 1.0000
	PHEOCHROMOCYTOMA, BENIGN	1/70 (48) 0.4387	0/60 (38) 1.0000	0/60 (37) 1.0000	1/70 (41) 0.7120
GLAND, MAMMARY	ADENOCARCINOMA	29/70 (55) 0.8249	16/60 (44) 0.9666	10/59 (40) 0.9985	18/70 (47) 0.9515
	ADENOMA	15/70 (52) 0.4748	4/60 (39) 0.9938	2/59 (37) 0.9995	10/70 (45) 0.8355
	FIBROADENOMA	41/70 (56) 1.0000	26/60 (46) 0.9760	21/59 (43) 0.9965	13/70 (45) 1.0000
	FIBROMA	1/70 (48) 1.0000	0/60 (38) 1.0000	0/59 (36) 1.0000	0/70 (41) 1.0000
Gland mammary	C_aden+adenocarci	37/70 (57) 0.7078	17/60 (44) 0.9977	10/60 (41) 1.0000	25/70 (50) 0.9605
GLAND, PARATHYROID	ADENOMA	3/66 (45) 0.9928	1/56 (36) 0.9104	0/55 (33) 1.0000	0/64 (37) 1.0000
GLAND, PITUITARY	ADENOMA	53/70 (67) 0.0837	45/60 (55) 0.4438	45/60 (55) 0.4438	59/70 (67) 0.1216
	CARCINOMA	0/70 (48) 0.2500	0/60 (38) NC	0/60 (37) NC	1/70 (41) 0.4607
	CRANIOPHARYNGIOMA, MALIGNANT	0/70 (48) 0.2500	0/60 (38) NC	0/60 (37) NC	1/70 (41) 0.4607
GLAND, THYROID	C-CELL ADENOMA	9/70 (49) 0.9221	2/60 (38) 0.9878	9/60 (38) 0.3649	2/70 (41) 0.9912
	C-CELL CARCINOMA	1/70 (48) 0.6682	3/60 (38) 0.2254	4/60 (37) 0.1099	1/70 (41) 0.7120
	FOLLICULAR CELL ADENOMA	2/70 (48) 1.0000	0/60 (38) 1.0000	0/60 (37) 1.0000	0/70 (41) 1.0000
Gland thyroid	C_ccell ade+carc	10/70 (49) 0.9399	5/60 (38) 0.8807	12/60 (39) 0.1927	3/70 (42) 0.9848

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Water vs. Low	10 mg/kg/day Med (N=60) P-Value - Water vs. Medium	30 mg/kg/day High (N=70) P-Value - Water vs. High
HEART	SCHWANNOMA, BENIGN	0/70 (48) 0.2914	1/60 (38) 0.4419	0/60 (37) NC	1/70 (41) 0.4607
	SCHWANNOMA, MALIGNANT	1/70 (48) 1.0000	0/60 (38) 1.0000	0/60 (37) 1.0000	0/70 (41) 1.0000
HEMOLYMPHORE TICULA	HISTIOCYTIC SARCOMA	1/70 (48) 0.9166	2/60 (39) 0.4218	0/60 (37) 1.0000	0/70 (41) 1.0000
	LEUKEMIA, GRANULOCYTIC	0/70 (48) 0.2500	0/60 (38) NC	0/60 (37) NC	1/70 (41) 0.4607
	LYMPHOMA, MALIGNANT	0/70 (48) 0.4788	0/60 (38) NC	1/60 (38) 0.4419	0/70 (41) NC
KIDNEY	LIPOMA	1/70 (48) 0.7299	0/60 (38) 1.0000	1/60 (38) 0.6914	0/70 (41) 1.0000
	TUBULAR CELL CARCINOMA	0/70 (48) 0.0190	0/60 (38) NC	1/60 (37) 0.4353	3/70 (43) 0.1016
LARGE INTESTINE, R	PAPILLOMA	0/8 (6) 0.2727	0/1 (1) NC	0/2 (1) NC	1/3 (3) 0.3333
LIVER	CHOLANGIOCARCINOMA	0/70 (48) 0.2500	0/60 (38) NC	0/60 (37) NC	1/70 (41) 0.4607
	HEMANGIOSARCOMA	0/70 (48) 0.0613	0/60 (38) NC	0/60 (37) NC	2/70 (41) 0.2094
	HEPATOCELLULAR ADENOMA	2/70 (48) 0.1121	0/60 (38) 1.0000	0/60 (37) 1.0000	3/70 (42) 0.4362
	HEPATOCELLULAR CARCINOMA	0/70 (48) 0.2500	0/60 (38) NC	0/60 (37) NC	1/70 (41) 0.4607
Multiple Organs	C_Lipomas+Liposarcomas	1/70 (48) 0.7714	1/60 (38) 0.6914	2/60 (38) 0.4122	0/70 (41) 1.0000
	C_hemangiosar+heman	0/70 (48) 0.0156	0/60 (38) NC	0/60 (37) NC	3/70 (42) 0.0977
	C_mesotheliomas	0/70 (48) 0.4788	0/60 (38) NC	1/60 (38) 0.4419	0/70 (41) NC
OVARY	HISTIOCYTIC SARCOMA	0/69 (47) 0.7099	1/60 (38) 0.4471	0/60 (37) NC	0/69 (40) NC
	LUTEOMA	0/69 (47) 0.4753	0/60 (38) NC	1/60 (37) 0.4405	0/69 (40) NC
	MIXED SEX CORD STROMAL TUMOR, BENIGN	0/69 (47) 0.7099	1/60 (38) 0.4471	0/60 (37) NC	0/69 (40) NC
	MIXED SEX CORD STROMAL TUMOR, MALIGNANT	0/69 (47) 0.2469	0/60 (38) NC	0/60 (37) NC	1/69 (40) 0.4598
	TUBULOSTROMAL CARCINOMA	0/69 (47) 0.2515	0/60 (38) NC	0/60 (37) NC	1/69 (41) 0.4659

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Water vs. Low	10 mg/kg/day Med (N=60) P-Value - Water vs. Medium	30 mg/kg/day High (N=70) P-Value - Water vs. High
Oral cavity+Tongue	C_papillo+carcinomas	1/70 (48) 0.3522	0/60 (38) 1.0000	2/60 (37) 0.4023	1/70 (41) 0.7120
PANCREAS	ADENOMA	2/70 (48) 0.9049	1/60 (38) 0.8310	1/60 (37) 0.8249	0/70 (41) 1.0000
	ADENOMA, ACINAR	1/70 (48) 0.5166	1/60 (38) 0.6914	0/60 (37) 1.0000	1/70 (41) 0.7120
	CARCINOMA	1/70 (48) 0.4387	0/60 (38) 1.0000	0/60 (37) 1.0000	1/70 (41) 0.7120
SKIN	BASAL CELL TUMOR, MALIGNANT	0/70 (48) 0.2704	1/60 (39) 0.4483	1/60 (37) 0.4353	1/70 (41) 0.4607
	HAIR FOLLICLE TUMOR, BENIGN	1/70 (48) 1.0000	0/60 (38) 1.0000	0/60 (37) 1.0000	0/70 (41) 1.0000
	POLYP	0/70 (48) 0.5950	1/60 (38) 0.4419	1/60 (38) 0.4419	0/70 (41) NC
	SQUAMOUS CELL CARCINOMA	0/70 (48) 0.1748	0/60 (38) NC	1/60 (37) 0.4353	1/70 (41) 0.4607
SMALL INTESTINE, J	LEIOMYOMA	2/69 (48) 1.0000	0/59 (38) 1.0000	0/59 (37) 1.0000	0/70 (41) 1.0000
SPLEEN	HEMANGIOSARCOMA	0/70 (48) 0.2515	0/59 (37) NC	0/60 (37) NC	1/70 (41) 0.4607
SUBCUTIS	FIBROMA	1/3 (3) 0.5238	0/3 (2) 1.0000	1/3 (2) 0.7000	0/1 (0) NC
	FIBROSARCOMA	2/3 (3) 0.7143	0/3 (2) 1.0000	1/3 (2) 0.9000	0/1 (0) NC
	LIPOMA	0/3 (2) 0.3333	1/3 (2) 0.5000	1/3 (2) 0.5000	0/1 (0) NC
	MELANOMA, MALIGNANT	0/3 (2) 0.1667	0/3 (2) NC	0/3 (1) NC	1/1 (1) 0.3333
THYMUS	THYMOMA, MALIGNANT	0/69 (47) 0.7117	1/60 (38) 0.4471	0/60 (37) NC	0/70 (41) NC
UTERUS	ENDOMETRIAL ADENOMA	0/70 (48) 0.7073	1/60 (38) 0.4419	0/60 (37) NC	0/70 (41) NC
	GRANULAR CELL TUMOR, MALIGNANT	0/70 (48) 0.4756	0/60 (38) NC	1/60 (37) 0.4353	0/70 (41) NC
	HISTIOCYTIC SARCOMA	0/70 (48) 0.7073	1/60 (38) 0.4419	0/60 (37) NC	0/70 (41) NC
	LEIOMYOSARCOMA	1/70 (48) 0.5152	1/60 (39) 0.6985	0/60 (37) 1.0000	1/70 (41) 0.7120
	POLYP	5/70 (48) 0.3966	4/60 (38) 0.6275	3/60 (38) 0.7776	5/70 (42) 0.5419

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-Value Trend	3 mg/kg/day Low (N=60) P-Value - Water vs. Low	10 mg/kg/day Med (N=60) P-Value - Water vs. Medium	30 mg/kg/day High (N=70) P-Value - Water vs. High
VAGINA	GRANULAR CELL TUMOR, BENIGN	0/69 (47) 0.7811	2/59 (37) 0.1910	0/59 (36) NC	0/70 (41) NC
	GRANULAR CELL TUMOR, MALIGNANT	0/69 (47) 0.4815	0/59 (37) NC	1/59 (37) 0.4405	0/70 (41) NC
	POLYP	0/69 (47) 0.2547	0/59 (37) NC	0/59 (36) NC	1/70 (41) 0.4659
	SQUAMOUS CELL CARCINOMA	0/69 (47) 0.7081	1/59 (37) 0.4405	0/59 (36) NC	0/70 (41) NC

Figure 1: Kaplan-Meier Survival Functions for Male Rats

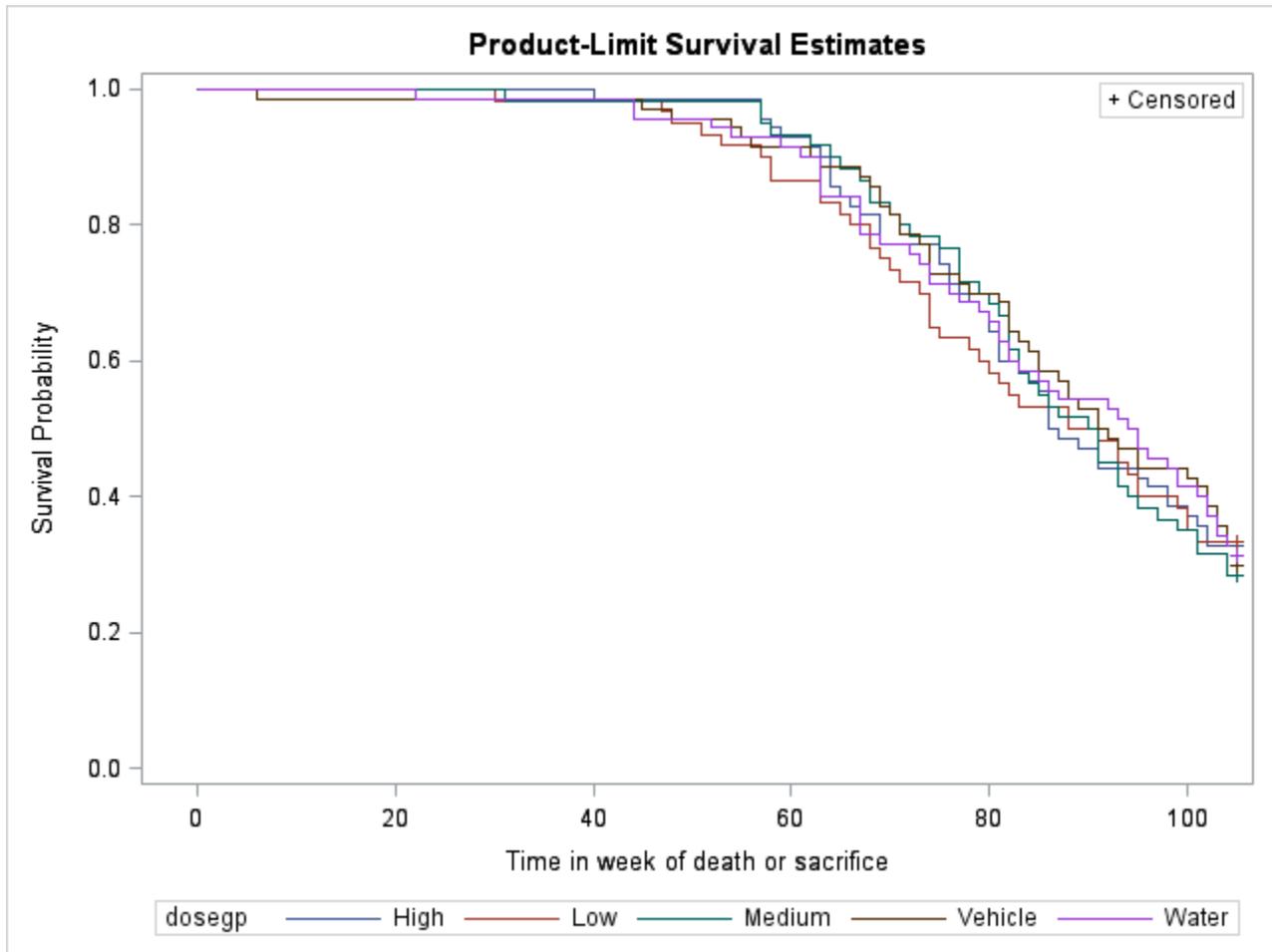
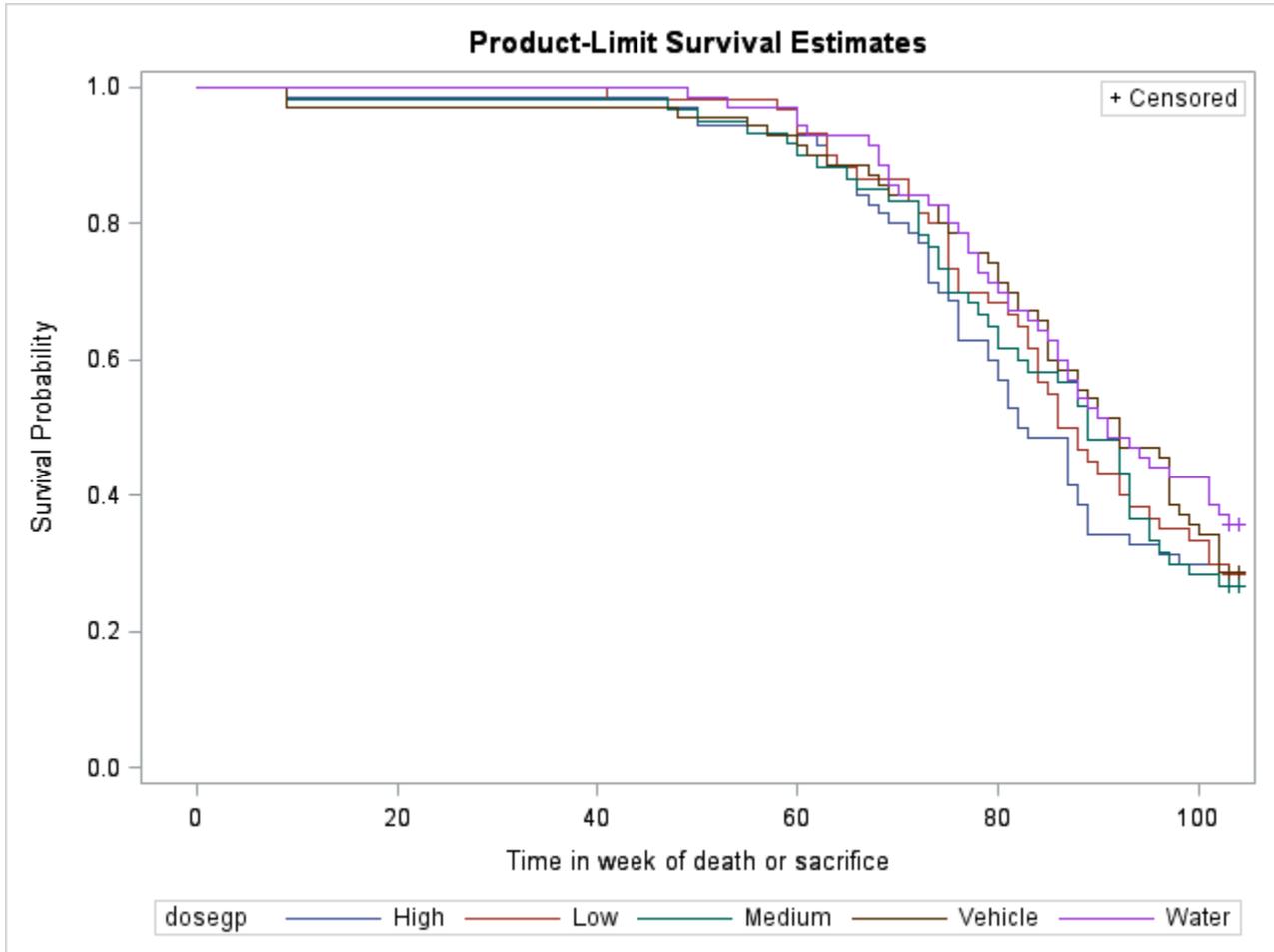


Figure 2: Kaplan-Meier Survival Functions for Female Rats



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Concur with review.

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