CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	203-858/N-000
Drug Name:	Lomitapide mesylate capsules
Indication(s):	Treatment of homozygous familial hypercholesterolemia
Applicant:	Aegerion Pharmaceuticals, Inc.
Date(s):	Received 02/29/12; user fee (10 months) 12/29/12
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
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Keywords:	NDA review, clinical studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Data from the pivotal Phase 3 trial have demonstrated that lomitapide was effective in reducing LDL-C, total cholesterol (TC), Apo B, triglycerides (TRIG), non-HDL-C, and VLDL-C in patients with HoFH after 26 weeks of treatment when used as an adjunct to a low-fat diet and other lipid-lowering therapies with or without LDL apheresis. The reductions seemed to be maintained through Week 56 for LDL-C, TC, ApoB, and non-HDL-C. Lomitapide was also shown to lower HDL-C during the 26-week dose-titration efficacy phase. However, the mean HDL-C at Week 56 was returned to its baseline level.

Evaluation of the data after Week 56 may be important for TRIG, VLDL-C, and especially HDL-C since the long-term effect of lomitapide on these parameters remains to be seen.

Labeling Comments: The following bullets summarize this reviewer's comments for the sponsor's proposed labeling in the Clinical Studies section.

- The sponsor stated the primary efficacy endpoint as "mean" percent change in LDL-C from baseline at Week 26. The "mean" should be omitted since it is not an endpoint; rather, it is an average of the endpoint values of the treated subjects in the study.

- Figure 1 is currently based on the ITT population with LOCF. This reviewer thinks that the graph should be based on the completers over time, with Week 26/LOCF values alongside.

- Table 5 presents the results for Week 26/LOCF (N = 29) and Week 56 (N = 23). It may be informative to include Week 26 (N = 23) results also so that there is a direct comparison between the 2 time points.

- The parameters listed in Table 5 should be clearly identified as the primary, key secondary, and other efficacy variables in the text. An asterisk (*) may be used to indicate a significant p-value for the primary and key secondary variables since their statistical analyses were prioritized.

1.2 Brief Overview of Clinical Studies

Aegerion Pharmaceuticals, Inc. has submitted an original NDA seeking approval of lomitapide mesylate capsules for the treatment of homozygous familial hypercholesterolemia (HoFH) when used as an adjunct to a low-fat diet and other lipid-lowering therapies with or without LDL apheresis. Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor. It has received an orphan drug designation for this indication on 10/23/2007. In

this NDA, the sponsor included the results from 24 clinical trials, ranging from Phase 1 to Phase 3, that were conducted in healthy subjects, adults with elevated LDL-C and other risk factors for CVD (without HoFH), adults with hepatic impairment, adults with end stage renal disease on dialysis, and adults with HoFH. The efficacy of lomitapide in patients with HoFH would be determined primarily based on the results from a pivotal Phase 3 study UP1002/AEGR-733-005 (29 patients) and a supportive Proof-of-Concept Phase 2 study UP1001 (6 patients) since the other trials were conducted in different populations.

The pivotal Phase 3 study was a 78-week, open-label, single-arm, dose-escalation (5, 10, 20, 40, 60 mg/day), multicenter, multinational trial, conducted at 11 sites located in US, Canada, South Africa, and Italy. The supportive Phase 2 study was a 16-week, open-label, single-arm, dose-escalation (0.03, 0.1, 0.3, 1.0 mg/kg/day), single-center (in US) trial. In the pivotal study, subjects were required to continue their concomitant lipid-lowering therapies through Week 26 (efficacy phase) and follow a diet with < 20% energy from fat; while in the supportive study, subjects were asked to stop all the lipid-lowering therapies prior to the Baseline visit but follow a rigorous low-fat diet with < 10% energy from fat.

At the time of the NDA submission, the pivotal trial was still ongoing. Therefore, the sponsor's clinical study report covers only the data and results through Week 56 based on the data cut-off date of 04/12/2011.

1.3 Statistical Issues and Findings

For Study UP1002/AEGR-733-005, a total of 29 subjects were enrolled and treated with lomitapide. As of 04/12/2011 the data cut-off date, 6 patients discontinued from the trial prior to Week 26; 23 of the 29 enrolled patients completed Week 56; and 18 of the 23 patients completed the entire 78-week trial. For Study UP1001, all the 6 enrolled subjects completed the trial.

As shown in Table 6 in the main body of this review, for the pivotal Phase 3 trial (Study UP1002/AEGR-733-005), the mean % decrease in LDL-C from baseline to Week 26 was about 40% for the ITT/LOCF population (N = 29) and 50% for the completers (N = 23). In addition, a total of 20 patients had a > 15% decrease in LDL-C at Week 26. Although the study was not designed as a dose-response trial, it was noted that the mean % reductions in LDL-C were increasing as doses were increased over the titration period (see Table 7 in the main body of this review). The reduction, however, reached a plateau at Week 18, but was sustained around 40-45% between Weeks 36 and 56 with the mean maximum tolerated dose (MTD) about 40 mg.

Note that the sponsor stated that there was a dose-response across patients whose maximum tolerated doses were 20, 40, and 60 mg with mean % changes from baseline to Week 26 in LDL-C of -33%, -48%, and -55%, respectively, based on the ITT/LOCF population (sponsor's CSR, page 108). This reviewer thinks that the statement is misleading because the patient who dropped out at 40 mg had a +17% change from baseline (see Table 8 in the main body of this review). In the completer cohort, the mean % changes at Week 26 were actually -38% (n = 5), -57% (n = 6), and -55% (n = 10) for the 20, 40, and 60 mg, respectively. In other words, the mean % reductions in LDL-C appear to be similar between the patients receiving 40 mg and 60 mg at Week 26.

There were statistically significant mean % reductions from baseline in TC, ApoB, and TRIG after 26 weeks of treatment with lomitapide (all $p \leq 0.01$). Significant mean % changes from baseline in non-HDL-C and VLDL-C at Week 26 favoring lomitapide were also observed (nominal $p < 0.05$). As in the case of LDL-C, the reductions in TC, ApoB, and non-HDL-C were seen as early as Week 2 and were continuously decreased until Week 18, then slightly went back up, but were sustained through Week 56 (see Figures 5 and 7 in the main body of this review). The reductions in TRIG and VLDL-C after Week 18 were, however, continuously reversed through Week 56.

There was no marked change in Lp(a) after 26 weeks of treatment with lomitapide when compared with baseline. There was, however, a beneficial reduction in Lp(a) after 56 weeks of treatment.

The mean % reduction in HDL-C at Week 26 was statistically significant in the completer cohort (-12.3%, nominal $p < 0.01$), but not in the ITT/LOCF population (-7.0%, nominal $p = 0.07$). The decrease in HDL-C after treatment with lomitapide was observed, but was reversed after Week 18, and gradually returned to the baseline level at Week 56.

Similar treatment effects on mean % changes from baseline in LDL-C at Week 26/LOCF were observed between males and females (-40% vs. -39%), age < 30 years and ≥ 30 years (-39% vs. -40%), White and non-White (-40% vs. -35%), US/Canada and other countries (-32% vs. -45%), baseline BMI < 30 and ≥ 30 kg/m^2 (-40% vs. -37%), and the use (yes or no) of apheresis at entry (-34% vs. -49%). There was a negative, but weak, correlation between the baseline LDL-C and % change from baseline in LDL-C at Week 26/LOCF in Study UP1002/AEGR-733-005.

Results from the supportive Phase 2 trial (Study UP1001) were similar to the results observed in the pivotal Phase 3 trial in general.

2. INTRODUCTION

2.1 Overview

Aegerion Pharmaceuticals, Inc. has submitted an original NDA seeking approval of lomitapide mesylate capsules for the treatment of homozygous familial hypercholesterolemia (HoFH) when used as an adjunct to a low-fat diet and other lipid-lowering therapies with or without LDL apheresis. Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor. It has received an orphan drug designation for this indication on 10/23/2007. In this NDA, the sponsor included the results from 24 clinical trials, ranging from Phase 1 to Phase 3, that were conducted in healthy subjects, adults with elevated LDL-C and other risk factors for CVD (without HoFH), adults with hepatic impairment, adults with end stage renal disease on dialysis, and adults with HoFH. The efficacy of lomitapide in patients with HoFH would be determined primarily based on the results from a pivotal Phase 3 study UP1002/AEGR-733-005 (29 patients) and a supportive Proof-of-Concept Phase 2 study UP1001 (6 patients) since the other trials were conducted in different populations. Therefore, this review focuses on the efficacy evaluation of these two studies.

2.2 Data Sources

The original clinical study reports and electronic data files are located in the sub-folders of EDR \\CDSESUB1\EVSPROD\NDA203858\0000. The sponsor provided datasets with SDTM format for individual studies and ADaM format for ISS and ISE. Since datasets with SDTM format contained multiple measurements from the same visit window for some patients, included data in the US unit for the US sites only, and did not have LOCF flag, this reviewer had to use the ISE dataset to extract study-specific data for the purpose of statistical analyses. However, there were some slight discrepancies between the results presented in the clinical study report (CSR) of the UP1002/AEGR-733-005 trial and the clinical overview (ISE). The sponsor stated in the August 1, 2012 submission that the differences were due to the baseline date used between the CSR and ISE analyses (\\CDSESUB1\EVSPROD\NDA203858\0020). In CSR, the lab assessment Visit 3 date was used as the baseline date to calculate subsequent visit windows; while in ISE, the first dose date was used as the baseline date. The differences in results for the primary efficacy endpoint between the CSR and ISE analyses appeared to be small.

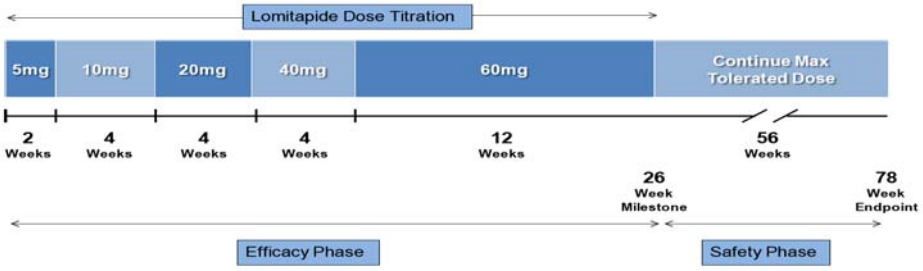
3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Protocol UP1002/AEGR-733-005 was a Phase 3, 78-week, open-label, single-arm, dose-escalation (5, 10, 20, 40, 60 mg/day), multicenter, multinational trial, conducted at 11 sites located in US (2 sites), Canada (2 sites), South Africa (3 sites), and Italy (4 sites). According to the sponsor, the dose escalation approach (see the schema below) was designed to achieve

the optimal individualized dose to maximize efficacy and minimize gastrointestinal side effects and transaminase elevations. Patients could have their dose titrated to 80 mg if they met strict safety and efficacy criteria. There was a 6-week run-in period where subjects were instructed to continue their concomitant lipid-lowering therapies (stable dose and regimen through Week 26), follow a diet with < 20% energy from fat, and start taking dietary supplements of vitamin E and fatty acids provided by the sponsor. After completing 26 weeks of treatment with lomitapide (Efficacy Phase), patients entered the Safety Phase at their established dose defined at Week 26 for an additional 52 weeks. The primary objective of this study was to evaluate the efficacy of lomitapide as defined by percent change from baseline in LDL-C at an individually-identified maximum tolerated dose after 26 weeks of treatment in patients with HoFH. Based on the assumptions of 25% change in LDL-C after 26 weeks of treatment with a 30% SD and 15% dropout rate, 29 subjects were enrolled to obtain at least 90% power for the study. The clinical study report covers only the data and results through Week 56 based on the data cut-off date of 04/12/2011.



Protocol UP1001 was a Phase 2, 16-week, open-label, single-arm, dose-escalation (0.03, 0.1, 0.3, 1.0 mg/kg/day), single-center (in US) trial. In contrast to Study UP1002/AEGR-733-005, subjects in this trial were required to stop all lipid-lowering therapies including apheresis within 4 weeks prior to the Baseline visit and throughout the trial. In addition, subjects were asked to follow a rigorous low-fat diet with < 10% energy from fat and were provided a standard multivitamin supplying 100% of the current dietary reference intake (DRI) for all essential vitamins and minerals. The primary objective of this study was to evaluate the safety and tolerability of 4 doses of lomitapide. Evaluation of the efficacy (lipid panel) was secondary.

3.1.2 Statistical Methods

For Study UP1002/AEGR-733-005, the primary efficacy endpoint was percent change from baseline in LDL-C at Week 26 and was analyzed using paired t-test by the sponsor. This reviewer also analyzed the data using Wilcoxon signed-rank test which can accommodate small sample sizes and non-normality. The proportions of LDL-C responders defined as greater than 15%, 25%, and 50% decreases from baseline to Week 26/LOCF were

summarized. There were 3 key secondary efficacy variables: total cholesterol (TC), Apo B, and triglycerides (TRIG). They were prioritized sequentially by the sponsor and analyzed using the same test to preserve the Type 1 error rate at $\alpha = 0.05$. Other lipid variables such as non-HDL-C, VLDL-C, Lp(a), and HDL-C were also analyzed in a similar fashion, but without multiplicity adjustment. The baseline value was calculated as the average of Week -2 and Week 0 values. The ITT population consisting of subjects who had received at least one dose of lomitapide, and had a baseline and a post-baseline LDL-value was the primary population for efficacy analyses. Missing data at Week 26 were imputed using the LOCF method. Analyses based on the completers at Week 26 as well as at Week 56 were also performed to evaluate the impact of dropouts on efficacy.

For Study UP1001, there was no formal statistical analysis plan developed. Although safety and tolerability were the primary interest of this study, percent change from baseline in LDL-C at Week 16 was the primary efficacy endpoint. For the ease of discussion, efficacy evaluation for this supportive study was performed similarly to the pivotal study.

3.1.3 Subject Disposition

For Study UP1002/AEGR-733-005, a total of 29 subjects were enrolled and treated with lomitapide. As of 04/12/2011 the data cut-off date, 6 patients discontinued from the trial prior to Week 26; 23 of the 29 enrolled patients completed Week 56; and 18 of the 23 patients completed the entire 78-week trial. Among the 6 dropouts (21%), 3 (10%) discontinued due to withdrawn consent, 2 (7%) due to adverse event, and 1 (3%) due to non-compliance or lack of cooperation. Their final titrated doses were 5 mg (n = 2), 10 mg (n = 2), 20 mg (n = 1), and 40 mg (n = 1). *For Study UP1001*, all the 6 enrolled subjects completed the trial.

3.1.4 Demographic and Baseline Characteristics

There were no geriatric (≥ 65 years) patients enrolled in these 2 studies. Most patients were White. Males and females were approximately equally distributed. Half of the population in each study had BMI < 25 kg/m^2. As shown in Table 1, the mean baseline LDL-C in Study UP1001 (614.2 mg/dL) was much higher than that in Study UP1002/AEGR-733-005 (337.0 mg/dL), as were the mean baseline values of TC, ApoB, and triglycerides. As explained by the sponsor, the high elevation in baseline lipids in Study UP1001 was due to the requirement of no lipid-lowering therapies within 4 weeks of the study entry; while in Study UP1002/AEGR-733-005, subjects were required to be on a stable regimen of their standard of care therapies during the run-in period. The majority of subjects in Study UP1002/AEGR-755-005 received their maximum tolerated doses of statins with or without ezetimibe at baseline.

Table 1 – Demographic and Baseline Characteristics – ITT Population

Characteristic		UP1002/AEGR-733-005 (N = 29)	UP1001 (N = 6)
Age (years):	Mean ± SD	30.7 ± 10.6	25.0 ± 9.2
	Median	30	21.0
	Range	18.0 – 55.0	17.0 – 39.0
Sex:	Male (%)	16 (55.2)	3 (50.0)
	Female (%)	13 (44.8)	3 (50.0)
Race:	White (%)	25 (86.2)	3 (50.0)
	Asian (%)	2 (6.9)	1 (16.7)
	Black or African American (%)	1 (3.4)	0
	Other (%)	1 (3.4)	2 (33.3)
Country:	USA (%)	7 (24.1)	6 (100.0)
	Canada (%)	5 (17.2)	0
	Italy (%)	6 (20.7)	0
	South Africa (%)	11 (37.9)	0
BMI (kg/m^2):	Mean ± SD	25.9 ± 5.5	24.9 ± 4.0
	Median	23.9	24.8
	Range	19.3 – 41.3	18.5 – 30.2
LDL-C (mg/dL):	Mean ± SD	337.0 ± 113.8	614.2 ± 105.8
	Median	357.1	622.5
	Range	152.4 – 565.0	480 – 789
TC (mg/dL):	Mean ± SD	430.4 ± 135.3	850.5 ± 194.8
	Median	459.5	796.5
	Range	191.4 – 721.6	684.0 – 1212.0
ApoB (mg/dL):	Mean ± SD	260.1 ± 80.1	310.0 ± 51.6
	Median	262.0	309.0
	Range	124.0 – 431.5	240.0 – 387.0
TRIG (mg/dL):	Mean ± SD	102.7 ± 47.8	282.8 ± 187.7
	Median	92.1	259.0
	Range	31.9 – 253.0	82.0 – 605.0
Use of Apheresis:	Yes (%)	18 (62.1)	NA
	No (%)	11 (37.9)	NA
Use of Statins:	Yes (%)	27 (93.1)	NA
	No (%)	2 (6.9)	NA
Use of Ezetimibe:	Yes (%)	22 (75.9)	NA
	No (%)	7 (24.1)	NA

3.1.5 Efficacy Results and Discussion

Unless otherwise stated, all the tables and graphs presented in this report were generated by this reviewer.

Primary Efficacy Endpoint. In Study UP1002\AEGR-733-005, after treatment with lomitapide, mean LDL-C in patients with HoFH was significantly reduced from 337.0 mg/dL at baseline to 191.3 mg/dL at Week 26 (Table 2). The mean % change from baseline in LDL-C at Week 26 in this pivotal trial was -40% based on the ITT/LOCF population ($p < 0.0001$) and the median % change was -50%. In Study UP1001, mean LDL-C was also significantly reduced from 614.2 mg/dL at baseline to 303.0 mg/dL at Week 16. The mean and median % changes from baseline in LDL-C at Week 16 in this supportive trial were -51% and -52%, respectively ($p < 0.0001$).

Table 2 – Statistical Results for LDL-C (mg/dL)

ITT/LOCF population		UP1002/AEGR-733-005 (26-week)	UP1001 (16-week)
Baseline	Mean ± SD (N)	337.0 ± 113.8 (29)	614.2 ± 105.8 (6)
	Median	357.1	622.5
	Min, Max	152.4, 565.0	480.0, 789.0
Endpoint	Mean ± SD (N)	191.3 ± 106.6 (29)	303.0 ± 81.3 (6)
	Median	169.4	303.5
	Min, Max	28.0, 442.8	201.0, 403.0
% Change	Mean ± SD (N)	-39.6 ± 32.0 (29)	-50.9 ± 9.3 (6)
	95% CI	(-51.8, -27.4)	(-60.7, -41.2)
	Median	-49.6	-52.3
	Min, Max	-92.6, 20.5	-62.4, -33.8
	Paired t-test p-value	< 0.0001	< 0.0001
	Signed-rank test p-value	< 0.0001	0.0313
Results were generated using the study-specific data extracted from the ISE ADaM dataset.			

There were 2 sites (Nos. 31 and 32, two patients each, all completers) showing larger mean % changes from baseline in LDL-C at Week 26 with very small standard deviations (-61% ± 2.5% and -52% ± 0.7%) when compared to the other sites in the study. When the 2 sites were excluded from the primary efficacy analysis, similar results were observed (-37% ± 34%, $N = 25$, $p < 0.0001$).

For the completer cohort in Study UP1002/AEGR-733-005 ($N = 23$), similar significant findings were also observed (mean % change at Week 26 = -50%, $p < 0.0001$). The following Figure 1 depicts that the mean % reductions from baseline in LDL-C were 9%, 15%, 27%, 44%, and 53% by Week 2, 6, 10, 14, and 18, respectively, where the

corresponding mean doses were 5, 10, 18, 33, and 40 mg, implying that the reductions in LDL-C were increasing as the doses were increased during the titration period. Then the mean % reduction was reduced to 50% by Week 26 with a mean dose of 45 mg, and further reduced to around 40%-45% between Weeks 36 and 56 with mean doses around 40 mg. At Week 26, the mean % reductions in LDL-C associated with the 5, 10, 20, 40, and 60 mg doses were 51% (n = 1), NA (n = 0), 38% (n = 5), 57% (n = 6), and 55% (n = 10), respectively. One patient received 80 mg at Week 26 and experienced a 29% reduction in LDL-C. In Study UP1001, the mean % reductions from baseline in LDL-C were small and insignificant during the 1st half of the study, which was probably due to the small doses used (2 mg at Week 4 and 7 mg at Week 8). By Week 12, the mean dose was increased to 20 mg and the mean % reduction was 25%. At the end of the 16-week study, 51% mean reduction in LDL-C was observed and it was associated with a higher mean dose of 67 mg.

Figure 1

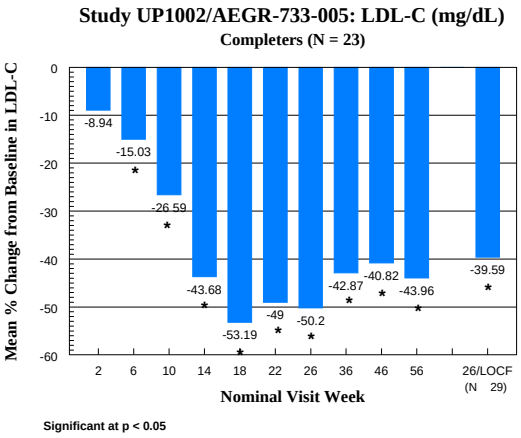
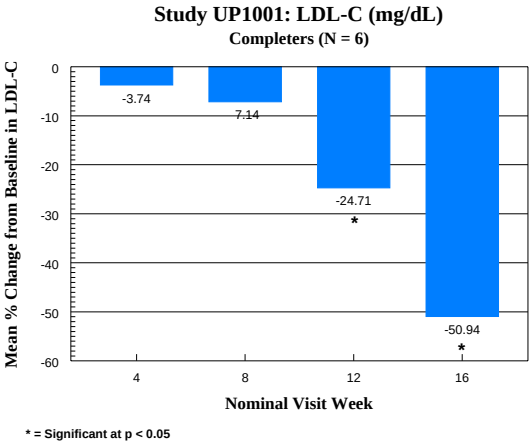


Figure 2



Slightly more than 2/3 of the 29 patients in the pivotal trial and all of the 6 enrolled patients in the supportive trial had greater than 15% of decrease in LDL-C from baseline at the end of the efficacy phase (Table 3). From Figures 3 and 4 below, one can easily obtain the % of subjects achieving a given level of response for any definition of responders. There were 4 patients (14%) in Study UP1002/AEGR-733-005 with an increased LDL-C from baseline after 26 weeks of treatment with lomitapide.

Table 3 – Responders for LDL-C (mg/dL)

	UP1002/AEGR-733-005		UP1001	
	Yes	No	Yes	No
> 15% reduction from baseline to Week 26/LOCF	20/29 (69%)	9/29 (31%)	6/6 (100%)	0
> 25% reduction from baseline to Week 26/LOCF	19/29 (66%)	10/29 (34%)	6/6 (100%)	0
> 50% reduction from baseline to Week 26/LOCF	14/29 (48%)	15/29 (52%)	5/6 (83%)	1/6 (17%)

Figure 3

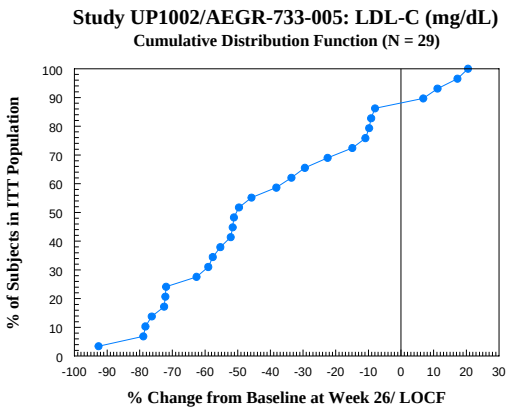
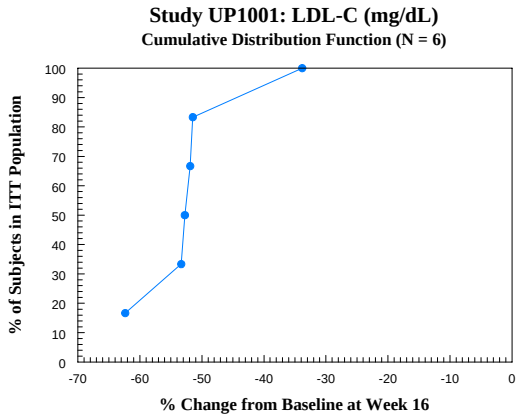


Figure 4



Key Secondary Efficacy Endpoints. As Table 4 shows, lomitapide significantly reduced total cholesterol (TC), ApoB, and triglycerides (TRIG) in patients with HoFH after 26 weeks of treatment in Study UP1002/AEGR-733-005 and after 16 weeks of treatment in Study UP1001 (all $p < 0.05$).

Table 4 – Statistical Results for % Change from Baseline for Key Secondary Efficacy Endpoints

Study	ITT/LOCF Population	TC (mg/dL)	ApoB (mg/dL)	TRIG (mg/dL)	Ln TRIG (mg/dL)
UP1002 /AEGR-733-005	Mean ± SD (N)	-35.7 ± 29.4 (29)	-39.3 ± 30.3 (29)	-28.2 ± 57.6 (29)	-0.60 ± 0.75 (29)
	95% CI	(-46.9, -24.5)	(-50.8, -27.8)	(-50.1, -6.3)	(-0.88, -0.31)
	Median	-40.0	-46.2	-44.5	-0.59
	Min, Max	-81.4, 24.2	-90.4, 19.0	-87.4, 169.4	-2.07, 0.99
	Paired t-test p	< 0.0001	< 0.0001	0.0136	0.0002
	Signed-rank test p	< 0.0001	< 0.0001	0.0023	< 0.0001
UP1001	Mean ± SD (N)	-58.4 ± 8.6 (6)	-55.6 ± 13.5 (6)	-65.2 ± 13.3 (6)	-1.12 ± 0.39 (6)
	95% CI	(-67.4, -49.3)	(-69.7, -41.4)	(-79.1, -51.3)	(-1.53, -0.71)
	Median	-56.7	-57.0	-68.2	-1.15
	Min, Max	-68.7, -50.3	-70.0, -36.8	-82.1, -43.9	-1.72, -0.58
	Paired t-test p	< 0.0001	0.0002	< 0.0001	0.0009
	Signed-rank test p	0.0313	0.0313	0.0313	0.0313

Results were generated using the study-specific data extracted from the ISE ADaM dataset.

Note: The raw TRIG data in Study UP1002/AEGR-733-005 were not normally distributed.

Ln TRIG = Log-transformed triglycerides

The response patterns of TC, ApoB, and TRIG over time in both studies (Figures 5 and 6) were similar to that of the primary efficacy variable, LDL-C (Figures 1 and 2). That is, in the

pivotal study, the reductions were seen as early as Week 2 and were continuously decreased until Week 18, then slightly went back up, but were sustained through Week 56 (except for TRIG of which reduction at Week 56 was smaller). In the supportive study, the reductions were continuous until the end of the trial.

Figure 5

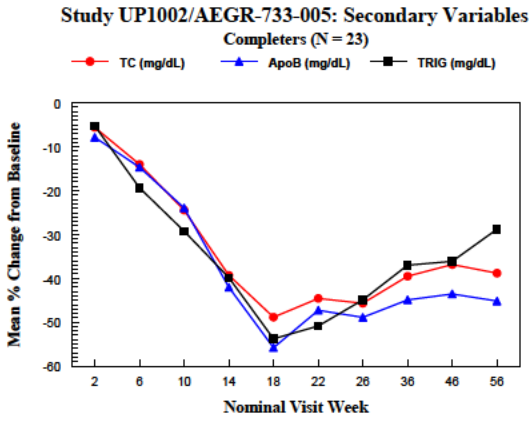
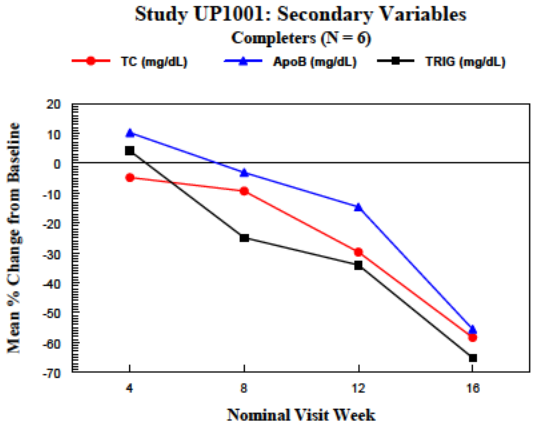


Figure 6



Other Efficacy Endpoints. As Table 5 shows, lomitapide also significantly reduced non-HDL-C and VLDL-C in patients with HoFH after 26 weeks of treatment in Study UP1002/AEGR-733-005 and after 16 weeks of treatment in Study UP1001 (nominal $p < 0.05$). The reductions in Lp(a) and HDL-C at the end of the efficacy phase in both studies were observed, but not statistically significant.

Table 5 – Statistical Results for % Change from Baseline for Other Efficacy Endpoints

Study	ITT/LOCF Population	Non-HDL-C (mg/dL)	VLDL-C (mg/dL)	Lp(a) (nmol/L)	HDL-C (mg/dL)
UP1002 /AEGR-733-005	Mean ± SD (N)	-39.2 ± 31.1 (29)	-27.9 ± 58.4 (29)	-10.6 ± 33.9 (29)	-7.0 ± 19.7 (29)
	95% CI	(-51.1, -27.4)	(-50.1, -5.7)	(-23.5, +2.3)	(-14.5, +0.6)
	Median	-47.7	-45.1	-13.4	-5.6
	Min, Max	-89.7, 25.9	-87.5, 175.0	-62.9, 88.1	-48.5, 28.3
	Paired t-test p	< 0.0001	0.0155	0.1034	0.0683
	Signed-rank test p	< 0.0001	0.0021	0.0324	0.0751
UP1001	Mean ± SD (N)	-60.1 ± 8.9 (6)	-78.7 ± 23.1 (6)	-10.5 ± 20.5 (6)	-2.2 ± 18.0 (6)
	95% CI	(-69.4, -50.8)	(-103.0, -54.5)	(-32.0, +11.0)	(-21.1, +16.7)
	Median	-58.7	-88.8	-16.1	-9.9
	Min, Max	-70.5, -52.1	-93.3, -33.3	-36.1, 18.8	-18.5, 30.0
	Paired t-test p	< 0.0001	0.0004	0.2632	0.7742
	Signed-rank test p	0.0313	0.0313	0.2188	0.5625

Results were generated using the study-specific data extracted from the ISE ADaM dataset.

Note: The raw VLDL-C data in both studies were not normally distributed.

Note: The raw Lp(a) data in Study UP1002/AEGR-733-005 were not normally distributed.

In the pivotal study, the response patterns of non-HDL-C and VLDL-C over time were similar to that of LDL-C and TRIG, respectively. As exhibited in Figure 7, the reductions in HDL-C from baseline were continued through Week 18, and then were gradually reversed to the baseline level at Week 56. In contrast to the pivotal study, mean HDL-C in the supportive study was increased from Week 4 to Week 12, and then decreased back to the baseline level at Week 16 (Figure 8).

Figure 7

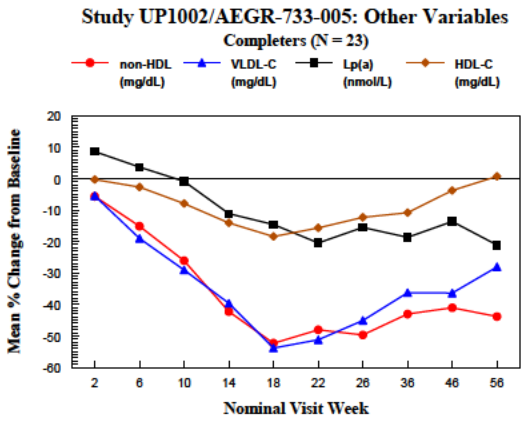
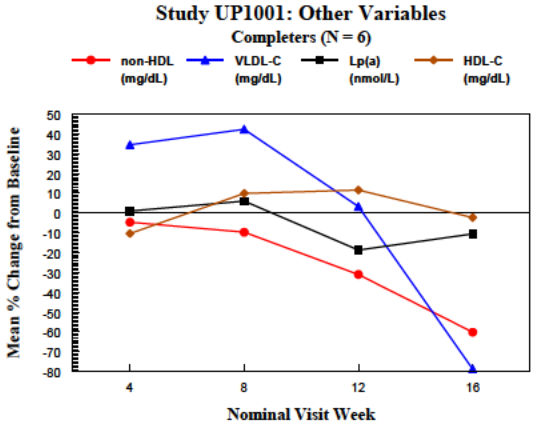


Figure 8



3.2 Evaluation of Safety

In consultation with the reviewing medical officer, there were no aspects of safety that required review by a statistician. See Dr. James Smith's report for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

In the pivotal study, mean % decreases from baseline in LDL-C at Week 26/LOCF were similar between males and females (-40% vs. -39%), between age < 30 years and ≥ 30 years (-39% vs. -40%), and between White and non-White (-40% vs. -35%).

4.2 Other Special/Subgroup Populations

In the pivotal study, mean % decreases from baseline in LDL-C at Week 26/LOCF were similar between US/Canada and other countries (-32% vs. -45%), between baseline BMI < 30 and ≥ 30 kg/m^2 (-40% vs. -37%), and between the use (yes or no) of apheresis at entry (-34% vs. -49%).

As seen in Figure 9, there was a negative, but weak, correlation between the baseline LDL-C (x-axis) and % change from baseline in LDL-C at Week 26/LOCF (y-axis) in Study UP1002/AEGR-733-005.

Figure 9

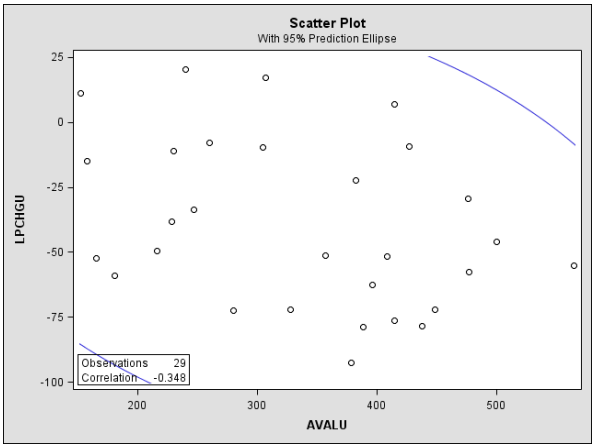
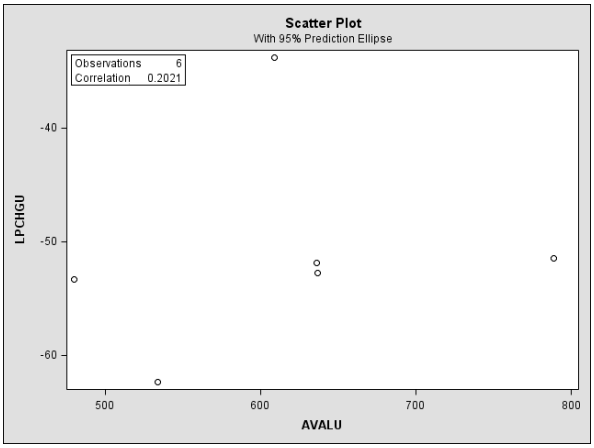


Figure 10



5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

As shown in Table 6, for the pivotal Phase 3 trial (Study UP1002/AEGR-733-005), the mean % decrease in LDL-C from baseline to Week 26 was about 40% for the ITT/LOCF population (N = 29) and 50% for the completers (N = 23). In addition, a total of 20 patients had a > 15% decrease in LDL-C at Week 26. Although the study was not designed as a dose-response trial, it was noted that the mean % reductions in LDL-C were increasing as doses were increased over the titration period (Table 7). The reduction, however, reached a plateau at Week 18, but was sustained around 40-45% between Weeks 36 and 56 with the mean maximum tolerated dose (MTD) about 40 mg.

Note that the sponsor stated that there was a dose-response across patients whose maximum tolerated doses were 20, 40, and 60 mg with mean % changes from baseline to Week 26 in LDL-C of -33%, -48%, and -55%, respectively, based on the ITT/LOCF population (sponsor's CSR, page 108). This reviewer thinks that the statement is misleading because the patient who dropped out at 40 mg had a +17% change from baseline (Table 8). In the completer cohort, the mean % changes at Week 26 were actually -38% (n = 5), -57% (n = 6), and -55% (n = 10) for the 20, 40, and 60 mg, respectively. In other words, the mean % reductions in LDL-C appear to be similar between the patients receiving 40 mg and 60 mg at Week 26.

Table 8 – Final Dose and % Change from Baseline in LDL-C of the Withdrawn Patients

5 mg	10 mg	20 mg	40 mg	60 mg
-9.8% +6.8%	-8.0% +11.2%	-10.9%	+17.3%	NA

There were statistically significant mean % reductions from baseline in TC, ApoB, and TRIG after 26 weeks of treatment with lomitapide (all $p \leq 0.01$, Table 6). Significant mean % changes from baseline in non-HDL-C and VLDL-C at Week 26 favoring lomitapide were also observed (nominal $p < 0.05$). As in the case of LDL-C, the reductions in TC, ApoB, and non-HDL-C were seen as early as Week 2 and were continuously decreased until Week 18, then slightly went back up, but were sustained through Week 56 (see Figures 5 and 7 above). The reductions in TRIG and VLDL-C after Week 18 were, however, continuously reversed through Week 56.

There was no marked change in Lp(a) after 26 weeks of treatment with lomitapide when compared with baseline. There was, however, a beneficial reduction in Lp(a) after 56 weeks of treatment.

The mean % reduction in HDL-C at Week 26 was statistically significant in the completer cohort (-12.3%, nominal $p < 0.01$), but not in the ITT/LOCF population (-7.0%, nominal $p = 0.07$). The decrease in HDL-C after treatment with lomitapide was observed, but was reversed after Week 18, and gradually returned to the baseline level at Week 56.

Results from the supportive Phase 2 trial (Study UP1001) were similar to the results observed in the pivotal Phase 3 trial in general.

5.2 Conclusions and Recommendations

Data from the pivotal Phase 3 trial have demonstrated that lomitapide was effective in reducing LDL-C, total cholesterol (TC), Apo B, triglycerides (TRIG), non-HDL-C, and VLDL-C in patients with HoFH after 26 weeks of treatment when used as an adjunct to a low-fat diet and other lipid-lowering therapies with or without LDL apheresis. The reductions seemed to be maintained through Week 56 for LDL-C, TC, ApoB, and non-HDL-C. Lomitapide was also shown to lower HDL-C during the 26-week dose-titration efficacy phase. However, the mean HDL-C at Week 56 was returned to its baseline level.

Evaluation of the data after Week 56 may be important for TRIG, VLDL-C, and especially HDL-C since the long-term effect of lomitapide on these parameters remains to be seen.

5.3 Labeling Comments

The following bullets summarize this reviewer's comments for the sponsor's proposed labeling in the Clinical Studies section.

- The sponsor stated the primary efficacy endpoint as "mean" percent change in LDL-C from baseline at Week 26. The "mean" should be omitted since it is not an endpoint; rather, it is an average of the endpoint values of the treated subjects in the study.

- Figure 1 is currently based on the ITT population with LOCF. This reviewer thinks that the graph should be based on the completers over time, with Week 26/LOCF values alongside.

- Table 5 presents the results for Week 26/LOCF (N = 29) and Week 56 (N = 23). It may be informative to include Week 26 (N = 23) results also so that there is a direct comparison between the 2 time points.

- The parameters listed in Table 5 should be clearly identified as the primary, key secondary, and other efficacy variables in the text. An asterisk (*) may be used to indicate a significant p-value for the primary and key secondary variables since their statistical analyses were prioritized.

Primary Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer: Todd Sahlroot, Ph.D.
Statistical Team Leader and Deputy Director of Biometrics II

CC: HFD-510/KJohnson, EColman, JSmith
HFD-715/TPermutt, TSahlroot, CLiu
HFD-700/LPatrician

Table 6 – Summary Statistics (Mean ± SD) and statistical results for Study UP1002/AEGR-733-005

Variable	Baseline (N=29)	Week 26 ITT/LOCF (N=29)	% Change from Baseline	p-value	Week 26 Completers (N=23)	% Change from Baseline	p-value	Week 56 Completers (N=23)	% Change from Baseline	p-value
LDL-C	337.0 ± 113.8	191.3 ± 106.6	-39.6 ± 32.0	< 0.01	167.7 ± 96.2	-50.2 ± 26.5	< 0.01	198.8 ± 122.7	-44.0 ± 29.8	< 0.01
TC	430.4 ± 135.3	261.1± 121.8	-35.7 ± 29.4	< 0.01	236.0 ± 112.4	-45.7 ± 23.7	< 0.01	274.3 ± 144.2	-38.8 ± 27.0	< 0.01
ApoB	260.1 ± 80.1	148.9 ± 74.9	-39.3 ± 30.3	< 0.01	132.9 ± 70.8	-48.9 ± 26.1	< 0.01	148.8 ± 83.1	-45.2 ± 27.6	< 0.01
TRIG	102.7 ± 47.8	63.7 ± 45.5	-28.2 ± 57.6	0.01	57.0 ± 37.6	-44.9 ± 36.8	< 0.01	81.2 ± 69.3	-28.8 ± 42.3	< 0.01
Non-HDL-C	386.4 ± 131.8	220.1 ± 116.6	-39.2 ± 31.1	< 0.01	196.3 ± 107.3	-49.7 ± 24.9	< 0.01	229.5 ± 138.7	-43.9 ± 29.4	< 0.01
VLDL-C	20.5 ± 9.6	12.7 ± 9.2	-27.9 ± 58.4	0.02	11.4 ± 7.6	-45.1 ± 36.6	< 0.01	16.3 ± 13.9	-28.1 ± 42.7	< 0.01
Lp(a)	78.2 ± 64.3	62.3 ± 41.1	-10.6 ± 33.9	0.10	60.7 ± 42.9	-15.5 ± 35.5	0.048	62.1 ± 51.4	-21.2 ± 23.4	< 0.01
HDL-C	44.0 ± 10.7	41.1 ± 13.5	-7.0 ± 19.7	0.07	39.8 ± 14.2	-12.3 ± 18.2	< 0.01	44.8 ± 15.5	+0.7 ± 32.3	0.92

All the variable units were mg/dL, except for Lp(a) where the unit was mmol/L.

p-value was based on paired t-test.

Table 7 – Association of % Reduction in LDL-C and Dose for Study UP1002/AEGR-733-005 – Completers (N = 23)

Week	2	6	10	14	18	22	26	36	46	56
% Reduction in LDL-C	9%	15%	27%	44%	53%	49%	50%	43%	41%	44%
Mean Dose (mg)	5	10	18	33	40	43	45	39	41	40
Median Dose (mg)	5	10	20	40	40	40	40	40	40	40
Minimum Dose (mg)	5	10	5	5	5	5	5	5	5	5
Maximum Dose (mg)	5	10	20	40	60	80	80	60	60	60

Dose information was obtained from the sponsor's clinical study report.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CYNTHIA Y LIU
11/30/2012

JON T SAHLROOT
11/30/2012
concur

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 STUDIES

IND/NDA Number:	IND 50,820/NDA 203858
Drug Name:	AEGR-733 (formerly known as BMS-201038)
Indication(s):	104 Week Carcinogenicity Studies in Rats and Mice
Applicant:	Sponsor: Aegerion Pharmaceuticals, Inc. 1140 Route 22 East, Suite 304 Bridgewater, New Jersey 08807
Documents Reviewed:	Electronic submission: Submission date March 11, 2011 Electronic data: March 11, 2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products
Reviewing Pharmacologist:	Tim Hummer, Ph.D.
Project Manager:	Kati Johnson
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of AEGR-733 (formerly known as BMS-201038) in rats and mice. The routes of administration were once daily by gavage for rats and dietary admixture for mice. The length of both studies was designed for 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Hummer.

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

2. 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 and one control group. Two hundred and forty Crl:CD(SD) rats of each sex were assigned randomly to treated and control groups in equal size of 60 animals per group. The dose levels for treated groups were 0.25, 1.7 and 7.5 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose group, respectively. The controls received the vehicle (75% polyethylene glycol 400 (PEG 400) solution (v/v) in reverse osmosis water) via oral gavage.

During the administration period all animals were checked twice daily for mortality, abnormalities, and signs of pain or distress. Detailed observations were done once during the predose phase, before dosing on Day 1, weekly thereafter, and on the day of scheduled sacrifice. Palpation for abnormal mass growth was done weekly. The bodyweights of individual rat were taken once during the predose phase, weekly during Weeks 1 through 14 of the dosing phase, and once every four weeks thereafter during the dosing phase.

As mention, the study was designed to continue for 104 weeks. However, because of low survival of female rats in low dose group (15 survivors), the low dose female rats were sacrificed on week 95. All remaining female rats were terminated on Week 97 because the number of surviving control females reached 20. All male carcinogenicity groups were terminated on Week 99 because the number of surviving controls reached 20.

2.1. Sponsor's analyses

2.1.1. Survival analysis

Survival function of each treatment group was estimated using the Kaplan-Meier product limit method and was presented graphically. Statistical analysis of the data was performed using the methodologies suggested by Cox-Tarone and Gehan-Breslow (Generalized Kruskal-Wallis test; Thomas et al., 1977) for testing the monotone trend and heterogeneity in censored survival data.

Sponsor's findings: Sponsor's analysis showed 33%, 28%, 47%, and 50% survival of male rats in the control, low, medium, and high dose groups, respectively and 33%, 25%, 53%, and 68% survival of female rats in the control, low, medium, and high dose groups, respectively. The sponsor analysis showed statistically significant negative dose response relationship in mortality among the female treated groups. The pairwise comparisons showed statistically significant lower mortality in medium and high dose groups compared to the control in female rats.

2.1.2. Tumor data analysis

The sponsor analyzed the tumor data using the Cochran-Armitage tests (Armitage 1955) for dose response relationship and Fisher-Irwin exact test for pairwise comparisons of treated groups with the control. For all tests, the one-sided probabilities for dose response relationship and group comparisons were evaluated at 5% level of significance.

Adjustment for multiple testing: The sponsor did not make any adjustment for multiple testing.

Sponsor's findings: Sponsor's analyses did not show statistically significant positive dose response relationship among the treated groups, or higher tumor incidences in the treated groups compared to the control in any of the observed tumor types in either sex.

2.2. Reviewer's analyses

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

2.2.1. Survival analysis

The survival distributions of animals in all four treatment groups were estimated by the Kaplan-Meier product limit method. 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 intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed 33%, 28%, 47%, and 50% survival of male rats in control, low, medium, and high dose groups, respectively and 33%, 25%, 53%, and 70% survival of female rats in control, low, medium, and high dose groups, respectively. This reviewer's analysis showed statistically significant negative dose response relationship in mortality across treatment groups in female rats. The pairwise comparisons in female rats showed statistically significant decreased mortality in medium and high dose group compared to the control.

Reviewer's comment: *The sponsor's analysis showed 68% survivors in female high dose group and this reviewer's analysis showed 70 % survivor. This difference is due to the fact that there was one animal (#B76900) that died naturally during the sacrifice week (Week 97). The sponsor did not consider this as a survivor while this reviewer considered it as a survivor.*

2.2.2. Tumor data analysis

The tumor data were analyzed for positive dose response relationships and pairwise comparisons of treated groups with control group to test significant increased incidence of any tumor types in the treated groups compared to the control. 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 Σs_h . As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, 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 3A and 3B 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 α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two species, and a significance level α=0.01 for common tumors and α=0.05 for rare tumors for a submission with one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control the FDA guidance the suggested the use of test levels α=0.01 for common tumors and α=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 tumor types showed p-values less than or equal to 0.05 either for dose response relationship or pairwise comparisons of control and treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons in Rats

Organ Name	Tumor Name	0 mg Cont N=60	0.25mg Low N=60	1.7mg Med N=60	7.5mg High N=60	P-Value Dose Resp	P-Value C vs L	P-Value C vs M	P-Value C vs H
Male									
Pancreas	B-Adenoma, Acinar Cell	7	5	5	15	0.0036*	0.6848	0.6848	0.0772
Thyroid	B-Adenoma, Follicular Cell	4	5	9	12	0.0172	0.5599	0.1747	0.0443
	Follicular cell adenom+carcin	5	6	9	13	0.0192	0.5667	0.2768	0.0556
Female									
Liver	B-Adenoma, Hepatocel	4	0	2	7	0.0404	0.9326	0.7338	0.4283

Based on the criteria of adjustment for multiple testing discussed above, the incidence of acinar cell B-Adenoma in Pancreas was considered to have statistically significant dose response relationship in male rats. None of the pairwise comparisons was considered to be statistically significant for the increased incidence of any of the observed tumor types in any of the treated groups in either sex compared to their respective control.

3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were five treated groups and one control group. Three hundred and sixty Crl:CD1 (ICR) mice of each sex were assigned randomly to treated and control groups in equal size of 60 animals per group. The dose levels for treated groups were 0.3, 1.5, 7.5, 15, and 45 mg/kg/day. In this review these dose groups were referred to as the low, mid-low, medium, mid-high, and high dose group, respectively. The controls remained untreated.

During the administration period all animals were checked twice daily for mortality, abnormalities, and signs of pain or distress. Detailed observations were done once during the predose phase, before dosing on Day 1, weekly thereafter, and on the day of scheduled sacrifice. Palpation for abnormal masses growth was done weekly. The bodyweights of individual mouse were taken once during the predose phase; weekly through Week 38; and every other week from Weeks 38 to Week 98 for Group 6 males, to Week 102 for Group 4 males; and to Week 104 for all remaining males; and to Week 100 for all females. Body weights were also taken on Week 105 for males in Groups 1, 2, 3, and 5.

As mention earlier, the study was designed to continue for 104 weeks. However, because of significantly increased mortality, the male mice given 45 mg/kg/day were sacrificed at Week 99. The male mice given 7.5 mg/kg/day were sacrificed at Week 102. Rest of the male mice was sacrificed at week 104-105. All female mice were sacrificed at Week 100. The Dosing of male rats in Groups 2, 3, 4, 5, and dosing of all rats from both sex in Group 6 was terminated early and were fed the drug free diet for 2 to 13 weeks prior to necropsy.

3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data from the mouse study were analyzed using the same statistical methodologies as were used to analyze the survival data from the rat study.

Sponsor's findings: Sponsor's analysis showed 32%, 32%, 28%, 25%, 23%, and 23% survival of male mice in control, low, mid-low, medium, mid-high and high dose groups, respectively and 25, 30%, 30%, 42%, 45%, and 28% survival of female mice in control, low, mid-low, medium, mid-high and high dose groups, respectively. The sponsor analysis showed statistically significant positive dose response relationship in mortality for male mice up to Week 99 ($p = 0.0160$). The sponsor commented that the dose response relationship was caused by the significant increased mortality of male mice in 45 mg/kg/day group.

3.1.2. Tumor data analysis

The sponsor analyzed the mouse tumor data using the methodology outlined by Peto et al. (1980). Following the National Toxicological Program (NTP) format, the sponsor used the fixed intervals of Weeks 0-52, 53-78, 79 -92, 93-109 and the terminal sacrifice to analyze the incidental tumors. For tumor types with less than or

equal to five total incidences, the permutation based exact tests were performed, otherwise asymptotic tests were conducted.

Sponsor's findings: Sponsor's analyses showed statistically significant increased incidence of hepatocellular carcinomas in male mice given ≥1.5 mg/kg/day and females given 7.5 or 15 mg/kg/day. The incidence of carcinomas was also increased in females given 45 mg/kg/day but did not achieve statistical significance. Statistically significantly increased incidences of hepatocellular adenomas were also observed in mice in both sexes given ≥7.5 mg/kg/day. The sponsor's analysis also showed increased incidences of small intestinal adenomas and/or carcinomas in all male mice, which reached statistical significance for male mice given ≥15 mg/kg/day. Statistically significant increased incidences of adenomas and/or carcinomas in the small intestine were also observed in females given 15 mg/kg/day.

3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses from the mouse study. For the mouse data analyses this reviewer used similar methodologies as he used to analyze the survival data from the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1. Survival analysis

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

Reviewer's findings: This reviewer's analysis showed 33%, 32%, 28%,27%, 25%,and 25% survival of male mice in control, low, mid-low, medium, mid-high, and high dose groups, respectively and 25%, 32%, 32%, 42%, 45%, and 28% survival of female mice in control, low, mid-low, medium, mid-high, and high dose groups, respectively. This reviewer's analysis showed statistically significant negative dose response relationship in the mortality across treatment groups in male mice. The pairwise comparisons did not show statistically significant increased mortality in any of the treated groups compared to the control.

Reviewer's comment: *Similar to the rat study, there were some discrepancies in the percentages of survivals in few treatment groups calculated by the sponsor and this reviewer. These differences are due to the fact that the following animals died naturally during the sacrifice week. The sponsor did not consider them as the survivors, while this reviewer considered them as the survivor.*

Sex	*Animal #*	*Group*	*Sex*	*Animal #*	*Group*
Male	*A28515*	*Medium*	*Female*	*A28884*	*Low*
	A28562	*Mid-High*		*A28992*	*Medium*
	A28591	*High*			

3.2.2. Tumor data analysis

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

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship or pairwise comparisons of control and treated groups.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons in Mice

Organ Name	Tumor Name	0 mg Cont N=60	0.3mg Low N=60	1.5mg MidLo N=60	7.5mg Med N=60	15mg MidHi N=60	45mg High N=60	P-Value Dose Resp	C V. L	C V. ML	C V. M	C V. MH	C V. H
Male													
Body, Whole/Cav	M-Hemangiosarcoma	1	1	7	3	2	1	0.7737	0.2534	0.0397	0.3071	0.5104	0.6875
	M-Histiocytic Sarcoma	0	1	5	0	1	0	0.9103	0.5135	0.0356*	.	0.5000	.
Duodenum	M-Carcinoma	0	0	0	0	2	2	0.0107*	.	.	.	0.2534	0.1875
Epididymis	B-Interstitial Cell Tumor	0	0	0	0	3	2	0.0184*	.	.	.	0.1197	0.1875
Jejunum	M-Carcinoma	0	0	1	1	6	3	0.0110*	.	0.5135	0.5000	0.0149*	0.0786
Liver	B-Adenoma+M-Carcinoma_Hepatoc	25	25	44	42	43	37	0.0131	0.4638	0.0061*	0.0024*	0.0071*	0.0103
	B-Adenoma, Hepatocellular	4	5	13	11	16	15	0.0011*	0.5000	0.0271	0.0462	0.0034*	0.0013*
	M-Carcinoma, Hepatocellular	23	22	40	38	36	30	0.0384	0.5457	0.0088*	0.0076*	0.0253	0.0307
Duodenum+Ileum + Jejunum	Adenomas+Carcinomas	0	2	1	2	9	5	0.0039*	0.2534	0.5135	0.2534	0.0019*	0.0144*
	Carcinomas	0	0	1	1	9	5	<0.001*	.	0.5135	0.5000	0.0019*	0.0144*
Female													
Liver	B-Adenoma+M-Carcinoma_Hepatoc	5	0	2	23	25	19	<0.001*	0.9751	0.8363	<0.001*	<0.001*	0.0025*
	B-Adenoma, Hepatocellular	1	0	1	12	12	10	<0.001*	0.5143	0.2888	0.0035*	0.0051*	0.0065*
	M-Carcinoma, Hepatocellular	4	0	1	17	16	11	0.0016*	0.9461	0.8598	0.0049*	0.0119	0.0513
Skin/Subcutis	M-Fibrosarcoma	0	0	0	0	0	2	0.0228*	.	.	.	.	0.2536
Duodenum+Ileum + Jejunum	Adenomas+Carcinomas	0	0	0	0	8	3	0.0111*	.	.	.	0.0083*	0.1304
	Carcinomas	0	0	0	0	5	3	0.0086*	.	.	.	0.0542	0.1304

Based on the multiple testing adjustment procedure discussed in the rat data analysis section, the incidences of M-carcinoma in duodenum, B-interstitial cell tumor in epididymis, M-carcinoma in jejunum, and hepatocellular B-adenoma in male mice; hepatocellular B-adenoma, hepatocellular M-carcinoma, and M-fibrosarcoma in skin/subcutis in female mice were considered to have statistically significant dose response relationship. The combined incidences of hepatocellular B-adenoma and hepatocellular M-carcinoma showed statistically significant dose response relationship in female mice. The incidence of M-carcinomas and combined incidences of adenomas and carcinomas jointly in duodenum, ileum and jejunum also showed statistically significant positive dose response in both sexes. All pairwise comparisons marked by the asterisks were considered to be statistically significant for the increased incidence of their respective tumor types compared to their respective control.

It may be worth noting that the incidences of bronchiolar-alveolar B-adenomas, bronchiolar-alveolar M-carcinomas, and combined incidences of bronchiolar-alveolar B-adenomas and bronchiolar-alveolar M-carcinomas showed statistically significant negative dose response relationship.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of AEGR-733 (formerly known as BMS-201038) in

rats and mice. The route of administration was once daily by gavage for rats and dietary admixture for mice. The length of both studies was designed for 104 weeks.

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

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 and one control group. Two hundred and forty Crl:CD(SD) rats of each sex were assigned randomly to treated and control groups in equal size of 60 animals per group. The dose levels for treated groups were 0.25, 1.7 and 7.5 mg/kg/day. The controls received the vehicle (75% polyethylene glycol 400 (PEG 400) solution (v/v) in reverse osmosis water) via oral gavage.

The study was designed to continue for 104 weeks. However, because of low survival of female rats in low dose group (15 survivors), the low dose female rats were sacrificed on week 95. All remaining female rats were terminated on Week 97 because the number of surviving control females reached 20. All male carcinogenicity groups were terminated on Week 99 because the number of surviving controls reached 20.

The tests showed statistically significant negative dose response relationship in mortality across treatment groups in female rats. The pairwise comparisons in female rats showed statistically significant decreased mortality in medium and high dose group compared to the control. The tests showed statistically significant dose response relationship in the incidence of acinar cell B-Adenoma in Pancreas in male rats. None of the pairwise comparisons was considered to be statistically significant for the increased incidence of any of the observed tumor types in any of the treated groups in either sex compared to their respective control.

Mouse Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were five treated groups and one control group. Three hundred and sixty Crl:CD1 (ICR) mice of each sex were assigned randomly to treated and control groups in equal size of 60 animals per group. The dose levels for treated groups were 0.3, 1.5, 7.5, 15, and 45 mg/kg/day. The controls remained untreated.

Similar to the rat study, the mouse study was also designed to continue for 104 weeks. However, because of significantly increased mortality, the male mice given 45 mg/kg/day were sacrificed at Week 99. The male mice given 7.5 mg/kg/day were sacrificed at Week 102. Rest of the male mice was sacrificed at week 104-105. All female mice were sacrificed at Week 100. The Dosing of male rats in Groups 2, 3, 4, 5, and dosing of all rats from both sex in Group 6 was terminated early and were fed the drug free diet for 2 to 13 weeks prior to necropsy.

Tests showed statistically significant negative dose response relationship in the mortality across treatment groups in male mice. The pairwise comparisons did not show statistically significant increased mortality in any of the treated groups compared to the control. Test showed statistically significant dose response relationship in the incidences of M-carcinoma in duodenum, B-interstitial cell tumor in epididymis, M-carcinoma in jejunum, and hepatocellular B-adenoma in male mice; hepatocellular B-adenoma, hepatocellular M-carcinoma, and M-fibrosarcoma in skin/subcutis in female mice. The combined incidences of hepatocellular B-adenoma and hepatocellular M-carcinoma showed statistically significant dose response relationship in female mice but not in male mice. The incidence of M-carcinomas and combined incidences of adenomas and carcinomas jointly in duodenum, ileum and jejunum also showed statistically significant positive dose response in both sexes.

The pairwise comparisons showed statistically significant increased incidences of the following tumor types in

the indicated dose groups compared to their respective control.

Sex	Organ Name	Tumor Name	Dose Groups Compared with Control
Male	Body, Whole/Cav	M-Histiocytic Sarcoma	Mid-low
	Jejunum	M-Carcinoma	Mid-High
	Liver	B-Adenoma+M-Carcinoma_Hepatoc	Mid-low, Medium, Mid-high
		B-Adenoma, Hepatocellular	Mid-high, high
		M-Carcinoma, Hepatocellular	Mid-low, Medium
	Duodenum + Ileum + Jejunum	Adenomas+Carcinomas	Mid-high, high
		Carcinomas	Mid-high, high
Female	Liver	B-Adenoma+M-Carcinoma_Hepatoc	Medium, Mid-high, high
		B-Adenoma, Hepatocellular	Medium, Mid-high, high
		M-Carcinoma, Hepatocellular	Medium
	Duodenum + Ileum + Jejunum	Adenomas+Carcinomas	Mid-high

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5. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

	0 mg|kg|day		0.25 mg|kg|day		1.70 mg|kg|day		7.50 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	4	6.67	2	3.33	3	5.00	4	6.67
53 - 78	14	30.00	10	20.00	8	18.33	11	25.00
79 - 91	16	56.67	15	45.00	13	40.00	9	40.00
92 - 98	6	66.67	16	71.67	8	53.33	6	50.00
Ter. Sac.	20	33.33	17	28.33	28	46.67	30	50.00
Total	N=60		N=60		N=60		N=60	

Table 1B: Intercurrent Mortality Rate
Female Rats

	0 mg|kg|day		0.25 mg|kg|day		1.70 mg|kg|day		7.50 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	4	6.67	4	6.67	1	1.67	2	3.33
53 - 78	17	35.00	18	36.67	12	21.67	5	11.67
79 - 91	11	53.33	20	70.00	7	33.33	9	26.67
92 - 96	8	66.67	3	75.00	8	46.67	2	30.00
Ter. Sac.*	20	33.33	15	25.00	32	53.33	42	70.00
Total	N=60		N=60		N=60		N=60	

***Female low dose group were sacrificed on Week 95**

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.0589
Homogeneity	Log-Rank	0.1214

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	<.0001
Homogeneity	Log-Rank	<.0001

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

Organ Name	Tumor Name	0 mg Cont N=60	0.25mg Low N=60	1.7mg Med N=60	7.5mg High N=60	P-Value Dose Resp	C vs L	C vs M	C vs H
Adrenal, Cortex	B-Adenoma	1	1	2	1	0.4583	0.2709	0.5436	0.2709
	M-Carcinoma	1	0	0	1	0.4512	0.5233	0.5287	0.2767
Adrenal, Medull	B-Pheochromocytoma	8	7	8	8	0.4909	0.5795	0.5303	0.4925
	M-Malignant Pheochromocytoma	1	2	3	2	0.4118	0.5446	0.3628	0.5446
Body, Whole/Cav	B-Hemangioma	0	0	1	1	0.1987	.	0.5349	0.5294
	M-Hemangiosarcoma	0	3	1	2	0.3268	0.1437	0.5349	0.2773
	M-Hibernoma, Malignant	0	1	0	0	0.5170	0.5294	.	.
	M-Histiocytic Sarcoma	1	2	3	0	0.8569	0.5353	0.3529	0.5233
	M-Liposarcoma	1	0	1	0	0.6487	0.5294	0.2832	0.5294
	M-Lymphosarcoma	0	1	1	1	0.3233	0.5294	0.5402	0.5349
	M-Malignant Mesothelioma	0	0	1	0	0.2557	.	0.5349	.
Bone, Other	B-Osteoma	0	0	0	1	0.2599	.	.	0.5349
Brain	B-Granular Cell Tumor	1	0	1	0	0.6443	0.5233	0.2767	0.5233
	M-Malignant Astrocytoma	0	0	2	1	0.2181	.	0.2890	0.5349
	M-Malignant Granular Cell Tu	0	0	0	1	0.2599	.	.	0.5349
	M-Meningeal Sarcoma	0	1	0	0	0.5170	0.5294	.	.
Eye	M-Melanoma	1	0	0	0	0.7727	0.5294	0.5349	0.5294
Heart	M-Endocardial Schwannoma	0	2	0	0	0.7682	0.2773	.	.
Jejunum	M-Carcinoma	0	0	0	1	0.2599	.	.	0.5349
Kidney	B-Adenoma, Tubule Cell	0	2	0	0	0.7682	0.2773	.	.
	M-Carcinoma, Tubule Cell	0	2	0	1	0.4664	0.2773	.	0.5349
Liver	B-Adenoma, Hepatocellular	1	0	2	2	0.1892	0.5294	0.5529	0.5529
	Hhepatocellular_adenoma+carci	2	2	2	5	0.0889	0.3539	0.3628	0.2787
	M-Carcinoma, Hepatocellular	1	2	0	3	0.1646	0.5446	0.5349	0.3628
	M-Cholangiocarcinoma	1	0	0	0	0.7727	0.5294	0.5349	0.5294
Mammary, Male	B-Adenoma	1	0	0	0	0.7684	0.5233	0.5287	0.5233
	B-Fibroadenoma	1	1	0	0	0.8325	0.2773	0.5349	0.5294
Mesentery	M-Sarcoma	0	0	0	1	0.2599	.	.	0.5349
Muscle, Bi Fem	M-Schwannoma	0	0	1	0	0.2557	.	0.5349	.
Pancreas	B-Adenoma, Acinar Cell	7	5	5	15	0.0036*	0.6848	0.6848	0.0772
	B-Adenoma, Islet Cell	5	5	0	8	0.0793	0.4306	0.9797	0.3388
	M-Carcinoma, Islet Cell	2	1	1	2	0.4212	0.5353	0.5436	0.3529
Parathyroid	B-Adenoma	0	1	2	1	0.3493	0.5294	0.2832	0.5349
Pituitary	B-Adenoma, Pars Distalis	37	41	39	43	0.2176	0.4313	0.5403	0.2670
	B-Adenoma, Pars Intermedia	1	2	1	1	0.5782	0.5353	0.2767	0.2767

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

Organ Name	Tumor Name	0 mg Cont N=60	0.25mg Low N=60	1.7mg Med N=60	7.5mg High N=60	P-Value Dose Resp	C vs L	C vs M	C vs H
Pituitary	M-Carcinoma	0	0	1	0	0.2557	.	0.5349	.
Prostate	M-Leiomyosarcoma	0	0	0	1	0.2599	.	.	0.5349
Skin/Subcutis	B-Basal Cell Tumor	1	0	0	0	0.7727	0.5294	0.5349	0.5294
	B-Fibroma	0	0	4	1	0.3821	.	0.0801	0.5294
	B-Keratoacanthoma	7	7	5	2	0.9753	0.4768	0.6989	0.9367
	B-Lipoma	1	1	0	0	0.8289	0.2709	0.5287	0.5233
	B-Papilloma, Squamous Cell	1	0	0	0	0.7684	0.5233	0.5287	0.5233
	B-Trichoepithelioma	1	2	0	0	0.9053	0.5446	0.5349	0.5294
	M-Fibrosarcoma	1	2	0	2	0.3502	0.5353	0.5287	0.5436
	M-Neural Crest Tumor, Malign	1	0	0	0	0.7684	0.5233	0.5287	0.5233
	M-Osteosarcoma	0	1	1	0	0.5143	0.5294	0.5402	.
	M-Sarcoma	0	0	1	0	0.2542	.	0.5402	.
Spleen	M-Leiomyosarcoma	0	1	0	0	0.5170	0.5294	.	.
Stomach, Nongl	B-Papilloma, Squamous Cell	0	1	0	0	0.5170	0.5294	.	.
	M-Carcinoma, Squamous Cell	0	0	1	0	0.2557	.	0.5349	.
Thyroid	B-Adenoma, C-cell	9	8	10	14	0.0775	0.5814	0.5870	0.2362
	B-Adenoma, Follicular Cell	4	5	9	12	0.0172	0.5599	0.1747	0.0443
	Follicular_cell_adenom+carcin	5	6	9	13	0.0192	0.5667	0.2768	0.0556
	M-Carcinoma, C-cell	1	1	1	0	0.7524	0.2709	0.2767	0.5233
	M-Carcinoma, Follicular Cell	1	2	0	3	0.1646	0.5446	0.5349	0.3628

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

Organ Name	Tumor Name	0 mg Cont N=60	0.25mg Low N=60	1.7mg Med N=60	7.5mg High N=60	P-Value Dose Resp	C vs L	C vs M	C vs H
Adrenal, Cortex	B-Adenoma	4	6	3	0	0.9982	0.3366	0.5885	0.9653
	M-Carcinoma	0	0	0	1	0.2905	.	.	0.5591
Adrenal, Medull	B-Ganglioneuroma	0	0	1	0	0.2905	.	0.5393	.
	B-Pheochromocytoma	0	2	1	3	0.1337	0.2282	0.5393	0.1703
	M-Malignant Pheochro	0	1	0	1	0.3639	0.4810	.	0.5591
Body, Whole/Cav	B-Hemangioma	0	0	1	0	0.2905	.	0.5393	.
	B-Hibernoma	2	0	0	1	0.6058	0.7339	0.7906	0.5963
	M-Hibernoma, Maligna	1	0	1	0	0.6831	0.4810	0.2880	0.5591
	M-Histiocytic Sarcom	1	1	0	2	0.3112	0.7339	0.5393	0.5963
	M-Lymphosarcoma	1	1	0	0	0.8507	0.7339	0.5393	0.5591
	M-Malignant Mesothel	0	2	0	0	0.8038	0.2345	.	.
Brain	M-Malignant Astrocyt	1	0	0	0	0.7709	0.4810	0.5393	0.5591
	M-Malignant Granular	0	0	0	1	0.2905	.	.	0.5591
	M-Meningeal Sarcoma	0	0	0	1	0.2944	.	.	0.5638
Cavity, Abdomin	M-Malignant Teratoma	0	1	0	0	0.5587	0.4810	.	.
Cervix	B-Polyp, Endometrial	0	0	1	0	0.2905	.	0.5393	.
	M-Leiomyosarcoma	0	0	0	1	0.2944	.	.	0.5638
	M-Sarcoma, Endometri	1	2	0	0	0.9248	0.4712	0.5393	0.5591
	M-Schwannoma, Malign	1	0	0	0	0.7709	0.4810	0.5393	0.5591
Kidney	B-Adenoma, Tubule Ce	0	0	1	0	0.2889	.	0.5444	.
	B-Lipoma	0	1	0	0	0.5587	0.4810	.	.
Liver	B-Adenoma, Hepatocel	4	0	2	7	0.0404	0.9326	0.7338	0.4283
	M-Carcinoma, Hepatoc	0	1	2	2	0.2028	0.4810	0.2880	0.3100
Mammary, Female	B-Adenoma	2	0	1	3	0.1923	0.7339	0.5672	0.6123
	B-Fibroadenoma	19	23	14	10	0.9996	0.2276	0.9070	0.9915
	M-Carcinoma	12	20	12	11	0.9604	0.0601	0.5731	0.6963
Ovary	B-Adenoma	1	0	0	0	0.7709	0.4810	0.5393	0.5591
	M-Malignant Granulos	1	0	0	0	0.7709	0.4810	0.5393	0.5591
Pancreas	B-Adenoma, Acinar Ce	0	2	1	3	0.1316	0.2345	0.5393	0.1703
	B-Adenoma, Islet Cel	1	1	5	2	0.5142	0.7339	0.1480	0.5963
	M-Carcinoma, Islet C	1	0	0	0	0.7709	0.4810	0.5393	0.5591
Parathyroid	B-Adenoma	0	0	1	0	0.2905	.	0.5393	.
Pituitary	B-Adenoma, Pars Dist	47	49	55	52	0.6642	0.5930	0.1130	0.4174
	M-Carcinoma	4	4	0	4	0.5276	0.6011	0.9562	0.4942
Rectum	M-Carcinoma	1	0	0	0	0.7709	0.4810	0.5393	0.5591
	M-Leiomyosarcoma	0	0	1	0	0.2889	.	0.5444	.

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

Organ Name	Tumor Name	0 mg Cont N=60	0.25mg Low N=60	1.7mg Med N=60	7.5mg High N=60	P-Value Dose Resp	C vs L	C vs M	C vs H
Skin/Subcutis	B-Fibroma	1	2	0	0	0.9248	0.4712	0.5393	0.5591
	B-Keratoacanthoma	0	1	1	0	0.5685	0.4810	0.5444	.
	M-Neural Crest Tumor	0	0	0	1	0.2905	.	.	0.5591
	M-Osteosarcoma	1	2	0	0	0.9248	0.4712	0.5393	0.5591
Thyroid	B-Adenoma, C-cell	9	2	1	6	0.5135	0.9643	0.9960	0.8457
	B-Adenoma, Follicula	1	0	1	2	0.2322	0.4810	0.2880	0.5893
	M-Carcinoma, C-cell	0	3	1	0	0.8719	0.1067	0.5393	.
Uterus	B-Polyp, Endometrial	1	1	2	1	0.5451	0.7339	0.5595	0.3153
	M-Carcinoma	0	0	1	0	0.2905	.	0.5393	.

Table 4A: Intercurrent Mortality Rate in Male Mice

	0mg|kg|day		0.3 mg|kg|day		1.5 mg|kg|day		7.5 mg|kg|day		15.0 mg|kg|day		4.5 0mg|kg|day	
Week	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 - 52	11	18.33	6	10.00	5	8.33	8	13.33	7	11.67	15	25.00
53 - 78	9	33.33	13	31.67	15	33.33	10	30.00	12	31.67	20	58.33
79 - 91	11	51.67	12	51.67	11	51.67	13	51.67	17	60.00	6	68.33
92 - 104	9	66.67	10	68.33	12	71.67	13	73.33	9	75.00	4	75.00
Ter. Sac*	20	33.33	19	31.67	17	28.33	16	26.67	15	25.00	15	25.00
Total	N=60		N=60		N=60		N=60		N=60		N=60	

***Male high dose group were sacrificed on Week 99 and**

Table 4B: Intercurrent Mortality Rate Female Mice

	0mg|kg|day		0.3 mg|kg|day		1.5 mg|kg|day		7.5 mg|kg|day		15.0 mg|kg|day		4.5 0mg|kg|day	
Week	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 - 52	10	16.67	12	20.00	8	13.33	7	11.67	5	8.33	7	11.67
53 - 78	17	45.00	10	36.67	11	31.67	9	26.67	12	28.33	20	45.00
79 - 91	12	65.00	11	55.00	10	48.33	15	51.67	13	50.00	12	65.00
92 - 99	6	75.00	8	68.33	12	68.33	4	58.33	3	55.00	4	71.67
Ter. Sac.	15	25.00	19	31.67	19	31.67	25	41.67	27	45.00	17	28.33
Total	N=60		N=60		N=60		N=60		N=60		N=60	

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.0044
Homogeneity	Log-Rank	0.0951

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.7655
Homogeneity	Log-Rank	0.0921

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

Organ Name	Tumor Name	0 mg Cont N=60	0.3mg Low N=60	1.5mg MidLo N=60	7.5mg Med N=60	15mg MidHi N=60	45mg High N=60	P-Value Dose Resp	C V. L	C V. ML	C V. M	C V. MH	C V. H
Adrenal, Cortex	B-Adenoma	2	0	1	0	4	1	0.2666	0.7534	0.5101	0.7466	0.3238	0.3952
	M-Carcinoma	0	0	0	0	2	0	0.2768	.	.	.	0.2465	.
Adrenal, Medull	B-Pheochromocytoma	0	1	0	0	0	0	0.6509	0.5135	.	.	.	.
Body, Whole/Cav	B-Hemangioma	1	3	0	0	0	0	0.9868	0.3281	0.5135	0.5000	0.5000	0.4375
	B-Lymphangioma	0	0	0	1	0	0	0.3033	.	.	0.5000	.	.
	M-Hemangiosarcoma	1	1	7	3	2	1	0.7737	0.2534	0.0397	0.3071	0.5104	0.6875
	M-Histiocytic Sarcoma	0	1	5	0	1	0	0.9103	0.5135	0.0356*	.	0.5000	.
	M-Leukemia, Erythrocytic	0	0	0	0	1	0	0.3066	.	.	.	0.5068	.
	M-Lymphosarcoma	5	5	3	2	3	2	0.7229	0.4014	0.6585	0.7503	0.6141	0.6270
	M-Osteosarcoma	0	0	0	1	0	0	0.3033	.	.	0.5000	.	.
Cecum	B-Adenoma	0	0	0	0	1	0	0.3033	.	.	.	0.5000	.
Colon	M-Carcinoma	0	0	0	0	1	0	0.3033	.	.	.	0.5000	.
Du+Il+Je	Adenomas	0	2	0	1	0	0	0.7962	0.2534	.	0.5068	.	.
	Adenomas+Carcinomas	0	2	1	2	9	5	0.0039*	0.2534	0.5135	0.2534	0.0019*	0.0144*
	Carcinomas	0	0	1	1	9	5	<0.001*	.	0.5135	0.5000	0.0019*	0.0144*
Duodenum	B-Adenoma	0	2	0	0	0	0	0.8814	0.2534	.	.	.	.
	M-Carcinoma	0	0	0	0	2	2	0.0107*	.	.	.	0.2534	0.1875
Epididymis	B-Interstitial Cell Tumor	0	0	0	0	3	2	0.0184*	.	.	.	0.1197	0.1875
Gallbladder	B-Adenoma	0	1	0	0	1	0	0.3970	0.5068	.	.	0.5000	.
Gl, Harderian	B-Adenoma	8	7	4	1	1	4	0.7115	0.5457	0.8622	0.9844	0.9844	0.6873
	M-Carcinoma	0	0	1	0	0	0	0.4717	.	0.5200	.	.	.
Heart	M-Rhabdomyosarcoma	0	0	0	1	0	0	0.3033	.	.	0.5000	.	.
Ileum	M-Carcinoma	0	0	0	0	1	0	0.3066	.	.	.	0.5068	.
Jejunum	B-Adenoma	0	0	0	1	0	0	0.3019	.	.	0.5068	.	.
	M-Carcinoma	0	0	1	1	6	3	0.0110*	.	0.5135	0.5000	0.0149*	0.0786
Kidney	B-Adenoma, Tubule Cell	0	2	0	0	0	0	0.8814	0.2534	.	.	.	.
	M-Carcinoma, Transitional Ce	0	1	0	0	0	0	0.6540	0.5068	.	.	.	.
	M-Carcinoma, Tubule Cell	0	0	0	0	0	1	0.1327	.	.	.	.	0.4375
Liver	B-Adenoma+M-Carcinoma_Hepatoc	25	25	44	42	43	37	0.0131	0.4638	0.0061*	0.0024*	0.0071*	0.0103
	B-Adenoma, Hepatocellular	4	5	13	11	16	15	0.0011*	0.5000	0.0271	0.0462	0.0034*	0.0013*
	M-Carcinoma, Hepatocellular	23	22	40	38	36	30	0.0384	0.5457	0.0088*	0.0076*	0.0253	0.0307
	M-Hepatocholangiocarcinoma	0	0	1	0	0	0	0.4739	.	0.5135	.	.	.
Lung	B-Adenoma+M-Carcinoma_Bronchi	23	16	14	11	10	3	0.9998	0.8438	0.9514	0.9824	0.9885	0.9998

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

Organ Name	Tumor Name	0 mg Cont N=60	0.3mg Low N=60	1.5mg MidLo N=60	7.5mg Med N=60	15mg MidHi N=60	45mg High N=60	P-Value Dose Resp	C V. L	C V. ML	C V. M	C V. MH	C V. H
Lung	B-Adenoma, Bronchiolar-Alveo	10	5	8	7	6	2	0.9540	0.8757	0.6528	0.7086	0.8004	0.9563
	M-Carcinoma, Bronchiolar-Alv	13	11	7	5	5	2	0.9952	0.5385	0.8900	0.9562	0.9502	0.9864
Omentum	M-Fibrosarcoma	1	0	0	0	0	0	0.8294	0.5068	0.5135	0.5000	0.5000	0.4375
Pancreas	B-Adenoma, Islet Cell	0	0	2	0	0	0	0.7221	.	0.2670	.	.	.
Parathyroid	M-Carcinoma	0	0	0	1	0	0	0.3019	.	.	0.5068	.	.
Pituitary	B-Adenoma	1	0	0	0	3	0	0.4549	0.5068	0.5135	0.5000	0.3177	0.4375
	M-Carcinoma	0	0	0	1	0	0	0.3019	.	.	0.5068	.	.
Seminal Vesicle	M-Leiomyosarcoma	0	1	0	0	0	0	0.6509	0.5135	.	.	.	.
		1	0	0	0	0	0	0.8294	0.5068	0.5135	0.5000	0.5000	0.4375
Skin/Subcutis	M-Carcinoma, Squamous Cell	0	0	0	1	0	0	0.3033	.	.	0.5000	.	.
	M-Osteosarcoma	0	1	0	0	0	0	0.6509	0.5135	.	.	.	.
	M-Sarcoma	0	0	0	0	1	0	0.3066	.	.	.	0.5068	.
Stomach, Gl	M-Carcinoma	0	1	0	0	0	0	0.6540	0.5068	.	.	.	.
	M-Sarcoma	0	0	0	0	0	1	0.1368	.	.	.	.	0.4462
Stomach, Nongl	M-Carcinoma, Squamous Cell	0	0	0	1	0	0	0.3033	.	.	0.5000	.	.
Testis	B-Interstitial Cell Tumor	1	0	1	2	1	1	0.3012	0.5068	0.2603	0.5000	0.7535	0.6875
Thyroid	B-Adenoma, C-cell	1	0	0	0	0	0	0.8294	0.5068	0.5135	0.5000	0.5000	0.4375
Urinary Bladder	M-Carcinoma, Transitional Ce	1	0	0	0	0	0	0.8255	0.5000	0.5067	0.4932	0.4932	0.4308

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

Organ Name	Tumor Name	0 mg Cont N=60	0.3mg Low N=60	1.5mg MidLo N=60	7.5mg Med N=60	15mg MidHi N=60	45mg High N=60	P-Value Dose Resp	C V. L	C V. ML	C V. M	C V. MH	C V. H
Adrenal, Cortex	B-Adenoma, Subcapsular Cell	0	0	1	0	1	0	0.3850	.	0.5405	.	0.5584	.
	M-Carcinoma	0	0	1	0	1	0	0.3850	.	0.5405	.	0.5584	.
Adrenal, Medull	B-Pheochromocytoma	2	0	1	0	0	0	0.9609	0.7677	0.5615	0.7978	0.8083	0.7609
Body, Whole/Cav	B-Hemangioma	3	3	5	6	4	2	0.7870	0.3774	0.4339	0.3407	0.6279	0.5136
	B-Lymphangioma	0	0	1	0	0	0	0.5197	.	0.5405	.	.	.
	M-Hemangiosarcoma	1	1	3	4	1	2	0.4381	0.2680	0.3714	0.2520	0.3086	0.5110
	M-Histiocytic Sarcoma	5	3	6	6	6	3	0.7140	0.6751	0.5935	0.6265	0.3881	0.6449
	M-Leukemia, Granulocytic	0	2	0	0	1	0	0.6786	0.2750	.	.	0.5584	.
	M-Lymphosarcoma	9	11	6	8	5	3	0.9832	0.4238	0.7517	0.5688	0.8704	0.9243
	M-Malignant Mesothelioma	0	0	0	0	1	0	0.3435	.	.	.	0.5641	.
Bone, Other	M-Sarcoma	0	0	1	0	0	0	0.5197	.	0.5405	.	.	.
Cavity, Abdomin	M-Sarcoma	0	0	0	0	0	1	0.1565	.	.	.	.	0.5143
Cavity, Thoraci	B-Osteoma	0	0	1	0	0	0	0.5197	.	0.5405	.	.	.
Cervix	B-Polyp, Endometrial Stromal	0	2	1	0	2	0	0.6865	0.2680	0.5405	.	0.3086	.
	M-Carcinoma	0	0	0	0	1	0	0.3406	.	.	.	0.5584	.
	M-Leiomyosarcoma	0	0	0	0	1	0	0.3406	.	.	.	0.5584	.
Du+Il+Je	Adenomas	0	0	0	0	3	0	0.3997	.	.	.	0.1687	.
	Adenomas+Carcinomas	0	0	0	0	8	3	0.0111*	.	.	.	0.0083*	0.1304
	Carcinomas	0	0	0	0	5	3	0.0086*	.	.	.	0.0542	0.1304
Duodenum	B-Adenoma	0	0	0	0	2	0	0.3175	.	.	.	0.3086	.
	M-Carcinoma	0	0	0	0	0	1	0.1528	.	.	.	.	0.5072
Gallbladder	B-Adenoma	2	1	0	0	0	0	0.9860	0.5107	0.7856	0.7912	0.8019	0.7536
Gl, Harderian	B-Adenoma	8	3	2	3	2	3	0.7515	0.9215	0.9742	0.9534	0.9823	0.9143
	M-Carcinoma	1	0	0	0	0	0	0.8515	0.5143	0.5405	0.5467	0.5584	0.5072
Gl, Mandib Sali	M-Carcinoma	1	0	0	0	0	0	0.8515	0.5143	0.5405	0.5467	0.5584	0.5072
Ileum	M-Carcinoma	0	0	0	0	0	1	0.1565	.	.	.	.	0.5143
Jejunum	B-Adenoma	0	0	0	0	2	0	0.3175	.	.	.	0.3086	.
	M-Carcinoma	0	0	0	0	5	1	0.1011	.	.	.	0.0542	0.5072
	M-Osteosarcoma	0	0	0	1	0	0	0.3406	.	.	0.5467	.	.
	M-Sarcoma	0	0	0	0	0	1	0.1528	.	.	.	.	0.5072
Liver	B-Adenoma+M-Carcinoma_Hepatoc	5	0	2	23	25	19	<0.001*	0.9751	0.8363	<0.001*	<0.001*	0.0025*
	B-Adenoma, Hepatocellular	1	0	1	12	12	10	<0.001*	0.5143	0.2888	0.0035*	0.0051*	0.0065*
	M-Carcinoma, Hepatocellular	4	0	1	17	16	11	0.0016*	0.9461	0.8598	0.0049*	0.0119	0.0513

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

Organ Name	Tumor Name	0 mg Cont N=60	0.3mg Low N=60	1.5mg MidLo N=60	7.5mg Med N=60	15mg MidHi N=60	45mg High N=60	P-Value Dose Resp	C V. L	C V. ML	C V. M	C V. MH	C V. H
Lung	B-Adenoma+M-Carcinoma_Bronchi	14	5	6	11	4	5	0.9289	0.9842	0.9818	0.8257	0.9979	0.9842
	B-Adenoma, Bronchiolar-Alveo	5	1	4	9	3	2	0.8185	0.9071	0.5863	0.3064	0.7641	0.7972
	M-Carcinoma, Bronchiolar-Alv	9	4	3	3	1	3	0.8847	0.8998	0.9628	0.9695	0.9973	0.9443
Mammary, Female	M-Carcinoma	1	0	1	0	0	0	0.8554	0.5143	0.2888	0.5467	0.5584	0.5072
Muscle, Other	M-Rhabdomyosarcoma	0	0	0	0	1	0	0.3406	.	.	.	0.5584	.
Nerve, Other	M-Malignant Schwannoma	0	0	1	0	0	0	0.5197	.	0.5405	.	.	.
Ovary	B-Adenoma	3	3	1	2	5	0	0.8844	0.3640	0.7415	0.5870	0.4777	0.8804
	M-Carcinoma	0	0	0	0	1	0	0.3435	.	.	.	0.5641	.
Pancreas	B-Adenoma, Islet Cell	0	0	1	0	0	0	0.5197	.	0.5405	.	.	.
Pituitary	B-Adenoma	2	0	1	0	0	1	0.4803	0.7677	0.5615	0.7978	0.8083	0.5110
	M-Meningeal Sarcoma	0	0	0	0	0	1	0.1565	.	.	.	.	0.5143
Rectum	M-Carcinoma	0	0	0	0	1	0	0.3435	.	.	.	0.5641	.
Skin/Subcutis	B-Adenoma, Sebaceous Gland	0	0	0	1	0	0	0.3406	.	.	0.5467	.	.
	B-Papilloma, Squamous Cell	2	1	0	0	0	0	0.9866	0.5321	0.7923	0.7978	0.8083	0.7609
	M-Carcinoma, Squamous Cell	0	1	0	0	0	0	0.6913	0.5211	.	.	.	.
	M-Fibrosarcoma	0	0	0	0	0	2	0.0228*	.	.	.	.	0.2536
	M-Sarcoma	0	1	1	0	0	0	0.7978	0.5211	0.5405	.	.	.
Stomach, Nongl	B-Papilloma, Squamous Cell	1	0	0	0	0	0	0.8515	0.5143	0.5405	0.5467	0.5584	0.5072
Thymus	B-Thymoma	0	0	0	1	0	0	0.3391	.	.	0.5526	.	.
Tongue	M-Carcinoma, Squamous Cell	0	0	1	0	0	0	0.5197	.	0.5405	.	.	.
Uterus	B-Leiomyoma	0	1	0	0	0	0	0.6913	0.5211	.	.	.	.
	B-Polyp, Endometrial Stromal	11	3	6	5	3	1	0.9971	0.9849	0.9201	0.9557	0.9930	0.9985
	M-Carcinoma	0	0	1	1	1	1	0.1915	.	0.5405	0.5467	0.5584	0.5072
	M-Leiomyosarcoma	0	0	1	0	1	0	0.3850	.	0.5405	.	0.5584	.
Vagina	B-Polyp	0	1	0	0	0	0	0.6913	0.5211	.	.	.	.

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

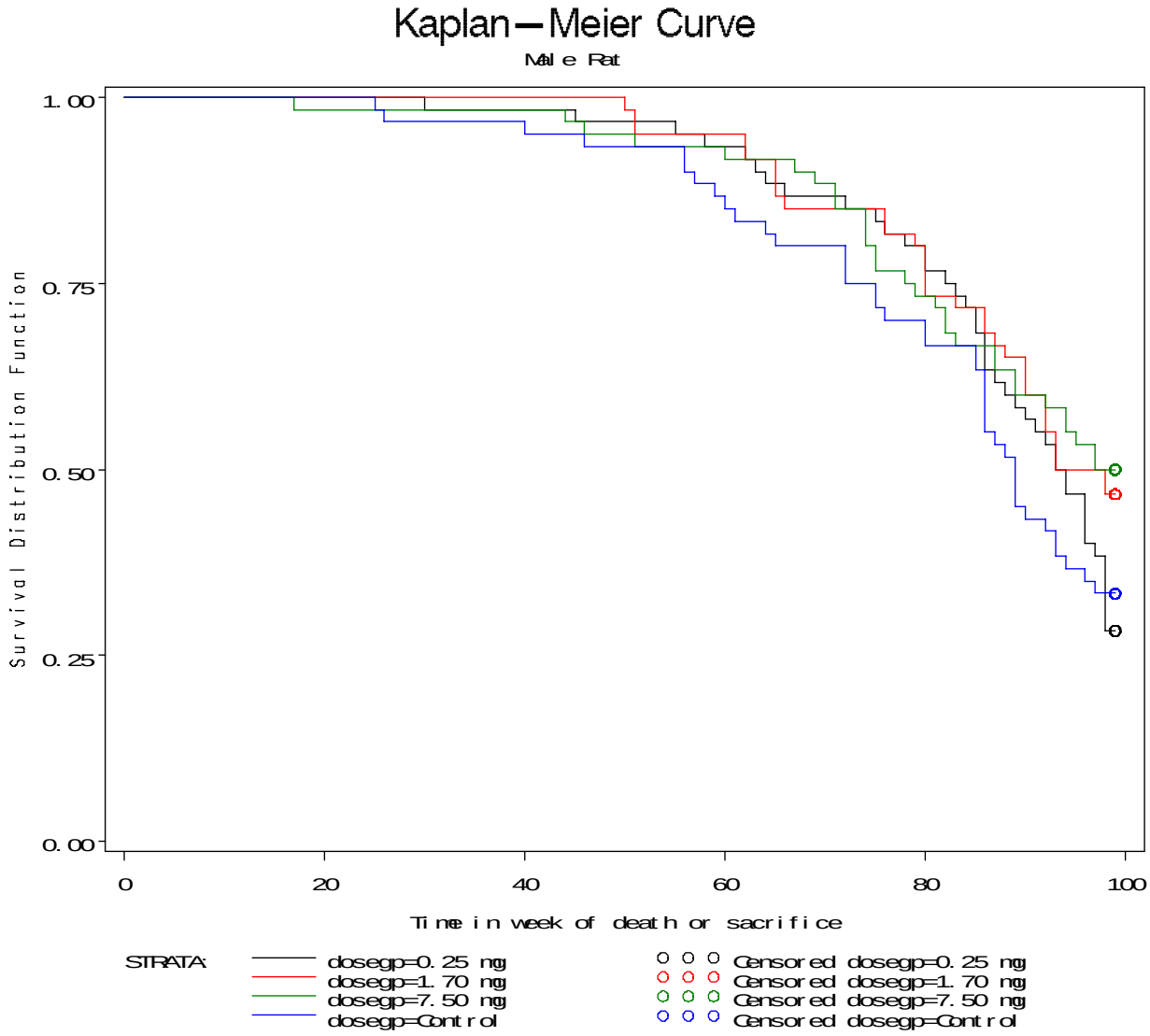


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

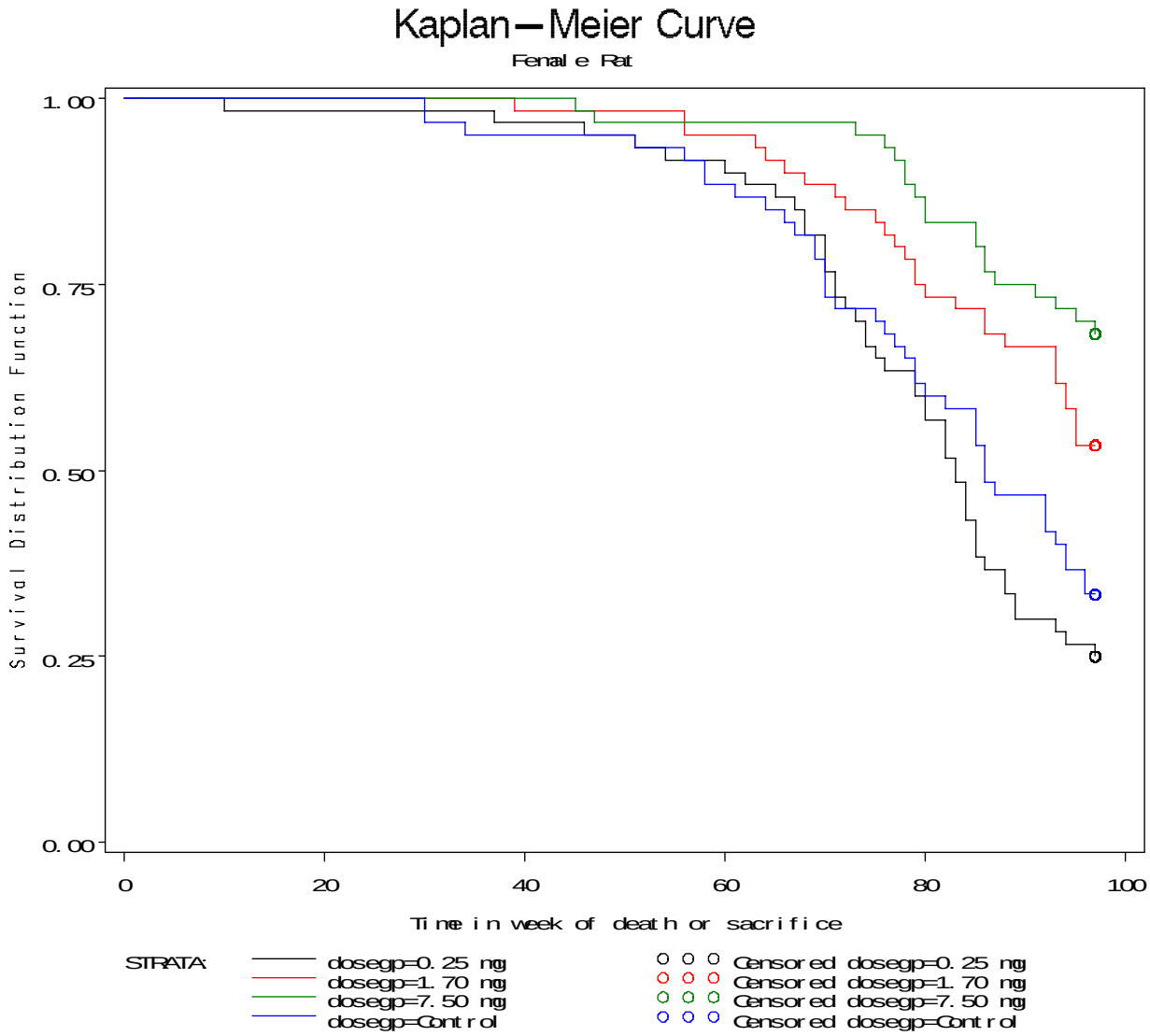


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

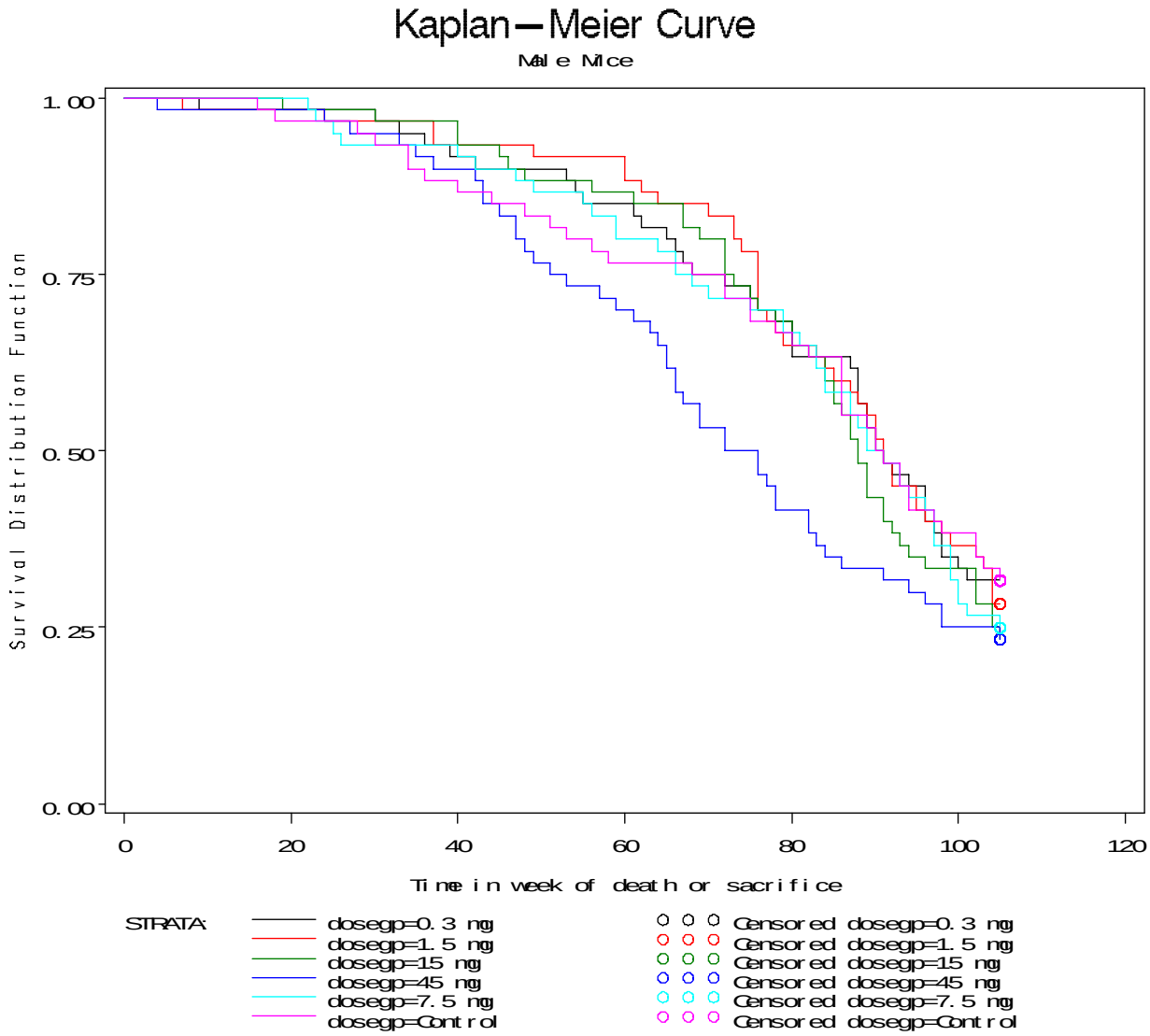
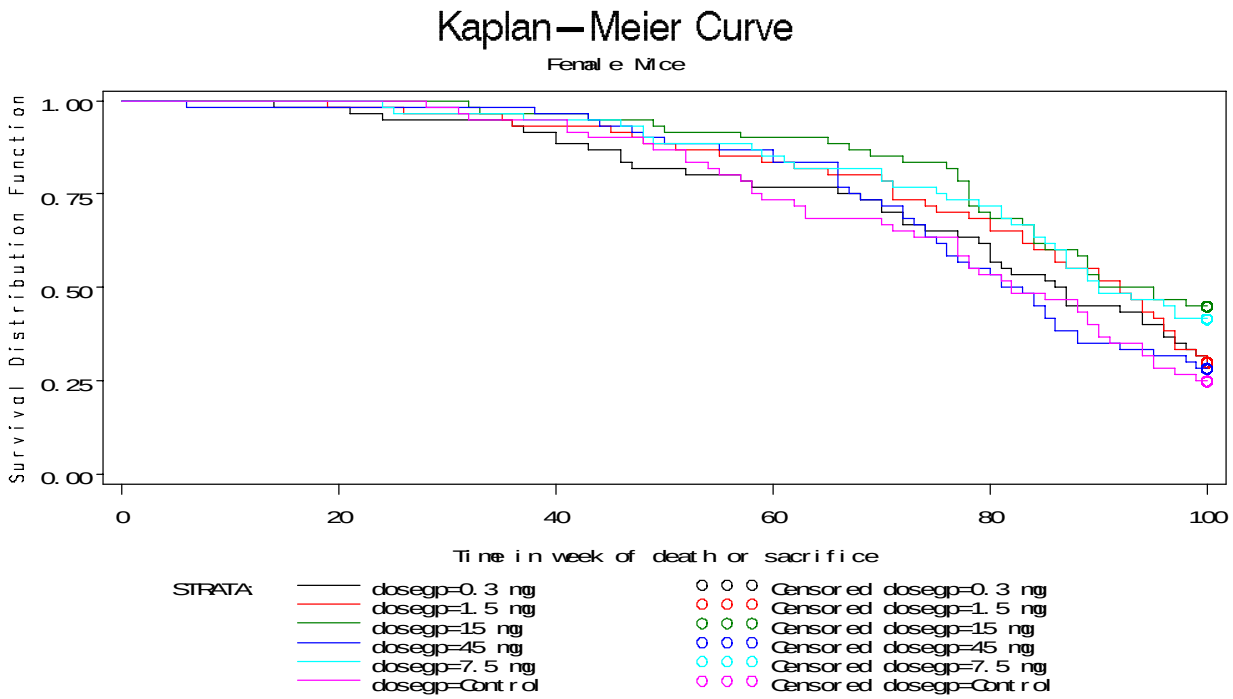


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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/s/

MOHAMMAD A RAHMAN
07/30/2012

KARL K LIN
08/01/2012
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA No.: 203858	**Applicant: Aegerion Pharmaceuticals, Inc.**	**Stamp Date: 02/29/2011**
Drug Name: Lomitapide mesylate capsules	**Indication: Treatment of HoFH**	**NDA Type: Standard**
Filing Meeting Date: 04/16/2012	**PDUFA goal date: 12/29/2012 (AC date: 10/17/2012)**	**Statistical Reviewer: Cynthia Liu**
Link to location of original submission in EDR \\CDSESUB1\EVSPROD\NDA203858\0000		

Background

Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor. The sponsor is submitting an original NDA seeking approval of lomitapide mesylate capsules for the treatment of homozygous familial hypercholesterolemia (HoFH) when used as an adjunct to a low-fat diet and other lipid-lowering therapies (LLT). Lomitapide has received an orphan drug designation for the indication on 10/23/2007. The safety and effectiveness of lomitapide in patients with HoFH are determined primarily based on the results from a pivotal Phase 3 study UP1002/AEGR-733-005 (29 patients) along with its extension trial AEGR-733-012 and a supportive Phase 2 study UP1001 (6 patients).

The pivotal Phase 3 study was a 26-week, open-label, single-arm, multicenter, multinational trial, conducted at 11 sites located in US (2 sites), Canada (2 sites), South Africa (3 sites), and Italy (4 sites). After completing Week 26, patients were eligible to enter the optional open-label extension study for 52 weeks to evaluate long-term efficacy and safety. As of 04/12/2011 the data cut-off date, 6 patients discontinued from the pivotal study prior to Week 26; 23 of the 29 enrolled patients had completed Week 56; and 18 of the 23 patients had completed the entire 78-week trial. The clinical study report submitted in this NDA covers only the data and results through Week 56.

The primary objective of the pivotal study was to evaluate the efficacy of lomitapide as defined by percent change from baseline in LDL-C at an individually-identified maximum tolerated dose after 26 weeks of treatment in patients with HoFH. The secondary objectives of the study were to evaluate percent changes in other lipid parameters, long-term safety, change in hepatic fat percent, and PK of lomitapide.

The primary efficacy endpoint, the percent change from baseline in LDL-C at Week 26, was analyzed using paired t-test. The key secondary efficacy parameters, TC, apo B, and triglycerides, were also analyzed using the same test in a sequential fashion in the order listed to preserve the Type 1 error rate at $\alpha = 0.05$.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

File-ability Checklist

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
Data sets in EDR are accessible and include adequate files for describing the data (e.g., define.pdf files).	X			SDTM format for individual study; ADaM format for ISS and ISE.
Data listings and intermediate analysis tables were sufficient to permit a statistical review.	X			
Safety and efficacy were investigated for subgroups based on gender, race, and age (including a subgroup for 65 and older) (if applicable).		X		Age (mean=31 yrs; 18-55 yrs) Race (25 pts Caucasian) Gender (16 pts M; 13 pts F)
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans and followed in the study reports.	X			
Designs utilized are appropriate for the indications requested.	X			
Intention-to-treat analysis was performed.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			Datasets for ISS submitted
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			The protocol specified an interim analysis at Week 56. The primary endpoint was Week 26. Therefore, there was no need for α adjustment.
Appropriate references for novel statistical methodology (if present) are included.			X	
Effects of dropouts on primary analyses were investigated.	X			LOCF; completers

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____YES____

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

Identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None at this moment.

Identify and list any potential review issues.
None at this moment.

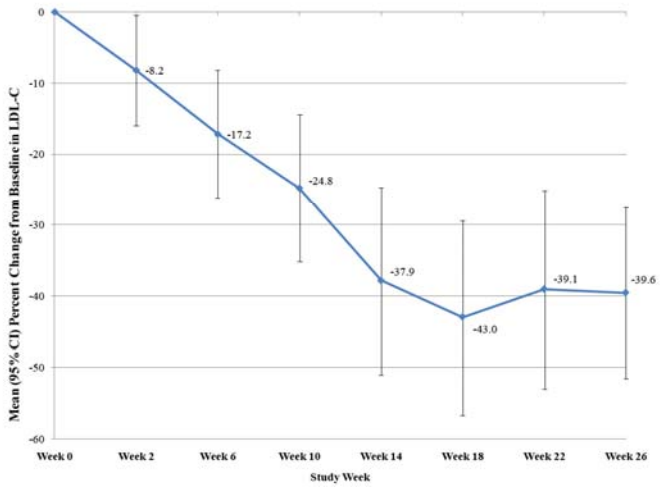
Table 12: Primary Efficacy Endpoint: LDL-C at Baseline and Week 26/LOCF (ITT Population)

TIME POINT STATISTIC	OBSERVED VALUE (MG/DL)	OBSERVED CHANGE (MG/DL)	PERCENT CHANGE (%)	P-VALUE[1]
Baseline				
N	29			
Mean (SD)	336.4 (113.54)	NA	NA	NA
Median	356.5			
Minimum, Maximum	152.0, 564.0			
[95% CI]	[293.3, 379.6]			
Week 26/LOCF				
N	29	29	29	
Mean (SD)	189.6 (104.24)	-146.9 (127.11)	-40.1 (31.25)	< 0.001
Median	169.0	-107.0	-49.5	
Minimum, Maximum	28.0, 442.0	-350.5, 49.0	-92.6, 20.4	
[95% CI]	[149.9, 229.2]	[-195.2, -98.5]	[-51.9, -28.2]	

Table 14: Mean (SD) LDL-C at Baseline and at Each Study Visit during the Efficacy and Safety Phases (Completers Population, N=23)

TIME POINT (N)	OBSERVED VALUE (MG/DL)	OBSERVED CHANGE (MG/DL)	P-VALUE[1]	PERCENT CHANGE (%)	P-VALUE[2]
Efficacy Phase					
Baseline (23)	351.9 (116.18)	NA	NA	NA	NA
Week 2 (22)	321.4 (125.71)	-36.7 (80.97)	0.046	-9.0 (21.53)	0.065
Week 6 (23)	294.7 (120.13)	-57.3 (88.86)	0.005	-15.0 (22.98)	0.005
Week 10 (23)	257.1 (129.47)	-94.8 (106.03)	< 0.001	-26.6 (26.08)	< 0.001
Week 14 (23)	201.8 (131.39)	-150.1 (121.08)	< 0.001	-43.7 (32.16)	< 0.001
Week 18 (21)	160.3 (107.75)	-197.3 (117.00)	< 0.001	-55.4 (31.95)	< 0.001
Week 22 (23)	179.2 (129.13)	-172.8 (131.90)	< 0.001	-49.0 (35.02)	< 0.001
Week 26 (23)	167.5 (96.09)	-184.5 (115.26)	< 0.001	-50.2 (26.47)	< 0.001
Safety Phase					
Week 36 (23)	202.4 (127.23)	-149.5 (108.81)	< 0.001	-42.9 (29.37)	< 0.001
Week 46 (23)	210.1 (133.84)	-141.8 (117.36)	< 0.001	-40.8 (29.38)	< 0.001
Week 56 (23)	198.6 (122.69)	-153.4 (113.51)	< 0.001	-44.0 (29.82)	< 0.001

Figure 6: Mean (95% CI) Percent Changes from Baseline in LDL-C in the Phase 3 Study UP1002/AEGR-733-005 through the Primary Endpoint of Week 26 using LOCF to Each Assessment (Full Analysis Set, N=29)



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/s/

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04/23/2012

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04/23/2012