CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21 - 316

STATISTICAL REVIEW(S)

Introduction

Lovastatin XL (LOV-XL) is an extended release formulation of lovastatin (an immediate release formulation marketed as Mevacor by Merck Pharmaceuticals). The sponsor is seeking indications for lowering total cholesterol (TC), LDL and triglycerides (TG) and raising HDL and —— and for slowing progression of atherosclerosis and —— of CHD. Indications for increasing —— and for slowing progression of atherosclerosis and —— of CHD are based on showing that lovastatin XL shows equivalent or comparable lipid effects or PK effects to Mevacor and therefore should receive comparable labeling.

The results of two controlled clinical trials have been submitted to support the efficacy and safety of lovastatin XL. These two trials (Studies 146-009 and 146-010, Table 1) are reviewed in detail here. Three additional clinical trials were described in the NDA but, by design, do not provide sufficient data to alone demonstrate the efficacy of lovastatin XL and are not reviewed in detail for the following reasons:

1. Study 146-006 is a small PK-PD study of only 26 patients and 4 weeks duration
2. Study 146-008 is an open label study
3. Study 146-011 is an extension study of Studies 146-009 and 146-010

Table 1. Lovastatin XL Clinical Trials

Study (# of centers)	Design	Treatment groups (N)	Duration of treatment
146-009 (12 US)	**DB, randomized, parallel group**	**Placebo (34)** **LOV-XL 10 mg (35)** **LOV-XL 20 mg (34)** **LOV-XL 40 mg (33)** **LOV-XL 60 mg (36)**	**4 wks diet/placebo run-in** **12 wks DB treatment**
146-010 (24 US)	**DB, randomized, 2-period crossover**	**LOV-XL 20/Mevacor 20 (90)** **Mevacor 20/ LOV-XL 20 (89)** **LOV-XL 60/Mevacor 60 (88)** **Mevacor 60/ LOV-XL 60 (91)**	**4 wks diet/placebo run-in** **12 weeks for each period** **6 wk washout between periods**
146-006 (1 US)	Single-blind, randomized, 2-period crossover, PK-PD	LOV-XL 40/Mevacor 40 (13) Mevacor 40/ LOV-XL 40 (13) LOV-XL given at bedtime Mevacor given with dinner	4 weeks for each period
146-008 (3 US)	Open-label, randomized, parallel group	LOV-XL 40 Before breakfast (22) After Dinner (23) At bedtime (23)	4 weeks
146-011 (36 US)	Extension of 146-009 and 146-010	LOV-XL 40 mg (70) LOV-XL 60 mg (159)	12 weeks

Reviewer's Methods

Data was obtained from two clinical trials, Studies 146-009 and 146-010, for analysis by this reviewer. All results for these studies, presented in this review, were created by this reviewer. These results were compared to the results presented in the NDA; differences between this reviewer's results and the sponsor's results were examined and are noted in this review.

The objective of this review primarily is to describe the treatment effect of lovastatin XL; the safety and efficacy of this product is fully reviewed by the medical reviewer, Dr. Pariser and is not in question. This reviewer has examined the treatment effect of the range of doses of lovastatin XL in order to make recommendations for the label. The estimates of the treatment effects in each study are also presented in the context of other data provided in the submission by the sponsor in the summary section of this review.

Only a brief overview of each trial is given here; for further details of these trials, see the medical review.

Study 146-009 (conducted 6/99 to 7/00)

Study 146-009 is a dose-response placebo-controlled study designed to assess the safety and efficacy of four doses of lovastatin XL (10 mg, 20 mg, 40 mg and 60 mg). After a 4-week placebo run-in, patients were randomized and treated for 12 weeks. The primary efficacy endpoint was percent change in LDL-C after 12 weeks of treatment. Secondary variables were percent change from baseline in HDL-C, triglycerides (TG) and total cholesterol (TC).

Less than 10% of the patients (3 or less in each group) dropped out of the trial (Tables 2 and 3).

Table 2. Study 146-009 Patient Disposition

	PLA	LOV-XL 10	LOV-XL 20	LOV-XL 40	LOV-XL 60
Randomized	34	35	34	33	36
Wk 4	34	33	34	33	35
Wk 8	34	32	32	32	34
Wk 11	33	32	31	32	34
Wk 12	32	32	31	32	33
Completers	32	32	31	32	33
Sponsor's ITT	34	33	34	33	35

The primary reason for dropout was adverse event (ADE, Table 3). No dropouts due to ADE were observed in the highest dose.

Table 3. Study 146-009 Reasons for discontinuation

	PLA (n=34)	LOV-XL 10 (n=35)	LOV-XL 20 (n=34)	LOV-XL 40 (n=33)	LOV-XL 60 (n=36)
ADE	2	1	2	1	0
Pt/Inv request	0	1	1	0	1
Prot. Viol.	0	0	0	0	0
Other	0	1	0	0	2

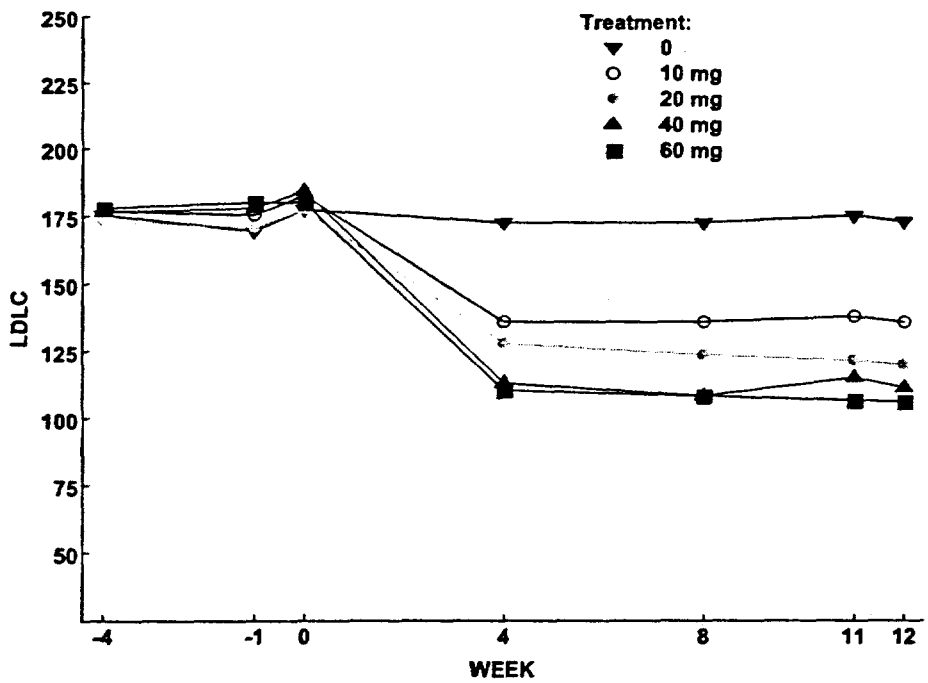
The treatment groups were sufficiently balanced regarding baseline demographics (Table 4). Less than half the patients were female except in the highest dose group. The average age of patients was about 57 years, 20% were 65 or older. About 90% of the patients were Caucasian.

Table 4. Study 146-009 Patient Demographics for All Randomized Patients

	PLA	LOV-XL 10	LOV-XL 20	LOV-XL 40	LOV-XL 60
Age					
Mean (SD)	56 (10)	56 (8)	57 (8)	57 (8)	57 (8)
Range	29-70	38-70	38-70	38-69	35-68
%≥65years	26%	15%	15%	15%	26%
Gender					
% female	47%	49%	44%	42%	56%
Race					
% white	91%	91%	91%	91%	83%

Statistically significant drops in LDL-C were seen after 4 weeks of treatment (Figure 1) for all doses of lovastatin XL compared to placebo.

Figure 1. Study 146-009 LDL-C (mg/dL) by week on study and treatment group (observed cases).



For analysis purposes, Weeks –1 and 0 were averaged for baseline and Weeks 11 and 12 were averaged for endpoint. Percent change from baseline was computed using these values. For the ITT analysis, the last observation on therapy was used (note that missing data was not an issue for this trial).

The mean baseline and the mean and median percent change from baseline for LDL,

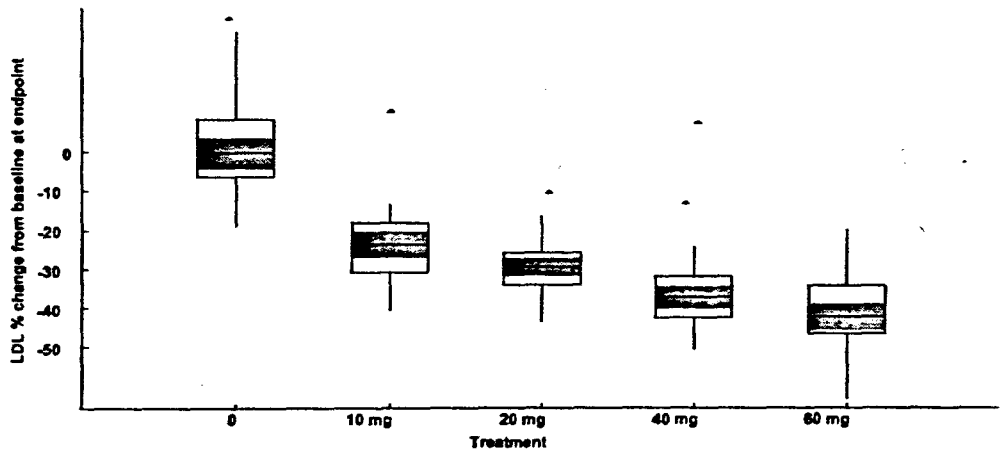
HDL, TC and TG are summarized in Table 5 below.

Table 5. Study 146-009 LDL-C Baseline and Week 12 % change from baseline LOCF

	PLA (n=34)	LOV-XL 10 (n=35)	LOV-XL 20 (n=34)	LOV-XL 40 (n=33)	LOV-XL 60 (n=36)
LDL					
Baseline	174 (28)	179 (26)	174 (22)	181 (34)	180 (35)
Week 12 LOCF					
Mean (SD)	+1.3% (12.6)	-23.8% (9.8)	-29.6% (7.4)	-35.8% (11.0)	-40.8% (10.0)
Median	-0.3%	-23.7%	-29.5%	-37.3%	-42.4%
HDL					
Baseline	43.5 (10.0)	45.1 (10.7)	45.1 (15.1)	44.0 (9.3)	48.9 (17)
Week 12 LOCF					
Mean (SD)	+5.6% (13.1)	+9.4% (13.6)	+12.0% (10.9)	+13.1% (10.9)	+11.6% (9.3)
Median	+4.6%	+8.2%	+12.1%	+11.2%	+8.9%
TC					
Baseline	253 (36.6)	259 (30)	261 (31)	263 (36)	264 (38)
Week 12 LOCF					
Mean (SD)	+3.4% (9.9)	-17.9% (8.5)	-20.9% (7.1)	-25.4% (9.1)	-29.2% (8.3)
Median	+0.6%	-18.1%	-21.2%	-27.6%	-29.5%
TG					
Baseline	175 (73)	175 (71)	206 (99)	189 (75)	174 (78)
Week 12 LOCF					
Mean (SD)	+8.7% (23.5)	-17.3% (26.7)	-13.0% (33)	-9.9% (34)	-25.1% (18.4)
Median	+2.3%	-23.3%	-22.4%	-18.1%	-28.4%

For **LDL**, each dose was significantly different from placebo at endpoint ($p<.0001$; ANCOVA with baseline as a covariate) and a clear dose response was evident ($p<.0001$, trend test for dose excluding placebo). In addition, the response at each dose was found to be significantly different from every other dose with the smallest difference observed between the 40 mg dose and the 60 mg dose ($p<.03$). The distribution of the responses at each dose further illustrates the dose response relationship (Figure 2).

Figure 2. Study 146-009 Boxplots of LDL % change from baseline at Week 12 LOCF



The results for **TC** were consistent with the LDL results; each dose was statistically different from placebo (p<.0001) and there was a significant dose response (p<.0001).

The results for **TG** and **HDL** are similar in that there is a significant effect for lovastatin XL over placebo (with the exception of HDL for the 10 mg dose) but no dose response relationship (p>.25) for either measure. From Table 5, it can be seen that there is some variability amongst the baselines for TG and HDL. (Pairwise tests revealed p-values less than .10 for the most extreme differences.) To examine the results (particularly the dose response) more carefully taking these baseline differences into consideration, this reviewer looked at the median response for change from baseline overall and stratifying on baseline. Figures 3 and 4 emphasize that there is no dose response relationship for lovastatin XL for HDL and TG.

Figure 3. Study 146-009 HDL-C (mg/dL) change from baseline (median) by week on study and treatment group (observed cases) overall and by baseline HDL.

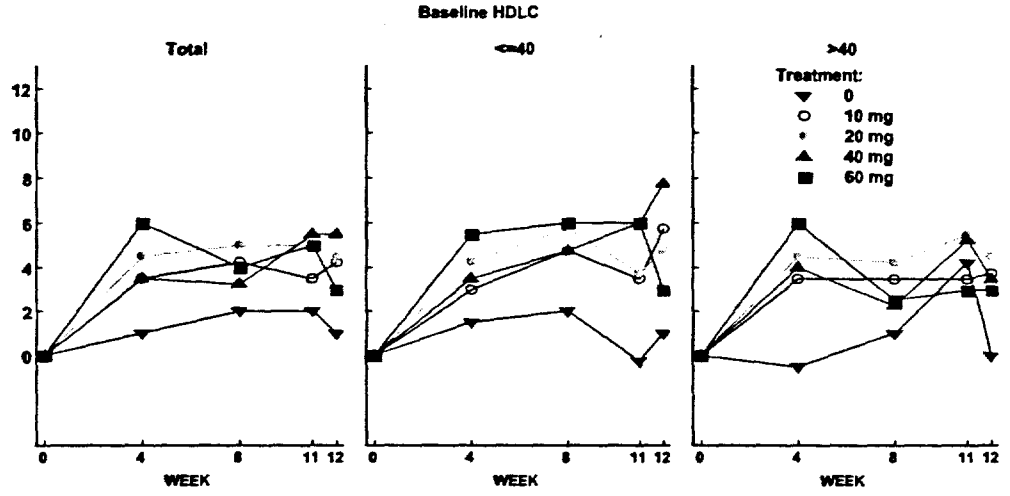
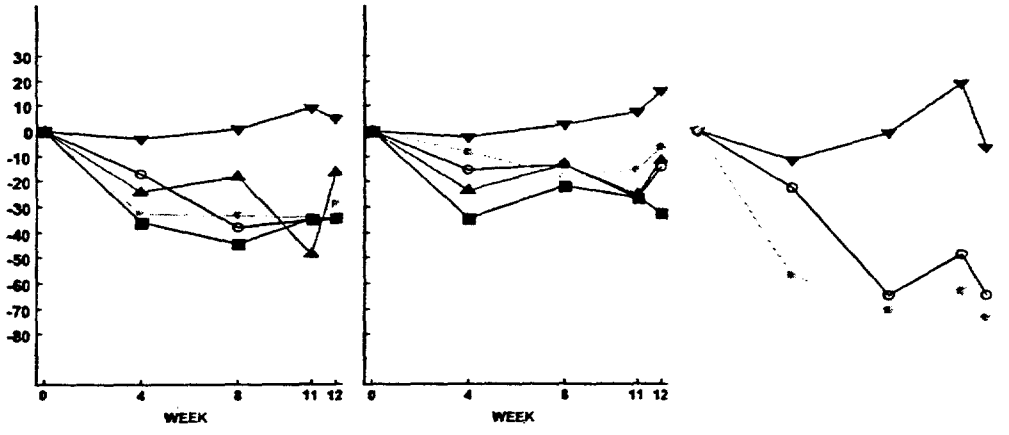


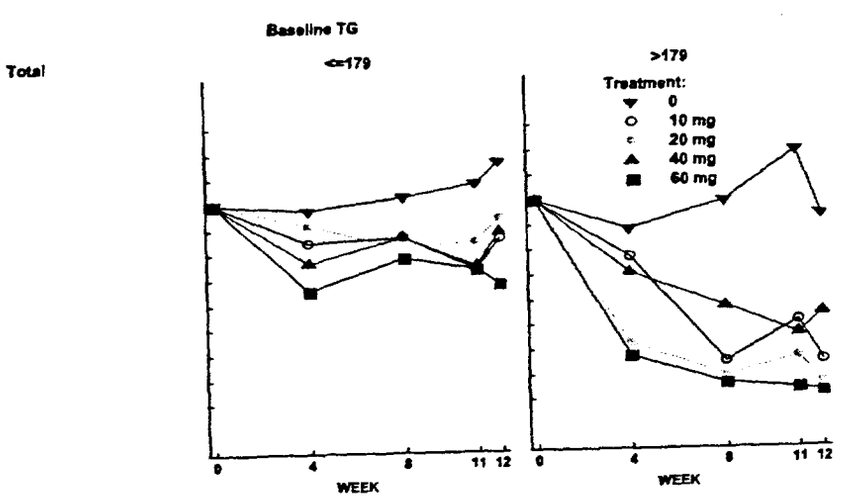
Figure 4. Study 146-009 TG (mg/dL) change from baseline (median) by week on study and treatment group (observed cases) overall and by baseline TG.



HDL change from baseline

TG change from baseline

Total



Study 146-010 (conducted 6/99 to 7/00)

Study 146-010 is a crossover study designed to compare two doses of lovastatin XL (LOV-XL; 20 mg and 60 mg) to two doses of Mevacor (MEV; also 20 mg and 60 mg). After a 4-week placebo run-in, patients were randomized to one of four treatment sequences (LOV-XL20/MEV20; MEV20/LOV-XL20; LOV-XL60/MEV60; MEV60/LOV-XL60). Each treatment period was 12 weeks long separated by a washout period of 6 weeks.

With 60 patients in each sequence (120 at each dose), this trial was powered at 90% to show a larger decrease for lovastatin XL over Mevacor of 3% or greater for LDL. The sponsor surpassed their proposed sample size with over 70 patients in each sequence (Table 6). The rate of dropout in this study was similar to the rate observed in Study 146-009 with about 10% of the patients dropping out during each 12 week period. Overall about 83% of the randomized patients were included in the ITT population; patients with baseline data and with observations in each period are included in the sponsor's ITT population. This reviewer's ITT analyses included all available data.

Table 6. Study 146-010 Patient Disposition

	LOV-XL20/MEV20	MEV20/LOV-XL20	LOV-XL60/MEV60	MEV60/LOV-XL60
Randomized	90 (100%)	89 (100%)	88 (100%)	91 (100%)
Period 1				
Wk 4	88	87	85	91
Wk 8	85	81	84	89
Wk 11	83	77	78	85
Wk 12	81	76	78	83
Washout				
Wk 17	77	72	72	79
Wk 18	77	72	72	79
Period 2				
Wk 22	77	72	70	76
Wk 26	76	71	69	76
Wk 29	76	70	69	75
Wk 30	76	69	68	75
Completers	76 (84%)	69 (78%)	68 (77%)	75 (82%)
Sponsor's ITT	77 (86%)	72 (81%)	71 (81%)	77 (85%)

The primary reasons for discontinuation (Table 7) were ADE or patient/investigator request. The two drugs did not differ with respect to reasons for discontinuation.

Table 7. Study 146-010 Reasons for discontinuation by treatment administered

	Lovastatin XL 20 (n=179)	Mevacor 20 (n=179)	Lovastatin XL 60 (n=179)	Mevacor 60 (n=179)
ADE	4	7	9	7
Pt/Inv request	5	9	7	4
Prot. Viol.	4	2	2	1
Other	2	1	4	2

The demographics in this study were similar to those in Study 146-009 (Table 8).

Table 8. Study 146-010 Patient Demographics for All Randomized Patients

	LOV-XL20/MEV20 N=90	MEV20/LOV-XL20 N=89	LOV-XL60/MEV60 N=88	MEV60/LOV-XL60 N=91
Age				
Mean	56	56	56	55
Range	36-70	32-71	31-70	30-70
%≥65years	14%	20%	20%	16%
Gender				
% female	38%	51%	42%	40%
Race				
% white	90%	81%	81%	87%

(Demographics for ITT patients are similar.)

LDL-C, the primary endpoint, is depicted in Figure 5 over the full duration of the trial. From this graph, the following is evident:

- Decreases in LDL primarily occur during the first 4 weeks of treatment
- LDL returns to baseline levels after about 5 weeks of washout.
- There is no evidence of carry-over
- Responses are similar for the two drugs

Figure 5 Study 146-010 Mean LDL by week on study

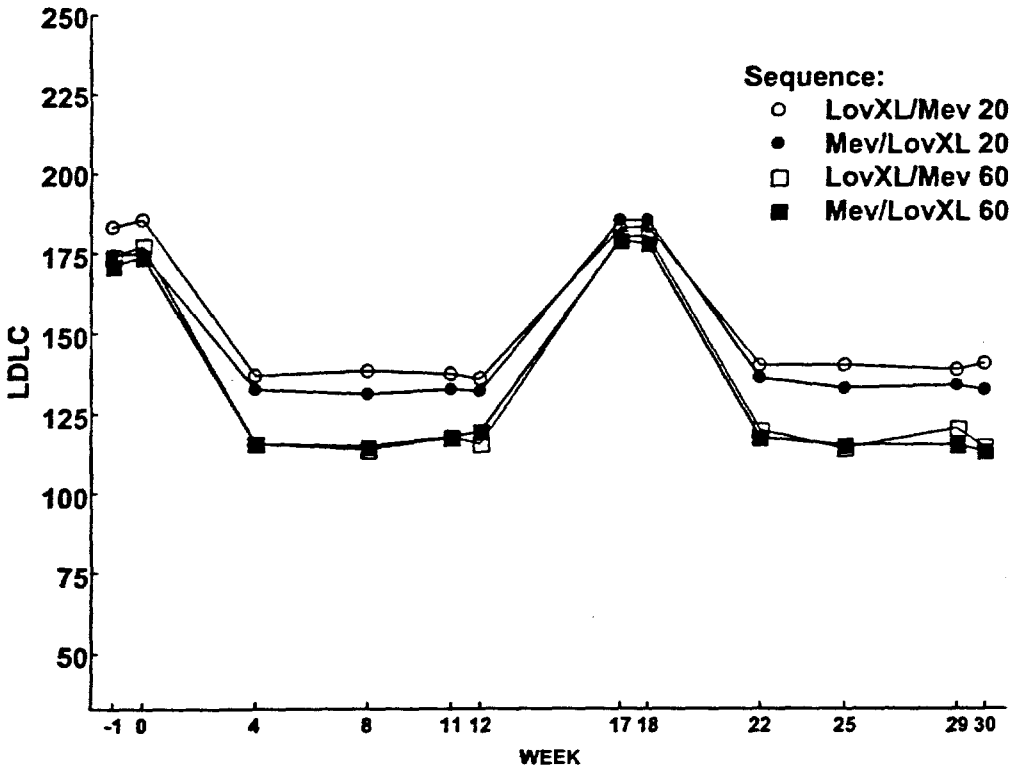
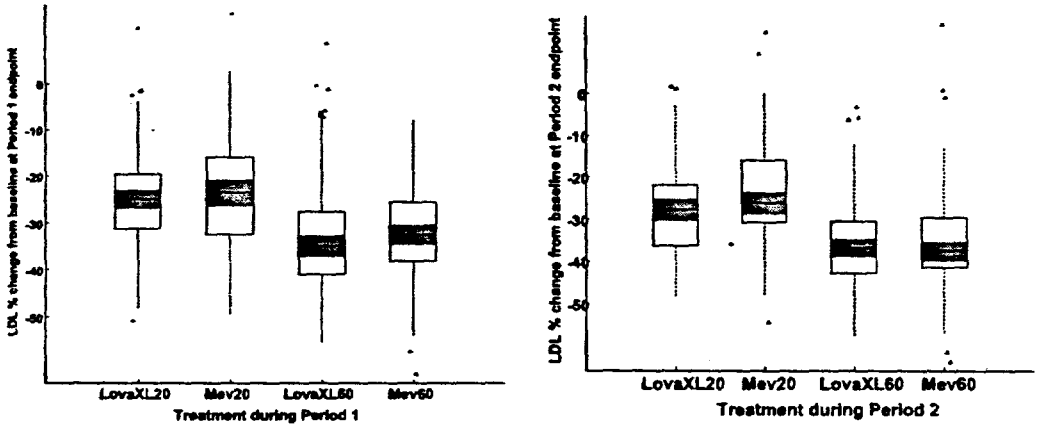


Figure 6 further illustrates the comparability of response of the two drugs within each period.

Figure 6 Study 146-010 Boxplots of LDL % change from baseline by period and treatment



In the absence of carryover, the treatment effects are estimated ignoring sequence and period. The lipid results, assuming no carryover, are summarized in Table 9 below. All available data was used to compute the descriptive statistics in Table 9. Comparing to the magnitude of responses seen for lovastatin XL 20 and 60 mg in Study 146-009, the values in this study are all smaller in absolute magnitude by about 2-8%.

Table 9. Study 146-010 Lipid parameters baseline and Week 12 % change from baseline LOCF

	Lovastatin XL 20 (n=160)	Mevacor 20 (n=164)	Lovastatin XL 60 (n=163)	Mevacor 60 (n=162)
LDL				
Baseline	185 (37)	179 (36)	177 (31)	176 (35)
Week 12 LOCF				
Mean (SD)	-26.1% (11.2)	-23.2% (11.8)	-34.3% (12.4)	-33.1% (11.8)
Median	-26.0%	-23.8%	-35.8%	-34.6%
HDL				
Baseline	46.5 (10.3)	46.0 (10.9)	46.0 (12.3)	45.4 (12.2)
Week 12 LOCF				
Mean (SD)	+3.8% (11.8)	+4.4% (12.0)	+5.6% (12.1)	+5.2% (11.5)
Median	+2.7%	+4.9%	+6.0%	+5.3%
TC				
Baseline	264 (40)	259 (39)	257 (37)	256 (39)
Week 12 LOCF				
Mean (SD)	-18.9% (9.2)	-17.1% (9.1)	-25.7% (9.4)	-25.1% (9.1)
Median	-19.7%	-18.0%	-27.3%	-25.6%
TG				
Baseline	166 (76)	171 (76)	166 (67)	174 (83)
Week 12 LOCF				
Mean (SD)	-7.9% (27.8)	-11.0% (24.6)	-18.7% (26)	-19.2% (27.1)
Median	-11.6%	-14.3%	-22.8%	-21.0%

The objective of this trial was to show that lovastatin XL lowered LDL more than Mevacor by 3% or more. For the 20 mg dose, the sponsor met their goal (Table 10, p=.005), but for the 60 mg dose, only about a 2% difference was observed. Lovastatin XL did not beat Mevacor on any other lipid parameter after making adjustments to alpha for multiple endpoints.

Table 10. Study 146-010 Paired differences at Week 12 endpoint for ITT patients

	LOV-XL 20 – Mevacor 20[1] (n=149)	LOV-XL 60 – Mevacor 60[1] (n=148)
LDL		
Mean	-3.2%	-1.7%
95% CI	-5.4%, -1.1%	-3.7%, 0.5%
Median	-3.0%	-3.8%
p-value[2]	.005	.055
HDL		
Mean	-0.3%	-0.2%
95% CI	-2.8%, +2.3%	-2.6%, +2.1%
Median	0	0
p-value[2]	.97	.87
TC		
Mean	-1.9%	-0.9%
95% CI	-3.7%, -0.1%	-2.7%, +0.9%
Median	-1.8%	-1.6%
p-value[2]	.03	.21
TG		
Mean	+2.8%	+1.1%
95% CI	-2.5%, +8.6%	-5.3%, +7.0%
Median	+2.6%	-1.4%
p-value[2]	.42	.77

[1] For LDL, TC and TG, negative differences favor lovastatin XL over Mevacor. For HDL, positive differences favor lovastatin XL over Mevacor.

[2]P-value is result of Wilcoxon signed rank test.

The 95% confidence intervals on the treatment difference for LDL, HDL and TC show that lovastatin XL is no worse than Mevacor by a margin of about 3% or less (Table 10). The results for TG do not show convincing comparability of the two drugs with potential differences in favor of Mevacor as high as 8.6%. With no a priori definitions of comparability, no definitive statements on the equivalence of the effects of the drug can be made. Nevertheless, if one was to assume that 3% was a clinically important difference based on the objective of the trial, one could conclude that the effect of lovastatin XL on LDL, HDL and TC is not inferior to the effect of Mevacor based on the boundaries of the 95% confidence intervals.

Assessment of treatment effect

In the sponsor's proposed label, only the results of Study 146-009 are presented. In this section of my review, I examine the treatment effect in both studies in order to ascertain whether the results of Study 146-009 fairly represent the efficacy of lovastatin- XL.

Larger treatment effects for LDL were seen in Study 146-009 than in Study 146-010 as can be seen in the table below.

Table 11. LDL % change from baseline at Week 12 LOCF in Studies 146-009 and 146-010

	Lova-XL 20 Mean (95% CI)	Lova-XL 60 Mean (95% CI)
Study 9	-29.6% (-31.9%, -27.3%) (n=34)	-40.8% (-44.2%, -37.4%) (n=36)
Study 10	-26.1% (-27.8%, -24.4%) (n=160)	-34.3% (-36.2%, -32.4%) (n=163)

This difference is illustrated further in Figure 7 There is a distinct difference between the study distributions of the response in each study for patients with low decreases (less than 10) or no decrease.

Figure 7 Boxplots of LDL % change from baseline at Week 12 LOCF by dose and study

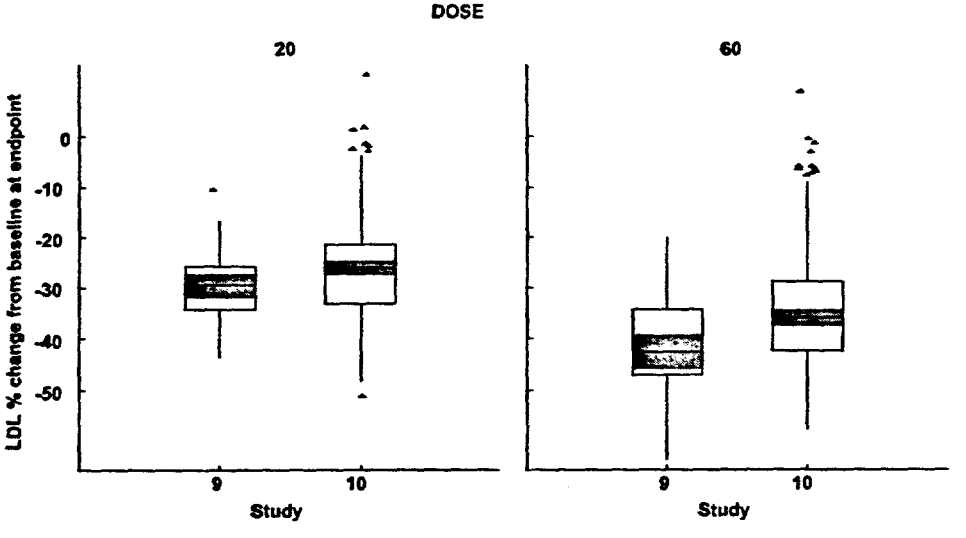


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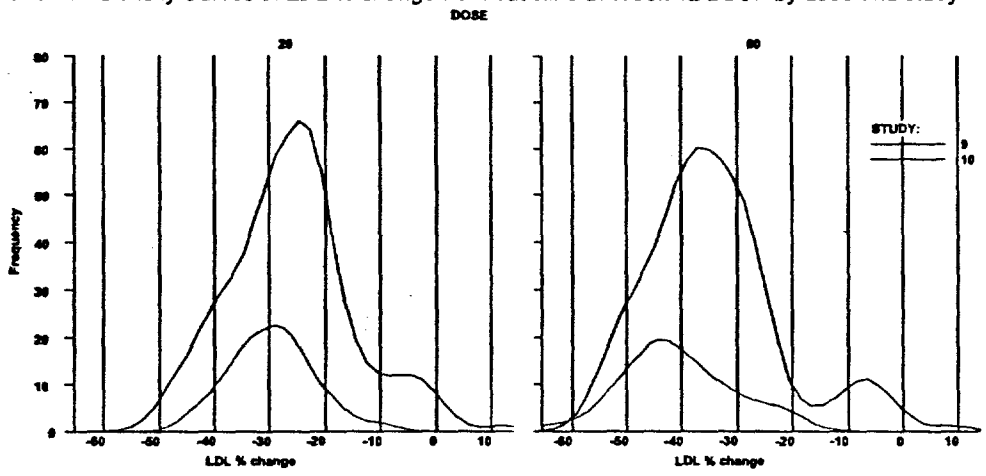
Figure 8, a plot of the kernel densities, shows clearly a second "hump" for Study 146-010 for those patients with low or no decreases indicating outliers in the right tail. The distribution of the remaining Study 146-010 patients is slightly shifted to the right of the distribution of Study 146-090 with about a 5% difference between peaks (close to the difference seen in the means).

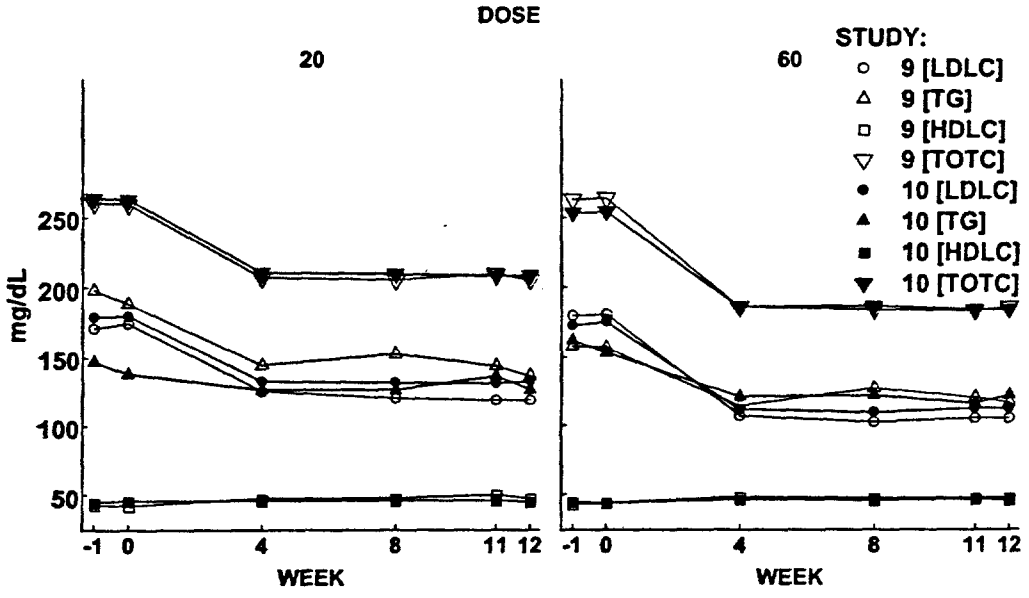
Figure 8 Kernel Density Curves of LDL % change from baseline at Week 12 LOCF by dose and study



This reviewer could find no pattern in the outliers of Study 146-010; that is, patients with low response were distributed across centers and not restricted to any specific subgroup defined by baseline demographics or baseline lipid parameters.

To look at all the lipid responses over time, this reviewer plotted the values by study and by dose in Figure 9. With the exception of triglycerides for the 20 mg dose groups, the pattern of responses in the two studies look similar.

Figure 9. LDL,HDL, TC and TG in Studies 146-009 and 146-010 for lovastatin-XL 20 mg and 60 mg



This reviewer concludes from examination of the data from both studies that the data from Study 146-009 fairly represents the efficacy of lovastatin-XL and though the responses are larger for LDL than was seen in Study 146-010, the results from the two studies cannot be interpreted as being inconsistent. Given the differences in design and sample size and the amount of variability inherent in the measures, the differences between the study results are not troubling. In addition, the results for the secondary lipid parameters are similar.

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Subgroups

LDL results by subgroups defined by gender, age, baseline LDL and baseline TG were consistent with the overall results observed in Study 146-009 (Table 12). A clear dose response is evident within each subgroup and magnitude of effects between subgroups are comparable.

Table 12. Study 146-009 LDL-C Week 12 LOCF % change from baseline (Mean)

	PLA (n=34)	LOV-XL 10 (n=35)	LOV-XL 20 (n=34)	LOV-XL 40 (n=33)	LOV-XL 60 (n=36)
Gender					
Female	-1.2% (n=16)	-24.1% (n=17)	-28.3% (n=15)	-38.6% (n=14)	-43.9% (n=20)
Male	+3.6% (n=18)	-23.4% (n=16)	-30.7% (n=18)	-33.8% (n=19)	-36.5% (n=15)
Age					
<65	+2.6% (n=25)	-24.4% (n=28)	-29.3% (n=28)	-34.9% (n=28)	-40.8% (n=26)
≥65	-2.3% (n=9)	-20.7% (n=5)	-31.8% (n=5)	-41.2% (n=5)	-40.8% (n=9)
Baseline LDL-C (by median)					
<174	+6.3% (n=16)	-21.4% (n=17)	-28.2% (n=18)	-31.5% (n=17)	-36.3% (n=15)
≥174	-3.0% (n=18)	-26.4% (n=16)	-31.3% (n=15)	-40.4% (n=16)	-44.1% (n=20)
Baseline TG (by median)					
<178.5	+5.2% (n=20)	-26.1% (n=17)	-28.4% (n=13)	-34.3% (n=14)	-42.2% (n=20)
≥178.5	-4.1% (n=14)	-21.0% (n=16)	-30.4% (n=20)	-36.9% (n=19)	-38.9% (n=15)

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Summary and Conclusions

The sponsor has conducted five clinical trials; two of these trials (Studies 146-009 and 146-010) were reviewed here) were well-controlled, randomized, blinded trials which demonstrated the efficacy of lovastatin-XL and were reviewed here. The other three trials offered some efficacy data but by design were not adequate to establish efficacy (Study 146-006 is a small PK-PD study; Study 146-008 is an open label study and Study 146-011 is an extension study of Studies 146-009 and 146-010) (see Table 1 for more details on all five studies).

The endpoint results for LDL percent change from baseline (the primary efficacy variable) for all five studies are summarized in Table 13. The administration of lovastatin-XL results in highly statistically significant drops in LDL compared to placebo in a dose-related manner ($p<.0001$, Study 146-009). The results for Study 146-009 are representative of the results from the other four studies (see Assessment of treatment effect for more details).

Table 13. Mean LDL % change from baseline at endpoint (≥4 weeks of treatment)[1]

	146-009	146-010	146-006	146-008	146-011
Placebo	+1%				
Lovastatin XL					
10	-24%				
20	-30%	-26%			
40	-36%		-41%	-37%	-34%
60	-41%	-34%			-33%
Mevacor					
20		-23%			
40			-37%		
60		-33%			

Efficacy results for total cholesterol (a secondary variable) were consistent with the LDL results.

The results for HDL and TG in Study 146-009 showed significant increases and decreases, respectively, compared to placebo but no dose-response. The response for these measures is clearly less predictable than for LDL and TC. The medical reviewer describes the HDL and TG results as modest clinical effects.

Table 14. Mean HDL and TG % change from baseline at endpoint (≥4 weeks of treatment)[1]

	146-009		146-010		146-006		146-008		146-011	
	HDL	TG (med)	HDL	TG (med)	HDL	TG (mean)	HDL	TG (mean)	HDL	TG (mean)
Placebo	+5%	+2%								
Lovastatin XL										
10	+9%	-23%								
20	+12%	-22%	+4%	-12%						
40	+13%	-18%			+8%	-21%	+11%	-20%	+7%	-20%
60	+12%	-28%	+6%	-23%					+6%	-15%
Mevacor										
20			+4%	-14%						
40										
60			+5%	-21%						

In conclusion, the results for Studies 146-009 and 146-010 provide sufficient statistical evidence to establish the efficacy of lovastatin-XL for the treatment of hyperlipidemia. Significant

1 Results for 146-009 and 146-010 were computed by the reviewer; results for the other three studies were computed by the sponsor.

dose-related responses for LDL and TC were seen after 4 weeks of treatment. Significant changes in HDL and TG were observed but the responses were variable over time and not dose-related (see Figure 3 and Figure 4).

Labeling Comments

This reviewer has the following comments on the sponsor's proposed label with modifications by the medical reviewer:

1. According to the draft guidance for labeling, terms that vaguely describe an effect should be avoided. The terms [redacted] should be deleted and the responses described either using numbers or characterized as "dose-related" or in other more precise terms.
2. Under the Geriatric and Gender sections, subgroup results should be described in the same way. The guidance recommends that subgroup results be summarized in the clinical studies section not in the special populations section.
3. The first paragraph of the Clinical Studies section should give an overview of the submission. For example, mention the number of patients in the database, etc.
4. The transition to immediate-release results seems confusing to me. Might the reader wonder why these results are here?
5. Should [redacted] included in indications given it was not measured in the sponsor's studies?
6. The sponsor's label contains results for Study 146-009 and not Study 146-010 in the Clinical Studies section. This is acceptable but information that reflects the variability of the data in Study 146-009 should be added. One way to do this is to include boxplots of the dose response (see Figure 2 of this review).

These comments will be shared with the medical reviewer.

Joy D. Mele, M.S.
Mathematical Statistician

Concur:

Todd Sahlroot, Ph.D.
Team Leader

APPEARS THIS WAY
ON ORIGINAL

Ed Nevius, Ph.D.
Director of DOB2

cc:
Archival NDA 21-316
HFD-510
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/s/

Joy Mele
12/14/01 01:35:38 PM
BIOMETRICS

S. Edward Nevius
12/22/01 11:42:42 AM
BIOMETRICS
Concur with review.

Todd Sahlroot
12/26/01 10:28:01 AM
BIOMETRICS