C. Methods and Specific Findings of Safety Review

The designs of the two controlled and the uncontrolled Phase III studies were quite different, making pooling of the studies difficult. Therefore, this Reviewer performed safety evaluations of the 3 Phase III studies separately (see subsections 2, 3 and 4 of this section for detailed safety reviews).

The sponsor performed a safety review with pooling of the safety results, however. The sponsor pooled the two controlled clinical trials (146-009 and 146-010) in one analysis, and pooled the uncontrolled trials (146-011 and 146-008) in another analysis. Study 146-006 was excluded from the pooled analysis of controlled trials as it was a smaller study (26 patients) of shorter duration (4 weeks for each treatment) designed to obtain PK and PD data. As the Phase I trials were single-dose studies performed in healthy volunteers, these studies were also analyzed separately. There were no notable findings, no SAEs and no discontinuations in the Phase I studies. [For methods of pooling, please see NDA #21-316, Volume 3.p, Section 2.2 in the 120-day Integrated Summary of Safety Update, page 36.]

The safety results for the pooled controlled trials and uncontrolled trials were similar in types and frequencies of Adverse Events, with no meaningful differences between the two analyses. Therefore, the sponsor's results for the pooled controlled studies only will be summarized below, which will then be followed by this Reviewer's safety review of the Phase III studies 146-009, 146-010, and 146-011.

1. Pooled Safety Results Performed by the Sponsor

The results for the pooled safety review for the two controlled trials (Protocols 146-009 and 146-010) performed by the sponsor are summarized as follows

a) Demographics

The baseline demographics for the pooled controlled studies were similar to the baseline demographics for studies 146-009, 146-010, and 146-011 alone, and for the pooled uncontrolled studies. Comparisons between the patients exposed to placebo, lovastatin XL, and Mevacor in the pooled controlled studies showed that baseline demographics were relatively well balanced across the groups. The baseline demographics by treatment exposure in the pooled controlled studies are summarized in the following table

Table 69: Pooled Controlled Studies Baseline Demographics

	All	Placebo	Lovastatin XL	Mevacor
ITT Patients, n =	530	34	467	329
Demographic Measure				
Gender, n (%)				
Male	296 (56)	18 (53)	265 (57)	193 (59)
Female	234 (44)	16 (47)	202 (43)	136 (41)
Age, years				
Mean	55.9	55.7	56.0	55.4
Age ≥ 65 years, n (%)	95 (18)	9 (26)	83 (18)	56 (17)
Ethnicity, n(%)				
Caucasian	457 (86)	31 (91)	403 (86)	278 (84)
Black	29 (5)	0	27 (6)	17 (5)
Asian	6 (1)	0	6 (1)	6 (2)
Other	38 (7)	3 (9)	31 (7)	28 (9)
Risk Factors (RF)				
≥2 CAD RF or CHD, n (%)	307 (58)	20 (59)	231 (49)	162 (49)
<2 CAD RF, n (%)	223 (42)	14 (41)	236 (51)	167 (51)
Mean BMI, kg/M^2	28.1	28.0	28.0	28.3
Baseline Lipid Value				
Mean LDL-C, mg/dL		174.5	177.7	176.2
Mean HDL-C, mg/dL		43.5	46.2	46.0
Mean TC, mg/dL		252.5	259.0	256.4
Mean TG, mg/dL		174.8	175.7	172.1

b) Dropouts

Dropouts were pooled by the sponsor for all studies including Protocols 146-006, 146-008, 146-009, 146-010, and 146-011. Of the 560 patients exposed to lovastatin XL in these studies, 47 patients (8%) discontinued prior to study completion compared to 36 of 354 patients (10%) exposed to Mevacor and 2 of 34 patients (6%) exposed to placebo. The most common reason for discontinuation was for an AE, followed by withdrawal of consent. There were no notable differences between the groups in frequency or reason for withdrawal. The patient discontinuations are summarized in the following table

Table 70: Pooled Patient Discontinuations

	Treatment		
	Placebo	**Lovastatin XL**	**Mevacor**
Randomized Patients, n =	34	560	354
Number of Withdrawals, n (%)	2 (6)	47 (8)	36 (10)
Reason for Dropout			
Adverse Event, n (%)	2 (6)	17 (3)	14 (4)
Withdrawal of Consent, n (%)	0	14 (3)	14 (4)
Protocol Violation , n (%)	0	6 (1)	3 (1)
Other, n (%)	0	10 (2)	5 (1)

c) Adverse Events

An Adverse Event was defined as any adverse change from the patient's pre-treatment condition after a test drug had been administered, whether considered related to treatment or not, and may have included an abnormal laboratory finding. Adverse events that occurred during active treatment of a crossover study were attributed only to the drug

taken at the time of onset of the event. Adverse events that occurred during the washout period of Studies 146-006 and 146-010 (crossover studies) were attributed to the treatment received during the first treatment period. Adverse Events were coded by body system and preferred term using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionary. Common AEs were defined as having an incidence of ≥2%.

Treatment emergent signs and symptoms (TESS) were defined as AEs that occurred for the first time after starting randomization to double-blind treatment, or existed prior to treatment and worsened after starting treatment.

For the pooled controlled studies, the incidence rates of patients reporting any TESS were similar across the treatment groups. The incidence of TESS by treatment group are summarized in the following table

Table 71: Pooled Controlled Study Patients Reporting Any TESS

	Treatment		
	Placebo	**Lovastatin XL**	**Mevacor**
Randomized Patients, n =	34	467	329
Reporting Any AE, n (%)	22 (65)	302 (65)	214 (65)

d) Adverse Events By Body System

The body systems with the greatest number of TESS were the Body as a Whole, Digestive, and Respiratory systems. There were no notable differences in the types and frequencies of TESS between the Mevacor and lovastatin XL treatment groups. The placebo group had somewhat higher rates of Musculoskeletal and Nervous system complaints than the lovastatin XL and Mevacor groups; however, the number of patients in the placebo group was small and no definite conclusions will be drawn from this. The incidence rates of TESS by treatment group by body system are summarized in the following table

Table 72: Pooled Controlled Study Patients, Incidence of TESS by Body System

	Treatment		
	Placebo	**Lovastatin XL**	**Mevacor**
Randomized Patients, n =	34	467	329
Body System			
Body as a Whole, n (%)	11 (32)	173 (37)	137 (42)
Cardiovascular, n (%)	1 (3)	26 (6)	20 (6)
Digestive, n (%)	4 (12)	74 (16)	56 (17)
Endocrine, n (%)	0	5 (1)	5 (2)
Hematologic and Lymphatic, n (%)	0	5 (1)	2 (1)
Metabolic and Nutritional, n (%)	1 (3)	14 (3)	12 (4)
Musculoskeletal, n (%)	8 (24)	50 (11)	46 (14)
Nervous, n (%)	10 (29)	50 (11)	26 (8)
Respiratory, n (%)	2 (6)	52 (11)	56 (17)
Skin and Appendages, n (%)	2 (6)	38 (8)	22 (7)
Special Senses, n (%)	3 (9)	28 (6)	14 (4)
Urogenital, n (%)	5 (15)	29 (6)	20 (6)

Infection, headache and accidental injury were the most frequently reported AE terms overall. There were no meaningful differences between the groups in frequency of AEs reported. Of particular interest in these studies were myalgias, myopathy, rhabdomyolysis, and hepatitis. There were no reported cases of myopathy, rhabdomyolysis, or hepatitis. Myalgias were more common in the placebo group, reported by 15% of placebo patients vs 3% of patients in the Mevacor and lovastatin groups. The most commonly reported (reported by ≥5% in any group) TESS by body system and COSTART term, by treatment group for the pooled controlled studies are listed in the following table [a complete list of common (≥2%) TESS by Body System and COSTART term, by treatment group, for the pooled controlled studies is in the Appendix]

Table 73: Pooled Controlled Studies TESS by Body System and COSTART Term, Most Common (≥5% in Any Group)

		Treatment		
		Placebo	**Lovastatin XL**	**Mevacor**
Randomized Patients, n =		34	467	329
Body System	**COSTART Term**			
Body as a Whole	Infection	3 (9)	52 (11)	52 (16)
	Accidental Injury	3 (9)	26 (6)	12 (4)
	Asthenia	2 (6)	12 (3)	6 (2)
	Headache	2 (6)	34 (7)	26 (8)
	Back Pain	1 (3)	23 (5)	18 (5)
	Flu Syndrome	1 (3)	24 (5)	18 (5)
	Pain	0	14 (3)	17 (5)
Digestive	Diarrhea	2 (6)	15 (3)	8 (2)
Musculoskeletal	Arthralgia	2 (6)	24 (5)	20 (6)
	Myalgia	5 (15)	14 (3)	11 (3)
Nervous	Dizziness	2 (6)	10 (2)	5 (2)
Respiratory	Sinusitis	1 (3)	17 (4)	20 (6)
Urogenital	Urinary Tract Infection	2 (6)	8 (2)	9 (3)

e) Adverse Events By Subgroup

Patients reporting any AE were also analyzed by subgroup. Female patients were more likely than male patients to report any AE in the lovastatin XL and placebo groups (any AE by female vs male were not available for the Mevacor patients). The results are summarized in the following table

Table 74: Pooled Patients Reporting Any AE, Male vs Female

	Treatment		
	Placebo	**Lovastatin XL**	**Mevacor**
Randomized Patients, n =	34	467	329
Randomized Patients Female (F), n =	F = 16	F = 202	F = 136
Randomized Patients Male (M), n =	M = 18	M = 265	M = 193
Females Reporting Any AE, n (%)	13 (81)	142 (70)	NA
Males Reporting Any AE, n (%)	8 (44)	160 (60)	NA

Geriatric patients were about as likely to report any AE as were non-geriatric patients in the placebo and lovastatin groups (results not available for the Mevacor patients). The results are summarized in the following table

Table 75: Pooled Patients Reporting Any AE, Geriatric vs Non-Geriatric

	Treatment		
	Placebo	**Lovastatin XL**	**Mevacor**
Randomized Patients, n =	34	467	329
Randomized Patients Non-Geriatric (NG), n =	NG = 25	NG = 384	NG = 273
Randomized Patients Geriatric (G), n =	G = 9	G = 83	G = 56
Non-Geriatric Reporting Any AE, n (%)	15 (60)	247 (66)	NA
Geriatric Reporting Any AE, n (%)	6 (67)	55 (66)	NA

f) Treatment Emergent Laboratory Abnormalities

(1) ALT and AST Elevations

The sponsor defined ALT and AST abnormalities as elevations >3 X ULN on 2 consecutive occasions or >3 X ULN on 1 occasion with no follow-up. By this definition, one patient (010-3094) had an AST elevation >3 X ULN in the setting of acute cholecystitis. There were no other AST or ALT elevations meeting this definition. For ALT >2 X ULN and ≤3 X ULN, there were 2 elevations in the lovastatin XL 60 mg group, and 3 elevations in the Mevacor 60 mg group. For AST elevations >2 X ULN and ≤3 X ULN, there were 2 elevations in the lovastatin 20 mg group and 1 elevation in the Mevacor 20 mg group. (Summaries of individual patients with AST or ALT elevations are in the individual study safety sections, to follow.) AST and ALT elevations by pooled treatment groups are summarized in the following table

Table 76: Pooled Controlled Studies ALT and AST Elevations

	Treatment		
	Placebo	**Lovastatin XL**	**Mevacor**
Randomized Patients, n =	34	467	329
ALT >1 X ULN, n (%)	2 (6)	61 (13)	41 (12)
ALT >2 X ULN, n (%)	0	2 (<1)	3 (1)
ALT >3 X ULN, n (%)	0	0	0
AST >1 X ULN, n (%)	1 (3)	31 (7)	20 (6)
AST >2 X ULN, n (%)	0	2 (<1)	1 (<1)
AST >3 X ULN, n (%)	0	0	0

(2) CPK Elevations

Patients with notable CPK elevations, defined by the sponsor as CPK >10 X ULN, occurred in 2 patients in the lovastatin 20 mg group, and 1 patient in the Mevacor 20 mg group. One patient each in the placebo, lovastatin XL 60 mg and Mevacor 20 mg groups had a CPK elevation >5 X ULN and ≤10 X ULN. (Summaries of individual patients with CPK elevations are in the individual study safety sections, to follow.) CPK elevations by pooled treatment groups are summarized in the following table

Table 77: Pooled Controlled Studies CPK Elevations

	Treatment		
	Placebo	Lovastatin XL	Mevacor
Randomized Patients, n =	34	467	329
CPK >1 X ULN, n (%)	7 (21)	153 (33)	100 (30)
CPK >5 X ULN, n (%)	1 (3)	3 (1)	2 (1)
CPK >10 X ULN, n (%)	0	2 (<1)	1 (<1)

There were no other notable laboratory abnormalities.

g) Sponsor's Summary of Pooled Safety Results from the Controlled Studies
In the Controlled studies, the frequency of TESS was similar in the Placebo, lovastatin XL and Mevacor groups. There were no meaningful differences in the frequencies of TESS in the different age groups. Of particular interest in this study, there was no increased frequency of myalgia in geriatric patients or in males or females, or in any subgroup defined by baseline lipid levels. Overall, the safety data show that lovastatin XL is as safe and well tolerated as Mevacor.

The 2 controlled studies 146-009 and 146-010, and the large, uncontrolled extension study will now be considered individually for safety.

2. Protocol 146-009

a) Adverse Events
An Adverse Event was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The sponsor defined a treatment emergent AE as an AE that occurred for the first time after starting double-blind treatment or existed prior to double-blind treatment and then worsened after starting double-blind treatment (See NDA #21-316, Study Report 146-009, Volume 1.56, page 40). Adverse Events in the data set included those occurring in randomized patients who took at least one dose of double-blind study medication through study completion/discontinuation. Recurrent or continuing AEs were counted only once. Adverse Event incidence rates were calculated using all randomized patients as the denominator. Clinical AEs were coded to body system and preferred term using the COSTART dictionary. Common AEs were defined as having an incidence of $\geq$2% (A complete list of common AEs is in the Appendix).

There were 98 different AE terms reported by 117 of 172 (68%) patients overall. There were the fewest reports of any AE in the lovastatin XL 20 mg (53%) and the most in the lovastatin XL 10 mg group (80%). The incidence rates of patients reporting any AE by treatment group are summarized in the following table

Table 78: 146-009 Patients Reporting Any AE

		Treatment				
	All	Placebo	Lova 10	Lova 20	Lova 40	Lova 60
Randomized Patients, n =	172	34	35	34	33	36
Reporting Any AE, n (%)	117 (68)	21 (62)	28 (80)	18 (53)	25 (76)	25 (72)

b) Adverse Events by Body System

Adverse Events occurring in the Body as a Whole, Nervous, and Musculoskeletal systems were the most commonly reported (with 32%, 29%, and 24% respectively of All patients reporting any AE in these body systems). Headache was the most commonly reported AE term, reported by 12% of patients overall. Adverse Events were relatively evenly distributed across treatment groups, with the exception of myalgia that was more common in the placebo group (reported by 18% of placebo patients), and arthralgia which was more common in the lovastatin XL 10 mg group (14%). However, as the incidence of any particular AE term reported by treatment group was small, no definite conclusions will be generated from these findings. The most commonly reported AEs by body system (occurring in ≥5% of patients overall) are listed in the following table

Table 79: 146-009 Incidence of Most Common (≥5%) Adverse Events by Body System

			Treatment				
		All	Placebo	Lova 10	Lova 20	Lova 40	Lova 60
Randomized Patients, n =		172	34	35	34	33	36
Body System	COSTART Term						
Body as a Whole	Headache	21 (12)	2 (6)	5 (14)	4 (12)	6 (18)	4 (12)
	Accidental injury	13 (8)	3 (9)	4 (11)	1 (3)	2 (6)	3 (9)
	Asthenia	9 (5)	2 (6)	0	2 (6)	2 (6)	3 (9)
	Infection	8 (5)	3 (9)	1 (3)	1 (3)	1 (3)	2 (6)
Musculoskeletal	Arthralgia	11 (6)	1 (3)	5 (14)	1 (3)	2 (6)	2 (6)
	Myalgia	10 (6)	6 (18)	0	2 (6)	1 (3)	1 (3)

Other AEs of particular interest in this study were myalgia, myopathy, rhabdomyolysis, and hepatitis. No cases of myopathy, rhabdomyolysis, or hepatitis, were reported during the study.

There were 10 patients who reported myalgia as an AE as follows:
Patients 2007, 2008, 2038, 2073, 2076, 2118, 2128, 2134, 2148, and 2182
Myalgia resulted in study drug discontinuation in one patient (2076)
Of these patients, only patients 2007, 2008, 2038 and 2076 had a CPK elevation >normal at any time during double-blind treatment. And of these patients, none had a CPK elevation >2 X ULN, except for patient 2076 (who had an elevation >8 X ULN – see CPK elevation section).

c) Adverse Events by Subgroup

Female patients were more likely than male patients to report any AE (77% vs 60% respectively) overall and by treatment group. Fewer female patients in the lovastatin XL 20 mg group reported any AE than in the other treatment groups, which accounted for the lower incidence of AEs reported in the lovastatin XL 20 mg group overall. Fewer males

in the placebo group reported any AE (44%) compared to the other groups (60% overall). Otherwise, reports of any AE did not differ across treatment groups by sex. There were too few non-Caucasian patients to analyze by race, and too few geriatric patients to analyze by age.

Table 80: 146-009 Patients Reporting Any Adverse Event, Male vs Female

		Treatment				
	All	**Placebo**	**Lova 10**	**Lova 20**	**Lova 40**	**Lova 60**
Randomized Patients, n =	172	34	35	34	33	36
Randomized Patients Female (F), n =	F = 82	F = 16	F = 17	F = 15	F = 14	F = 20
Randomized Patients Male (M), n =	M = 90	M = 18	M = 18	M = 19	M = 19	M = 16
Females Reporting Any AE, n (%)	63 (77)	13 (81)	15 (88)	8 (53)	12 (86)	15 (75)
Males Reporting Any AE, n (%)	54 (60)	8 (44)	13 (72)	10 (53)	13 (68)	10 (63)

Overall, females were more likely than males to complain of headache (18% vs 7% respectively), and headache was more common in females exposed to lovastatin XL than in females exposed to placebo (10-36% vs 6%). Arthralgias were more common in females in the lovastatin XL 10 mg group (24%) than in the other treatment groups (7% overall), and myalgias were more common in both males (17%) and females (19%) in the placebo group than in the other groups (5-7% overall). Given the small number of patients in each subgroup, however, no definite conclusions will be drawn from these findings. Otherwise, there were no notable differences between male vs female patients, or between treatment groups. The incidence rates of the most commonly reported (≥5% overall) AEs by body system, male vs female, are summarized in the following table [A complete listing of the incidence of common AEs (≥2%) by body system, male vs female, is in the Appendix]

Table 81: 146-009 Incidence of Most Common (≥5%) AEs by Body System, Male vs Female

				Treatment				
			All	**Placebo**	**Lova 10**	**Lova 20**	**Lova 40**	**Lova 60**
Randomized Patients Female (F) , n =			F = 82	F = 16	F = 17	F = 15	F = 14	F = 20
Randomized Patients Male (M) , n =			M = 90	M = 18	M = 18	M = 19	M = 19	M = 16
Body System	**COSTART Term**	**F/M**						
Body as a Whole	Headache	F	15 (18)	1 (6)	4 (24)	3 (20)	5 (36)	2 (10)
		M	6 (7)	1 (6)	1 (6)	1 (5)	1 (5)	2 (13)
	Accidental injury	F	8 (10)	3 (19)	2 (12)	0	1 (7)	2 (10)
		M	5 (6)	0	2 (11)	1 (5)	1 (5)	1 (6)
	Asthenia	F	5 (6)	1 (6)	0	1 (7)	1 (7)	2 (10)
		M	4 (4)	1 (6)	0	1 (5)	1 (5)	1 (6)
	Infection	F	4 (5)	1 (6)	1 (6)	0	1 (7)	1 (5)
		M	4 (4)	2 (11)	0	1 (5)	0	1 (6)
Musculoskeletal	Arthralgia	F	6 (7)	0	4 (24)	0	1 (7)	1 (5)
		M	5 (6)	1 (6)	1 (6)	1 (5)	1 (5)	1 (6)
	Myalgia	F	4 (5)	3 (19)	0	1 (7)	0	0
		M	6 (7)	3 (17)	0	1 (5)	1 (5)	1 (6)

d) Adverse Events Resulting in Drug Discontinuation

Twelve (12) of the 172 randomized patients (7%) discontinued study medication prior to study completion. Of the 12 patients who discontinued, 6 discontinued due to an AE. Discontinuations due to AEs were relatively evenly distributed over the treatment groups

(0-2 patients discontinued per treatment group). Discontinuations due to AEs in the Digestive system were the most common, and abdominal pain, diarrhea, and CPK elevation were the AE terms most frequently reported as the reason for discontinuation (2 patients each). Patients could report more than one AE per discontinuation. Patients reporting an AE as the reason for discontinuation are as follows

- In the Placebo group: Patient 2076 Caucasian Male age 65 (depression, impotence, myalgia, abnormal ejaculation, and CPK elevation); and Patient 2114 Caucasian female age 46 (gastroenteritis)
- In the Lovastatin XL 10 mg group: Patient 2153 61 year old (yo) Caucasian (rectal hemorrhage)
- In the Lovastatin XL 20 mg group: Patient 2158 66 yo Hispanic female (diarrhea and abdominal pain); and Patient 2039 65 yo Caucasian female (CPK increased)
- In the Lovastatin XL 40 mg group: Patient 2126 56 yo Caucasian male (eructation, flatulence, abdominal pain, diarrhea, and nausea)
- No patients in the Lovastatin XL 60 mg withdrew due to an AE

As the number of discontinuations due to AEs was small, no conclusions will be generated from these findings. Adverse Events resulting in drug discontinuation are summarized in the following table

Table 82: 146-009 Discontinuations Due to Adverse Events

			Treatment				
		All	Placebo	Lova 10	Lova 20	Lova 40	Lova 60
Randomized Patients, n =		172	34	35	34	33	36
Number of Withdrawals, n (%)		12 (7)	2 (6)	3 (9)	3 (9)	1 (3)	3 (8)
Discontinued for AE*, n (%)		6 (3)	2 (6)	1 (3)	2 (6)	1 (3)	0
Body System	**COSTART Term**						
Body as a Whole	Abdominal pain	2 (1)	0	0	1 (3)	1 (3)	0
Digestive	Diarrhea	2 (1)	0	0	1 (3)	1 (3)	0
	Eructation	1 (1)	0	0	0	1 (3)	0
	Flatulence	1 (1)	0	0	0	1 (3)	0
	Gastroenteritis	1 (1)	1 (3)	0	0	0	0
	Nausea	1 (1)	0	0	0	1 (3)	0
	Rectal hemorrhage	1 (1)	0	1 (3)	0	0	0
Metabolic & Nutritional	CPK increased	2 (1)	1 (3)	0	1 (3)	0	0
Musculoskeletal	Myalgia	1 (1)	1 (3)	0	0	0	0
Nervous	Depression	1 (1)	1 (3)	0	0	0	0
Urologic	Abnormal ejaculation	1 (1)	1 (3)	0	0	0	0
	Impotence	1 (1)	1 (3)	0	0	0	0

*Patients may have reported more than one AE term per discontinuation

e) Serious Adverse Events

There were 3 Serious Adverse Events (SAEs) occurring in 2 patients [Patient 2101 and Patient 2003]. There were no deaths. All SAEs occurred in the Cardiovascular system, which is not unexpected in this high risk group of patients. The SAEs are summarized as follows

Table 83: 146-009 Serious Adverse Events

Treatment	Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days) drug/drug	Invest. Attrib.	Drug D/C?
Lovastatin XL 10 mg	2101	M	59	Myocardial infarction (MI)	CV	36	NR	No
Lovastatin XL 20 mg	2003	M	58	Coronary artery disorder	CV	81	NR	No
Lovastatin XL 20 mg	2003	M	58	MI	CV	81	NR	No

f) Other Significant Adverse Events

There were no other significant Adverse Events.

g) Treatment Emergent Laboratory Abnormalities

Treatment emergent laboratory abnormalities (TELAs) of particular interest in this study were ALT, AST, and CPK. TELAs were defined by this Reviewer as laboratory values outside the normal ranges during study drug treatment.

(1) ALT and AST Elevations

No patient experienced an ALT or AST elevation ≥2 X ULN during study drug treatment. Eighteen (18) patients (10%) experienced an ALT elevation >1 X ULN at any time during double-blind treatment, and 9 patients (5%) experienced an AST elevation >1 X ULN. There were no notable differences in ALT and AST elevations between the treatment groups. No patient was discontinued for an ALT or AST elevation. The incidence of treatment emergent AST and ALT elevations by treatment group are as follows

Table 84: 146-009 Incidence of Treatment Emergent ALT and AST Elevations

		Treatment				
	All	Placebo	Lova 10	Lova 20	Lova 40	Lova 60
Randomized Patients, n =	172	34	35	34	33	36
ALT >1 X ULN, n (%)	18 (10)	2 (6)	5 (14)	4 (12)	3 (9)	4 (11)
ALT ≥2 X ULN, n (%)	0	0	0	0	0	0
AST >1 X ULN, n (%)	9 (5)	1 (3)	2 (6)	2 (6)	1 (3)	3 (8)
AST ≥2 X ULN, n (%)	0	0	0	0	0	0

ALT normal range: 6-48 IU/L
AST normal range: 10-45 IU/L

(2) CPK Elevations

Minor elevations (>normal) in CPK were common, occurring in 27% of patients overall. These elevations were evenly distributed across the treatment groups, and were of no clinical importance. No patient had a CPK elevation ≥10 X ULN, and 1 patient (Patient 2076; placebo group) had a CPK ≥5 X ULN during study drug treatment (see below). The incidence of treatment emergent CPK elevations by treatment group is summarized in the following table

Table 85: 146-009 Incidence of Treatment Emergent CPK Elevations

		Treatment				
	All	**Placebo**	**Lova 10**	**Lova 20**	**Lova 40**	**Lova 60**
Randomized Patients, n =	172	34	35	34	33	36
CPK >1 X ULN, n (%)	46 (27)	7 (21)	12 (34)	6 (18)	7 (21)	14 (39)
CPK ≥5 X ULN, n (%)	1 (1)	1 (3)	0	0	0	0
CPK ≥10 X ULN, n (%)	0	0	0	0	0	0

CPK normal range: Male 24-195 IU/L; Female 24-170 IU/L

One patient (2076; placebo) experienced a CPK elevation >5 X ULN and was discontinued (dc'd) from the study, and one patient (2039; lovastatin XL 20 mg) was discontinued due to a CPK elevation. These patients are summarized as follows:

Table 86: 146-009 Patient With Clinically Significant CPK Elevations (≥5 X ULN or Resulting in Discontinuation)

Patient	Treatment	Visit	CPK (IU/L)	Elevation	Relevant History
2076	Placebo	1 (screening)	137		65 yo male who complained of myalgias
		2 (placebo run-in)	121		in both legs at baseline. Myalgias
		3	155		increased in severity on Day 78 and
		4 (randomization)	148		patient was dc'd. CPK at ET visit noted to
		5	201	>normal	be elevated. 2 days after dc, pain
		6	149		decreased to moderate and CPK
		7 (early termination)	1617	≥5 X ULN	decreased (iso 100% MM). 19 days post
		7 (retest)	144		dc, CPK was WNL and myalgia resolved.
2039	Lova 20 mg	1 (screening)	274	>normal	65 yo female, dc'd on Day 58 for an
		2 (placebo run-in)	498	>normal	elevated CPK. Asymptomatic. Referred
		3	285	>normal	for cardiac work-up for increased
		4 (randomization)	546	>normal	isozymes (9% MB), with normal ECG
		5	260	>normal	and Echocardiogram. Developed chest
		6	807	>normal	pain on Day 72 diagnosed as non-cardiac.
		6 (retest)	424	>normal	Follow-up CPK returned to baseline.
		6 (retest)	306	>normal	
		6 (early termination)	225	>normal	

(3) Other Laboratory Abnormalities

There were no other clinically significant laboratory abnormalities during the study.

h) Overall Safety Conclusions for Protocol 146-009

In general, lovastatin XL was well tolerated. Lovastatin XL patients were about as likely as placebo patients to report any AE during study drug treatment, and there was no increase in the incidence of AEs with increasing doses of lovastatin XL. Most AEs were not serious or severe. Adverse Events occurring in the Body as a Whole and Musculoskeletal systems were the most commonly reported, with headache occurring more commonly in lovastatin-exposed patients than in placebo patients, and myalgias occurring more commonly in the placebo group than in the lovastatin groups. There were no reports of myopathy, rhabdomyolysis or hepatitis during the study. Female patients were more likely than male patients to report any AE regardless of treatment group, and female lovastatin-exposed patients were more likely to report headache than female placebo patients. There were 6 discontinuations during the study for AEs, with complaints in the Digestive system being the most common. There were no notable

differences in numbers of patients discontinued by treatment group, with 0-2 patients discontinued per group. Three (3) SAEs occurred in 2 patients during the study. All 3 SAEs were in the Cardiovascular system. Clinically significant treatment emergent laboratory abnormalities were uncommon. There were no AST or ALT elevations ≥2 X ULN during study drug treatment. One patient in the placebo group experienced a CPK elevation ≥5 X ULN, and this patient was discontinued from the study. There were no other clinically significant laboratory abnormalities during the study.

3. Protocol 146-010

a) Adverse Events

The sponsor defined a treatment emergent AE as an AE that occurred for the first time after starting active treatment or existed prior to active treatment and then worsened after starting active treatment (See NDA #21-316, Study Repot 146-010, Volume 1.63, page 45). Adverse Events in the data set included those occurring in randomized patients who took at least one dose of study medication through study completion/discontinuation. Recurrent or continuing AEs were counted only once. Adverse Event incidence rates were calculated using all randomized patients as the denominator. Clinical AEs were coded to body system and preferred term using the COSTART dictionary. Common AEs were defined as having an incidence of ≥2%.

There were 179 different AE terms reported by 289 of 358 (81%) patients overall. The incidence rates for patients reporting any AE during study drug treatment were assessed in three different ways: 1) pooled by treatment received, e.g., patients receiving lovastatin XL 20 mg in Period 1 were pooled with patients receiving lovastatin XL 20 mg in Period 2; 2) by treatment group assignment, e.g., Lov/Mev 20 mg group received lovastatin XL 20 mg in Period 1 and Mevacor 20 mg in Period 2; and 3) by treatment received in each treatment period. When AEs were assessed by any of these three groupings, the incidence rates for any AE reported were similar across the treatment groups. The incidence rates of patients reporting any AE are summarized in the following tables.

By treatment received:

Table 87: 146-010 Incidence of Any Adverse Event by Treatment Received

	Treatment			
	20 mg		60 mg	
	Lovastatin XL	Mevacor	Lovastatin XL	Mevacor
Randomized Patients, n =	162	166	167	163
Patients reporting any AE, n (%)	128 (79)	123 (74)	127 (76)	128 (79)

By treatment group assignment:

Table 88: 146-010 Incidence of Any Adverse Event by Treatment Group Assignment

		Treatment			
		20 mg		60 mg	
	All	Lovastatin XL	Mevacor	Lovastatin XL	Mevacor
Randomized Patients, n =	358	90	89	88	91
Patients reporting any AE, n (%)	289 (81)	72 (80)	73 (82)	68 (77)	76 (84)

By treatment received in each treatment period (Note: in Period 2, patients would have received the treatment listed second, e.g., in the Lov/Mev 20 mg group, patients received lovastatin XL 20 mg in Period 1, and Mevacor 20 mg in Period 2):

Table 89: 146-010 Incidence of Any Adverse Event by Treatment Received in Each Treatment Period

		Treatment			
		20 mg		60 mg	
	All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =	358	90	89	88	91
Patients reporting any AE in Treatment Period 1, n (%)	289 (81)	72 (80)	73 (82)	68 (77)	76 (84)
Patients reporting any AE in Treatment Period 2, n (%)	217 (61)	50 (56)	56 (64)	52 (59)	59 (65)

b) Adverse Events by Body System

Adverse events were analyzed by the sponsor "...by treatment group by combining all events occurring with a particular treatment during both treatment periods. For example, to obtain the total adverse events for the Lovastatin XL 20 mg treatment group, all adverse events occurring during Period 1 in the Lovastatin XL/Mevacor 20 mg treatment sequence group were combined with the adverse events occurring during Period 2 in the Mevacor/Lovastatin XL 20 mg treatment sequence group." (see NDA #21316, Study Report 146-010, volume 1.63, page 59). This Reviewer also analyzed the incidence rates of AEs by treatment group assignment and by treatment received in each treatment period.

There were no notable differences between the groups in types or frequencies of AEs reported, nor was there a trend by dose. Adverse Events were most commonly reported in the Body as a Whole and Digestive systems. Infection was the most commonly reported AE term in all treatment groups, followed by flu syndrome, and back pain. The most commonly reported (by ≥5% of patients overall) AEs are summarized in the following tables.

By pooled treatment received:

Table 90: 146-010 Incidence of Common Adverse Events (>2%) by Pooled Treatment Received

		Treatment			
		20 mg		60 mg	
		Lovastatin XL	Mevacor	Lovastatin XL	Mevacor
Randomized Patients, n =		162	166	167	163
Body System	**COSTART Term**				
Body as a Whole	Infection	22 (14)	25 (15)	26 (16)	31 (19)
	Back Pain	15 (9)	7 (4)	8 (5)	10 (6)
	Flu Syndrome	13 (8)	7 (4)	8 (5)	11 (7)
Musculoskeletal	Arthralgia	11 (7)	12 (7)	8 (5)	5 (3)
Respiratory	Rhinitis	8 (5)	5 (3)	5 (3)	8 (5)

By treatment group assignment:

Table 91: 146-010 Incidence of Most Common Adverse Events (≥5%) by Treatment Group Assignment by Body System

			Treatment			
			20 mg		60 mg	
		All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =		358	90	89	88	91
Body System	**COSTART Term**					
Body as a Whole	Infection	92 (26)	19 (21)	22 (25)	22 (25)	29 (32)
	Headache	39 (11)	5 (6)	13 (15)	8 (9)	13 (14)
	Flu Syndrome	38 (11)	8 (9)	11 (12)	9 (10)	10 (11)
	Back Pain	37 (10)	11 (12)	10 (11)	9 (10)	7 (8)
	Accidental Injury	28 (8)	5 (6)	6 (7)	7 (8)	10 (11)
	Pain	25 (7)	5 (6)	5 (6)	5 (6)	10 (11)
Digestive	Dyspepsia	20 (6)	4 (4)	4 (4)	6 (7)	6 (7)
	Diarrhea	18 (5)	5 (6)	6 (7)	4 (5)	3 (3)
	Nausea	18 (5)	4 (4)	4 (4)	7 (8)	3 (3)
Musculoskeletal	Arthralgia	30 (8)	11 (12)	8 (9)	7 (8)	4 (4)
	Myalgia	19 (5)	5 (6)	4 (4)	3 (3)	7 (8)
Respiratory	Sinusitis	29 (8)	6 (7)	9 (10)	6 (7)	8 (9)
	Rhinitis	24 (7)	7 (8)	5 (6)	4 (5)	8 (9)

By treatment received in each treatment period:
Period 1:

Table 92: 146-010 Incidence of Adverse Events in Period 1 by Treatment Received

			Treatment			
			20 mg		60 mg	
		All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =		358	90	89	88	91
Body System	**COSTART Term**					
Body as a Whole	Infection	74 (21)	14 (16)	19 (21)	17 (19)	24 (26)
	Back pain	27 (8)	9 (10)	5 (6)	7 (8)	6 (7)
	Flu syndrome	27 (8)	8 (9)	7 (8)	5 (6)	7 (8)
	Headache	27 (8)	3 (3)	12 (13)	7 (8)	5 (5)
Musculoskeletal	Arthralgia	19 (5)	6 (7)	5 (6)	6 (7)	2 (2)
Respiratory	Sinusitis	20 (6)	4 (4)	7 (8)	3 (3)	6 (7)

Period 2:

Table 93: 146-010 Incidence of Adverse Events in Period 2 by Treatment Received

			Treatment			
			20 mg		60 mg	
		All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =		358	90	89	88	91
Body System	**COSTART Term**					
Body as a Whole	Infection	30 (8)	6 (7)	8 (9)	7 (8)	9 (10)
	Headache	21 (6)	4 (4)	3 (3)	4 (5)	10 (11)
Musculoskeletal	Arthralgia	17 (5)	7 (8)	5 (6)	3 (3)	2 (2)

Other AEs of particular interest in this study were myalgias, myopathy, rhabdomyolysis and hepatitis. No cases of myopathy, rhabdomyolysis, or hepatitis were reported. Nineteen (19) patients (5% overall) reported myalgia, which had a similar incidence across the treatment group groups. One patient with myalgia (3150) also had a CPK elevation >10 X ULN, which resolved. Three (3) patients (3009, 3329, and 3415) were discontinued due to myalgia prior to study completion, and none of these discontinuations was associated with a CPK elevation.

c) Adverse Events Resulting in Drug Discontinuation

Seventy (70) of the 358 (20%) randomized patients discontinued study medication prior to study completion. Of the 70 patients who discontinued, 27 discontinued due to an AE. Discontinuations due to an AE were slightly more common in the Lov/Mev 60 mg group (11% vs 8% overall) and slightly less common in the Lov/Mev 20 mg group (4% vs 8% overall). However, the numbers of patients who discontinued in each treatment group was small and no conclusions will be drawn from this. Adverse Events resulting in discontinuations occurred most frequently in the Body as a Whole and Digestive systems. Nausea was the most frequently reported AE term resulting in discontinuation (4 patients), followed by asthenia, chest pain, arthralgia and myalgia (3 patients each). One patient was discontinued for a laboratory abnormality (ALT/SGPT increased; Patient 3326; Lov/Mev 60 mg). The most commonly reported AEs (reported in >1 patient), by treatment group assignment, are summarized in the following table (a complete list of discontinuations due to AEs is in the Appendix)

Table 94: 146-010 Discontinuations Due to Adverse Events, Most Common

			Treatment			
			20 mg		60 mg	
		All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =		358	90	89	88	91
All Discontinuations, n (%)		70 (20)	14 (16)	20 (22)	20 (23)	16 (18)
Discontinuations for AE*, n (%)		27 (8)	4 (4)	7 (8)	10 (11)	6 (7)
Body System	**COSTART Term**					
Body as a Whole	Asthenia	3 (1)	0	2 (2)	0	1 (1)
	Chest pain	3 (1)	1 (1)	1 (1)	0	1 (1)
	Abdominal pain	2 (1)	0	1 (1)	0	1 (1)
	Headache	2 (1)	0	1 (1)	0	1 (1)
Cardiovascular	MI	2 (1)	0	1 (1)	1 (1)	0
Digestive	Nausea	4 (1)	2 (2)	0	1 (1)	1 (1)
Musculoskeletal	Arthralgia	3 (1)	0	0	3 (3)	0
	Myalgia	3 (1)	0	1 (1)	1 (1)	1 (1)
Nervous	Hypesthesia	2 (1)	0	0	2 (2)	0

*Patients may have reported more than one AE term per discontinuation

When evaluated by drug treatment received at the time of study discontinuation, the discontinuations remain relatively balanced across treatment groups, as follows

1) Lovastatin XL 20 mg: 5 patients (3%)
2) Mevacor 20 mg: 6 patients (4%)
3) Lovastatin XL: 8 patients (5%)
4) Mevacor 60 mg: 8 patients (5%)

d) Serious Adverse Events

There were 13 Serious Adverse Events (SAEs) occurring in 9 patients [Patient 3284: chest pain and chest pain costochondritis was listed twice by the sponsor (see table below)]. There were no deaths. Two of these SAEs occurred prior to randomization (Patient 3383: left knee arthritis; and Patient 3381: gallstones) [listed separately] and will not be counted by this Reviewer towards the total number of SAEs. Body as a Whole and the Cardiovascular system were the body systems most frequently affected (4 SAEs each). One SAE (Patient 2094: cholecystitis) was assessed by the Investigator as being possibly related to study medication, and two patients (Patient 3377: MI; and Patients 3296: ARDS and MI) were discontinued from study treatment due to an AE.

As most patients crossed-over and received treatment with both lovastatin XL and Mevacor during the study, SAEs are grouped in two ways: 1) by treatment group assignment; and 2) by treatment received at time of the SAE. By treatment group assignment, there were no SAEs occurring in the patients assigned to Mev/Lov 60 mg. By treatment received at the time of the SAE, the SAEs were relatively evenly distributed across the treatment groups. Given the relatively small number of SAEs, no trends or conclusions can be generated from these findings.

SAEs are listed by treatment group assignment in the following table

Table 95: 146-010 Serious Adverse Events by Treatment Group Assignment

Treatment	Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days) drug/drug	Invest. Attrib.	Drug D/C?
Lov/Mev 20 mg	3295	M	61	Transient Ischemic Attack (TIA)	CV	54/-	NR	No
Lov/Mev 20 mg	3295	M	61	Angina	CV	54/-	NR	No
Lov/Mev 20 mg	3382	F	55	Uterine Fibroids	Uro	3/-	NR	No
Lov/Mev 20 mg	3094	F	56	Cholecystitis	Dig	38/-	Possibly	No
Lov/Mev 20 mg	3122	M	68	Avulsion left elbow	Body	20/-	NR	No
Mev/Lov 20 mg	3020	M	68	Ruptured Disc (L4-L5)	Body	89/43	NR	No
Mev/Lov 20 mg	3307	M	68	Knee pain; DJD	MS	57/-	NR	No
Mev/Lov 20 mg	3377	M	49	Myocardial Infarction (MI)	CV	58/-	NR	Yes
Lov/Mev 60 mg	3296	F	66	Cholecystitis	Dig	85/80	NR	No
Lov/Mev 60 mg	3296	F	66	Adult Respiratory Distress Syndrome (ARDS)	Resp	85/80	NR	Yes
Lov/Mev 60 mg	3296	F	66	MI	CV	85/80	NR	Yes
Lov/Mev 60 mg	3063	M	55	Quadriceps disruption R knee	Body	22/-	NR	No
Lov/Mev 60 mg	3284	F	46	Chest pain	Body	85/	NR	No
Lov/Mev 60 mg	3284	F	46	Chest pain (costochondritis)	MS	85/	NR	No

By treatment received at time of SAE:

Table 96: 146-010 Serious Adverse Events by Treatment Received at Time of SAE

Treatment	Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days) drug/drug	Invest. Attrib.	Drug D/C?
Lovastatin XL 20 mg	3295	M	61	Transient Ischemic Attack (TIA)	CV	54	NR	No
Lovastatin XL 20 mg	3295	M	61	Angina	CV	54	NR	No
Lovastatin XL 20 mg	3382	F	55	Uterine Fibroids	Uro	3	NR	No
Lovastatin XL 20 mg	3094	F	56	Cholecystitis	Dig	38	Possibly	No
Lovastatin XL 20 mg	3122	M	68	Avulsion left elbow	Body	20	NR	No
Lovastatin XL 20 mg	3020	M	68	Ruptured Disc (L4-L5)	Body	43	NR	No
Mevacor 20 mg	3307	M	68	Knee pain; DJD	MS	57	NR	No
Mevacor 20 mg	3377	M	49	Myocardial Infarction (MI)	CV	58	NR	Yes
Lovastatin XL 60 mg	3063	M	55	Quadriceps disruption R knee	Body	22	NR	No
Lovastatin XL 60 mg	3284	F	46	Chest pain	Body	85	NR	No
Lovastatin XL 60 mg	3284	F	46	Chest pain (costochondritis)	MS	85	NR	No
Mevacor 60 mg	3296	F	66	Cholecystitis	Dig	80	NR	No
Mevacor 60 mg	3296	F	66	Adult Respiratory Distress Syndrome (ARDS)	Resp	80	NR	Yes
Mevacor 60 mg	3296	F	66	MI	CV	80	NR	Yes

The SAEs that occurred prior to randomization are listed as follows

Table 97: 146-010 Serious Adverse Events Occurring Prior to Randomization

Treatment	Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days) drug/drug	Invest. Attrib.	Drug D/C?
Lov/Mev 60 mg	3383	M	56	Left knee arthritis	MS	-/-	NR	No
Mev/Lov 60 mg	3381	F	60	Gallstones	Dig	-33/-	NR	No

e) Treatment Emergent Laboratory Abnormalities

Treatment emergent laboratory abnormalities (TELAs) of particular interest in this study were ALT, AST and CPK. TELAs were defined by this Reviewer as laboratory values that were outside the normal ranges during study drug treatment.

(1) ALT and AST Elevations

Treatment emergent ALT and AST elevations >normal occurred in 18% and 10% respectively of patients overall. ALT and AST elevations >2 X ULN were uncommon (2% and 1% respectively). There was one patient (patient 3094 – see below) with an ALT elevation >3 X ULN occurring in the Lov/Mev 20 mg group. This patient was receiving lovastatin XL 20 mg at the time of the elevation. There was one patient (3094) with an AST elevation >3 X ULN also occurring in the Lov/Mev 20 mg group. This patient was receiving lovastatin XL 20 mg at the time of elevation. Elevations were relatively balanced across the treatment groups. Incidence rates of treatment emergent ALT and AST elevations, by treatment group assignment, are as follows

Table 98: 146-010 Incidence of Treatment Emergent ALT and AST Elevations by Treatment Group Assignment

		Treatment			
		20 mg		60 mg	
	All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =	358	90	89	88	91
ALT >1 X ULN, n (%)	63 (18)	17 (19)	16 (18)	15 (17)	15 (16)
ALT >2 X ULN, n (%)	6 (2)	1 (1)	0	3 (3)	2 (2)
ALT >3 X ULN	1 (<1)	1 (1)	0	0	0
AST >1 X ULN, n (%)	36 (10)	10 (11)	10 (11)	6 (7)	10 (11)
AST >2 X ULN, n (%)	3 (1)	3 (3)	0	0	0
AST >3 X ULN, n (%)	1 (<1)	1 (1)	0	0	0

ALT normal range: 6-37 IU/L
AST normal range: 10-45 IU/L

Patients with ALT elevations >2 X ULN are summarized in the following table

Table 99: 146-010 Patients with Treatment Emergent ALT Elevations >2 X ULN

Patient	Treatment	Visit	ALT (IU/L)	Elevation	Relevant History
3094	Lov/Mev 20 mg	1 (screening)	17		56 year old female, receiving lovastatin
		2 (placebo run-in)	19		XL 20 mg at time of elevation. The
		3	16		patient discontinued from the study and
		4	15		4 days later was diagnosed with
		5 (randomization)	16		cholecystitis, choledocolithiasis and
		5 retest	567	>15 X ULN	gallstone pancreatitis.
3079	Lov/Mev 60 mg	1(screening)	42	>normal	51 year old female receiving lovastatin
		2 (placebo run-in)	66	>normal	XL 60 mg at time of elevation. Patient
		3	40	>normal	completed the study.
		4	33		
		5 (randomization)	45	>normal	
		6	79	>2 X ULN	
		7	51	>normal	
		8	66	>normal	
		9	44	>normal	
		10	46	>normal	

Table 99: 146-010 Patients with Treatment Emergent ALT Elevations >2 X ULN

Patient	Treatment	Visit	ALT (IU/L)	Elevation	Relevant History
3079 cont.		11	42	>normal	
3326	Lov/Mev 60 mg	1 (screening)	50	>normal	32 year old male receiving lovastatin XL 60 mg at time of elevation. The patient was discontinued due to ALT elevation.
		2 (placebo run-in)	59	>normal	
		3	65	>normal	
		4	61	>normal	
		5 (randomization)	50	>normal	
		6	85	>normal	
		6 retest	120	>2 X ULN	
		6 retest	89	>normal	
3389	Lov/Mev 60 mg	1 (screening)	28		59 year old female receiving Mevacor 60 mg at time of elevation. Patient completed the study.
		2 (placebo run-in)	24		
		3	27		
		4	28		
		5 (randomization)	40	>normal	
		6	40	>normal	
		7	50	>normal	
		7 retest	36		
		8	34		
		9	35		
		10	45	>normal	
		10A	77	>2 X ULN	
		11	52	>normal	
		11 retest	30		
3325	Mev/Lov 60 mg	1 (screening)	50	>normal	50 year old male receiving Mevacor 60 mg at time of elevation. Patient completed the study.
		2 (placebo run-in)	22		
		3	38		
		4	30		
		5 (randomization)	35		
		6	97	>2 X ULN	
		6 retest	52	>normal	
		7	44		
		8	39		
		9	42		
		10	52	>normal	
		11	42		
3415	Mev/Lov 60 mg	1 (screening)	40	>normal	59 year old female receiving Mevacor 60 mg at time of elevation. Patient discontinued due to depression and myalgia.
		2 (placebo run-in)	35		
		3	21		
		4	ND		
		4 retest	22		
		5 (randomization)	33		
		6	44	>normal	
		7	77	>2 X ULN	
		7 retest	32		
		7 retest	26		

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Patients with AST elevations >2 X ULN are summarized in the following table

Table 100: 146-010 Patients with Treatment Emergent AST Elevations >2 X ULN

Patient	Treatment	Visit	AST (IU/L)	Elevation	Relevant History
3062	Lov/Mev 20 mg	1 (screening)	31		40 year old male receiving lovastatin XL 20 mg at the time of elevation. Patient completed the study.
		2 (placebo run-in)	25		
		3	24		
		4	21		
		5 (randomization)	99	>2 X ULN	
		6	29		
		7	23		
		8	25		
		9	30		
		10	26		
		11	25		
3094	Lov/Mev 20 mg	1 (screening)	20		56 year old female receiving lovastatin XL 20 mg at the time of elevation. The patient discontinued from the study and 4 days later was diagnosed with cholecystitis, choledocolithiasis and gallstone pancreatitis.
		2 (placebo/run-in)	18		
		3	14		
		4	14		
		5 (randomization)	13		
		5 retest	251	>6 X ULN	
3150	Lov/Mev 20 mg	1 (screening)	19		59 year old male completed lovastatin XL 20 mg and in placebo/washout phase at time of elevation.
		2 (placebo run-in)	17		
		3	19		
		4	17		
		5 (randomization)	18		
		6	20		
		7	16		
		8	113	>2 X ULN	
		8 retest	126	>2 X ULN	
		8 retest	20		
		9	20		
		10	22		
		11	19		

(2) CPK Elevations

Minor elevations (>normal) in CPK were common, occurring in 40% of patients overall. These elevations were evenly distributed across the treatment groups, and were of no clinical importance. There were 2 patients with CPK elevations >5 X ULN and <10 X ULN, and 2 patients (3062 and 3150) with CPK elevations >10 X ULN, both of whom were in the Lov/Mev 20 mg treatment group. One patient (3062) was receiving lovastatin XL 20 mg at the time of elevation, and one patient (3150) had completed treatment with lovastatin XL 20 mg and was in the placebo/washout phase at the time of elevation. Both patients completed the study. The incidence rates of treatment emergent CPK elevations by treatment group assignment are summarized in the following table

Table 101: 146-010 Incidence of Treatment Emergent CPK Elevations by Treatment Group Assignment

		Treatment			
		20 mg		60 mg	
	All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =	358	90	89	88	91
CPK >1 X ULN, n (%)	144 (40)	33 (37)	36 (40)	42 (48)	33 (36)
CPK >5 X ULN, n (%)	4 (1)	1 (1)	2 (2)	0	1 (1)
CPK >10 X ULN, n (%)	2 (1)	2 (2)	0	0	0

CPK normal range: Male 24-195 IU/L; Female 24-170 IU/L

Patients with CPK elevations >5 X ULN are summarized as follows

Table 102: 146-010 Patients with Treatment Emergent CPK Elevations >2 X ULN

Patient	Treatment	Visit	CPK (IU/L)	Elevation	Relevant History
3075	Lov/Mev 20 mg	1 (screening)	485	>2 X ULN	59 year old male receiving
		2 (placebo run-in)	394	>2 X ULN	Mevacor 20 mg at the time of
		3	302	>normal	elevation. Patient completed
		4	597	>3 X ULN	the study
		5 (randomization)	557	>2 X ULN	
		6	736	>3 X ULN	
		7	316	>normal	
		8	494	>2 X ULN	
		9	776	>3 X ULN	
		10	1156	>5 X ULN	
		10 retest	495	>2 X ULN	
		11	326	>normal	
3062	Lov/Mev 20 mg	1 (screening)	462	>2 X ULN	40 year old male receiving
		2 (placebo run-in)	315	>normal	lovastatin XL 20 mg at the time
		3	177		of elevation. Strenuous
		4	101		exercise 1 day prior to
		5 (randomization)	4310	>22 X ULN	elevation.
		5 retest	651	>3 X ULN	
		6	93		
		7	191		
		8	142		
		9	117		
		10	121		
		11	99		
3150	Lov/Mev 20 mg	1 (screening)	147		59 year old male who
		2 (placebo run-in)	172		completed lovastatin XL 20 mg
		3	163		and was in the placebo/washout
		4	171		phase at the time of elevation.
		5 (randomization)	148		The patient complained of
		6	148		myalgia prior to and after the
		7	168		CPK elevation. Patient
		8	7330	>37 X ULN	restarted vigorous exercise
		8 retest	2638	>13 X ULN	prior to Period 2. The patient
		8 retest	207	>normal	completed the study.
		9	171		
		10	207	>normal	
		11	187		
3014	Mev/Lov 60 mg	1 (screening)	136		43 year old male receiving
		2 (placebo run-in)	281	>normal	lovastatin XL 60 mg at time of
		3	355	>normal	elevation. The patient
		4	208	>normal	completed the study.
		5 (randomization)	224	>normal	
		6	271	>normal	
		7	151		
		8	179		
		9	1527	>7 X ULN	
		9 retest	315	>normal	
		10	256	>normal	
		11	344	>normal	

(3) Other Laboratory Abnormalities

There were no other clinically significant laboratory abnormalities during the study.

f) Overall Safety Conclusions for Protocol 146-010

In general, lovastatin XL was well tolerated with a safety profile similar to that of Mevacor. Lovastatin XL and Mevacor patients were about as likely to report any AE during the study, and the types and incidence rates of AEs were also similar. Adverse Events occurring in the Body as a Whole and Digestive systems were the most commonly reported, and infection, flu syndrome, and back pain were the most commonly reported AE terms. Myalgias occurred in about 5% of patients overall, with no notable difference in incidence rates between the treatment groups. Twenty-seven (27) patients discontinued due AEs, with nausea (4 patients), and asthenia, chest pain, arthralgia, and myalgia (3 patients each) being the most common reasons for discontinuations. When evaluated by treatment received at the time of study discontinuation, the discontinuations were relatively evenly balanced across the treatment groups. There were 13 Serious Adverse Events in 9 patients throughout the study. No trends or patterns by SAE or treatment groups were noted. Clinically significant treatment emergent laboratory abnormalities were uncommon. ALT and AST elevations >3 X ULN occurred in <1% of patients overall, and 1 patient discontinued due to an ALT elevation. CPK elevations >10 X ULN occurred in 2 patients (1%), one of whom also complained of myalgias. Both patients completed the study. There were no other clinically significant laboratory abnormalities.

4. Protocol 146-011

a) Adverse Events

An Adverse Event was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The sponsor defined a treatment emergent AE as an AE that occurred for the first time after starting study drug treatment or existed prior to study drug treatment and then worsened after starting treatment. Adverse Events in the data set included those occurring in enrolled patients who took at least one dose of study medication through study completion/discontinuation. Recurrent or continuing AEs were counted only once. Adverse Event incidence rates were calculated using all enrolled patients as the denominator. Clinical AEs were coded to body system and preferred term using the COSTART dictionary. Common AEs were defined as having an incidence of ≥2% (A complete list of common AEs is in the Appendix).

There were 157 different AE terms reported by 270 of 365 patients (74%) overall at anytime during the extension study. The incidence rates of patients reporting any AE by treatment group were relatively evenly balanced between the two treatment groups, and are summarized in the following table

Table 103: 146-011 Patients Reporting Any AE

	All	Treatment	
		Lovastatin XL 40 mg	Lovastatin XL 60 mg
All Enrolled Patients, n =	365	128	237
Reporting Any AE, n (%)	270 (74)	92 (72)	178 (75)

b) Adverse Events by Body System

Adverse Events occurring in the Body as a Whole, Digestive, and Musculoskeletal body systems were the most commonly reported (with 34%, 20%, and 13% respectively of all patients reporting any AE in these body systems). Arthralgia was the most commonly reported AE term, reported by 12% of patients overall. Adverse Events were relatively evenly distributed across treatment groups. The most commonly reported AEs by body system (occurring in ≥5% of patients overall) are listed in the following table

Table 104: 146-011 Incidence of Most Common (>5%) Adverse Events by Body System

			Treatment	
		All	Lovastatin XL 40 mg	Lovastatin XL 60 mg
All Enrolled Patients, n =		365	128	237
Body System	**Preferred Term**			
Body as a Whole	Accidental Injury	33 (9)	13 (10)	20 (8)
	Back Pain	32 (9)	8 (6)	24 (10)
	Infection	31 (8)	14 (10)	17 (7)
	Asthenia	20 (5)	7 (5)	13 (5)
	Headache	17 (5)	7 (5)	10 (4)
	Pain	17 (5)	6 (5)	11 (5)
Musculoskeletal	Arthralgia	43 (12)	13 (10)	30 (13)
Respiratory	Sinusitis	18 (5)	8 (6)	10 (4)

AEs of particular interest to this study were hepatitis, myalgia, myopathy, and rhabdomyolysis. There were no reports of hepatitis, myopathy or rhabdomyolysis during the study.

Thirteen (13) patients reported myalgia during the extension study as follows: Patients 2023, 2071, 2084, 2089, 2095, 2118, 2127, 2128, 2150, 2167, 2191, 3013, and 3282. Myalgia results in study drug discontinuation in one patient (2084).
Of these patients, six patients (2084, 2095, 2118, 2150, 2191, and 3282) had a CPK elevation >normal at anytime during study drug treatment. Only two of these patients (2095) had a CPK elevation >5 X ULN (see CPK elevations section).

c) Adverse Events by Subgroup

Female patients were more likely than male patients to report any AE (81% vs 69% respectively) at anytime during the study. The results were similar overall and by treatment group. There were too few non-Caucasians patients to analyze by race, and too few geriatric patients to analyze by age. Incidence rates for patients reporting any AE, male vs female, are summarized in the following table

Table 105: 146-011 Incidence Rates of Patients Reporting Any Adverse Event, Male vs Female

		Treatment	
	All	**Lovastatin XL 40 mg**	**Lovastatin XL 60 mg**
All Enrolled Patients, n =	365	128	237
Enrolled Patients Female (F), n =	F = 143	F = 54	F = 89
Enrolled Patients Male (M), n =	M = 222	M = 74	M = 148
Females Reporting Any AE, n (%)	116 (81)	44 (81)	72 (81)
Males Reporting Any AE, n (%)	154 (69)	48 (65)	106 (72)

Females were more likely than males to report most AEs (by preferred term), both overall and by treatment group, with the exception of arthralgias which were more common in males. There were no notable differences in the incidence of AEs reported by sex between treatment groups. The incidence rates of the most commonly reported (≥5% overall) AEs by body system, male vs female, are summarized in the following table [a complete listing of the incidence of common AEs (≥2%) by body system, male vs female, is in the Appendix]

Table 106: 146-011 Incidence of Most Common (≥5%) AEs by Body System, Male vs Female

				Treatment	
			All	**Lovastatin XL 40 mg**	**Lovastatin XL 60 mg**
Enrolled Patients Female (F), n =			F = 143	F = 54	F = 89
Enrolled Patients Male (M), n =			M = 222	M = 74	M = 148
Body System	**Preferred Term**	F/M			
Body as a Whole	Accidental Injury	F	16 (11)	7 (13)	9 (10)
		M	17 (8)	6 (8)	11 (7)
	Back Pain	F	18 (13)	6 (11)	12 (13)
		M	14 (6)	2 (3)	12 (8)
	Infection	F	15 (10)	7 (13)	8 (9)
		M	16 (7)	7 (9)	9 (6)
	Asthenia	F	11 (8)	3 (6)	8 (9)
		M	9 (4)	4 (5)	5 (3)
	Headache	F	11 (8)	6 (11)	5 (6)
		M	6 (3)	1 (1)	5 (3)
	Pain	F	8 (6)	3 (6)	5 (6)
		M	9 (4)	3 (4)	6 (4)
Musculoskeletal	Arthralgia	F	16 (11)	6 (11)	10 (11)
		M	27 (12)	7 (9)	20 (14)
Respiratory	Sinusitis	F	9 (6)	4 (7)	5 (6)
		M	9 (4)	4 (5)	5 (3)

d) Adverse Events Resulting in Drug Discontinuation

Twenty-five (25) of the 365 enrolled patients (7%) discontinued study medication prior to study completion. Of the 25 patients who discontinued, 14 discontinued due to an AE. Discontinuations due to AEs were slightly more common in the lovastatin XL 40 mg group than the lovastatin XL 60 mg group [8 patients (6%) vs 6 patients (3%) respectively]; however, as the number of discontinuations due to AEs was small, no conclusions will be generated from this. A number of different AE terms were reported as the reason for discontinuation, with discontinuations due to asthenia (3 patients), MI (2 patients), and somnolence (2 patients) being the most commonly reported (reported by >1

patient). One patient (2084) discontinued due to myalgias, fatigue and lethargy which began 3 days after starting in the extension study. This patient's CPK increased to 470 IU/L (ULN 195 IU/L). These symptoms eventually resolved after about 22 days.

Patients could report more than one AE per discontinuation. Patients reporting an AE as the reason for discontinuation are as follows

In the lovastatin XL 40 mg group:
Patient 3122 68 yo Caucasian male (MI)
Patient 2003 59 yo Caucasian male (coronary artery disease [CAD], MI)
Patient 2025 48 yo Caucasian male (SGPT increased, SGOT increased)
Patient 2084 63 yo Caucasian male (asthenia, somnolence, myalgia)
Patient 2017 69 yo Hispanic male (dizziness)
Patient 2095 69 yo Caucasian male (increased CPK)
Patient 2040 42 yo Caucasian female (dyspepsia)
Patient 2062 59 yo Caucasian female (mouth ulceration)

In the lovastatin XL 60 mg group:
Patient 3020 69 yo Caucasian male (infection, bacterial)
Patient 3143 44 yo Caucasian male (back pain)
Patients 2001 51 yo Caucasian female (taste perversion, asthenia, halitosis)
Patient 2086 55 yo Caucasian female (conjunctivitis, liver function tests, abnormal, asthenia, flatulence, diarrhea, somnolence, eye disorder)
Patient 2161 61 yo Caucasian female (melena)
Patient 2070 52 yo Black female (dry mouth)

The most common (occurring in >1 patient) Adverse Events resulting in drug discontinuation are summarized in the following table [A complete listing of AEs resulting in drug discontinuation is in the Appendix]

Table 107: 146-011 Discontinuations Due to Adverse Events, Most Common (Occurring in >1 Patients)

			Treatment	
		All	**Lovastatin XL 40 mg**	**Lovastatin XL 60 mg**
Enrolled Patients, n =		365	128	237
Number of Withdrawals, n (%)		25 (7)	12 (9)	13 (5)
Discontinued for AE*, n (%)		14 (4)	8 (6)	6 (3)
Body System	**Preferred Term**			
Body as a Whole	Asthenia	3 (1)	1 (1)	2 (1)
Cardiovascular	MI	2 (1)	2 (2)	0
Nervous	Somnolence	2 (1)	1 (1)	1 (<1)

*Patients may have reported more than one AE term per discontinuation

e) Serious Adverse Events

There were 11 SAEs occurring in 7 patients during the study. Three (3) patients (7 SAEs) were in the lovastatin XL 40 mg group and 4 patients (4 SAEs) were in the lovastatin XL 60 mg group. SAEs occurred most commonly in the Cardiovascular system (5 SAEs). Two (2) SAEs resulted in study drug discontinuation (MI and Staph

infection), and no SAE was attributed by the Investigator as being study drug related. There were no deaths. The SAEs are summarized as follows

Table 108: 146-011 Serious Adverse Events

Treatment	Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days) drug/drug	Invest. Attrib.	Drug D/C?
Lova XL 40 mg	3122	M	68	Myocardial Infarction (MI)	CV	25	NR	Yes
Lova XL 40 mg	2163	F	66	Chest Pain	Body	75	NR	No
Lova XL 40 mg	2163	F	66	Coronary Artery Disorder (CAD)	CV	48	NR	No
Lova XL 40 mg	2163	F	66	Dyspnea	Resp	75	NR	No
Lova XL 40 mg	2163	F	66	MI	CV	49	NR	No
Lova XL 40 mg	2163	F	66	CAD	CV	49	NR	No
Lova XL 40 mg	2032	M	67	Cholelithiasis	Dig	84	NR	No
Lova XL 60 mg	3020	M	69	Staph Infection	Body	36	NR	Yes
Lova XL 60 mg	3409	M	69	Colitis	Dig	88	NR	No
Lova XL 60 mg	3045	M	63	Cholelithiasis	Dig	22	NR	No
Lova XL 60 mg	3067	M	63	Arteriosclerosis	CV	16	NR	No

Two other SAEs (in one patient) were listed in the sponsor's study report. These SAEs occurred in the 146-009 study, prior to extension study entry, and have previously been listed in the 146-009 section. These SAEs are as follows

Table 109: 146-011 Serious Adverse Events Occurring before Extension Study Entry

Treatment	Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days) drug/drug	Invest. Attrib.	Drug D/C?
Lova XL 40 mg	2003	M	59	CAD	CV	-12	NR	Yes
Lova XL 40 mg	2003	M	59	MI	CV	-12	NR	Yes

f) Treatment Emergent Laboratory Abnormalities

Abnormalities for ALT, AST and CPK were defined by this Reviewer as any values outside the normal laboratory ranges during study drug treatment.

(1) ALT and AST Elevations

No patient experienced an ALT or AST elevation >3 X ULN during the extension study. Forty-seven (47) patients (13%) experienced an ALT elevation >1 X ULN at any time during double-blind treatment, and 25 patients (7%) experienced an AST elevation > 1 X ULN at any time. Six (6) patients (2%) experienced an ALT elevation >2 X ULN at any time during double-blind treatment, and 3 patients (1%) experienced an AST elevation > 2 X ULN at any time. There were no notable differences in ALT and AST elevations between the treatment groups. Additionally, there were no notable differences between male and female patients [see table in the Appendix]. The incidence rates of treatment emergent ALT and AST elevations by treatment group are as follows

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Table 110: 146-011 ALT and AST Elevations

		Treatment	
	All	**Lovastatin XL 40 mg**	**Lovastatin XL 60 mg**
All Enrolled Patients, n =	365	128	237
ALT > 1X ULN, n (%)	47 (13)	19 (15)	28 (12)
ALT > 2 X ULN, n (%)	6 (2)	4 (3)	2 (1)
ALT > 3 X ULN, n (%)	0	0	0
AST > 1X ULN, n (%)	25 (7)	14 (11)	11 (5)
AST > 2 X ULN, n (%)	3 (1)	2 (2)	1 (<1)
AST > 3 X ULN, n (%)	0	0	0

ALT normal range: Male 6-48 IU/L; Female 6-37 IU/L
AST normal range: Male 10-45 IU/L; Female 10-36 IU/L

One patient (2025) in the lovastatin XL 40 mg group was discontinued for ALT and AST elevations. This patient is summarized as follows

Table 111: 146-011 Patient Discontinued for ALT and AST Elevation

Patient Number	Sex	Lovastatin XL dose	Visit	ALT	AST	History
2025	M	40 mg	1	27	33	Prior to the LFT elevations, patient
			2	28	39	experienced severe accidental trauma treated
			3	137	120	with narcotics, acetaminophen and an
			3 retest	140	95	NSAID. Patient DC'd study medication after
			3 retest	95	50	Visit 3, and labs returned to WNL 15 days
			3 retest	30	23	later. The patient was DC'd from the study.

(2) CPK Elevations

Minor elevations (>1 X ULN) were common, occurring in 32% of patients overall. These elevations were somewhat more common in the lovastatin XL 60 mg group (34% vs 29% in the lovastatin XL 40 mg group), but were of no clinical importance. No patient had a CPK elevation ≥10 X ULN, and 3 patients had CPK elevations ≥5 X ULN. The incidence of treatment emergent CPK elevations by treatment group is summarized in the following table

Table 112: 146-011 CPK Elevations

		Treatment	
	All	**Lovastatin XL 40 mg**	**Lovastatin XL 60 mg**
All Enrolled Patients, n =	365	128	237
CPK > 1X ULN, n (%)	118 (32)	37 (29)	81 (34)
CPK > 5 X ULN, n (%)	3 (11)	1 (1)	2 (1)
CPK > 10 X ULN, n (%)	0	0	0

CPK normal range: Male 24-195 IU/L; Female 24-170 IU/L

Minor CPK elevations (>1 X ULN) were more common in male than in female patients overall (41% vs 20% respectively). There were no notable differences by sex by treatment group, however. The incidence of treatment emergent CPK elevations, male vs female, by treatment group is summarized as follows

Table 113: 146-011 CPK Elevations, Male vs Female

		Treatment	
	All	**Lovastatin XL 40 mg**	**Lovastatin XL 60 mg**
Enrolled Patients Female (F), n =	F = 143	F = 54	F = 89
Enrolled Patients Male (M), n =	M = 222	M = 74	M = 148
CPK > 1 X ULN			
Female, n (%)	28 (20)	8 (15)	20 (8)
Male, n (%)	90 (41)	29 (39)	61 (41)
CPK ≥ 5 X ULN			
Female, n (%)	0	0	0
Male, n (%)	3 (1)	1 (1)	2 (1)

Three patients (2095, 3216, and 3499) experienced CPK elevations >5 X ULN during the study, and one patient (2095) was discontinued due to a CPK elevation. One patient (2095) was in the lovastatin XL group and the other 2 patients (3216 and 3499) were in the lovastatin XL 60 mg group. These patients are summarized as follows

Table 114: 146-011 Patients with Clinically Significant CPK (≥ 5 X ULN or Resulting in Study Discontinuation)

Patient Number	Sex	Lovastatin XL dose	Visit	CPK (IU/L)	Elevation	History
2095	M	40 mg	1	48		Patient reported working out on exercise equipment 2-3 days prior to study visit and reported muscle soreness at the time. The patient DC'd study drug and muscle soreness resolved 1 day later. The patient's CPK returned to WNL 18 days after DC of study medication.
			2	1873	>5 X ULN	
			2 retest	213	>normal	
			2 retest	55		
3216	M	60 mg	1	302	>normal	Not available
			2	1057	>5 X ULN	
			3	360	>normal	
			5	289	>normal	
3499	M	60 mg	1	244	>normal	Not available
			2	1635	>5 X ULN	
			2 retest	202	>normal	
			3	140		
			5	138		

(3) Other Laboratory Abnormalities

There were no other clinically significant laboratory abnormalities during the study.

g) Overall Safety Conclusions for Protocol 146-011

In general, lovastatin XL was well tolerated. Most AEs were not serious or severe, and did not result in study drug discontinuation or interruption. Adverse Events occurring in the Body as a Whole, Digestive and Musculoskeletal systems were the most commonly reported, with arthralgia being the most frequently reported AE term. There were no reported cases of myopathy, rhabdomyolysis, or hepatitis. There were no notable differences in incidence of AEs between the two treatment groups. Adverse Events were more common in females patients than in male patients, with female patients more likely to report any AE term than males with the exception of arthralgias. There were 14

discontinuations (4%) during the study for AEs, with complaints or asthenia, MI and somnolence being the most common (occurring in 3, 2, and 2 patients respectively). One patient discontinued for myalgia. Eleven (11) SAEs occurred in 7 patients during the study, which occurred most commonly in the Cardiovascular system (5 SAEs). Clinically significant treatment emergent laboratory abnormalities were uncommon. No patient experienced an ALT or AST elevation >3 X ULN, and no patient experienced a CPK elevation >10 X ULN. Two (2) patients were discontinued due to laboratory abnormalities: one patient for AST and ALT elevations, and one patient for a CPK elevation. There were no other clinically significant laboratory abnormalities during the study.

D. Adequacy of Safety Testing

The safety testing was adequate to assess common AEs and TELAs frequently seen with lovastatin, and in this regard, the sponsor has demonstrated a safety profile similar to Mevacor. However, the sponsor has proposed a number of changes to the warning and precautions sections of the labeling that would differ from the Mevacor label regarding safety that were not adequately addressed by the sponsor's clinical program and by the data submitted.

The sponsor is proposing [redacted] of liver enzyme monitoring. The current Mevacor labeling recommends liver enzyme testing occur 6 and 12 weeks after initiation of treatment or increase in dose and then periodically thereafter. The sponsor is proposing that liver enzymes be measured [redacted] The sponsor cites as justification for this change current labeling for Lipitor, Pravachol, and Zocor, and that rates of liver enzyme elevations were similar in the AFCAPs and EXCEL trials as are reported for other statins. The relatively small number of patients exposed to lovastatin XL for a short duration of time, in addition to the available clinical literature for Mevacor, do not support a change regarding liver enzyme monitoring from the Mevacor label. Therefore, liver enzyme monitoring recommendations should be consistent with those for Mevacor, that is, "It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation of dose, and periodically thereafter (e.g., semiannually)." [Mevacor package insert]

Additionally, the sponsor did not include in the package insert other safety warnings and precautions currently included in the Mevacor label, including:

- Warning regarding concomitant administration with Verapamil may increase the risk of myopathy
- Endocrine function
- CNS toxicity, specifically cataracts in dogs

As no new data presented and no testing performed with lovastatin XL, warnings and precautions should remain the same as for Mevacor.

In addition, no drug-interaction data with lovastatin XL were submitted to the NDA. Given the delayed and extended-release properties of the extended-release formulation,

assumptions on drug interactions cannot necessarily be made from lovastatin IR data. This is particularly relevant for lovastatin XL at a dose of 60 mg, as the drug exposure is greater than that of lovastatin IR 80 mg (the maximum recommended dose), and therefore, the severity and magnitude of drug interactions with lovastatin XL 60 mg are not known. Therefore, it is recommended that the label for lovastatin XL contain wording advising the treating physician that precautions and recommendations for the concomitant administration of lovastatin IR with other drugs be interpreted with caution [see Proposed Labeling section in the Appendix].

E. Summarize Critical Safety Findings and Limitations of Data

Adverse Events were analyzed by individual study, and pooled by controlled studies or uncontrolled studies. The results for all these analyses were similar, and in general, lovastatin XL was found to be well tolerated with a safety profile similar to that of Mevacor. Lovastatin XL patients were about as likely as Mevacor and placebo patients to report any AE during the clinical studies. Most AEs were not serious or severe, and there was no increase in the incidence of AEs reported with increasing doses of lovastatin XL. Adverse Events occurring in the Body as a Whole body system were the most commonly reported, and the types and frequencies of AEs were similar across the treatment groups. The Musculoskeletal and Digestive systems were of particular interest in this study, especially myalgias, myopathy, rhabdomyolysis, and hepatitis. Patients in the lovastatin XL and Mevacor groups were no more likely to report myalgias than placebo patients, and there were no reported cases of myopathy, rhabdomyolysis, or hepatitis in any of the clinical studies. Discontinuations from any of the clinical studies for AEs were in any of the treatment groups, and most patients who entered the studies completed study drug treatment. Female patients were more likely to report any AE than male patients across all treatment groups; however, there did not appear to be an increased incidence of AEs in the lovastatin XL treatment groups compared to placebo. Lovastatin XL appeared to be as well tolerated in Geriatric vs Non-Geriatric patients. Serious Adverse Events were infrequent, and were most commonly observed in the Cardiovascular system. This is not unexpected in this high-risk group of patients. Clinically significant treatment emergent laboratory abnormalities were also uncommon. AST and ALT elevations $\geq$3 X ULN in one patient (010-3094), and CPK elevations $\geq$10 X ULN occurred in 2 patients, both of whom were receiving lovastatin XL 20 mg (010-3062 and 010-3150).

As stated in Section VIII, subsection D Adequacy of Safety Testing (see above), the safety data submitted to this NDA did not address the long-term or less frequently observed safety findings previously seen with Mevacor (such as long-term liver enzyme elevations or drug interactions). Therefore, it is recommended that the labeling of lovastatin XL include the same warnings and precautions as Mevacor.

VIII. Dosing, Regimen, and Administration Issues

Lovastatin XL is being proposed for use once daily at bedtime, in a dosage range of 10-60 mg. It is recommended that the starting dose for lovastatin XL be the same as that of Mevacor, that is 20 mg once daily, with titration of the dose based on NCEP III treatment

goals after a minimum of 4 weeks of treatment. A starting dose of 10 mg may be considered for patients requiring smaller reductions.

IX. Use in Special Populations

A. Critically Evaluate Sponsor's Gender Effects Analyses and Adequacy of Investigation

Approximately 45% of patients studied in the controlled studies were female, and 55% were male. The lipid-altering response in females and males was similar, with no meaningful differences in lipid-altering effects noted between males and females. Although females were more likely than males to report any AE during the clinical studies, there was no increased incidence of AEs in females in the lovastatin XL group compared to the placebo group.

B. Critically Evaluate Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Eighty-six percent (86%) of randomized patients in the controlled trials were Caucasian. The number of non-Caucasian patients was too small to evaluate by race.

The number of geriatric patients was also small, but analysis by subgroup for patients ≥65 years of age vs age <65 years did not reveal any meaningful differences in safety or efficacy between the two groups.

C. Evaluate Pediatric Program

The clinical trials submitted to the NDA were all performed in patients ages >18 years of age, and no data, including PK data, were submitted for pediatric patients. The sponsor has, however, submitted a proposal for a pediatric study to be performed in children ages — years of age. The proposed study is an

[ ]

Experience with immediate-release lovastatin in pediatric patients consists mainly of small clinical trials, usually performed in children with familial hypercholesterolemia. The lipid-altering effects and the safety of immediate-release lovastatin in children appear to be similar to those seen in adults[20, 21].

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[20] Stein EA, Illingworth DR, Kwiterovich PO Jr, Liacouras CA, Siimes MA, Jacobson MS, Brewster TG, Hopkins P, Davidson M, Graham K, Arensman F, Knopp RH, DuJovne C, Williams CL, Isaacsohn JL, Jacobsen CA, Laskarzewski PM, Ames S, Gormley GJ. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. JAMA 1999; 281(2):180-181.

[21] Lambert M, Lupien PJ, Gagne C, Levy E, Blaichman S, Langlois S, Hayden M, Rose V, Clarke JT, Wolfe BM, Clarson C, Parsons H, Stephure DK, Potvin D, Lambert J. Treatment of familial

D. Comment on Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

No clinical trials submitted to the NDA were performed in patients with compromised hepatic function. As lovastatin is extensively metabolized by the liver, further data would need to be submitted prior to the recommended use of lovastatin XL in patients with compromised hepatic function.

In a study of patients with severe renal insufficiency (creatinine clearance 10-30 mL/min), the plasma concentrations of total inhibitors after a single dose of lovastatin were approximately 2-fold higher than those in healthy volunteers. Studies in patients with end-stage renal disease on hemodialysis have not been conducted.

hypercholesterolemia in children and adolescents: effect of lovastatin. Canadian Lovastatin in Children Study Group. Pediatrics 1996;97(5):619-628.

X. Conclusions and Recommendations

A. Conclusions

The data from the clinical safety and efficacy studies submitted to NDA 21-316 support the approval of lovastatin XL as a treatment to lower TC, LDL-C, and TG, and to increase HDL-C; and as a treatment to slow the progression of coronary atherosclerosis in patients with CHD. Lovastatin XL was found to have a similar safety and efficacy profile to Mevacor, and the label for lovastatin XL should contain similar warnings, precautions, and recommendations for use as the label for Mevacor.

B. Recommendations

It is recommended by this Reviewer that lovastatin XL receive approval as a treatment to lower TC, LDL-C, and TG, and to increase HDL-C; and as a treatment to slow the progression of coronary atherosclerosis in patients with CHD. It is recommended that lovastatin XL receive this approval pending changes to the proposed labeling. See Appendix A for a detailed discussion of the proposed labeling.

XI. Appendices

A. Proposed Label

The following is the sponsor's proposed labeling for lovastatin XL that was submitted to the NDA. This Reviewer's comments will appear in text boxes in the appropriate sections and are not intended to appear in the final label. Recommended changes that are intended to appear in the final label will appear as edit track-changes within the labeling text. The recommended changes and comments were the result of discussions and recommendations from the entire lovastatin XL team, including the Chemistry, Biopharmaceutics, Pharmacotoxicology, and Biostatistics Reviewers. As labeling will likely be an ongoing discussion with the sponsor, the editing changes and comments below may be altered as a result of these discussions and should not be considered as final at this time.

The labeling changes and comments below represent changes up to the labeling teleconference held with the sponsor on 08-Jan-2002 and additional changes are expected. For further labeling changes and discussions after this date, please refer to meeting minutes for subsequent labeling teleconferences.

Proposed Text of the Labeling

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Draft

Labeling

B. Common Adverse Events

1. Protocol 146-009

Table 115: 146-009 Incidence of Common AEs (>2%) by Body System

			Treatment				
		All	Placebo	Lova 10	Lova 20	Lova 40	Lova 60
Randomized Patients, n =		172	34	35	34	33	36
Body System	**COSTART Term**						
Body as a Whole	Headache	21 (12)	2 (6)	5 (14)	4 (12)	6 (18)	4 (11)
	Accidental injury	13 (8)	3 (9)	4 (11)	1 (3)	2 (6)	3 (8)
	Asthenia	9 (5)	2 (6)	0	2 (6)	2 (6)	3 (8)
	Infection	8 (5)	3 (9)	1 (3)	1 (3)	1 (3)	2 (6)
	Abdominal pain	7 (4)	0	1 (3)	1 (3)	4 (12)	1 (3)
	Allergic reaction	7 (4)	1 (3)	1 (3)	2 (6)	1 (3)	2 (6)
	Flu syndrome	5 (3)	1 (3)	2 (6)	1 (3)	0	1 (3)
	Back pain	4 (2)	1 (3)	1 (3)	0	1 (3)	1 (3)
	Chest pain	4 (2)	0	2 (6)	1 (3)	1 (3)	0
	Neck pain	4 (2)	1 (3)	2 (6)	1 (3)	0	0
	Pain	4 (2)	0	0	2 (6)	2 (6)	0
Digestive	Diarrhea	6 (3)	2 (6)	0	1 (3)	2 (6)	1 (3)
	Nausea	5 (3)	1 (3)	0	0	1 (3)	3 (8)
	Flatulence	3 (2)	0	0	0	2 (6)	1 (3)
Metabolic & Nutritional	CPK increased	5 (3)	1 (3)	0	1 (3)	0	3 (8)
Musculoskeletal	Arthralgia	11 (6)	1 (3)	5 (14)	1 (3)	2 (6)	2 (6)
	Myalgia	10 (6)	6 (18)	0	2 (6)	1 (3)	1 (3)
	Arthritis	4 (2)	1 (3)	1 (3)	0	1 (3)	1 (3)
	Leg cramps	4 (2)	1 (3)	2 (6)	0	0	1 (3)
Nervous	Dizziness	7 (4)	2 (6)	2 (6)	0	0	3 (8)
	Insomnia	7 (4)	1 (3)	4 (11)	1 (3)	1 (3)	0
	Somnolence	7 (4)	2 (6)	1 (3)	1 (3)	2 (6)	1 (3)
	Anxiety	4 (2)	1 (3)	2 (6)	1 (3)	0	0
	Dry mouth	4 (2)	1 (3)	0	1 (3)	1 (3)	1 (3)
	Depression	3 (2)	2 (6)	0	0	0	1 (3)
Respiratory	Sinusitis	6 (3)	1 (3)	1 (3)	0	3 (9)	1 (3)
	Bronchitis	3 (2)	0	1 (3)	1 (3)	1 (3)	0
Skin & Appendages	Contact dermatitis	3 (2)	1 (3)	1 (3)	0	1 (3)	0
	Sweating	3 (2)	0	1 (3)	1 (3)	0	1 (3)
Special Senses	Otitis media	3 (2)	0	0	2 (6)	1 (3)	0
Urogenital	Urinary frequency	3 (2)	1 (3)	0	0	2 (6)	0
	Urinary tract infection	3 (2)	2 (6)	0	0	0	1 (3)

2. Protocol 146-010

a) By Treatment Group Assignment

Table 116: 146-010 Incidence of Common Adverse Events (≥2%) by Treatment Group Assignment

			Treatment			
			20 mg		60 mg	
		All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =		358	90	89	88	91
Body System	**COSTART Term**					
Body as a Whole	Infection	92 (26)	19 (21)	22 (25)	22 (25)	29 (32)
	Headache	39 (11)	5 (6)	13 (15)	8 (9)	13 (14)
	Flu Syndrome	38 (11)	8 (9)	11 (12)	9 (10)	10 (11)
	Back Pain	37 (10)	11 (12)	10 (11)	9 (10)	7 (8)
	Accidental Injury	28 (8)	5 (6)	6 (7)	7 (8)	10 (11)
	Pain	25 (7)	5 (6)	5 (6)	5 (6)	10 (11)
	Abdominal pain	14 (4)	2 (2)	4 (4)	5 (6)	3 (3)
	Allergic reaction	11 (3)	7 (8)	1 (1)	1 (1)	2 (2)
	Asthenia	10 (3)	0	4 (4)	2 (2)	4 (4)
	Chest pain	10 (3)	3 (3)	1 (1)	3 (3)	3 (3)
	Cyst	6 (2)	0	2 (2)	2 (2)	2 (2)
	Hernia	6 (2)	4 (4)	0	1 (1)	1 (1)
Cardiovascular	Hypertension	11 (3)	1 (1)	3 (3)	3 (3)	4 (4)
	Migraine	7 (2)	1 (1)	0	4 (5)	2 (2)
Digestive	Dyspepsia	20 (6)	4 (4)	4 (4)	6 (7)	6 (7)
	Diarrhea	18 (5)	5 (6)	6 (7)	4 (5)	3 (3)
	Nausea	18 (5)	4 (4)	4 (4)	7 (8)	3 (3)
	Gastroenteritis	15 (4)	4 (4)	4 (4)	2 (2)	5 (5)
	Tooth disorder	12 (3)	3 (3)	3 (3)	3 (3)	3 (3)
	Flatulence	9 (3)	1 (1)	2 (2)	3 (3)	3 (3)
	Constipation	7 (2)	3 (3)	2 (2)	0	2 (2)
	Vomiting	7 (2)	2 (2)	2 (2)	2 (2)	1 (1)
Metabolic & Nutritional	Peripheral edema	12 (3)	4 (4)	2 (2)	1 (1)	5 (5)
Musculoskeletal	Arthralgia	30 (8)	11 (12)	8 (9)	7 (8)	4 (4)
	Myalgia	19 (5)	5 (6)	4 (4)	3 (3)	7 (8)
	Arthritis	12 (3)	3 (3)	2 (2)	2 (2)	5 (5)
	Joint disorder	6 (2)	2 (2)	1 (1)	1 (1)	2 (2)
Nervous	Dizziness	10 (3)	2 (2)	4 (4)	3 (3)	1 (1)
	Insomnia	10 (3)	3 (3)	3 (3)	3 (3)	1 (1)
	Depression	7 (2)	0	3 (3)	1 (1)	3 (3)
Respiratory	Sinusitis	29 (8)	6 (7)	9 (10)	6 (7)	8 (9)
	Rhinitis	24 (7)	7 (8)	5 (6)	4 (5)	8 (9)
	Cough increased	15 (4)	4 (4)	1 (1)	3 (3)	7 (8)
	Pharyngitis	13 (4)	2 (2)	5 (6)	1 (1)	5 (5)
Skin & Appendages	Rash	12 (3)	2 (2)	4 (4)	5 (6)	1 (1)
Urogenital	Urinary tract infection	15 (4)	4 (4)	4 (4)	4 (5)	3 (3)

b) By Pooled Treatment Received

Table 117: 146-010 Incidence of Common Adverse Events (>2%) Pooled by Treatment Received

		Treatment			
		20 mg		60 mg	
		Lovastatin XL	Mevacor	Lovastatin XL	Mevacor
Randomized Patients, n =		162	166	167	163
Body System	**COSTART Term**				
Body as a Whole	Infection	22 (14)	25 (15)	26 (16)	31 (19)
	Back Pain	15 (9)	7 (4)	8 (5)	10 (6)
	Flu Syndrome	13 (8)	7 (4)	8 (5)	11 (7)
	Accidental Injury	7 (4)	4 (2)	11 (7)	6 (4)
	Allergic reaction	6 (4)	2 (1)	0	3 (2)
	Headache	6 (4)	16 (10)	17 (10)	9 (6)
	Pain	4 (2)	7 (4)	5 (3)	10 (6)
	Asthenia	3 (2)	1 (1)	3 (2)	3 (2)
	Hernia	3 (2)	1 (1)	2 (1)	0
	Abdominal pain	2 (1)	5 (3)	4 (2)	5 (3)
	Chest pain	1 (1)	3 (2)	3 (2)	3 (2)
	Cyst	1 (1)	1 (1)	1 (1)	3 (2)
Cardiovascular	Hypertension	3 (2)	1 (1)	2 (1)	5 (3)
	Migraine	1 (1)	0	5 (3)	1 (1)
Digestive	Diarrhea	6 (4)	5 (3)	3 (2)	4 (2)
	Gastroenteritis	6 (4)	3 (2)	5 (3)	3 (2)
	Constipation	4 (2)	1 (1)	2 (1)	0
	Dyspepsia	4 (2)	5 (3)	9 (5)	7 (4)
	Tooth disorder	4 (2)	2 (1)	2 (1)	5 (3)
	Flatulence	3 (2)	1 (1)	2 (1)	4 (2)
	Vomiting	3 (2)	1 (1)	0	3 (2)
	Nausea	2 (1)	6 (4)	6 (4)	4 (2)
Metabolic & Nutritional	Peripheral edema	1 (1)	6 (4)	3 (2)	4 (2)
Musculoskeletal	Arthralgia	11 (7)	12 (7)	8 (5)	5 (3)
	Myalgia	6 (4)	3 (2)	6 (4)	5 (3)
	Arthritis	4 (2)	2 (1)	4 (2)	5 (3)
	Joint disorder	2 (1)	1 (1)	0	3 (2)
Nervous	Dizziness	2 (1)	4 (2)	3 (2)	3 (2)
	Insomnia	5 (3)	1 (1)	2 (1)	2 (1)
	Depression	3 (2)	0	2 (1)	2 (1)
Respiratory	Sinusitis	7 (4)	9 (5)	6 (4)	9 (6)
	Rhinitis	8 (5)	5 (3)	5 (3)	8 (5)
	Cough increased	4 (2)	1 (1)	6 (4)	4 (2)
	Pharyngitis	1 (1)	6 (4)	3 (2)	3 (2)
Skin & Appendages	Rash	3 (2)	3 (2)	3 (2)	4 (2)
Urogenital	Urinary tract infection	1 (1)	7 (4)	4 (2)	3 (2)

c) In Period 1

Table 118: 146-010 Incidence of Adverse Events in Period 1 by Treatment Received

			Treatment			
			20 mg		60 mg	
		All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =		358	90	89	88	91
Body System	**COSTART Term**					
Body as a Whole	Infection	74 (21)	14 (16)	19 (21)	17 (19)	24 (26)
	Back pain	27 (8)	9 (10)	5 (6)	7 (8)	6 (7)
	Flu syndrome	27 (8)	8 (9)	7 (8)	5 (6)	7 (8)
	Headache	27 (8)	3 (3)	12 (13)	7 (8)	5 (5)
	Accidental injury	16 (4)	4 (4)	3 (3)	5 (6)	4 (4)
	Pain	13 (4)	1 (1)	3 (3)	2 (2)	7 (8)
	Abdominal pain	9 (3)	1 (1)	3 (3)	3 (3)	2 (2)
	Chest pain	8 (2)	1 (1)	1 (1)	3 (3)	3 (3)
	Allergic reaction	7 (2)	5 (6)	0	0	2 (2)
Cardiovascular	Hypertension	8 (2)	1 (1)	1 (1)	2 (2)	4 (4)
Digestive	Diarrhea	14 (4)	4 (4)	4 (4)	3 (3)	3 (3)
	Dyspepsia	13 (4)	2 (2)	2 (2)	5 (6)	4 (4)
	Nausea	11 (3)	2 (2)	4 (4)	4 (5)	1 (1)
	Tooth disorder	8 (2)	2 (2)	1 (1)	2 (2)	3 (3)
	Gastroenteritis	7 (2)	3 (3)	1 (1)	1 (1)	2 (2)
Metabolic & Nutritional	Peripheral edema	6 (2)	1 (1)	2 (2)	0	3 (3)
Musculoskeletal	Arthralgia	19 (5)	6 (7)	5 (6)	6 (7)	2 (2)
	Arthritis	10 (3)	3 (3)	1 (1)	2 (2)	4 (4)
	Myalgia	9 (3)	3 (3)	1 (1)	2 (2)	3 (3)
Nervous	Dizziness	8 (2)	1 (1)	3 (3)	3 (3)	1 (1)
	Insomnia	7 (2)	3 (3)	1 (1)	2 (2)	1 (1)
Respiratory	Sinusitis	20 (6)	4 (4)	7 (8)	3 (3)	6 (7)
	Rhinitis	16 (4)	5 (6)	3 (3)	2 (2)	6 (7)
	Cough increased	8 (2)	4 (4)	1 (1)	1 (1)	2 (2)
	Pharyngitis	8 (2)	0	4 (4)	1 (1)	3 (3)
Skin & Appendages	Rash	7 (2)	2 (2)	3 (3)	2 (2)	0
Urogenital	Urinary tract infection	8 (2)	1 (1)	4 (4)	2 (2)	1 (1)

d) In Period 2

Table 119: 146-010 Incidence of Adverse Events in Period 2 by Treatment Received

			Treatment			
			20 mg		60 mg	
		All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =		358	90	89	88	91
Body System	**COSTART Term**					
Body as a Whole	Infection	30 (8)	6 (7)	8 (9)	7 (8)	9 (10)
	Headache	21 (6)	4 (4)	3 (3)	4 (5)	10 (11)
	Back pain	13 (4)	2 (2)	6 (7)	4 (5)	1 (1)
	Pain	13 (4)	4 (4)	3 (3)	3 (3)	3 (3)
	Accidental injury	12 (3)	1 (1)	3 (3)	2 (2)	6 (7)
	Flu syndrome	12 (3)	0	5 (6)	4 (5)	3 (3)
	Abdominal pain	7 (2)	2 (2)	1 (1)	3 (3)	1 (1)
Digestive	Dyspepsia	12 (3)	3 (3)	2 (2)	3 (3)	4 (4)
	Gastroenteritis	10 (3)	2 (2)	3 (3)	1 (1)	4 (4)
	Nausea	7 (2)	2 (2)	0	3 (3)	2 (2)
Metabolic & Nutritional	Peripheral edema	8 (2)	4 (4)	0	1 (1)	3 (3)
Musculoskeletal	Arthralgia	17 (5)	7 (8)	5 (6)	3 (3)	2 (2)
	Myalgia	11 (3)	2 (2)	3 (3)	2 (2)	4 (4)
Respiratory	Sinusitis	11 (3)	2 (2)	3 (3)	3 (3)	3 (3)
	Rhinitis	10 (3)	2 (2)	3 (3)	2 (2)	3 (3)
	Cough increased	7 (2)	0	0	2 (2)	5 (5)
Urogenital	Urinary tract infection	7 (2)	3 (3)	0	2 (2)	2 (2)

3. Protocol 146-011

Table 120: 146-011 Incidence of Common (≥2%) Adverse Events by Body System

			Treatment	
		All	Lovastatin XL 40 mg	Lovastatin XL 60 mg
All Enrolled Patients, n =		365	128	237
Body System	**Preferred Term**			
Body as a Whole	Accidental Injury	33 (9)	13 (10)	20 (8)
	Back Pain	32 (9)	8 (6)	24 (10)
	Infection	31 (8)	14 (11)	17 (7)
	Asthenia	20 (5)	7 (5)	13 (5)
	Headache	17 (5)	7 (5)	10 (4)
	Pain	17 (5)	6 (5)	11 (5)
	Allergic Reaction	13 (4)	4 (3)	9 (4)
	Abdominal Pain	10 (3)	4 (3)	6 (3)
	Chest Pain	6 (2)	2 (2)	4 (2)
	Flu Syndrome	6 (2)	2 (2)	4 (2)
Cardiovascular	Hypertension	11 (3)	5 (4)	6 (3)
Digestive	Dyspepsia	15 (4)	9 (7)	6 (3)
	Diarrhea	14 (4)	6 (5)	8 (3)
	Nausea	11 (3)	3 (2)	8 (3)
	Constipation	7 (2)	1 (1)	6 (3)
	Flatulence	7 (2)	2 (2)	5 (2)
	Gastroenteritis	7 (2)	2 (2)	5 (2)
	Tooth Disorder	7 (2)	4 (3)	3 (1)
Metabolic and Endocrine	Peripheral Edema	13 (4)	4 (3)	9 (4)
Musculoskeletal	Arthralgia	43 (12)	13 (10)	30 (13)
	Myalgia	13 (4)	8 (6)	5 (2)
	Arthritis	10 (3)	3 (2)	7 (3)
	Leg cramps	8 (2)	2 (2)	6 (3)
Nervous	Insomnia	12 (3)	7 (5)	5 (2)
	Somnolence	9 (2)	6 (5)	3 (1)
	Depression	8 (2)	4 (3)	4 (2)
	Anxiety	6 (2)	3 (2)	3 (1)
	Dizziness	6 (2)	3 (2)	3 (1)
Respiratory	Sinusitis	18 (5)	8 (6)	10 (4)
	Pharyngitis	12 (3)	7 (5)	5 (2)
	Cough Increased	7 (2)	3 (2)	4 (2)
Skin and Appendages	Rash	13 (4)	7 (5)	6 (3)
	Fungal Dermatitis	9 (2)	4 (3)	5 (2)
	Sweating	7 (2)	2 (2)	5 (2)
	Contact Dermatitis	6 (2)	2 (2)	4 (2)
Special Senses	Conjunctivitis	7 (2)	3 (2)	4 (2)
Urogenital	Urinary Frequency	6 (2)	3 (2)	3 (1)

4. Pooled, Controlled Studies

Table 121: Pooled Controlled Studies TESS by Body System and COSTART Term, Most Common (≥2%)

		Treatment		
		Placebo	Lovastatin XL	Mevacor
Randomized Patients, n =		34	560	354
Body System	**COSTART Term**			
Body as a Whole	Abdominal Pain	0	11 (2)	11 (3)
	Accidental Injury	3 (9)	26 (5)	12 (3)
	Allergic Reaction	1 (3)	11 (2)	7 (2)
	Asthenia	2 (6)	12 (2)	6 (2)
	Back Pain	1 (3)	23 (4)	18 (5)
	Chest Pain	0	10 (2)	4 (1)
	Flu Syndrome	1 (3)	24 (4)	18 (5)
	Headache	2 (6)	34 (6)	26 (7)
	Infection	3 (9)	52 (9)	52 (15)
	Pain	0	14 (3)	17 (5)
Cardiovascular	Hypertension	0	5 (1)	7 (2)
Digestive	Diarrhea	2 (6)	15 (3)	8 (2)
	Dyspepsia	0	13 (2)	10 (3)
	Flatulence	0	5 (1)	7 (2)
	Gastroenteritis	1 (3)	8 (1)	9 (3)
	Nausea	1 (3)	16 (3)	7 (2)
	Tooth Disorder	0	6 (1)	7 (2)
Metabolic and Nutritional	Peripheral Edema	0	6 (1)	9 (3)
Musculoskeletal	Arthralgia	2 (6)	24 (4)	20 (6)
	Arthritis	1 (3)	5 (1)	10 (3)
	Myalgia	5 (15)	14 (3)	11 (3)
Nervous	Dizziness	2 (6)	10 (2)	5 (1)
	Insomnia	1 (3)	11 (2)	6 (2)
Respiratory	Cough Increased	0	7 (1)	10 (3)
	Pharyngitis	0	8 (1)	7 (2)
	Rhinitis	1 (3)	11 (2)	15 (4)
	Sinusitis	1 (3)	17 (3)	20 (6)
Skin and Appendages	Rash	0	11 (2)	5 (1)
Urogenital	Urinary Tract Infection	2 (6)	8 (1)	9 (3)

APPEARS THIS WAY
ON ORIGINAL

C. Discontinuations for Adverse Events

1. Protocol 146-010: By Treatment Group Assignment

Table 122: 146-010 All Discontinuations Due to Adverse Events by Treatment Group Assignment

			Treatment			
			20 mg		60 mg	
		All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =		358	90	89	88	91
All Discontinuations, n (%)		70 (20)	14 (16)	20 (22)	20 (23)	16 (18)
Discontinuations for AE*, n (%)		27 (8)	4 (4)	7 (8)	10 (11)	6 (7)
Body System	COSTART Term					
Body as a Whole	Asthenia	3 (1)	0	2 (2)	0	1 (1)
	Chest pain	3 (1)	1 (1)	1 (1)	0	1 (1)
	Abdominal pain	2 (1)	0	1 (1)	0	1 (1)
	Headache	2 (1)	0	1 (1)	0	1 (1)
	Pain	1 (1)	0	0	1 (1)	0
	Viral Infection	1 (1)	0	1 (1)	0	0
Cardiovascular	MI	2 (1)	0	1 (1)	1 (1)	0
	Hypertension	1 (1)	0	0	0	1 (1)
	Palpitations	1 (1)	1 (1)	0	0	0
Digestive	Nausea	4 (1)	2 (2)	0	1 (1)	1 (1)
	Constipation	1 (1)	0	0	0	1 (1)
	Dyspepsia	1 (1)	1 (1)	0	0	0
	Flatulence	1 (1)	0	0	0	1 (1)
	Pancreatitis	1 (1)	0	0	1 (1)	0
	Vomiting	1 (1)	1 (1)	0	0	0
Metabolic & Nutritional	Edema	1 (1)	1 (1)	0	0	0
	SGPT Increased	1 (1)	0	0	1 (1)	0
	Weight gain	1 (1)	0	1 (1)	0	0
Musculoskeletal	Arthralgia	3 (1)	0	0	3 (3)	0
	Myalgia	3 (1)	0	1 (1)	1 (1)	1 (1)
Nervous	Hypesthesia	2 (1)	0	0	2 (2)	0
	Depression	1 (1)	0	0	0	1 (1)
	Dizziness	1 (1)	1 (1)	0	0	0
	Insomnia	1 (1)	0	1 (1)	0	0
Respiratory	ARDS	1 (1)	0	0	1 (1)	0
	Sinusitis	1 (1)	0	0	0	1 (1)
Skin & Appendages	Alopecia	1 (1)	1 (1)	0	0	0
	Furunculosis	1 (1)	1 (1)	0	0	0
	Rash	1 (1)	0	1 (1)	0	0
	Urticaria	1 (1)	0	1 (1)	0	0
	Pruritis	1 (1)	0	0	1 (1)	0
Special Senses	Conjunctivitis	1 (1)	0	0	0	1 (1)
Urogenital	Breast neoplasm	1 (1)	0	0	0	1 (1)

*Patients may have reported more than one AE term per discontinuation

2. Protocol 146-011

Table 123: 146-011 Discontinuations Due to Adverse Events

			Treatment	
		All	Lovastatin XL 40 mg	Lovastatin XL 60 mg
Enrolled Patients, n =		365	128	237
Number of Withdrawals, n (%)		25 (7)	12 (9)	13 (5)
Discontinued for AE*, n (%)		14 (4)	8 (6)	6 (3)
Body System	**Preferred Term**			
Body as a Whole	Asthenia	3 (1)	1 (1)	2 (1)
	Back Pain	1 (<1)	0	1 (<1)
	Halitosis	1 (<1)	0	1 (<1)
	Staph Infection	1 (<1)	0	1 (<1)
Cardiovascular	CAD	1 (<1)	1 (1)	0
	MI	2 (1)	2 (2)	0
Digestive	Abnormal LFTs	1 (<1)	0	1 (<1)
	Diarrhea	1 (<1)	0	1 (<1)
	Dyspepsia	1 (<1)	1 (1)	0
	Flatulence	1 (<1)	0	1 (<1)
	Melena	1 (<1)	0	1 (<1)
	Mouth Ulceration	1 (<1)	1 (1)	0
Metabolic and Nutritional	Increased SGOT	1 (<1)	1 (1)	0
	Increased SGPT	1 (<1)	1 (1)	0
	Increased CPK	1 (<1)	1 (1)	0
Musculoskeletal	Myalgia	1 (<1)	1 (1)	0
Nervous	Dizziness	1 (<1)	1 (1)	0
	Dry Mouth	1 (<1)	0	1 (<1)
	Somnolence	2 (1)	1 (1)	1 (<1)
Special Senses	Conjunctivitis	1 (<1)	0	1 (<1)
	Eye Disorder	1 (<1)	0	1 (<1)
	Taste Perversion	1 (<1)	0	1 (<1)

*Patients may have reported more than one AE term per discontinuation

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D. Adverse Events by Subgroup

1. Protocol 146-009: AEs by Body System, Male vs Female

Table 124: 146-009 Incidence of Common AEs by Body System, Male vs Female

				Treatment				
			All	Placebo	Lova 10	Lova 20	Lova 40	Lova 60
Randomized Patients Female (F) , n =			F = 82	F = 16	F = 17	F = 15	F = 14	F = 20
Randomized Patients Male (M) , n =			M = 90	M = 18	M = 18	M = 19	M = 19	M = 16
Body System	**COSTART Term**	**F/M**						
Body as a Whole	Headache	F	15 (18)	1 (6)	4 (24)	3 (20)	5 (36)	2 (10)
		M	6 (7)	1 (6)	1 (6)	1 (5)	1 (5)	2 (13)
	Accidental injury	F	8 (10)	3 (19)	2 (12)	0	1 (7)	2 (10)
		M	5 (6)	0	2 (11)	1 (5)	1 (5)	1 (6)
	Asthenia	F	5 (6)	1 (6)	0	1 (7)	1 (7)	2 (10)
		M	4 (4)	1 (6)	0	1 (5)	1 (5)	1 (6)
	Infection	F	4 (5)	1 (6)	1 (6)	0	1 (7)	1 (5)
		M	4 (4)	2 (11)	0	1 (5)	0	1 (6)
	Abdominal pain	F	6 (7)	0	1 (6)	1 (7)	3 (21)	1 (5)
		M	1 (1)	0	0	0	1 (5	0
	Allergic reaction	F	4 (5)	0	1 (6)	1 (7)	0	2 (10)
		M	3 (3)	1 (6)	0	1 (5)	1 (5)	0
	Flu syndrome	F	2 (2)	1 (6)	0	1 (7)	0	0
		M	3 (3)	0	2 (11)	0	0	1 (6)
	Back pain	F	3 (4)	0	1 (6)	0	1 (7)	1 (5)
		M	1 (1)	1 (6)	0	0	0	0
	Chest pain	F	2 (2)	0	0	1 (7)	1 (7)	0
		M	2 (2)	0	2 (11)	0	0	0
	Neck pain	F	0	0	0	0	0	0
		M	4 (4)	1 (6)	2 (11)	1 (5)	0	0
	Pain	F	1 (1)	0	0	1 (7)	0	0
		M	3 (3)	0	0	1 (5)	2 (14)	0
Digestive	Diarrhea	F	5 (6)	2 (13)	0	1 (7)	1 (7)	1 (5)
		M	1 (1)	0	0	0	1 (5)	0
	Nausea	F	2 (2)	1 (6)	0	0	0	1 (5)
		M	3 (3)	0	0	0	1 (5)	2 (13)
	Flatulence	F	2 (2)	0	0	0	1 (7)	1 (5)
		M	1 (1)	0	0	0	1 (5)	0
Metabolic & Nutritional	CPK increased	F	3 (4)	0	0	1 (7)	0	2 (10)
		M	2 (2)	1 (6)	0	0	0	1 (6)
Musculoskeletal	Arthralgia	F	6 (7)	0	4 (24)	0	1 (7)	1 (5)
		M	5 (6)	1 (6)	1 (6)	1 (5)	1 (5)	1 (6)
	Myalgia	F	4 (5)	3 (19)	0	1 (7)	0	0
		M	6 (7)	3 (17)	0	1 (5)	1 (5)	1 (6)
	Arthritis	F	3 (4)	1 (6)	1 (6)	0	0	1 (5)
		M	1 (1)	0	0	0	1 (5)	0
	Leg cramps	F	3 (4)	1 (6)	1 (6)	0	0	1 (5)
		M	1 (1)	0	1 (6)	0	0	0
Nervous	Dizziness	F	3 (4)	0	2 (12)	0	0	1 (5)
		M	4 (4)	2 (11)	0	0	0	2 (13)
	Insomnia	F	3 (4)	0	2 (12)	1 (7)	0	0
		M	4 (4)	1 (6)	2 (11)	0	1 (5)	0
	Somnolence	F	4 (5)	2 (13)	0	0	1 (7)	1 (5)
		M	3 (3)	0	1 (6)	1 (5)	1 (5)	0

Table 124: 146-009 Incidence of Common AEs by Body System, Male vs Female

				Treatment				
			All	Placebo	Lova 10	Lova 20	Lova 40	Lova 60
	Anxiety	F	1 (1)	0	1 (6)	0	0	0
		M	3 (3)	1 (6)	1 (6)	1 (5)	0	0
	Dry mouth	F	0	0	0	0	0	0
		M	4 (4)	1 (6)	0	1 (5)	1 (5)	1 (6)
	Depression	F	2 (2)	1 (6)	0	0	0	1 (5)
		M	1 (1)	1 (6)	0	0	0	0
Respiratory	Sinusitis	F	4 (5)	0	1 (6)	0	2 (14)	1 (5)
		M	2 (2)	1 (6)	0	0	1 (5)	0
	Bronchitis	F	3 (4)	0	1 (6)	1 (7)	1 (7)	0
		M	0	0	0	0	0	0
Skin & Appendages	Contact dermatitis	F	1 (1)	1 (6)	0	0	0	0
		M	2 (2)	0	1 (6)	0	1 (5)	0
	Sweating	F	1 (1)	0	0	1 (7)	0	0
		M	2 (2)	0	1 (6)	0	0	1 (6)
Special Senses	Otitis media	F	2 (2)	0	0	1 (7)	1 (7)	0
		M	1 (1)	0	0	1 (5)	0	0
Urogenital	Urinary frequency	F	3 (4)	1 (6)	0	0	2 (14)	0
		M	0	0	0	0	0	0
	Urinary tract infection	F	3 (4)	2 (13)	0	0	0	1 (6)
		M	0	0	0	0	0	0

2. Protocol 146-011

a) AEs by Body System, Male vs Female

Table 125: 146-011 Incidence of Most Common (≥2%) AEs by Body System, Male vs Female

				Treatment	
			All	Lovastatin XL 40 mg	Lovastatin XL 60 mg
Randomized Patients Female (F), n =			F = 143	F = 54	F = 89
Randomized Patients Male (M), n =			M = 222	M = 74	M = 148
Body System	**Preferred Term**	F/M			
Body as a Whole	Accidental Injury	F	16 (11)	7 (13)	9 (10)
		M	17 (8)	6 (8)	11 (7)
	Back Pain	F	18 (13)	6 (11)	12 (13)
		M	14 (6)	2 (3)	12 (8)
	Infection	F	15 (10)	7 (13)	8 (9)
		M	16 (7)	7 (9)	9 (6)
	Asthenia	F	11 (8)	3 (6)	8 (9)
		M	9 (4)	4 (5)	5 (3)
	Headache	F	11 (8)	6 (11)	5 (6)
		M	6 (3)	1 (1)	5 (3)
	Pain	F	8 (6)	3 (6)	5 (6)
		M	9 (4)	3 (4)	6 (4)
	Allergic Reaction	F	3 (2)	1 (2)	2 (2)
		M	10 (5)	3 (4)	7 (5)
	Abdominal Pain	F	7 (5)	4 (7)	3 (3)
		M	3 (1)	0	3 (2)
	Chest Pain	F	2 (1)	1 (2)	1 (1)
		M	4 (2)	1 (1)	3 (2)
	Flu Syndrome	F	3 (2)	2 (4)	1 (1)
		M	3 (1)	0	3 (2)
Cardiovascular	Hypertension	F	5 (3)	2 (4)	3 (3)

		M	6 (3)	3 (4)	3 (2)
Digestive	Dyspepsia	F	10 (7)	8 (15)	2 (2)
		M	5 (2)	1 (1)	4 (3)
	Diarrhea	F	8 (6)	3 (6)	5 (6)
		M	6 (3)	3 (4)	3 (2)
	Nausea	F	5 (3)	1 (2)	4 (4)
		M	6 (3)	2 (3)	4 (3)
	Constipation	F	5 (3)	0	5 (6)
		M	2 (1)	1 (1)	1 (1)
	Flatulence	F	5 (3)	1 (2)	4 (4)
		M	2 (1)	1 (1)	1 (1)
	Gastroenteritis	F	4 (3)	2 (4)	2 (2)
		M	3 (1)	0	3 (2)
	Tooth Disorder	F	3 (2)	2 (4)	1 (1)
		M	4 (2)	2 (3)	2 (1)
Metabolic and Endocrine	Peripheral Edema	F	5 (3)	2 (4)	3 (3)
		M	8 (4)	2 (3)	6 (4)
Musculoskeletal	Arthralgia	F	16 (11)	6 (11)	10 (11)
		M	27 (12)	7 (9)	20 (14)
	Myalgia	F	5 (3)	3 (6)	2 (2)
		M	8 (4)	5 (7)	3 (2)
	Arthritis	F	7 (5)	3 (6)	4 (4)
		M	3 (1)	0	3 (2)
	Leg Cramps	F	2 (1)	0	2 (2)
		M	6 (3)	2 (3)	4 (3)
Nervous	Insomnia	F	7 (5)	4 (7)	3 (3)
		M	5 (2)	3 (4)	2 (1)
	Somnolence	F	6 (4)	3 (6)	3 (3)
		M	3 (1)	3 (4)	0
	Depression	F	4 (3)	3 (6)	1 (1)
		M	4 (2)	1 (1)	3 (2)
	Anxiety	F	1 (1)	1 (2)	0
		M	5 (2)	2 (3)	3 (2)
	Dizziness	F	2 (1)	1 (2)	1 (1)
		M	4 (2)	2 (3)	2 (1)
Respiratory	*Sinusitis*	F	9 (6)	4 (7)	5 (6)
		M	9 (4)	4 (5)	5 (3)
	Pharyngitis	F	5 (3)	5 (9)	0
		M	7 (3)	2 (3)	5 (3)
	Cough Increased	F	3 (2)	2 (4)	1 (1)
		M	4 (2)	1 (1)	3 (2)
Skin and Appendages	Rash	F	7 (5)	4 (7)	3 (3)
		M	6 (3)	3 (4)	3 (2)
	Fungal Dermatitis	F	2 (1)	1 (2)	1 (1)
		M	7 (3)	3 (4)	4 (3)
	Sweating	F	3 (2)	0	3 (3)
		M	4 (2)	2 (3)	2 (1)
	Contact Dermatitis	F	3 (2)	0	3 (3)
		M	3 (1)	2 (3)	1 (1)
Special Senses	Conjunctivitis	F	4 (3)	2 (4)	2 (2)
		M	3 (1)	1 (1)	2 (1)
Urogenital	Urinary Frequency	F	4 (3)	2 (4)	2 (2)
		M	2 (1)	1 (1)	1 (1)

b) Protocol 146-011: ALT and AST Elevations, Male vs Female

Table 126: 146-011 ALT and AST Elevations, Male vs Female

		Treatment	
	All	**Lovastatin XL 40 mg**	**Lovastatin XL 60 mg**
Enrolled Patients Female (F), n =	F = 143	F = 54	F = 89
Enrolled Patients Male (M), n =	M = 222	M = 74	M = 148
ALT > 1 X ULN			
Female, n (%)	22 (15)	9 (17)	13 (15)
Male, n (%)	25 (11)	10 (14)	15 (10)
ALT > 2 X ULN			
Female, n (%)	3 (2)	2 (4)	1 (1)
Male, n (%)	3 (1)	2 (3)	1 (1)
AST > 1 X ULN			
Female, n (%)	12 (8)	6 (11)	6 (7)
Male, n (%)	13 (6)	8 (11)	5 (3)
AST > 2 X ULN			
Female, n (%)	2 (1)	1 (2)	1 (1)
Male, n (%)	1 (<1)	1 (1)	0

ALT normal range: Male 6-48 IU/L; Female 6-37 IU/L
AST normal range: Male 10-45 IU/L; Female 10-36 IU/L

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/s/

Anne Pariser
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Mary Parks
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