Table 30: Risk Factors for Heart Disease

Age: 45 years or older for men, 55 years or older for women or women with premature menopause without estrogen replacement
Family history of premature CHD: Myocardial Infarction (MI) before the age of 55 in male first-degree relatives, or before age of 65 in female first-degree relatives
Current cigarette smoking
Low HDL-C (less than 35 mg/dL) at Visit 1
High blood pressure (BP) [defined as diastolic BP >90 mm Hg at Visit 1 or taking antihypertensive medication]
Diabetes mellitus* (DM)

*DM is an exclusion criterion in this study

6) Patient had a fasting plasma TG <350 mg/dL at Visit 1
7) CPK value was ≤3 X ULN (≤585 IU/L for male patients and ≤510 IU/L for female patients) at Visit 1

(b) Exclusion Criteria

1) Patient had received any lipid-modifying agent within 3 weeks prior to Visit 1
2) Premenopausal women, unless surgically sterile or using an effective method of contraception. Any patient who became pregnant during the study was discontinued.
3) Patient had previously demonstrated intolerance to HMG Co-A reductase inhibitors
4) Patient had clinically significant hepatic, renal, gastrointestinal, metabolic, neurologic, pulmonary, endocrine or psychiatric disorders
5) Patient had a history within the past 5 years or current diagnosis of malignancy, except for non-melanoma skin cancer
6) Patient had experienced acute MI, coronary revascularization procedure, or acute coronary insufficiency within 2 years preceding study entry
7) Patient had uncontrolled hypertension (treated or untreated) with either systolic BP >160 mm Hg or diastolic BP >95 mm Hg at Visit 1
8) Patient had a current diagnosis of secondary hypercholesterolemia or DM (defined as fasting glucose level >126 mg/dL on diet alone, or anyone on hypoglycemic medication)
9) Patient was currently taking any of the following medications:
   a) inconstant doses of psyllium (e.g., Metamucil);
   b) cimetidine or regularly used antacids;
   c) anticoagulants (antiplatelet agents are permitted), except aspirin;
   d) immunosuppressive agents, including cyclosporine;
   e)chronic systemic glucocorticoid therapy;
   f) macrolide antibiotics including erythromycin and clarithromycin;
   g) systemic azole antifungal agents (itraconazole, ketoconazole, etc.);
   h) cyclic estrogen replacement therapy (ERT), cyclic hormone replacement therapy (HRT), a depot progesterone injection or any oral contraceptive therapy (OCT). However, patients were eligible if they were receiving a stable dose of ERT or HRT which had been constant for at least 3 months prior to Visit 1 and was to remain unchanged for the duration of the study.
   i) Thyroid medication unless on a stable dose for 3 months prior to Visit 1

j) Nefazodone hydrochloride (Serzone)

10) Patient had a history of underlying hepatic disease or elevations of serum ALT or AST >1.5 X ULN at Visit 1
11) Patient had failed to maintain a 90% compliance rate at Visit 3 (end of 3-week diet/placebo run-in) and an 85% compliance rate at Visit 4 (end of 4-week diet/placebo run-in)
12) Patient had a history of alcohol or drug abuse
13) Patient had participated in another clinical research study within 30 days prior to Visit 1
14) Patient had a history of non-compliance to medical regimens and patients who were considered potentially unreliable
15) Patient had a positive screening tests for Hepatitis B or C
16) Body Mass Index (BMI) >36, determined by:
BMI = [weight (kg)/height^2 (m^2)]
17) Patient had any other diagnosis or characteristic that could be expected to impair the patient's compliance or response to the study medication, or confound the interpretation of the study results
18) Any patient who had previously been screened and found ineligible for participation in this study
19) Patient had an abnormal serum free T4 or TSH at the Screening Visit

(4) Study Visits and Procedures

The study visits and procedures are summarized below and in the following tables. All study visits could occur with ±3 days of the designated study day.

Table 31: 146-010 Study Visits and Procedures

	Screening	Diet/Placebo Run-in		Randomization	Double-Blind Treatment			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**6A**	**7**
Study Week (Study Day)	**-4 to -1 (-28 to -7)**	**0 (0)**	**3 (21)**	**4 (28)**	**8 (56)**	**12 (84)**	**15 (105)**	**16 (112)**
Procedure								
Informed Consent	X							
Diet Instruction		X						
Medical History	X							
Physical Exam				X				X
ECG				X				X
Concomitant Medications	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X		X
Dispense Study Medication		X		X	X	X		X
Study Medication Compliance			X	X	X	X		X
Adverse Events		X	X	X	X	X	X	X
Serum Lipids	X	X	X	X	X	X	X	X
Clinical Laboratory Tests								
Serum ALT, AST, CPK	X	X	X	X	X	X		X
Serum Chemistry	X			X				X
Hematology	X			X				X
Urinalysis	X			X				X
Serum free T4 and TSH	X							
Serum Beta-HCG	X			X		X		X
Hepatitis B and C	X							

Table 32: 146-010 Study Visits and Procedures Continued

	Washout		Double-Blind Treatment			
Visit	**7A**	**8**	**9**	**10**	**10A**	**11**
Study Week (Study Day)	**21 (147)**	**22 (154)**	**26 (182)**	**30 (210)**	**33 (231)**	**34 (238)**
Procedure Informed Consent						
Diet Instruction						
Medical History						
Physical Exam		X				X
ECG		X				X
Concomitant Medications	X	X	X	X	X	X
Vital Signs		X	X	X		X
Dispense Study Medication		X	X	X		
Study Medication Compliance		X	X	X		X
Adverse Events	X	X	X	X	X	X
Serum Lipids	X	X	X	X	X	X
Clinical Laboratory Tests						
Serum ALT, AST, CPK		X	X	X		X
Serum Chemistry		X				X
Hematology		X				X
Urinalysis		X				X
Serum free T4 and TSH						
Serum Beta-HCG		X		X		X
Hepatitis B and C						

(a) Screening/Visit 1 (Weeks –4 to –1; Days –28 to –7)

Patients taking lipid-lowering drugs were seen on or before Day –28 to obtain informed consent and begin drug washout. All patients returned on Day –7 for all remaining Visit 1 procedures. Patients reported to the study center before breakfast following at least a 10-hour fast and underwent the following procedures:

- Informed Consent
- Medical history and demographic data
- Concomitant medications record
- Vital signs (BP, pulse, and body temperature)
- Blood samples for lipids, serum AST and ALT, CPK, serum chemistry and hematology, free T4, TSH, serum beta-HCG (females only), Hepatitis B, and Hepatitis C
- Urinalysis

Qualifying patients were assigned an enrollment number and started in the diet/placebo run-in phase of the study. Patients were eligible for entry in the diet/placebo run-in period based on screening (Visit 1) laboratory, medical history, and concomitant medication assessments.

(b) Diet/Placebo Run-In Period/Visits 2 and 3 (Weeks 0 and 3; Days 0 and 21)

(i) Visit 2 (Week 0; Day 0)

At Visit 2, patients reported to the study center before breakfast, after at least a 10-hour fast. The following procedures were performed:

- Study and NCEP Step I diet instructions
- Concomitant medications record
- Vital signs (BP, pulse, and body temperature)
- Dispensing of study medication for Visits 2 and 3
- AE assessment
- Blood samples for lipids, AST, ALT, and CPK

(ii) Visit 3 (Week 3; Day 21)

At Visit 3, patients reported to the study center before breakfast, after at least a 10-hour fast. Compliance was assessed by a count of unused study medication, and patients with at least 90% compliance underwent the following procedures:

- Concomitant medications record
- Vital signs (BP, pulse, and body temperature)
- AE assessment
- Diet reinforcement
- Redispensing of study medication for Visits 2 and 3
- Blood samples for lipids, AST, ALT and CPK

(c) Randomization Visit/Visit 4 (Week 4; Day 28)

At Visit 4, patients reported to the study center before breakfast, after at least a 10-hour fast. Compliance was assessed by a count of unused study medication, and patients with at least 85% compliance underwent the following procedures:

- Physical examination
- ECG
- Concomitant medications record
- Vital signs (BP, pulse, temperature)
- AE Assessment
- Determine if patient meets all inclusion and none of the exclusion criteria
- Randomization number assigned to eligible patients
- Dispensing of study medication for Visit 4
- Diet reinforcement
- Blood samples for lipids, AST, ALT, CPK, serum chemistry and hematology, serum beta-HCG (Females only)
- Urinalysis

(d) Visit 5 (Week 8; Day 56), Visit 6 (Week 12; Day 84), and Visit 6A (Week 15; Day 105)

At Visits 5, 6, and 6A, patients reported to the study center before breakfast, after at least a 10-hour fast. Compliance was assessed by a count of unused study medication, and patients with at least 80% compliance underwent the following procedures:

- Concomitant medications record*
- Vital signs (BP, pulse, and body temperature)
- AE assessment*
- Diet reinforcement
- Dispensing of study medication for Visits 5 and 6
- Blood samples for lipids*, AST, ALT, CPK, and beta-HCG (females only)

* For Visit 6A, only procedures with an * were performed

(e) Visit 7 (Week 16; Day 112), Visit 7A (Week 21; Day 147), and Visit 8 (Week 22; Day 154)

At Visits 7, 7A, and 8, patients reported to the study center before breakfast, after at least a 10-hour fast. Compliance was assessed by a count of unused study medication, and patients with at least 80% compliance underwent the following procedures:

- Physical examination
- ECG
- Concomitant medications record*
- Vital signs (BP, pulse, and body temperature)
- AE assessment*
- Diet Reinforcement
- Dispensing of study medication for Visits 7 and 8
- Blood samples for lipids*, AST, ALT, CPK, and serum beta-HCG (females only)
- Urinalysis

* For Visit 7A, only procedures with an * were performed

(f) Visit 9 (Week 26; Day 182), Visit 10 (Week 30; Day 210), and Visit 10A (Week 33; Day 238)

At Visits 9, 10, and 10A, patients reported to the study center before breakfast, after at least a 10-hour fast. Compliance was assessed by a count of unused study medication, and patients with at least 80% compliance underwent the following procedures:

- Concomitant medications record*
- Vital signs (BP, pulse, and body temperature)
- AE assessment*
- Diet Reinforcement
- Dispensing of study medication for Visits 9 and 10
- Blood samples for lipids*, AST, ALT, CPK, and serum beta-HCG (females only; Visit 10 only)

* For Visit 10A, only procedures with an * were performed

(g) End of Study/Visit 11(Week 34; Day 238) or Early Termination

At Visit 11, patients reported to the study center before breakfast, after at least a 10-hour fast. All patients underwent the following procedures:

- Physical examination
- ECG
- Concomitant medications record
- Vital signs (BP, pulse, temperature)
- AE Assessment
- Blood samples for lipids, AST, ALT, CPK, serum chemistry and hematology, and serum beta-HCG (Females only)
- Urinalysis

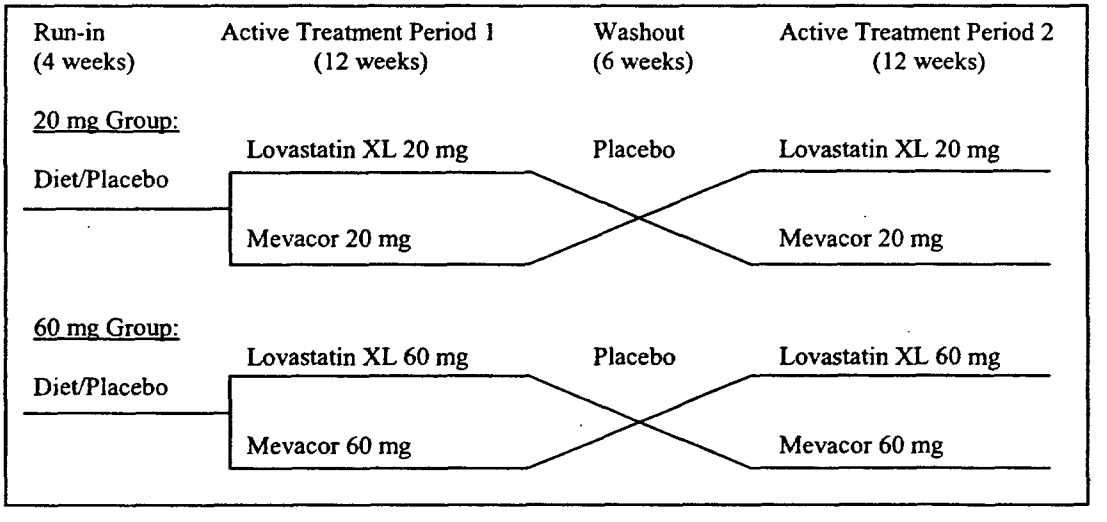
(5) Study Medication Dispensing and Compliance

During the placebo/run-in phase, all patients received placebo in a single-blind manner. At Visit 4 (Randomization Visit), patients were assigned in a 1:1 ratio to either the 20 mg or 60 mg dose group. Patients were randomized to 1 of 4 treatment sequence groups as follows:

Treatment sequence A: Lovastatin XL/Mevacor 20 mg once daily
Treatment sequence B: Mevacor/Lovastatin XL 20 mg once daily
Treatment sequence C: Lovastatin XL/Mevacor 60 mg once daily
Treatment sequence D: Mevacor/Lovastatin XL 60 mg once daily

Study dosing is summarized in the following schematic:

Figure 7: 146-010 Treatment Schedule



Randomization occurred at the study sites using blocks of four dispensed sequentially by blinded study personnel. Study medication was supplied as 2 capsules dosed one capsule after dinner and one capsule at bedtime. In order to maintain the blind, all study medications (including lovastatin XL, Mevacor, and placebo) were placed in capsules that could not be differentiated based on outside appearance. Capsules were packaged on blister cards and dispensed for a 2-week period + 4 days extra medication. Unused medication was collected at the following study visit, and compliance was determined by a tablet count.

(6) Efficacy and Endpoint Measures

(a) Primary

The primary efficacy variable was percent change in LDL-C from baseline to endpoint. Baseline was defined as the average of the last 2 values before starting each active treatment period (Visits 3 and 4 for Period 1, Visits 7A and 8 for Period 2). Endpoint was defined as the average of the last 2 values during active treatment (Visits 6A and 7 for Period 1, and Visits 10A and 11 for Period 2). For each efficacy parameter (LDL-C, HDL-C, TC, and TG), the null hypothesis of interest was that there was no difference between the treatments (lovastatin XL and Mevacor) in the mean percent change from baseline to endpoint.

(b) Secondary

The secondary efficacy variables were percent change in HDL-C, TC and TG from baseline to endpoint.

(c) Safety

Safety was assessed by the incidence and frequency of adverse events, and changes in vital signs, physical examinations, ECGs, and clinical laboratory values.

(d) Study Population

All Randomized patients included all patients who were randomized and received at least one dose of study medication. The ITT population included All Randomized patients who had at least 1 baseline observation from the first placebo period and 1 observation from both active treatment periods. The ITT population was the sponsor's primary efficacy analysis population.

b) Results

Seven-hundred ninety (790) patients were screened at 24 study sites. Three-hundred fifty-eight (358) patients were randomized between 19-Jul-1999 and 03-Jan-2001. All Randomized and ITT patients by study treatment are summarized in the following table

Table 32: 146-010 Randomized and ITT Patients by Treatment Group

		Treatment			
		20 mg		60 mg	
	All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
All Randomized Patients, n =	358	90	89	88	91
ITT Patients, n =	297	77	72	71	77

(1) Baseline Characteristics and Demographics

Overall, 60% of ITT patients were male and 85% were Caucasian. Patient ages ranged from 30 to 71 years. Demographic data for All Randomized patients were similar to the ITT population. Demographic data were not provided for the non-randomized (screen failure) patients. There were slight imbalances between treatment groups as follows:

1) There were more female than male patients in the Mev/Lov 20 mg group compared to the other groups (Mev/Lov 20 mg: 49% male and 51% female; All ITT patients: 60% male and 40% female)
2) There was a higher percentage of non-Caucasians in the Mev/Lov 20 mg group compared to the other groups (Mev/Lov 20 mg: 69% Caucasian; All ITT patients: 85% Caucasian)

These imbalances are minor however, and are unlikely to have affected the overall results.

Baseline characteristics and demographics for the treatment groups are summarized as follows

Table 33: 146-010 Baseline Characteristics and Demographics

		Treatment			
	ITT	20 mg		60 mg	
	All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
ITT Patients, n =	297	77	72	71	77
Demographic Measure					
Gender, n (%)					
Male	177 (60)	51 (66)	35 (49)	42 (59)	49 (64)
Female	120 (40)	26 (34)	37 (51)	29 (41)	28 (36)
Age, years					
Mean	55.4	56.0	55.8	55.2	54.4
Median	57.0	57.0	58.0	58.0	54.0
min, max	30, 71	36, 70	32, 71	31, 70	30, 69
Age ≥ 65 years, n (%)*	63 (18)	13 (14)	17 (19)	18 (20)	15 (16)
Ethnicity, n(%)					
Caucasian	252 (85)	70 (91)	59 (69)	56 (79)	67 (87)
Black	15 (5)	3 (4)	2 (3)	8 (11)	2 (3)
Asian	6 (2)	2 (3)	4 (6)	0	0
Other	24 (8)	2 (3)	7 (10)	7 (10)	8 (10)
Risk Factors (RF)					
≥2 CAD RF or CHD, n (%)	143 (48)	46 (60)	30 (42)	29 (41)	38 (49)
<2 CAD RF, n (%)	154 (52)	31 (40)	42 (58)	42 (59)	39 (51)
Mean BMI, kg/M^2	28.2	27.7	29.0	27.9	28.2
Baseline Lipid Value					
Mean LDL-C, mg/dL	-	183.3	178.9	177.9	178.2
Mean HDL-C, mg/dL	-	46.5	46.2	45.9	45.6
Mean TC, mg/dL	-	263.1	259.5	257.2	257.4
Mean TG, mg/dL	-	166.4	171.9	166.5	169.1

*Data extracted from Randomized patients n (%)

(2) Patient Disposition

(a) Screening and Randomization

Of the 790 patients screened for the study, 432 (55% of total screened) were not randomized. The most common reason for failing to meet eligibility criteria for randomization was a failure to have an appropriate lipid level per inclusion criteria, which occurred in 205 screen failure patients (47% of all screen failures). Patients failing to meet eligibility criteria are summarized in the following table

Table 34: 146-010 Patients Failing to Meet Eligibility Criteria

Eligibility criteria not met, n = 432	n (%)
Failure to have appropriate lipid levels per inclusion criteria	205 (47)
Abnormal laboratory value	99 (23)
Withdrawal of consent	52 (12)
Lost to Follow-up	14 (3)
Other	62 (14)

(b) Dropouts

Of the 358 patients randomized to a treatment group, 288 patients completed the study and 70 patients (20%) discontinued treatment prior to study completion. Of the 70 patients who discontinued, 27 patients (8%) discontinued for an AE, and 25 patients (7%) withdrew consent. The percentage of patients discontinuing and the reasons for discontinuation were relatively evenly distributed across the treatment groups. It is therefore unlikely that dropouts significantly affected the overall study results. Patient discontinuations by treatment group are summarized in the following table

Table 35: 146-010 Patients Discontinued

		Treatment			
		20 mg		60 mg	
	All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =	358	90	89	88	91
Number of Withdrawals, n (%)	70 (20)	14 (16)	20 (22)	20 (23)	16 (18)
Reason for Dropout					
Adverse event, n (%)	27 (8)	4 (4)	7 (8)	10 (11)	6 (7)
Withdrew consent, n (%)	25 (7)	6 (7)	8 (9)	6 (7)	5 (5)
Protocol Violation, n (%)	7 (2)	2 (2)	3 (3)	1 (1)	1 (1)
Other, n (%)	11 (3)	2 (2)	2 (2)	3 (3)	4 (4)

(3) Concomitant Medications

Concomitant medications (conmeds) were medications that were either started prior to randomization and continued during study drug treatment, or were started during study drug treatment. Overall, 344 of the 358 randomized patients (96%) reported the use of any concomitant medication during the study. Patients reporting any concomitant medication use during the study, by treatment group, are summarized in the following table

Table 36: 146-010 Patients With Any Concomitant Medication Use

		Treatment			
		20 mg		60 mg	
	All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =	358	90	89	88	91
Any conmed use, n (%)	344 (96)	83 (92)	86 (97)	86 (98)	89 (98)

A large number of different medications were used during the study (over 450 different medications were reported), with the majority of these medications used by a small number of patients (used by $\leq$5 patients per medication, or by $\leq$1% of patients overall). The most commonly reported concomitant medications used during the study were acetylsalicylic acid (by 41% of patients overall) and multivitamins (31%). Concomitant medication use appeared to be relatively well balanced across the treatment groups, and it is unlikely that the concomitant medications used affected the overall study results. The most commonly used concomitant medications (used by $\geq$5% of patients overall) are summarized overall and by treatment group in the following table

Table 37: 149-010 Concomitant Medications, Most Common (≥5%) Overall and by Treatment Group

		Treatment			
		20 mg		60 mg	
	All	Lov/Mev	Mev/Lov	Lov/Mev	Mev/Lov
Randomized Patients, n =	358	90	89	88	91
Medication					
Acetylsalicylic Acid	147 (41)	38 (42)	32 (36)	43 (49)	34 (37)
Multivitamins	111 (31)	25 (28)	27 (30)	31 (35)	28 (31)
Ibuprofen	85 (24)	21 (23)	22 (25)	21 (24)	21 (23)
Tocopherol	82 (23)	22 (24)	18 (20)	22 (25)	20 (22)
Ascorbic Acid	64 (18)	15 (17)	14 (16)	22 (25)	13 (14)
Paracetamol	58 (16)	12 (13)	16 (18)	10 (11)	20 (22)
Calcium	51 (14)	9 (10)	17 (19)	15 (17)	10 (11)
Naproxen	31 (9)	11 (12)	5 (6)	5 (6)	11 (12)
Estrogen	29 (8)	4 (4)	5 (6)	12 (14)	8 (9)
Influenza Virus Vaccine	28 (8)	12 (13)	5 (6)	5 (6)	6 (7)
Loratadine	28 (7)	8 (9)	7 (8)	6 (7)	7 (8)
Pseudoephedrine	24 (6)	5 (6)	6 (7)	3 (3)	10 (11)
Hydrochlorothiazide	23 (6)	5 (6)	7 (8)	6 (7)	5 (5)
Amoxicillin	22 (6)	5 (6)	5 (6)	4 (5)	8 (9)
Diphenhydramine	20 (6)	4 (4)	6 (7)	5 (6)	5 (5)
Vicodin	18 (5)	6 (7)	4 (4)	7 (8)	1 (1)
Celecoxib	17 (5)	7 (8)	4 (4)	1 (1)	5 (5)
General Nutrients	17 (5)	5 (6)	5 (6)	5 (6)	2 (2)
Nyquil	17 (5)	3 (3)	6 (7)	3 (3)	5 (5)
Omeprazole	17 (5)	3 (3)	6 (7)	3 (3)	5 (5)

(4) Patient Compliance

Compliance was assessed by pill counts at each study visit. Patient compliance with study medications in the active treatment periods was ≥95% in all treatment groups.

(5) Efficacy Results

(a) Primary Efficacy Analysis: Mean Percent Change in LDL-C

The sponsor's primary efficacy variable was the percent change in LDL-C from baseline to endpoint. Efficacy comparisons were made between the lovastatin XL 20 mg and Mevacor 20 mg treatment groups, and between the lovastatin XL 60 mg and Mevacor 60 mg treatment groups. The sponsor's primary comparison was for the percent change in LDL-C from baseline to endpoint by treatment group for treatment Periods 1 and 2 combined. Results were also evaluated for Period 1 alone, Period 2 alone, and results for each treatment group by treatment group assignment. These results are summarized below, as follows

(i) Combined Groupings by Treatment Received (ITT Population)

The results for mean percent decreases in LDL-C from baseline to endpoint by treatment group are shown below when the results for Period 1 and Period 2 were pooled by treatment received. For example, patients receiving lovastatin XL 20 mg in Period 1 (lov/Mev 20 mg group) and patients receiving lovastatin XL 20 mg in Period 2 (Mev/lov

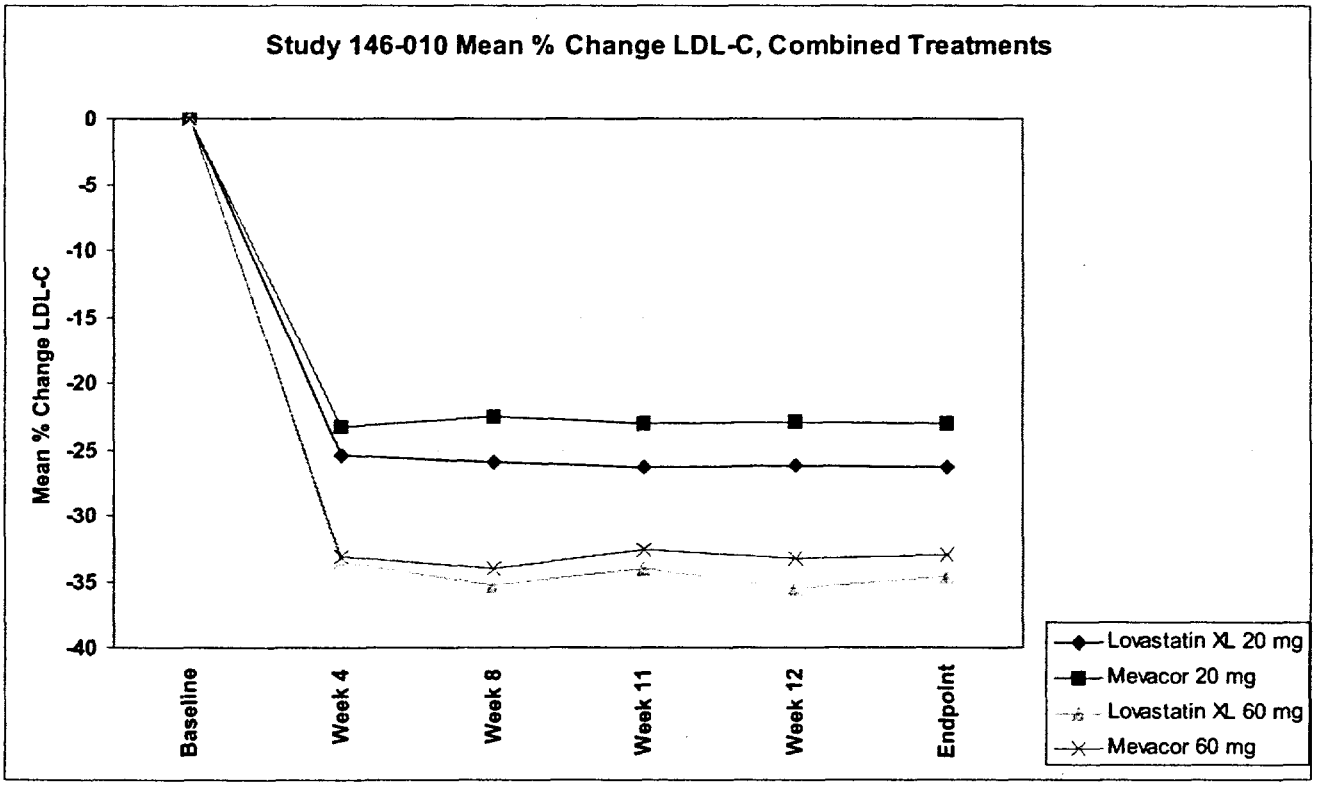
20 mg group) were combined to make the lovastatin XL 20 mg group. The results show that patients who received lovastatin XL 20 mg had a significantly greater decrease in LDL-C than the Mevacor 20 mg group (-26% and –23% respectively). The lovastatin XL 60 mg group and the Mevacor 60 mg groups had similar results for LDL-C (-35% and -33% respectively). The mean percent change in LDL-C from baseline to endpoint, by treatment group, are summarized in following table and graph

Table 38: 146-010 Mean Percent Change from Baseline in LDL-C (ITT Population) Pooled Results by Treatment Received

		Week				
Treatment	**Baseline**	**4**	**8**	**11**	**12**	**Endpoint**
Lovastatin XL 20 mg, n =	149	149	147	141	143	149
Mean	183.3 mg/dL	-25.4%	-25.9%	-26.3%	-26.2%	-26.3%*
Standard Deviation (SD)	35.5	13.7	12.9	11.9	12.7	11.1
Mevacor 20 mg, n =	146	146	147	143	147	149
Mean	179.1 mg/dL	-23.3%	-22.5%	-23.1%	-22.9%	-23.1%
SD	37.3	13.0	13.2	13.3	13.1	12.2
Lovastatin XL 60 mg, n =	146	146	147	144	143	148
Mean	177.6 mg/dL	-33.5%	-35.3%	-34.0%	-35.6%	-34.7%
SD	31.6	12.4	13.7	14.1	12.3	12.3
Mevacor 60 mg, n =	147	147	144	141	143	148
Mean	178.6 mg/dL	-33.2%	-34.1%	-32.7%	-33.3%	-33.0%
SD	33.4	11.6	11.8	13.2	11.8	11.6

*statistically significant vs Mevacor 20 mg

Figure 8: 146-010 Mean % Change LDL-C, Combined Treatments



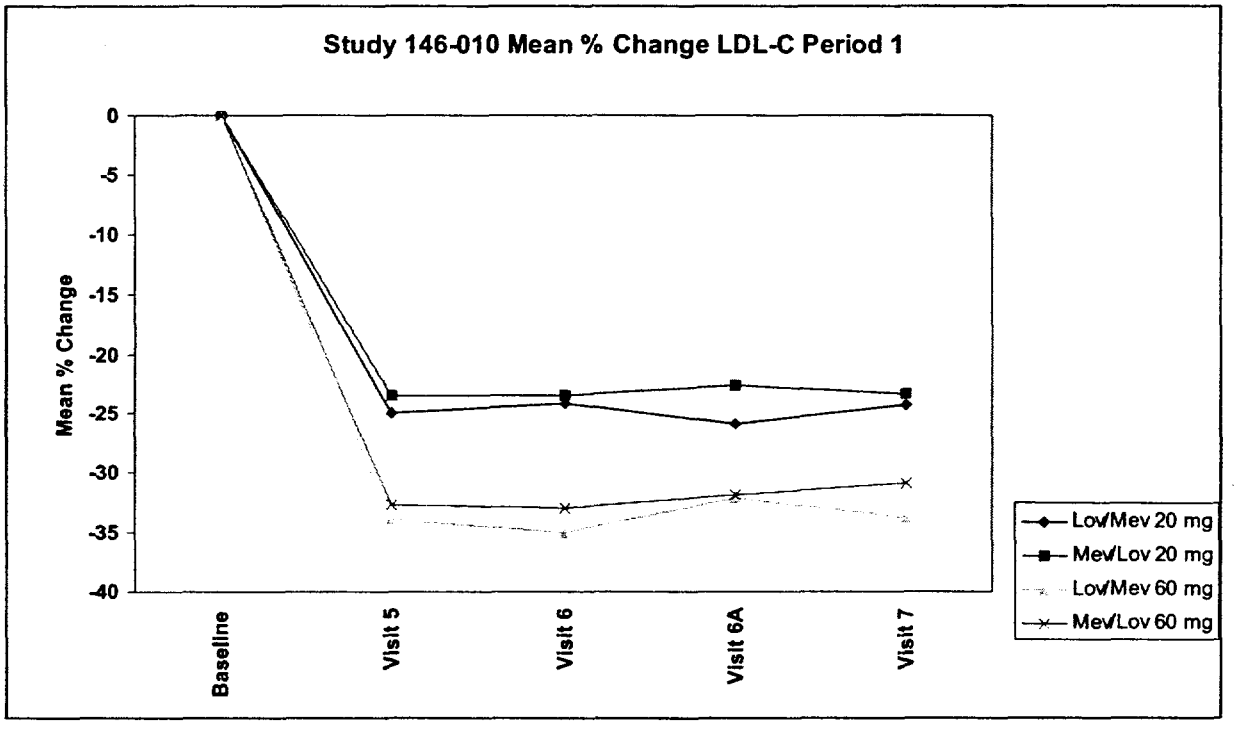
(ii) Period 1

The Period 1 (Visit 5 through Visit 7) show mean percent decreases in LDL-C for each treatment group. During Period 1, subjects would have received the treatment listed first in the treatment assignment, e.g., for the Lov/Mev 20 mg treatment group, subjects would have received lovastatin XL 20 mg. The results show a similar decrease in LDL-C from baseline to Visit 7 for the lovastatin XL and Mevacor 20 mg treatment groups (-24% and –23 % respectively). The lovastatin XL 60 mg group had about a 3% greater decrease in LDL-C than the Mevacor 60 mg group (-34% and –31% respectively). The mean percent change in LDL-C from baseline by visit for Period 1, by treatment group, are summarized in following table and graph

Table 39: 146-010 Mean Percent Change from Baseline in LDL-C (All Randomized Population) Period 1

		Visit			
Treatment	**Baseline**	**5**	**6**	**6A**	**7**
Lov/Mev 20 mg, n =	87	87	85	80	80
Mean	182.5 mg/dL	-24.9%	-24.1%	-25.9%	-24.3%
Standard Deviation (SD)	38.0	13.8	13.7	11.7	12.4
Mev/Lov 20 mg, n =	84	84	81	76	76
Mean	174.7 mg/dL	-23.5%	-23.5%	-22.7%	-23.3%
SD	32.9	11.8	14.4	12.3	13.4
Lov/Mev 60 mg, n =	85	85	83	77	76
Mean	175.4 mg/dL	-33.9%	-35.0%	-32.2%	-33.7%
SD	33.0	11.6	12.6	15.6	13.2
Mev/Lov 60 mg, n =	91	91	88	81	84
Mean	172.7 mg/dL	-32.7%	-33.0%	-31.8%	-30.9%
SD	34.5	10.8	11.1	13.2	10.4

Figure 9: 146-010 Mean % Change LDL-C Period 1



(iii) Period 2

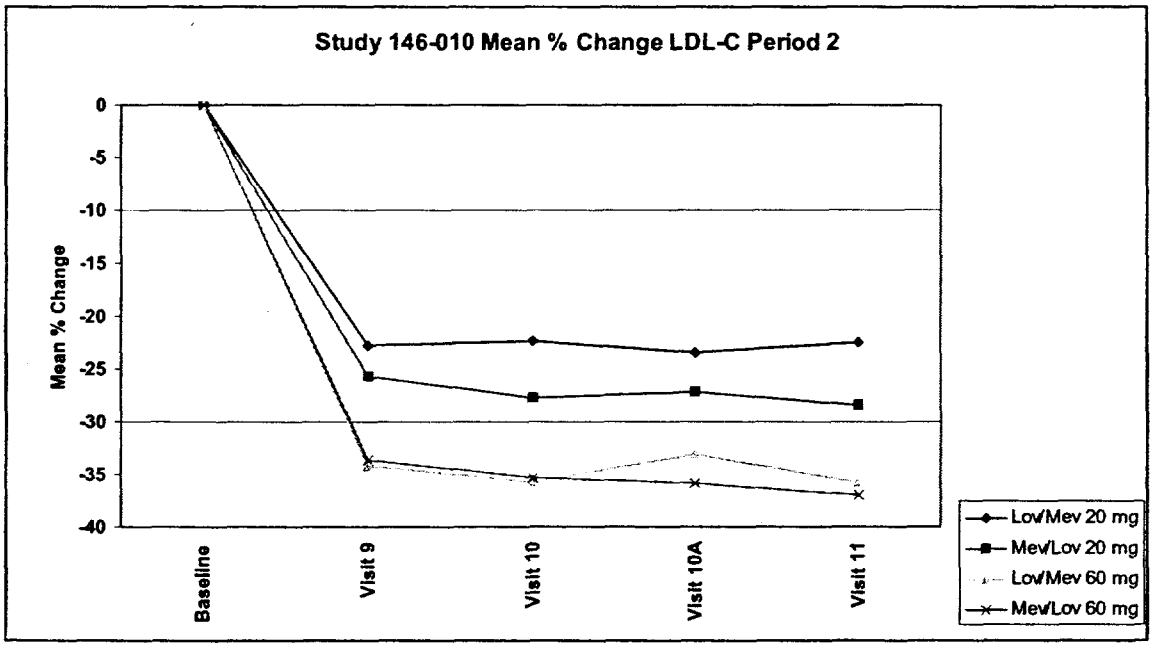
The Period 2 (Visit 9 through Visit 7) show mean percent decreases in LDL-C for each treatment group. During Period 2, subjects would have received the treatment listed ***second*** in the treatment assignment, e.g., for the Lov/Mev 20 mg treatment group, subjects would have received Mevacor 20 mg. The results show about a 5 percent greater decrease in LDL-C from baseline to Visit 11 for patients receiving lovastatin XL 20 mg than for the patients receiving Mevacor 20 mg (-23% and -29% respectively). The patients receiving lovastatin XL 60 mg and those receiving Mevacor 60 mg had similar decreases (-36% and –37% respectively). The mean percent change in LDL-C from baseline by visit for Period 2, by treatment group, are summarized in following table and graph

Table 40: 146-010 Mean Percent Change from Baseline in LDL-C (All Randomized Population) Period 2

		Visit			
Treatment	**Baseline**	**9**	**10**	**10A**	**11**
Lov/Mev 20*mg, n =	75	75	75	71	75
Mean	183.1 mg/dL	-22.9%	-22.4%	-23.5%	-22.5%
Standard Deviation (SD)	39.4	14.0	11.5	14.2	12.7
Mev/Lov 20 mg*, n =	72	72	70	67	68
Mean	185.7 mg/dL	-25.7%	-27.8%	-27.3%	-28.5%
SD	33.8	13.6	11.9	12.6	12.5
Lov/Mev 60 mg*, n =	70	70	68	68	67
Mean	183.0 mg/dL	-34.2%	-35.7%	-33.1%	-35.7%
SD	33.9	12.3	13.4	13.6	13.2
Mev/Lov 60 mg*, n =	75	75	76	73	73
Mean	178.7 mg/dL	-33.6%	-35.3%	-35.8%	-37.0%
SD	29.3	12.5	14.7	11.9	11.3

*Note: Results in Period 2 are for the drug listed second, e.g., for Lov/Mev 20 mg, patients received Mevacor 20 mg

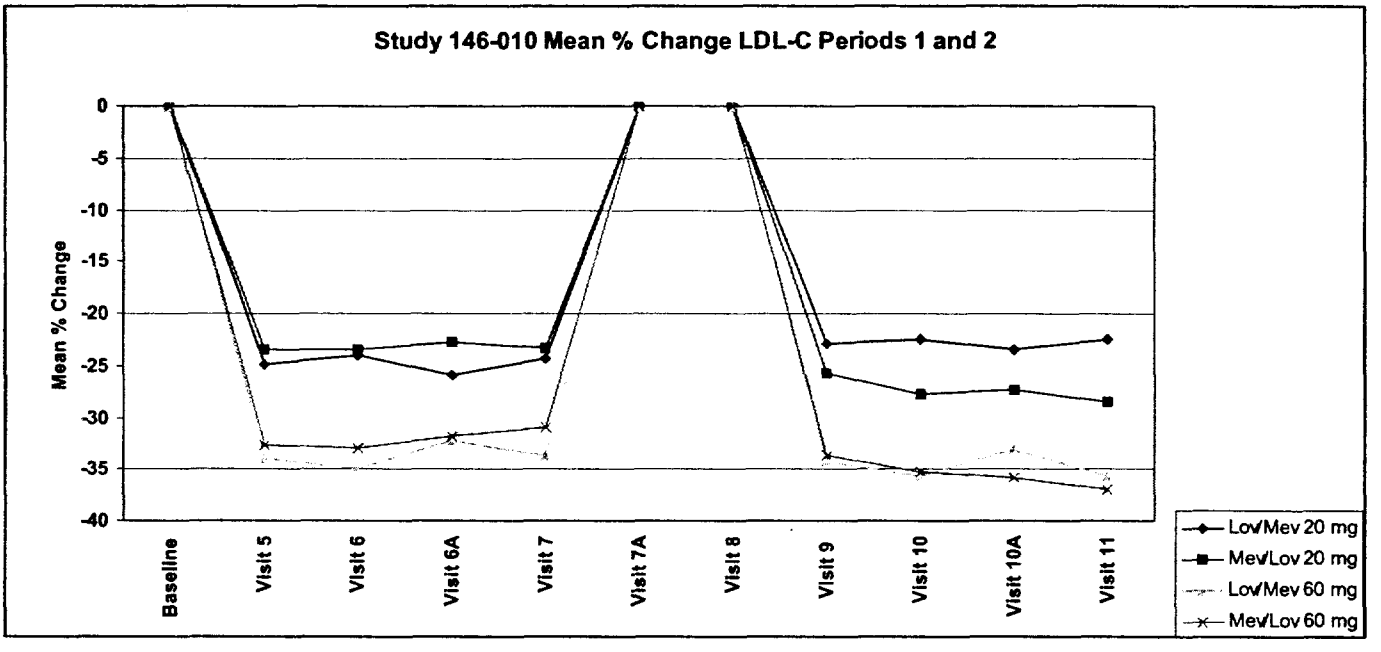
Figure 10: 146-010 Mean % Change LDL-C Period 2



Results are also depicted graphically for the crossover treatments, by treatment group assignment over the full duration of the trial [Assumption: mean percent change from baseline was assumed to be zero during the placebo washout period at Visits 7A and 8]. The results show that:

- The decreases in LDL-C occur primarily during the first 4 weeks of treatment;
- LDL-C returns to baseline after about 5 weeks of washout (not shown, please refer to Statistical Review);
- There was no evidence of carry-over from Period 1 to Period 2; and
- The responses for the 2 drugs are similar

Figure 11: 146-010 Mean % Change LDL-C by Treatment Group Assignment for Periods 1 and 2



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(b) Secondary Efficacy Analysis

Secondary Efficacy Variables were the percent change in HDL-C, TC, and TG from baseline to endpoint in the ITT population. Comparisons were also made between the lovastatin XL 20 mg and Mevacor 20 mg treatment groups, and between the lovastatin XL 60 mg and Mevacor 60 mg treatment groups.

(i) Mean Percent Change in HDL-C

Efficacy comparisons were made between the lovastatin XL 20 mg and Mevacor 20 mg treatment groups, and between the lovastatin XL 60 mg and Mevacor 60 mg treatment groups. The sponsor's primary comparison was for the percent change in HDL-C from baseline to endpoint by treatment group for treatment Periods 1 and 2 combined. Results were also evaluated for Period 1 alone, Period 2 alone, and results for each treatment group by treatment group assignment. These results are summarized below, as follows

Combined Groupings by Treatment Received (ITT Population)

The results for mean percent increases in HDL-C from baseline to endpoint by treatment group are shown below when the results for Period 1 and Period 2 were pooled by treatment received. The results show that patients who received lovastatin XL 20 mg and Mevacor 20 mg had similar results for HDL-C (+4% in both groups). Similar results were also shown for both the lovastatin XL 60 mg and Mevacor 60 mg treatment groups (+5% in both groups). The mean percent change in HDL-C from baseline to endpoint, by treatment group, are summarized in following table and graph

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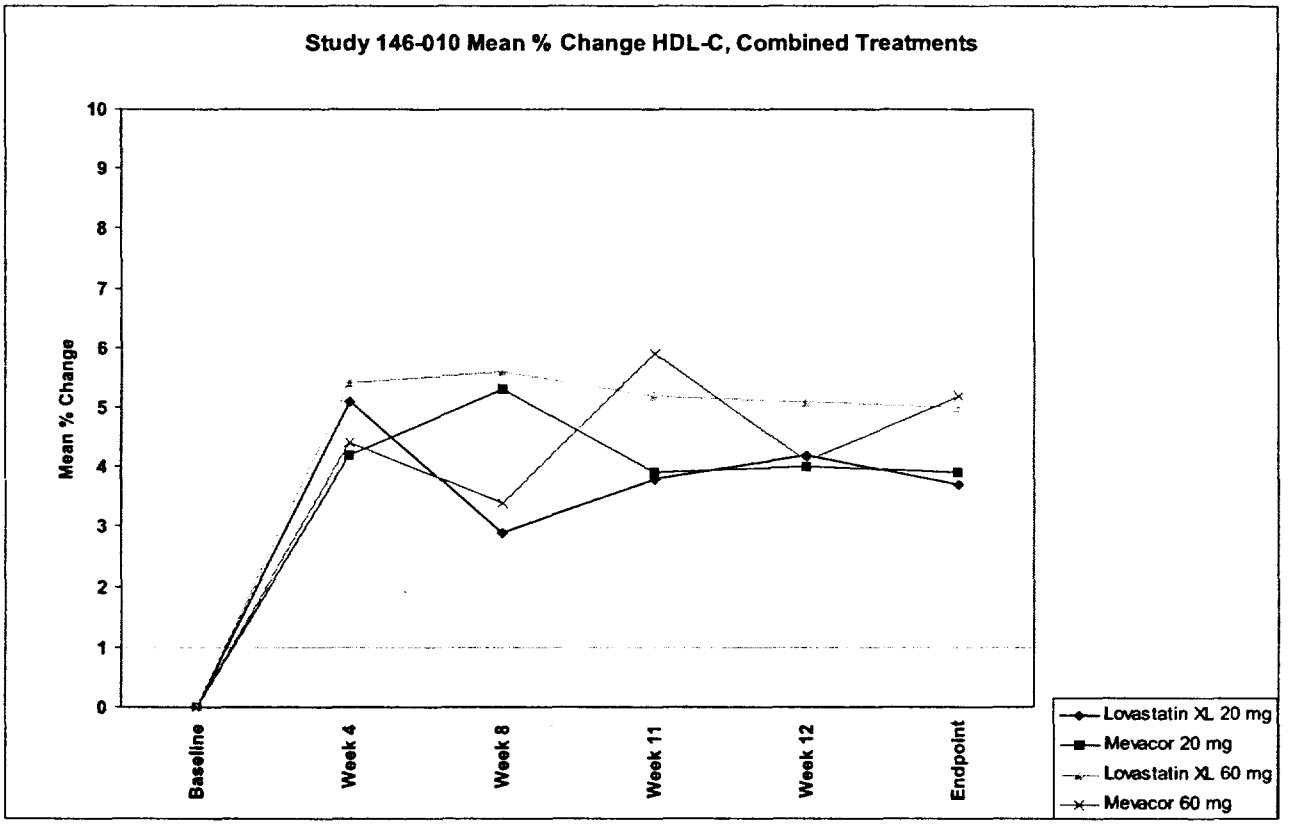
Table 41: 146-010 Mean Percent Change from Baseline in HDL-C (ITT Population) Combined Treatments

		Week				
Treatment	**Baseline**	**4**	**8**	**11**	**12**	**Endpoint**
Lovastatin XL 20 mg, n =	149	149	147	142	144	149
Mean	46.5 mg/dL	5.1%	2.9%	3.8%	4.2%	3.7%
Standard Deviation (SD)	10.4	11.8	10.8	12.4	12.5	11.2
Mevacor 20 mg, n =	146	146	147	144	147	149
Mean	46.1 mg/dL	4.2%	5.3%	3.9%	4.0%	3.9%
SD	11.0	13.4	12.8	13.3	12.7	12.0
Lovastatin XL 60 mg, n =	147	147	147	144	143	148
Mean	46.0 mg/dL	5.4%	5.6%	5.2%	5.1%	5.0%
SD	12.3	12.2	15.0	13.8	13.3	12.1
Mevacor 60 mg, n =	147	147	144	141	142	148
Mean	45.6 mg/dL	4.4%	3.4%	5.9%	4.1%	5.2%
SD	12.2	12.0	13.5	12.6	12.9	11.5

Figure 12: 146-010 Mean % Change HDL-C by Treatment Received



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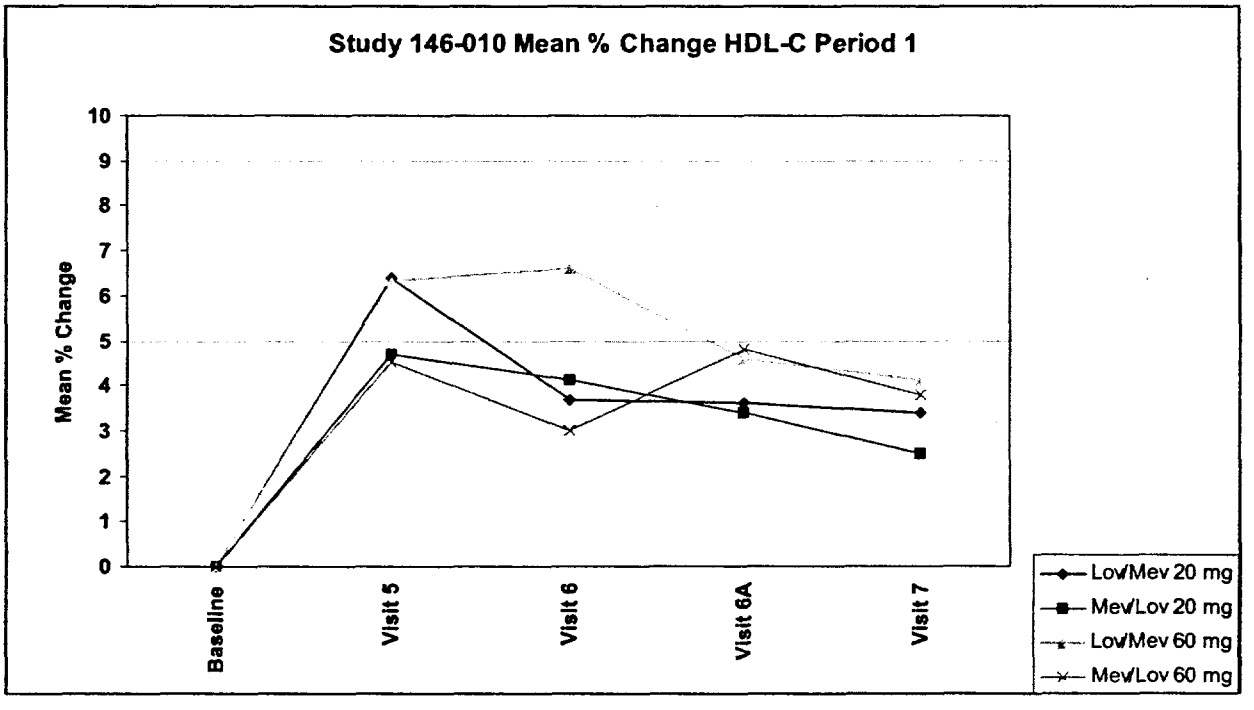
Period 1

The Period 1 (Visit 5 through Visit 7) show mean percent increases in HDL-C for each treatment group. The results show a similar increase in HDL-C from baseline to Visit 7 for the lovastatin XL and Mevacor 20 mg treatment groups (+4% and +3% respectively). There were also similar results for the lovastatin XL 60 mg and Mevacor 60 mg treatment groups (+4% for both groups). The mean percent change in HDL-C from baseline by visit for Period 1, by treatment group, are summarized in following table and graph

Table 42: 146-010 Mean Percent Change from Baseline in HDL-C (All Randomized Population) Period 1

	Visit				
Treatment	**Baseline**	**5**	**6**	**6A**	**7**
Lov/Mev 20 mg, n =	87	87	85	81	81
Mean	44.5 mg/dL	6.4%	3.7%	3.6%	3.4%
Standard Deviation (SD)	9.9	12.6	12.4	11.8	12.8
Mev/Lov 20 mg, n =	84	84	81	76	76
Mean	48.2 mg/dL	4.7%	4.1%	3.4%	2.5%
SD	10.9	14.1	13.6	12.9	12.9
Lov/Mev 60 mg, n =	85	85	83	77	76
Mean	46.1 mg/dL	6.3%	6.6%	4.6%	4.1%
SD	12.6	10.9	11.2	14.3	11.7
Mev/Lov 60 mg, n =	91	91	88	81	84
Mean	45.6 mg/dL	4.5%	3.0%	4.8%	3.8%
SD	12.3	11.8	13.0	14.3	13.6

Figure 13: 146-010 Mean % Change HDL-C Period 1



Period 2

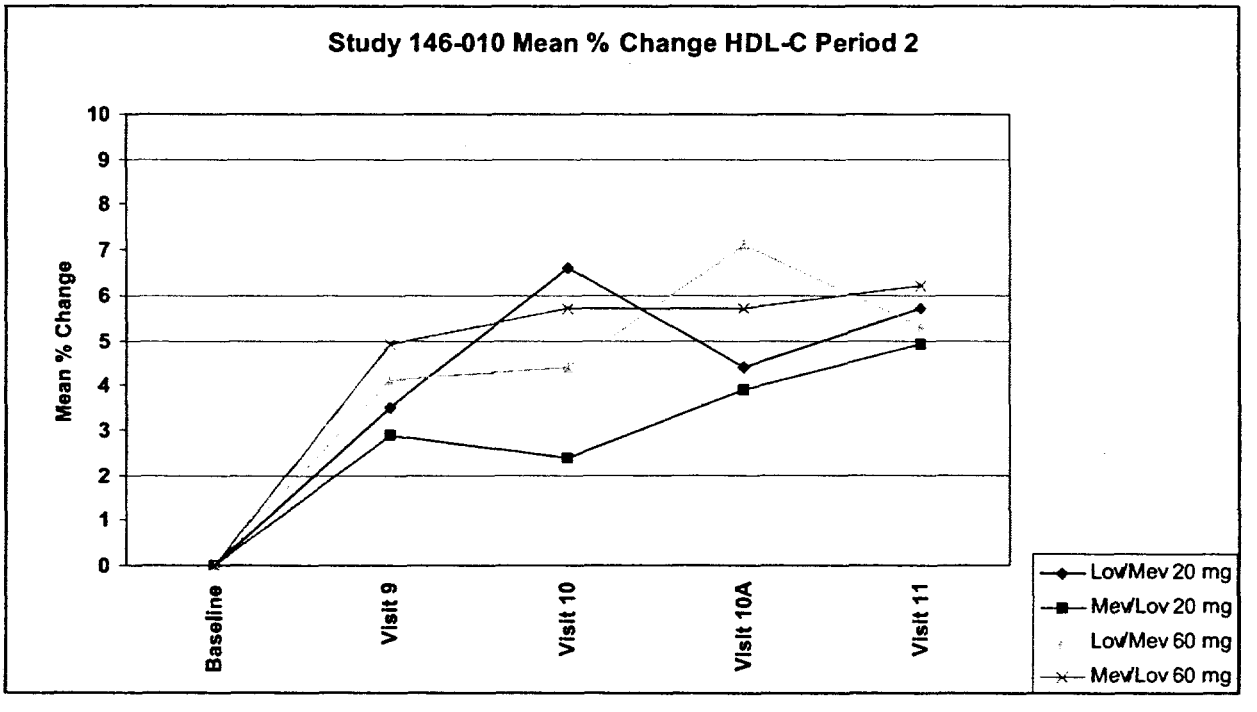
The Period 2 (Visit 9 through Visit 11) results show that the mean percent increases in HDL-C are similar when compared between the lovastatin XL 20 mg and the Mevacor 20 mg treatment groups (+5% and +6% respectively), and between the lovastatin XL 60 mg and the Mevacor 60 mg treatment groups (+6% and +5% respectively). The mean percent change in HDL-C from baseline by visit for Period 2, by treatment group, are summarized in following table and graph

Table 43: 146-010 Mean Percent Change from Baseline in HDL-C (All Randomized Population) Period 2

		Visit			
Treatment	**Baseline**	**9**	**10**	**10A**	**11**
Lov/Mev 20 mg*, n =	75	75	75	72	75
Mean	43.4 mg/dL	3.5%	6.6%	4.4%	5.7%
Standard Deviation (SD)	10.3	12.2	11.6	13.8	12.7
Mev/Lov 20 mg*, n =	72	72	70	67	68
Mean	48.6 mg/dL	2.9%	2.4%	3.9%	4.9%
SD	10.1	10.2	10.5	12.7	12.2
Lov/Mev 60 mg*, n =	70	70	68	68	66
Mean	45.3 mg/dL	4.1%	4.4%	7.1%	5.3%
SD	12.3	12.2	14.1	11.0	12.5
Mev/Lov 60 mg*, n =	76	76	76	73	73
Mean	46.0 mg/dL	4.9%	5.7%	5.7%	6.2%
SD	12.4	13.3	18.1	13.1	14.6

*Note: Results in Period 2 are for the drug listed second, e.g., for Lov/Mev 20 mg, patients received Mevacor 20 mg

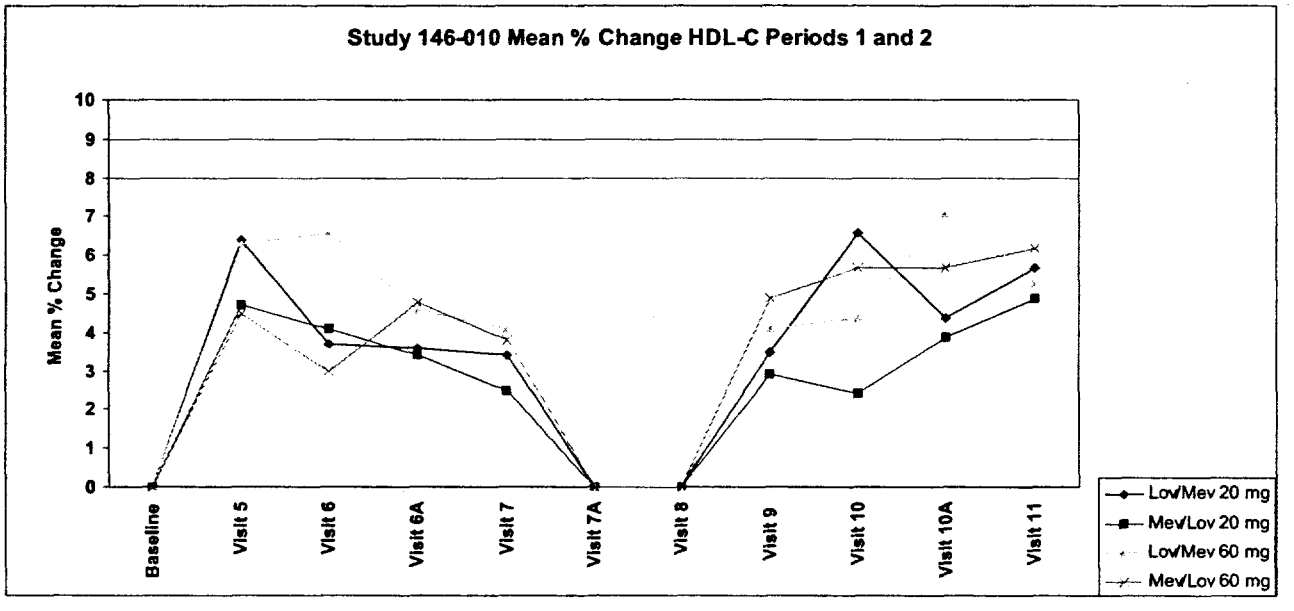
Figure 14: 146-010 Mean % Change HDL-C Period 2



Results are also depicted graphically for the crossover treatments, by treatment group assignment over the full duration of the trial [Assumption: mean percent change from baseline was assumed to be zero during the placebo washout period at Visits 7A and 8]. The results show that:

- The increases in HDL-C occur primarily during the first 4 weeks of treatment;
- There was no evidence of carry-over from Period 1 to Period 2; and
- The responses for the 2 drugs are similar

Figure 15: 146-010 Mean % Change HDL-C by Treatment Group Assignment for Periods 1and 2



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(ii) Mean Percent Change in TC

Efficacy comparisons were made between the lovastatin XL 20 mg and Mevacor 20 mg treatment groups, and between the lovastatin XL 60 mg and Mevacor 60 mg treatment groups. The sponsor's primary comparison was for the percent change in TC from baseline to endpoint by treatment group for treatment Periods 1 and 2 combined. Results were also evaluated for Period 1 alone, Period 2 alone, and results for each treatment group by treatment group assignment. These results are summarized below, as follows

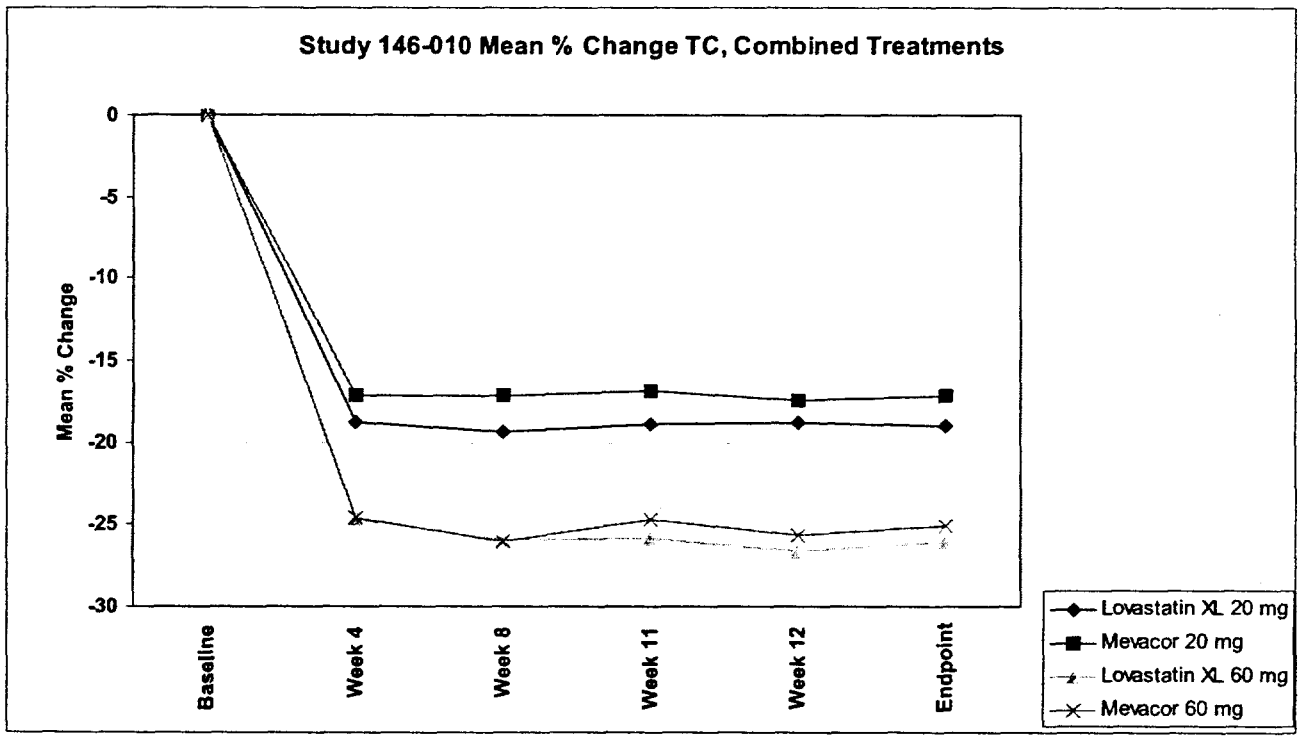
Combined Groupings by Treatment Received (ITT Population)

The results for mean percent decreases in TC from baseline to endpoint by treatment group are shown below when the results for Period 1 and Period 2 were pooled by treatment received. The results show that patients who received lovastatin XL 20 mg and Mevacor 20 mg had similar results for TC (-19% and –17% respectively). Similar results were also shown for both the lovastatin XL 60 mg and Mevacor 60 mg treatment groups (-26% and –25% respectively). The mean percent change in TC from baseline to endpoint, by treatment group, are summarized in following table and graph

Table 44: 146-010 Mean Percent Change from Baseline in TC (ITT Population) Combined Treatments

		Week				
Treatment	**Baseline**	**4**	**8**	**11**	**12**	**Endpoint**
Lovastatin XL 20 mg, n =	149	149	147	142	144	149
Mean	263.1 mg/dL	-18.8%	-19.4%	-18.9%	-18.8%	-19.0%
Standard Deviation (SD)	38.9	10.3	10.2	8.8	10.8	9.0
Mevacor 20 mg, n =	146	146	147	144	147	149
Mean	259.8 mg/dL	-17.1%	-17.1%	-16.8%	-17.4%	-17.1%
SD	40.3	9.8	10.0	10.3	10.1	9.4
Lovastatin XL 60 mg, n =	147	147	147	144	143	148
Mean	257.0 mg/dL	-24.7%	-25.9%	-25.8%	-26.6%	-26.0%
SD	37.0	9.2	11.4	11.0	9.6	9.5
Mevacor 60 mg, n =	147	147	144	141	143	148
Mean	257.7 mg/dL	-24.6%	-26.0%	-24.7%	-25.6%	-25.1%
SD	38.6	9.1	10.1	10.2	9.2	9.0

Figure 16: 146-010 Mean Percent Change from Baseline in TC Combined Treatments



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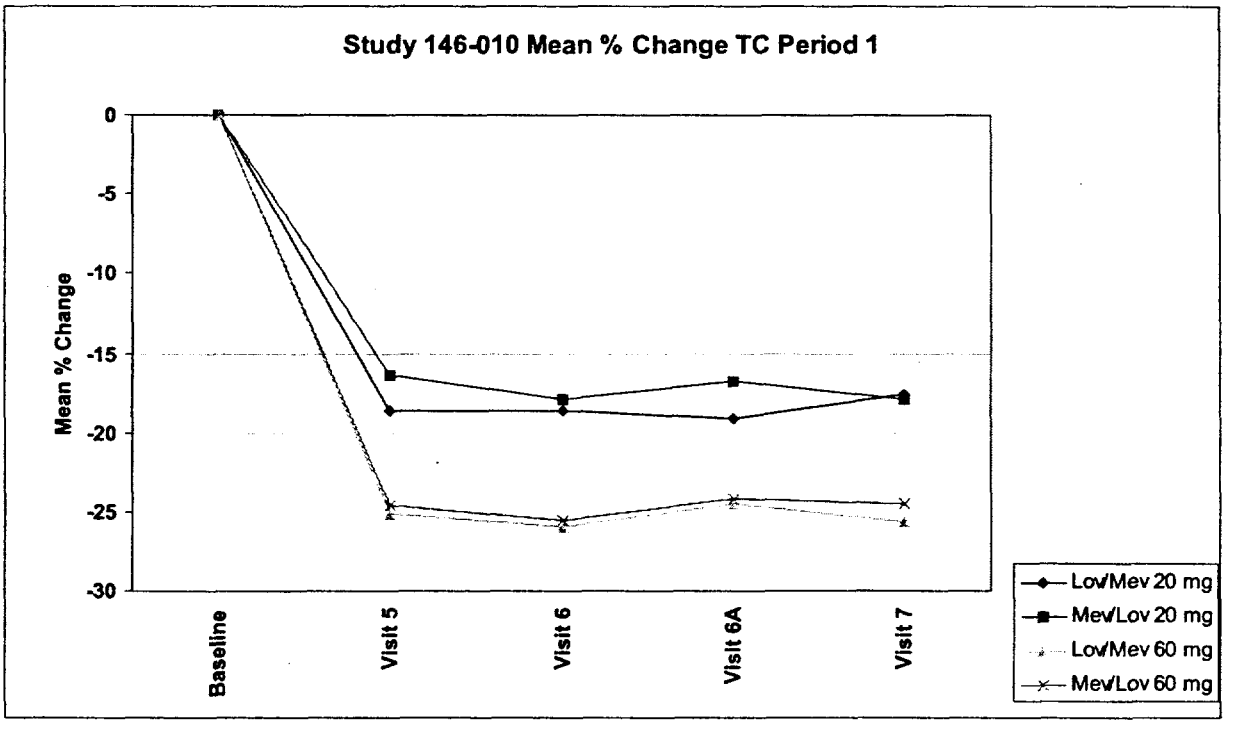
Period 1

The Period 1 (Visit 5 through Visit 7) show similar mean percent decreases in TC from baseline to Visit 7 for the lovastatin XL 20 mg and Mevacor 20 mg treatment groups (-17% and -18% respectively). There were also similar results for the lovastatin XL 60 mg and Mevacor 60 mg treatment groups (-26% and –25% respectively). The mean percent change in TC from baseline by visit for Period 1, by treatment group, are summarized in following table and graph

Table 45: 146-010 Mean Percent Change from Baseline in TC (All Randomized Population) Period 1

		Visit			
Treatment	**Baseline**	**5**	**6**	**6A**	**7**
Lov/Mev 20 mg, n =	87	87	85	81	81
Mean	260.9 mg/dL	-18.6%	-18.6%	-19.1%	-17.6%
Standard Deviation (SD)	41.5	9.6	10.9	9.1	11.2
Mev/Lov 20 mg, n =	84	84	81	76	76
Mean	256.7 mg/dL	-16.4%	-17.9%	-16.8%	-17.9%
SD	36.0	10.2	11.0	9.6	10.4
Lov/Mev 60 mg, n =	85	85	83	77	76
Mean	253.8 mg/dL	-25.1%	-25.9%	-24.5%	-25.6%
SD	39.8	8.5	9.5	12.5	10.4
Mev/Lov 60 mg, n =	91	91	88	81	84
Mean	254.7 mg/dL	-24.6%	-25.5%	-24.2%	-24.5%
SD	39.3	8.9	8.7	9.8	8.6

Figure 17: 146-010 Mean Percent Change TC Period 1



Period 2

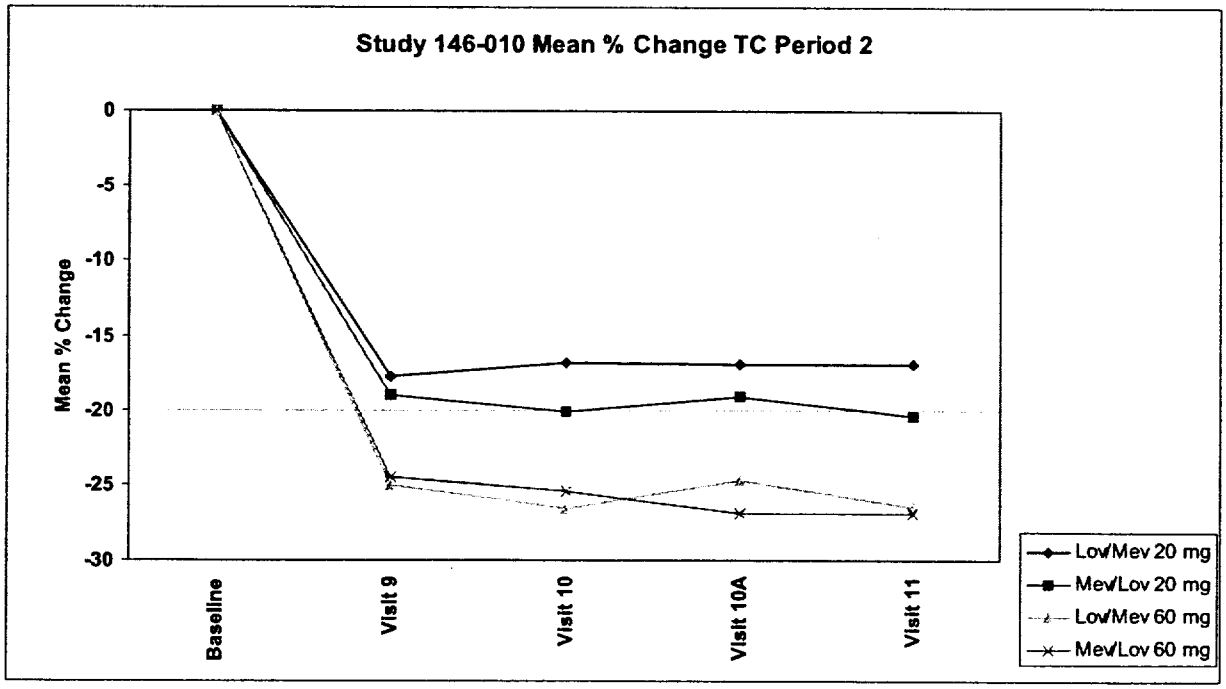
The Period 2 (Visit 9 through Visit 11) show mean percent decreases in TC for each treatment group. The results show about a 4 percent greater decrease in TC from baseline to Visit 11 for the patients receiving lovastatin XL 20 mg than for those receiving Mevacor 20 mg (-21% and -17% respectively). The patients receiving lovastatin XL 60 mg and those receiving Mevacor 60 mg had similar decreases (-27% for both groups). The mean percent change in TC from baseline by visit for Period 2, by treatment group, are summarized in following table and graph

Table 46: 146-010 Mean Percent Change from Baseline in TC (All Randomized Population) Period 2

	Visit				
Treatment	**Baseline**	**9**	**10**	**10A**	**11**
Lov/Mev 20 mg*, n =	75	75	75	72	75
Mean	261.7	-17.7	-16.8	-16.9	-16.9
Standard Deviation (SD)	42.7	9.2	8.7	11.0	9.7
Mev/Lov 20 mg*, n =	72	72	70	67	68
Mean	266.8	-19.0	-20.1	-19.1	-20.5
SD	36.5	11.2	9.8	9.2	10.1
Lov/Mev 60 mg*, n =	70	70	68	68	67
Mean	259.8	-25.0	-26.6	-24.7	-26.5
SD	39.1	9.1	12.1	10.4	10.1
Mev/Lov 60 mg*, n =	76	76	76	73	73
Mean	258.7	-24.5	-25.4	-26.9	-26.9
SD	33.9	9.5	12.9	9.0	8.9

*Note: Results in Period 2 are for the drug listed second, e.g., for Lov/Mev 20 mg, patients received Mevacor 20 mg

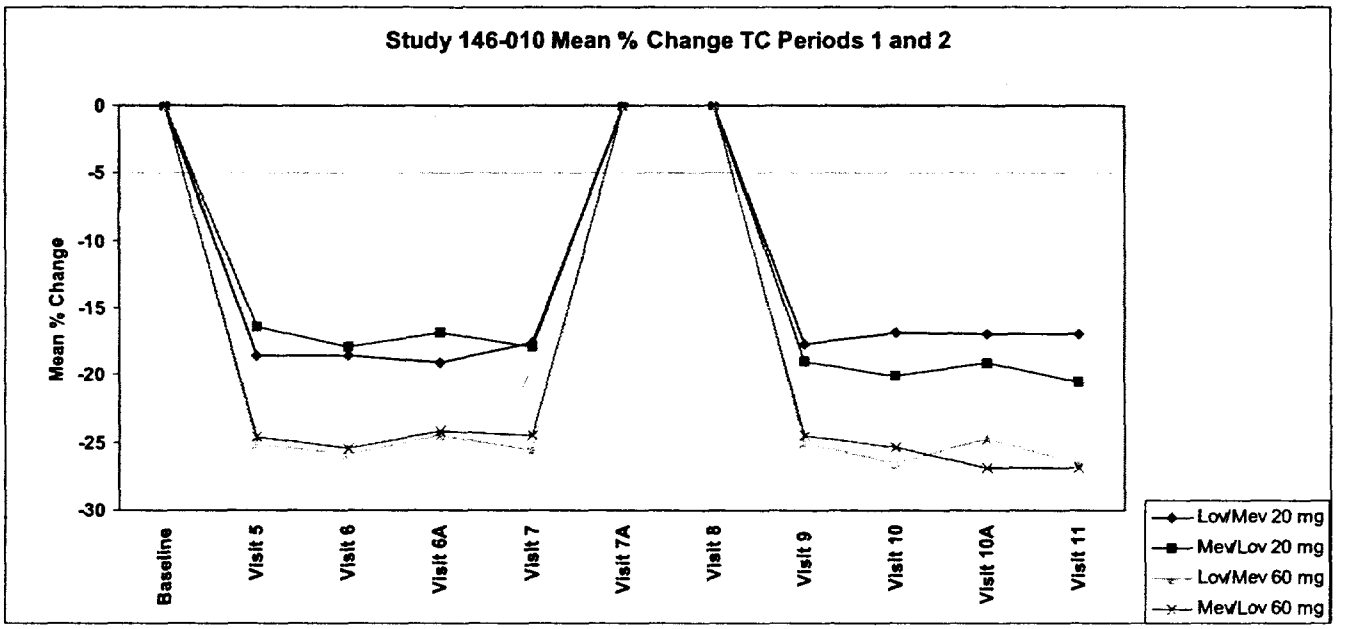
Figure 18: 146-010 Mean Percent Change TC Period 2



Results are also depicted graphically for the crossover treatments, by treatment group assignment over the full duration of the trial [Assumption: mean percent change from baseline was assumed to be zero during the placebo washout period at Visits 7A and 8]. The results show that:

- The decreases in TC occur primarily during the first 4 weeks of treatment;
- There was no evidence of carry-over from Period 1 to Period 2; and
- The responses for the 2 drugs are similar

Figure 19: 146-010 Mean % Change TC Periods 1 and 2 by Treatment Group Assignment



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(iii) Mean Percent Change in TG

Efficacy comparisons were made between the lovastatin XL 20 mg and Mevacor 20 mg treatment groups, and between the lovastatin XL 60 mg and Mevacor 60 mg treatment groups. The sponsor's primary comparison was for the mean percent change in TG from baseline to endpoint by treatment group for treatment Periods 1 and 2 combined . Results were also evaluated for Period 1 alone, Period 2 alone, and results for each treatment group by treatment group assignment. These results are summarized below, as follows

Combined Groupings by Treatment Received (ITT Population)

The results for mean percent decreases in TG from baseline to endpoint by treatment group are shown below when the results for Period 1 and Period 2 were pooled by treatment received. The results show that patients who received lovastatin XL 20 mg had a 3% greater decrease in TG at endpoint than patients who received Mevacor 20 (-8% and -11% respectively). Similar results were shown between the lovastatin XL 60 mg and Mevacor 60 mg treatment groups at endpoint (-18% and -19% respectively). It should be noted, however, that the results for TG, as expected, were variable in all treatment groups from Visit to Visit. The mean percent change in TG from baseline to endpoint, by treatment group, are summarized in following table and graph

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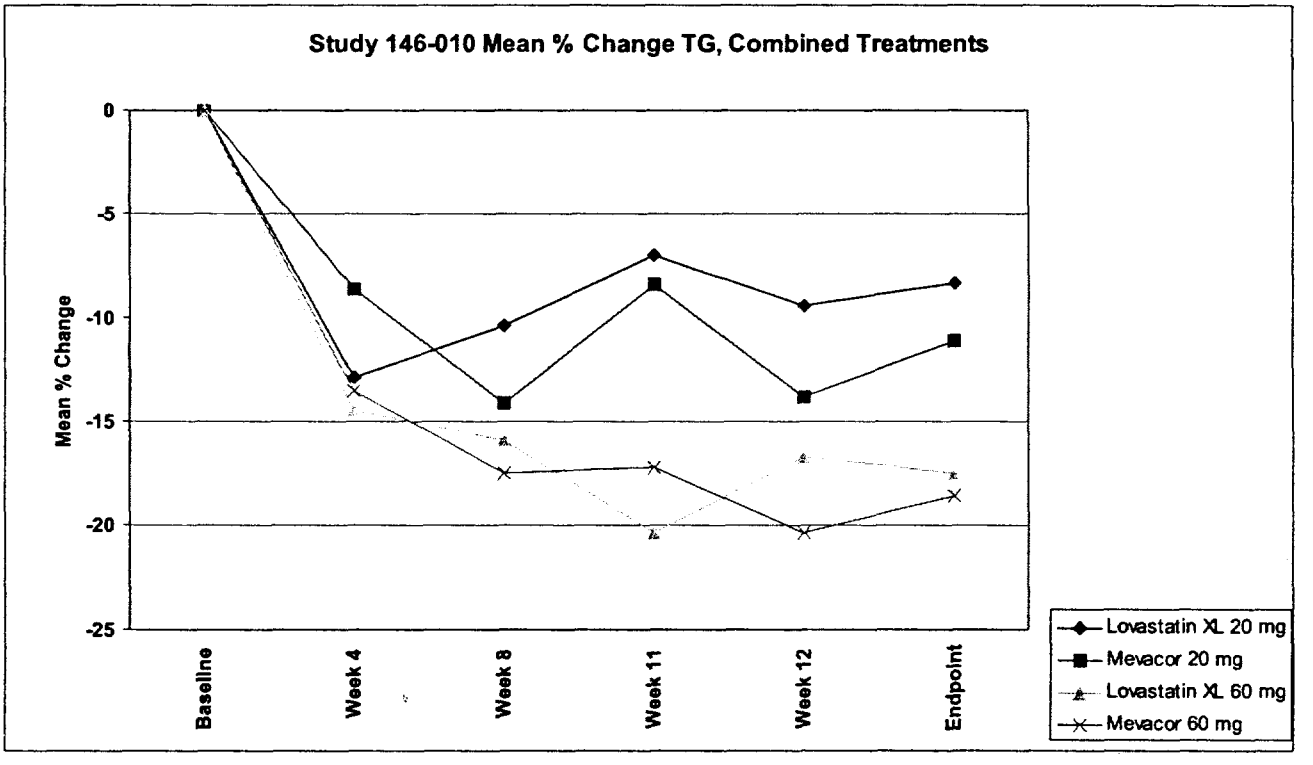
Table 47: 146-010 Mean Percent Change from Baseline in TG (ITT Population) Combined Treatments

		Week				
Treatment	**Baseline**	**4**	**8**	**11**	**12**	**Endpoint**
Lovastatin XL 20 mg, n =	149	149	147	142	144	149
Mean	166.4 mg/dL	-12.9%	-10.4%	-7.0%	-9.4%	-8.3%
Standard Deviation (SD)	75.8	25.2	28.0	30.1	30.6	26.2
Mevacor 20 mg, n =	146	146	147	144	147	149
Mean	173.1 mg/dL	-8.6%	-14.1%	-8.4%	-13.8%	-11.1%
SD	78.7	34.3	27.9	27.8	25.2	22.4
Lovastatin XL 60 mg, n =	147	147	147	144	143	148
Mean	165.6 mg/dL	-14.5%	-15.9%	-20.4%	-16.7%	-17.5%
SD	66.8	31.4	29.4	25.6	37.2	26.3
Mevacor 60 mg, n =	147	147	144	141	143	148
Mean	168.7 mg/dL	-13.5%	-17.5%	-17.2%	-20.4%	-18.6%
SD	82.3	33.5	29.7	28.6	29.5	27.7

Figure 20: 146-010 Mean % Change TG by Pooled Treatment Groups



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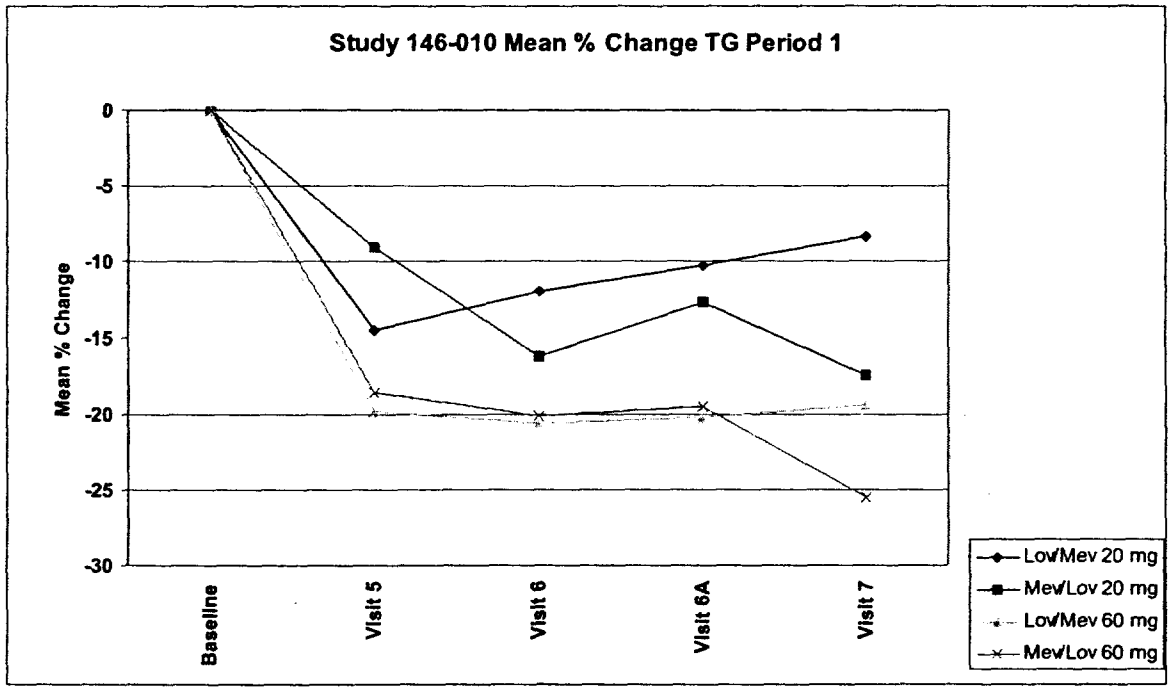
Period 1

The Period 1 (Visit 5 through Visit 7) show mean percent decreases in TG for each treatment group. The results show about a 10 percent greater decrease in mean TG from baseline to Visit 7 for the lovastatin XL 20 mg treatment than the Mevacor 20 mg treatment (-8% and -18% respectively). For the 60 mg groups there was about a 7% greater decrease in mean TG from baseline in the Mevacor 60 mg group than in the lovastatin XL 60 mg group (-26% and –19% respectively). The results from Visit to Visit were quite variable in all treatment groups, which may explain the differences in TG lowering between the Mevacor and lovastatin XL groups at each dosage level. The mean percent change in TG from baseline by visit for Period 1, by treatment group, are summarized in following table and graph

Table 48: 146-010 Mean Percent Change from Baseline in TG (All Randomized Population) Period 1

		Visit			
Treatment	**Baseline**	**5**	**6**	**6A**	**7**
Lov/Mev 20 mg, n =	87	87	85	81	81
Mean	167.9 mg/dL	-14.5%	-12.0%	-10.3%	-8.3%
Standard Deviation (SD)	74.0	22.9	23.8	28.3	37.1
Mev/Lov 20 mg, n =	84	84	81	76	76
Mean	171.5 mg/dL	-9.1%	-16.3%	-12.7%	-17.5%
SD	73.8	39.6	31.6	22.8	23.4
Lov/Mev 60 mg, n =	85	85	83	77	76
Mean	161.3 mg/dL	-19.8%	-20.6%	-20.2%	-19.4%
SD	57.1	24.3	22.3	26.5	30.2
Mev/Lov 60 mg, n =	91	91	88	81	84
Mean	183.5 mg/dL	-18.6%	-20.1%	-19.5%	-25.5%
SD	87.5	25.8	26.5	25.9	24.0

Figure 21: 146-010 Mean Percent Change TG Period 1



Period 2

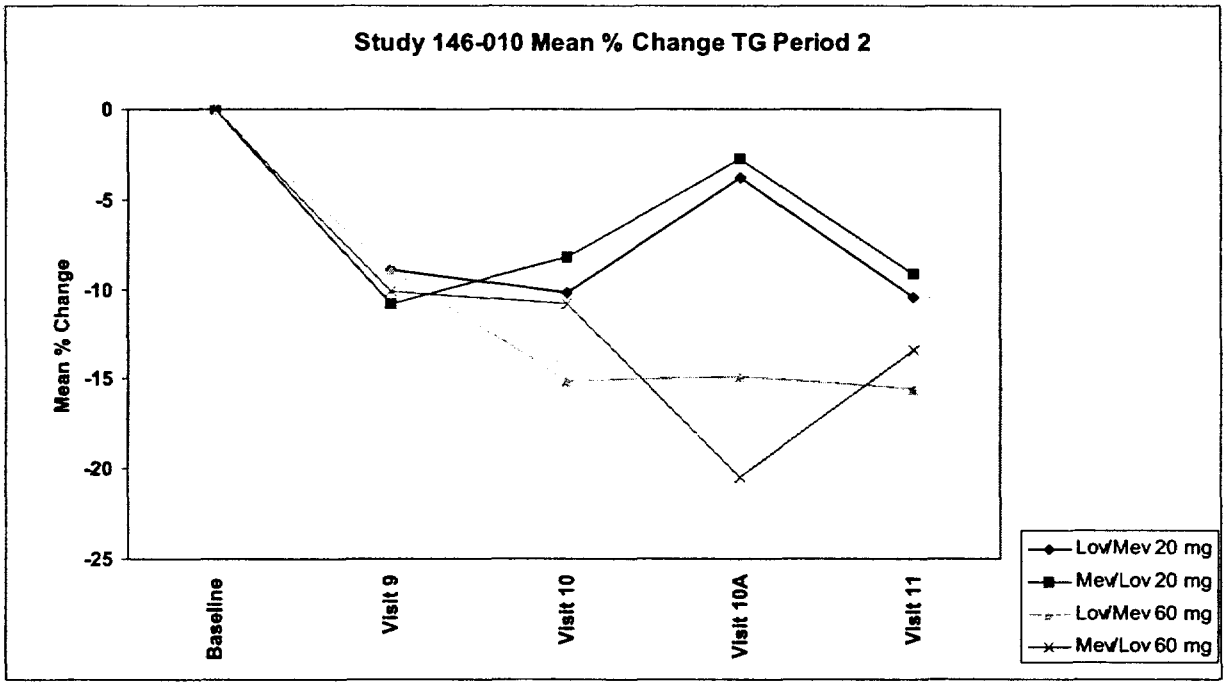
The Period 2 (Visit 9 through Visit 11) show mean percent decreases in TG for each treatment group. The results show a similar mean percent decrease in TG from baseline to Visit 7 for the patients receiving lovastatin XL 20 mg and those receiving Mevacor 20 mg (-9% and -11% respectively). For the 60 mg groups there was about a 3% greater decrease in mean TG from baseline for the patients receiving Mevacor 60 mg than for those receiving lovastatin XL 60 mg (-16% and -13% respectively). As previously noted, the results from Visit to Visit were quite variable in all treatment groups, which may explain the differences in TG lowering between the Mevacor and lovastatin XL groups in each dosage level. The mean percent change in TG from baseline by visit for Period 2, by treatment group, are summarized in following table and graph

Table 49: 146-010 Mean Percent Change from Baseline in TG (All Randomized Population) Period 2

		Visit			
Treatment	**Baseline**	**9**	**10**	**10A**	**11**
Lov/Mev 20 mg*, n =	75	75	75	72	75
Mean	173.6 mg/dL	-8.9%	-10.2%	-3.8%	-10.5%
Standard Deviation (SD)	79.9	26.4	27.1	31.9	26.5
Mev/Lov 20 mg*, n =	72	72	70	67	68
Mean	164.1 mg/dL	-10.8%	-8.2%	-2.8%	-9.2%
SD	77.6	27.6	32.5	33.2	29.7
Lov/Mev 60 mg*, n =	70	70	68	68	67
Mean	157.9 mg/dL	-8.9%	-15.1%	-14.9%	-15.6%
SD	73.8	39.1	31.9	31.2	34.2
Mev/Lov 60 mg*, n =	76	76	76	73	73
Mean	167.2 mg/dL	-10.1%	-10.8%	-20.5%	-13.4%
SD	72.7	36.1	34.4	24.3	42.0

*Note: Results in Period 2 are for the drug listed second, e.g., for Lov/Mev 20 mg, patients received Mevacor 20 mg

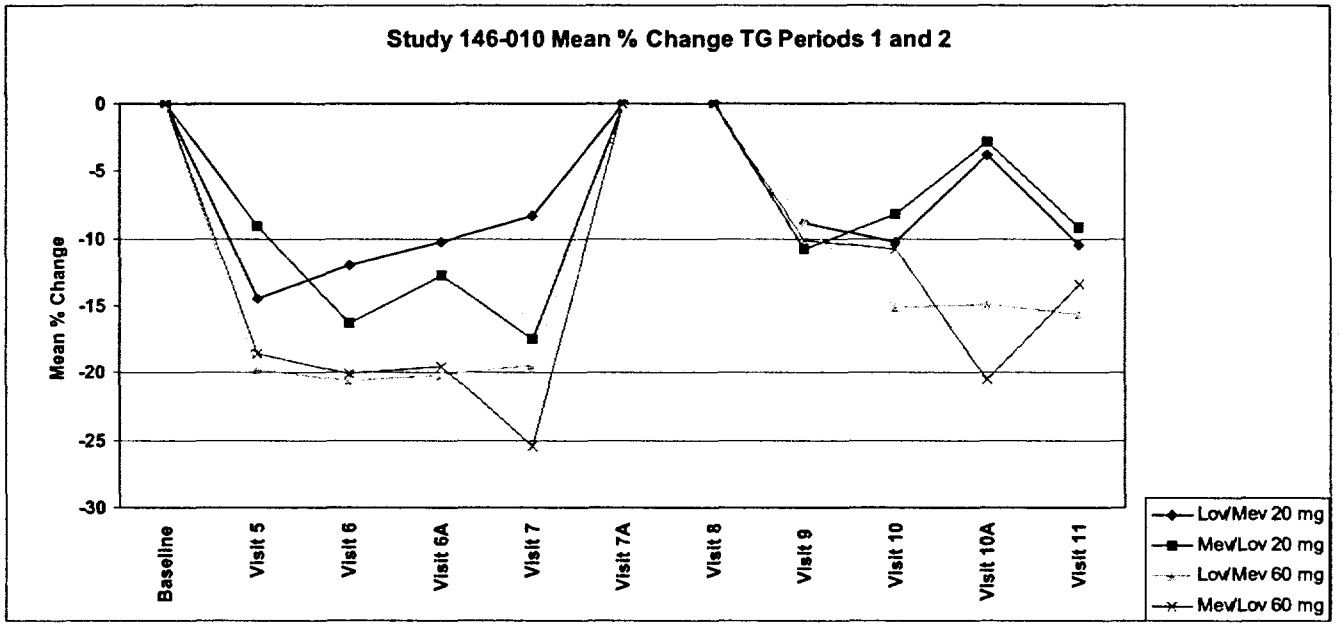
Figure 22: 146-010 Mean % Change TG Period 2



Results are also depicted graphically for the crossover treatments, by treatment group assignment over the full duration of the trial [Assumption: mean percent change from baseline was assumed to be zero during the placebo washout period at Visits 7A and 8]. The results show that:

- The decreases in TC occur primarily during the first 4 weeks of treatment;
- There was no evidence of carry-over from Period 1 to Period 2; and
- The responses for the 2 drugs are similar

Figure 23: 146-010 Mean % Change TC Periods 1 and 2 by Treatment Group Assignment



(c) Statistical Reviewer Findings

The findings of the Statistical Reviewer for the mean percent changes from baseline to endpoint for LDL-C, TC, TG, and HDL-C were the same as the sponsor's results, as summarized above. [Please refer to the Statistical Review prepared by: Mele, Joy M.S. Division of Biometrics, CDER, FDA, NDA #21-316, 14-Dec-2001, for the complete Statistical Review.]

(d) Conclusions on Efficacy Results for Protocol 146-010

The efficacy results for study 146-010 show that:

1. For the Primary efficacy variable (mean percent change from baseline for LDL-C):
   a) When the treatments were pooled, treatment with lovastatin XL 20 mg resulted in a significantly greater LDL-C lowering than Mevacor 20 mg, of about –3%. Lovastatin XL 20 mg had a mean percent lowering of LDL-C of –26% vs a mean percent lowering of –23% for Mevacor 20 mg. There was no significant difference between treatment with lovastatin XL 60 mg and Mevacor 60 mg, with mean percent LDL-lowering of –35% and –33% respectively.
   b) The majority of the LDL-lowering was seen within the first 4 weeks of treatment with minor changes seen during active treatment throughout the rest of the study.

2. For the secondary efficacy endpoints:
   a) When treatments were pooled, HDL-C increases of 4% were seen in both the lovastatin XL 20 mg and Mevacor 20 mg groups, and 5% increases were seen in both the 60 mg treatment groups. The majority of HDL-C raising was seen by the 4th week of treatment, with little change throughout the active treatment portions of the study.
   b) When the treatments were pooled, treatment with lovastatin XL 20 mg resulted in a significantly greater, but clinically minor, TC lowering than Mevacor 20 mg, of about –2%. Lovastatin XL 20 mg had a mean percent lowering of TC of –19% vs a mean percent lowering of –17% for Mevacor 20 mg. There was no significant difference between treatment with lovastatin XL 60 mg and Mevacor 60 mg, with mean percent lowering of –26% and –25% respectively. The majority of TC lowering was seen within the first 4 weeks of active treatment.
   c) When the treatments were pooled, TG decreases of –8 to –11% were seen in both the lovastatin XL 20 mg and Mevacor 20 mg groups, and –18 to –19% decreases were seen in the lovastatin XL 60 mg and Mevacor 60 mg treatment groups. There were no significant differences between the treatment groups at each dose level. Results for TG lowering were variable from Visit to Visit in all treatment groups.

   In summary, there was a statistically significantly greater, but clinically minor, decrease in LDL-C with treatment with lovastatin XL 20 mg vs Mevacor 20 mg. There was no difference in LDL-lowering between the lovastatin XL and Mevacor 60 mg treatment groups. For TC and TG lowering, and HDL-raising, there were no meaningful differences between the lovastatin XL and Mevacor treatment groups at each dosage level.

3. Protocol 146-011

a) Study Design for Protocol 146-011

(1) Study Design

Protocol 146-011 "An extended safety, efficacy and tolerability study of lovastatin XL in patients with hypercholesterolemia" was a multi-center, randomized, double-blind parallel-group extension study conducted at 36 clinical sites nationally. Treatment was for an additional 12-week period after successful completion of either the dose response study (Study 146-009) or the comparative, crossover study with Mevacor (Study 146-010). The study evaluated the efficacy and safety of lovastatin XL 40 mg or 60 mg in 229 patients with hypercholesterolemia.

(2) Study Objectives

The objectives of the study were to evaluate the extended safety, efficacy, and tolerability of lovastatin XL over an additional 12 weeks of treatment. The primary efficacy endpoint was the mean percent change in LDL-C from baseline to endpoint. Secondary efficacy endpoints were the percent changes in TC, HDL-C and TG from baseline to endpoint.

(3) Eligibility Criteria

(a) Inclusion Criteria

Patients were eligible for inclusion in the study if they had successfully completed either Study 146-009 or Study 146-010.

(b) Exclusion Criteria

Patients were excluded from the study if they had not completed either Study 146-009 or Study 146-010.

(4) Study Visits and Procedures

The study visits and procedures are summarized below and in the following table. All study visits were to occur within ±3 days of the designated study day.

Table 50: 146-011 Study Visits and Procedures

	Extension Treatment				
Visit	**1**	**2**	**3**	**4**	**5**
Study Week (Study Day)	**0 (0)**	**4 (28)**	**8 (56)**	**11 (77)**	**12 (84)**
Procedure					
Informed Consent	X				
Physical Examination	X				X
ECG	X				X
Concomitant Medications	X	X	X	X	X
Vital Signs	X	X	X		X
Dispense Study Medication	X	X	X		
Study Medication Compliance	X	X	X		X
Adverse Events	X	X	X	X	X
Serum Lipids	X	X	X	X	X
Clinical Laboratory Tests					
Serum ALT, AST, CPK	X	X	X		X
Serum Chemistry	X				X
Hematology	X				X
Urinalysis	X				X
Serum beta-HCG (females only)	X	X	X		X

(a) Visit 1 (Week 0; Day 0)

Visit 1 procedures were the same as those performed at Visit 8 in Study 146-009 and Visit 11 in Study 146-010 (End of Study Visit for both studies). Patients reported to the study center before breakfast, after at least a 10-hour fast. All patients underwent the following procedures:

- Informed consent
- Physical examination
- ECG
- Concomitant medications record
- Vital signs (BP, pulse, temperature)
- AE Assessment
- Blood samples for lipids, AST, ALT, CPK, serum chemistry and hematology, and serum beta-HCG (females only)
- Urinalysis
- Dispensing of study medication for Visit 1

(b) Visit 2 (Week 4; Day 28) and Visit 3 (Week 8; Day 56)

At Visits 2 and 3, patients reported to the study center before breakfast, after at least a 10-hour fast. All patients underwent the following procedures:

- Concomitant medications record
- Vital signs (BP, pulse, and body temperature)

- AE assessment
- Dispensing of study medication for Visits 2 and 3
- Blood samples for lipids, AST, ALT, CPK, and beta-HCG (females only)

(c) Visit 4 (Week 11; Day 77)

At Visit 4, patients reported to the study center before breakfast, after at least a 10-hour fast. All patients underwent the following procedures:

- Concomitant medications record
- AE assessment
- Blood samples for lipids, AST, ALT, CPK, and beta-HCG (females only)

(d) Visit 5/End of Study Visit (Week 12; Day 84)

At Visit 5, patients reported to the study center before breakfast, after at least a 10-hour fast. All patients underwent the following procedures:

- Physical examination
- ECG
- Concomitant medications record
- Vital signs (BP, pulse, temperature)
- AE Assessment
- Blood samples for lipids, AST, ALT, CPK, serum chemistry and hematology, and serum beta-HCG (females only)
- Urinalysis

(5) Study Medication Dispensing and Compliance

At Visit 1, patients were assigned to one of 2 treatment groups:

Treatment A: lovastatin XL 40 mg per day
Treatment B: lovastatin XL 60 mg per day

A computerized randomization scheme was generated before studies 146-009 and 146-010 were initiated, and treatment group assignment for Study 146-011 was performed in the following manner:

Patients previously in Study 146-009 were assigned to lovastatin XL 40 mg or 60 mg treatment groups in the extension study as follows:

1) Patients already receiving lovastatin XL 40 mg per day or 60 mg per remained on the same treatment in the extension study
2) Patients receiving placebo, lovastatin XL 10 mg or lovastatin XL 20 mg were re-randomized to receive lovastatin XL 40 or 60 mg per day in the extension study

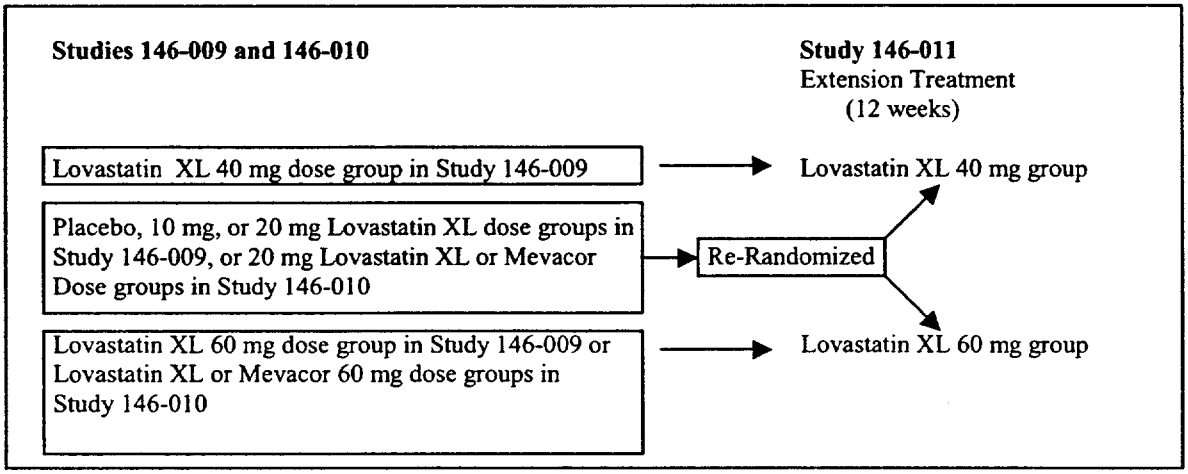
Patients previously in Study 146-010 were assigned to lovastatin XL 40 mg or 60 mg treatment groups in the extension study as follows:

1) Patients receiving lovastatin XL or Mevacor 60 mg per day received lovastatin XL 60 mg per day in the extension study

2) Patients receiving lovastatin XL or Mevacor 20 mg per day were re-randomized to receive lovastatin XL 40 or 60 mg per day in the extension study

Treatment group assignment for Study 146-011 is represented schematically in the following figure

Figure 24: 146-011 Randomization Scheme



Study medication was supplied as lovastatin XL 20 mg and 40 mg tablets, and matching placebo tablets. All patients took 3 tablets daily. Tablets were supplied in blister cards and dispensed in a double-blind manner. Unused medication was collected at the following study visit, and compliance was determined by a tablet count.

(6) Efficacy and Endpoint Measures

(a) Primary

The primary efficacy variable was mean percent change in LDL-C from baseline to endpoint. Baseline was defined as the average of the last 2 values before starting active treatment (Visits 3 and 4 in Study 146-009 or Study 146-010). Endpoint was defined as the average value after 11 and 12 weeks of extension treatment in Study 146-011.

(b) Secondary

Secondary efficacy variables were percent changes in HDL-C, TC, and TG from baseline to endpoint.

(c) Safety

Safety was assessed by the incidence and frequency of adverse events, and by changes in vital signs, physical examinations, ECGs, and clinical laboratory values.

(d) Study Population

Enrolled patients were defined as patients who were enrolled in the extension study and received at least one dose of study medication. The ITT population was defined as Enrolled patients who had at least one protocol-defined efficacy measurement after Visit 1. The ITT population was the sponsor's primary efficacy analysis population.

b) Results

Four-hundred forty-eight (448) patients completed the original studies: 160 patients in Study 146-009 and 288 patients in Study 146-010. Of these 448 patients, 365 patients were enrolled in the extension study: 136 patients from 146-009 and 229 from 146-010.

Interim Report

Two-hundred twenty-nine (229) of the 365 patients were included in the interim report for Study 146-011, which was submitted with the original NDA. As of the Interim Report, 208 patients had completed the extension study, and 21 patients had discontinued during the extension study. Two-hundred twenty (220) of these patients were included in the ITT population. There were few differences in overall findings between the interim report and the final report (see below).

Final Report

The final results for Study 146-011 were submitted as an updated report dated 26-Jul-2001. Three-hundred sixty-five (365) patients were enrolled in the extension study as follows:

Lovastatin XL 40 mg group: 128 patients (31 patients from Protocol 146-009 lovastatin XL 40 mg group, and 97 patients were re-randomized from the other groups)

Lovastatin XL 60 mg group: 237 patients [138 patients were already receiving lovastatin 60 mg (25 patients from Protocol 146-009, and 113 patients from Protocol 146-010), and 99 patients were re-randomized from the other groups].

Enrolled and ITT patients are summarized as follows:

Table 51: 146-011 Enrolled and ITT Patients by Treatment Group

		Treatment	
	All	**Lovastatin XL 40 mg**	**Lovastatin XL 60 mg**
Enrolled Patients, n =	365	128	237
ITT Patients, n =	356	124	232
At same dose as original study, n (%)	169 (46)	31 (24)	138 (58)
Re-randomized, n (%)	196 (54)	97 (76)	99 (42)

(1) Baseline Characteristics and Demographics

Overall, 61% of enrolled patients were male and 87% were Caucasian. Patients ranged in age from 29 to 71 years, with a mean age of 56.6 years. The treatment groups were relatively well balanced. When compared to the 146-009 and 146-010 study populations, baseline characteristics and demographics were similar between the extension (146-011)

study and the original treatment populations. Baseline characteristics and demographics for the Enrolled patients in the extension (146-011) study are summarized in the following table

Table 52: 146-011 Baseline Characteristics and Demographics

	All	Lovastatin XL 40 mg	Lovastatin XL 60 mg
Enrolled Patients, n =	365	128	237
Demographic Measure			
Gender, n (%)			
Male	222 (61)	74 (58)	148 (62)
Female	143 (39)	54 (42)	89 (38)
Age, years			
Mean	56.6	57.3	56.2
Median	58.0	59.0	57.0
Min, max	29, 71	36, 71	29, 71
Age ≥ 65 years, n (%)	75 (21)	27 (21)	48 (20)
Ethnicity, n(%)			
Caucasian	318 (87)	118 (92)	200 (84)
Black	18 (5)	6 (5)	12 (5)
Asian	4 (1)	2 (2)	2 (1)
Other	25 (7)	2 (2)	23 (10)
Risk Factors (RF)			
≥2 CAD RF or CHD, n (%)	191 (52)	70 (55)	121 (51)
<2 CAD RF, n (%)	174 (48)	58 (45)	116 (49)
Mean BMI, kg/M^2	28.1	27.9	28.3
Baseline Lipid Value			
Mean LDL-C, mg/dL		179.4	176.8
Mean HDL-C, mg/dL		45.8	45.2
Median Triglycerides, mg/dL		261.4	256.1
Mean Lp(a), mg/dL		179.1	171.7

(2) Patient Disposition

(a) Entry/Randomization

Of the 448 patients eligible for the study, 83 patients declined participation in the extension study. Reasons were not always supplied, but it appeared that the most common reason for not continuing in the extension study was for withdrawal of consent (77/83 patients). The remaining patients (6/83) withdrew due to AEs experienced in the 146-009 and 146-010 studies.

(b) Dropouts

Of the 365 patients enrolled in the extension study, 340 patients completed the study and 25 patients discontinued treatment prior to study completion. Of the 25 patients who discontinued, 14 patients (4%) discontinued due to an AE, 8 patients (2%) withdrew consent, and 4 patients (1%) withdrew for other reasons (not provided). The withdrawals occurred in 12 patients (9%) in the lovastatin XL 40 mg group and 13 patients (5%) in the lovastatin XL 60 mg group. Patient discontinuations by treatment group are summarized in the following table

Table 53: 146-011 Patients Discontinued

		Treatment	
	All	**Lovastatin XL 40**	**Lovastatin XL 60**
Enrolled Patients, n =	365	128	237
Number of Withdrawals, n (%)	25 (7)	12 (9)	13 (5)
Reason for Dropout			
Adverse Event	14 (4)	8 (6)	6 (3)
Withdrew Consent	8 (2)	4 (3)	4 (2)
Other	4 (1)	3 (2)	7 (3)

(3) Concomitant Medications

Concomitant medication use was common during the extension study. Overall, 338 of the 365 enrolled patients (93%) reported the use of any concomitant medication during the extension study. Patients reporting any concomitant medication use during the study, by treatment group, are summarized in the following table

Table 54: 146-011 Patients With Any Concomitant Medication Use

		Treatment	
	All	**Lovastatin XL 40**	**Lovastatin XL 60**
Enrolled Patients, n =	365	128	237
Any conmed use, n (%)	338 (93)	117 (91)	221 (93)

A large number of different medications were used during the study (over 350 medications were reported), with the majority used by a small number of patients (used by $\leq$5 patients, or $\leq$1% of patients overall). The most commonly reported concomitant medications used during the extension study were acetylsalicylic acid (by 36% of patients overall) and multivitamins (35%). There were no reports of any patient using a prohibited lipid-altering medication during the study. Concomitant medication use appeared to be relatively well balance across the two treatment groups. It is unlikely that the concomitant medications used affected the overall study results. The most commonly used concomitant medication (used by $\geq$5% of patients overall) are summarized in the following table

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Table 55: 146-011 Concomitant Medications, Most Common (≥5%) Overall and by Treatment Group

		Treatment	
	All	**Lovastatin XL 40**	**Lovastatin XL 60**
Enrolled Patients, n =	365	128	237
Medication			
Acetylsalicylic Acid	130 (36)	48 (38)	82 (35)
Multivitamins	129 (35)	43 (34)	85 (36)
Tocopherol	90 (25)	32 (25)	58 (24)
Ibuprofen	83 (23)	35 (27)	48 (20)
Ascorbic Acid	66 (18)	27 (21)	39 (16)
Calcium	52 (14)	23 (18)	29 (12)
Paracetamol	46 (13)	20 (16)	26 (11)
Estrogen	24 (7)	10 (8)	14 (6)
Diphenhydramine	23 (6)	11 (9)	12 (5)
Hydrochlorothiazide	23 (6)	10 (8)	13 (5)
Levothyroxine	23 (6)	11 (9)	12 (5)
Naproxen	22 (6)	10 (8)	12 (5)
Loratadine	19 (5)	6 (5)	13 (5)
General Nutrients	17 (5)	7 (5)	10 (4)
Pseudoephedrine	17 (5)	5 (4)	12 (5)

(4) Patient Compliance

Compliance was assessed by pill counts at each study visit. Patient compliance with study medication was >95% for both treatment groups during the extension study.

(5) Efficacy Analysis

(a) Primary Efficacy Analysis: Mean Percent Change in LDL-C

The primary efficacy variable was the percent change in LDL-C from baseline to endpoint for the ITT population. The results show statistically significant mean percent decreases in LDL-C for both treatment groups. There was no difference in LDL-C decreases comparing the lovastatin XL 40 mg group to the lovastatin XL 60 mg group, with a
–33.3% decrease from baseline in LDL-C in the lovastatin XL 40 mg group and a –33.7% decrease from baseline in the lovastatin XL 60 mg group. The mean percent change in LDL-C from baseline to endpoint by treatment group is summarized in the following table

Table 56: 146-011 Mean Percent Change in LDL-C Baseline to Endpoint, ITT Population

Treatment	**n**	**Baseline mean LDL-C ± SD (mg/dL)**	**Endpoint mean LDL-C ±SD (mg/dL)**	**Mean Percent Change ± SD (%)**	**p-value**
Lovastatin XL 40 mg	124	179.4 ± 34.0	118.8 ± 27.4	-33.3 ± 11.7	p ≤.0001
Lovastatin XL 60 mg	232	176.8 ± 30.1	115.9 ± 29.0	-33.7 ± 15.6	p ≤.0001

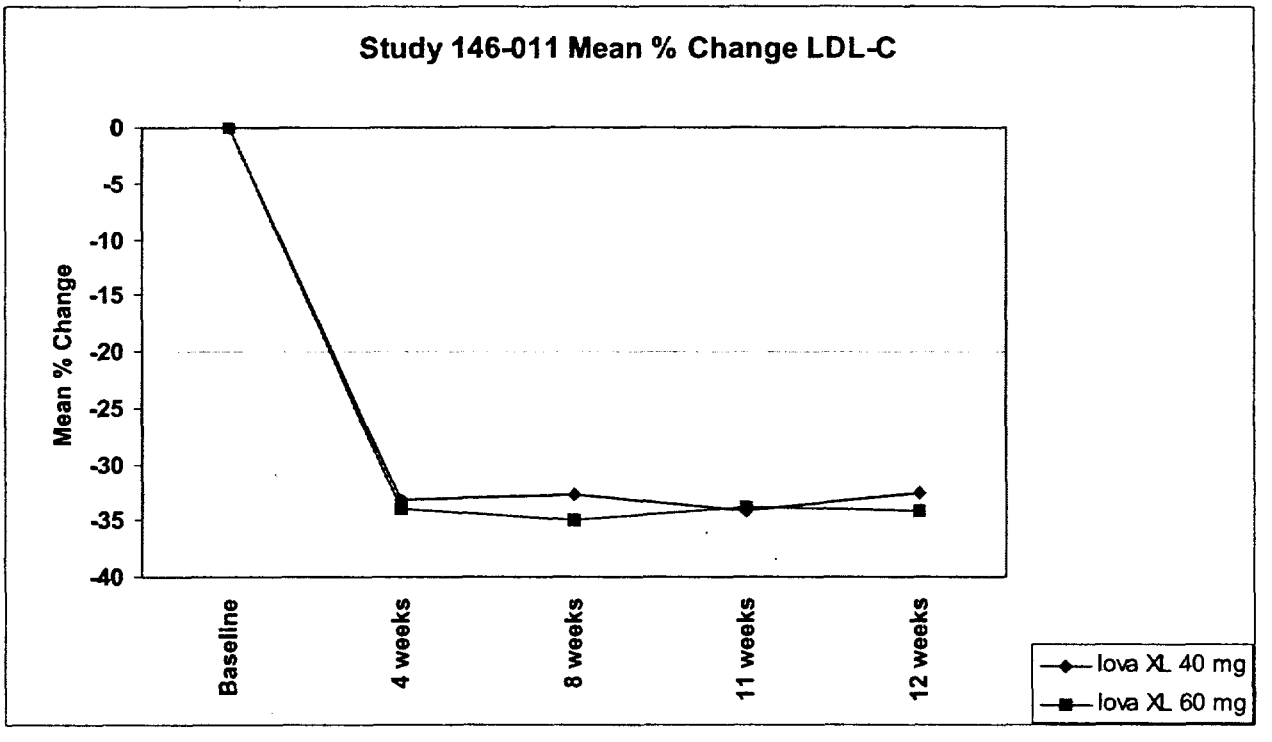
Mean percent decrease in LDL-C is also shown by treatment visit. The results show that the decreases in LDL-C are sustained throughout the extension study with little change from Weeks 4 through 12. As previously stated, there was no meaningful difference in

mean percent decrease in LDL-C between the lovastatin XL 40 mg and 60 mg groups. The results are summarized in the following table and graph

Table 57: 146-011 Mean Percent Change from Baseline in LDL-C (ITT Population)

		Weeks of Treatment			
Treatment	**Baseline**	**4**	**8**	**11**	**12**
Lovastatin XL 40 mg, n =	122	122	117	112	114
Mean	179.6 mg/dL	-33.1%	-32.7%	-34.1%	-32.5%
SD	34.3	12.5	12.8	12.3	12.9
Lovastatin XL 60 mg, n =	227	227	226	221	219
Mean	176.6 mg/dL	-34.0%	-34.9%	-33.9%	-34.1%
SD	30.3	16.2	14.4	16.8	14.9

Figure 25: 146-011 Mean % Change LDL-C



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(b) Secondary Efficacy Analysis

Secondary efficacy variables were the percent change in HDL-C, TC, and TG from baseline to endpoint in the ITT population.

(i) Mean Percent Change in HDL-C

The results show statistically significant mean percent increases in HDL-C for both lovastatin XL treatment groups from baseline to endpoint. As with the LDL-C results, there was no difference in the percent increases in HDL-C when the lovastatin XL 40 mg group was compared to the lovastatin XL 60 mg group, with both groups achieving a +7.1% increase in HDL-C. The mean percent change in HDL-C from baseline to endpoint by treatment group is summarized in the following table

Table 58: 146-011 Mean Percent Change in HDL-C Baseline to Endpoint, ITT Population

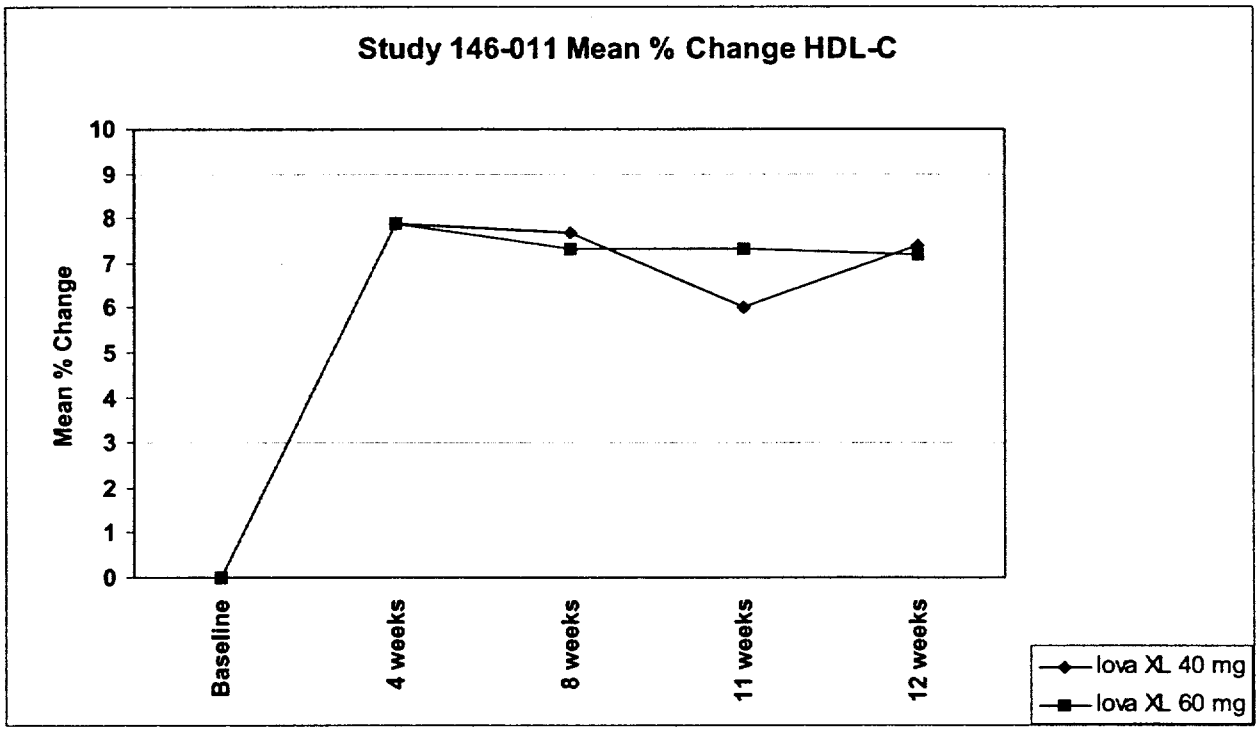
Treatment	n	Baseline mean HDL-C ± SD (mg/dL)	Endpoint mean HDL-C ±SD (mg/dL)	Mean Percent Change ± SD	p-value
Lovastatin XL 40 mg	124	45.8 ± 11.0	48.6 ± 11.5	7.1 ± 14.0	p ≤.0001
Lovastatin XL 60 mg	232	45.2 ± 12.0	48.2 ± 13.2	7.1 ± 13.2	p ≤.0001

Mean percent increase in HDL-C is also shown by treatment visit. The results show that the increases in HDL-C remain relatively unchanged throughout the 12 weeks of treatment in the extension study. As previously stated, there was no meaningful difference in mean percent increase in HDL-C between the lovastatin XL 40 mg and 60 mg groups. The results are summarized in the following table and graph

Table 59: 146-011 Mean Percent Change from Baseline in HDL-C (ITT Population)

		Weeks of Treatment			
Treatment	**Baseline**	**4**	**8**	**11**	**12**
Lovastatin XL 40 mg, n =	122	122	117	112	114
Mean	45.9 mg/dL	7.9%	7.7%	6.0%	7.4%
SD	11.0	13.6	15.9	15.3	13.9
Lovastatin XL 60 mg, n =	228	228	227	222	219
Mean	45.2 mg/dL	7.9%	7.3%	7.3%	7.2%
SD	12.1	14.8	13.8	14.5	13.8

Figure 26: 146-011 Mean % Change HDL-C



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(ii) Mean Percent Change TC

The results show statistically significant mean percent decreases in TC for both treatment groups. There was no difference in TC decreases comparing the lovastatin XL 40 mg group to the lovastatin XL 60 mg group, with a –24.6% decrease from baseline in TC in the lovastatin XL 40 mg group and a –24.8% decrease from baseline in the lovastatin XL 60 mg group. The mean percent change in TC from baseline to endpoint by treatment group is summarized in the following table

Table 60: 146-011 Mean Percent Change in TC Baseline to Endpoint, ITT Population

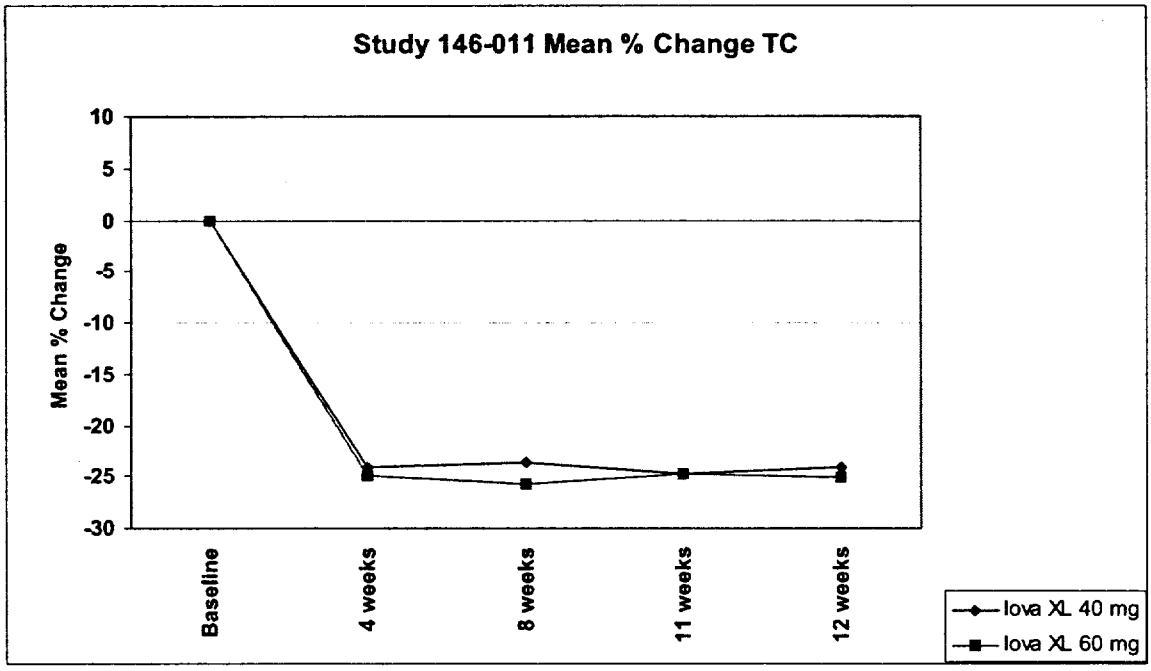
Treatment	n	Baseline mean TC ± SD (mg/dL)	Endpoint mean TC ±SD (mg/dL)	Mean Percent Change ± SD	p-value
Lovastatin XL 40 mg	124	261.4 ± 36.3	196.7 ± 32.1	-24.6 ± 8.2	p ≤.0001
Lovastatin XL 60 mg	232	256.1 ± 34.7	191.5 ± 33.7	-24.8 ± 11.8	p ≤.0001

Mean percent decrease in TC is also shown by treatment visit. The results show that the decreases in TC are sustained throughout the extension study with little change from Weeks 4 through 12. As previously stated, there was no meaningful difference in mean percent decrease in TC between the lovastatin XL 40 mg and 60 mg groups. The results are summarized in the following table and graph

Table 61: 146-011 Mean Percent Change from Baseline in TC (ITT Population)

		Weeks of Treatment			
Treatment	**Baseline**	**4**	**8**	**11**	**12**
Lovastatin XL 40 mg, n =	123	123	117	112	114
Mean	261.6 mg/dL	-24.1%	-23.7%	-24.8%	-24.2%
SD	36.3	9.0	10.5	8.8	9.3
Lovastatin XL 60 mg, n =	228	228	227	223	220
Mean	256.1 mg/dL	-25.0%	-25.7%	-24.8%	-25.2%
SD	34.9	12.0	11.2	12.5	11.4

Figure 27: 146-011 Mean % Change TC



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(iii) Mean Percent Change TG

The results show statistically significant mean percent decreases in TG for both treatment groups. There was no difference in TG decreases comparing the lovastatin XL 40 mg group to the lovastatin XL 60 mg group, with a –14.2% decrease from baseline in TG in the lovastatin XL 40 mg group and a –14.7% decrease from baseline in the lovastatin XL 60 mg group. The mean percent change in TG from baseline to endpoint by treatment group is summarized in the following table

Table 62: 146-011 Mean Percent Change in TG Baseline to Endpoint, ITT Population

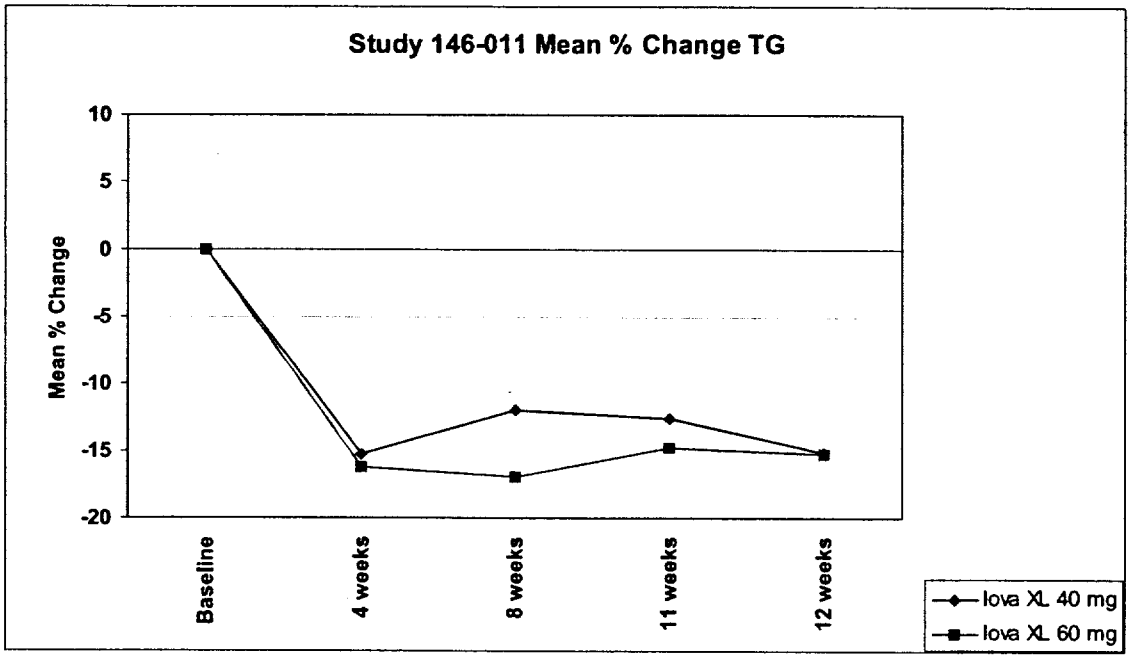
Treatment	N	Baseline mean TG ± SD (mg/dL)	Endpoint mean TG ±SD (mg/dL)	Mean Percent Change ± SD	p-value
Lovastatin XL 40 mg	124	179.1 ± 82.6	147.1 ± 66.2	-14.2 ± 26.2	p ≤.0001
Lovastatin XL 60 mg	232	171.7 ± 74.5	137.8 ± 62.8	-14.7 ± 30.8	p ≤.0001

Mean percent decrease in TG is also shown by treatment visit. The results show that the decreases in TG are sustained throughout the extension study with little change from Weeks 4 through 12. As previously stated, there was no meaningful difference in mean percent decrease in TG between the lovastatin XL 40 mg and 60 mg groups. The results are summarized in the following table and graph

Table 63: 146-011 Mean Percent Change from Baseline in TG (ITT Population)

		Weeks of Treatment			
Treatment	**Baseline**	**4**	**8**	**11**	**12**
Lovastatin XL 40 mg, n =	123	123	117	112	114
Mean	179.5 mg/dL	-15.3%	-11.9%	-12.5%	-15.1%
SD	82.8	24.1	36.3	28.1	29.6
Lovastatin XL 60 mg, n =	228	228	227	223	220
Mean	172.3 mg/dL	-16.2%	-16.9%	-14.7%	-15.3%
SD	74.9	32.5	31.6	35.0	34.4

Figure 28: 146-011 Mean % Change TG



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(c) Conclusions on Efficacy Results for Protocol 146-011

The results show that both lovastatin XL treatment groups experienced significant decreases in mean percent LDL-C (primary endpoint) from baseline to endpoint, and that these decreases were maintained throughout the extension study. There was no significant difference in LDL-C lowering between the lovastatin XL 40 mg and lovastatin XL 60 mg treatment groups, however. For the secondary endpoints, there were significant increases in HDL-C, and significant decreases in TC and TG in both treatment groups from baseline to endpoint, that were sustained throughout the extension study. As with the LDL-C results, there were no differences in these endpoints between the lovastatin XL 40 mg and lovastatin XL 60 mg treatment groups.

D. Conclusion on Review of NDA 21-316

The efficacy results for the lovastatin XL clinical program show:

For the primary endpoint:

1) Lovastatin XL produced statistically significant (and clinically relevant) decreases in LDL-C from baseline to endpoint, and significant decreases in LDL-C compared to placebo.
2) There was a dose-response effect with progressive decreases in LDL-C with increasing doses of lovastatin XL. There was about a 6% further decrease in LDL-C with a doubling of the lovastatin XL dose from 10 mg to 20 mg, and from 20 mg to 40mg, and about a 3% decrease with a dose increase from 40 mg to 60 mg.
3) The majority of the decrease in LDL-C was seen after 4 weeks of treatment.

For the secondary endpoints:

1) Lovastatin XL produced significant increases in HDL-C from baseline to endpoint, and significant increases in HDL-C compared to placebo for all doses of lovastatin XL except for the 10 mg dose. The increase in HDL-C plateaued from the 20 mg to 60 mg doses, with little change in HDL-C despite increasing doses of lovastatin XL.
2) Lovastatin XL produced significant decreases in TC from baseline to endpoint, and compared to placebo. The decrease in TC was progressive with increasing doses of lovastatin XL.
3) Lovastatin XL produced significant decreases in TG from baseline to endpoint, and significant decreases in TG compared to placebo. There was no dose-response effect seen with mean TG decreases, and the results were variable from week to week.
4) The majority of the lipid-altering effects of lovastatin XL for all parameters measured were seen after 4 weeks of treatment.

The results (for Protocol 146-009) are summarized in the following table

Table 64: Protocol 146-009 Efficacy Results, Summary

		Mean % Change From Baseline to Endpoint			
Treatment	**n**	**LDL-C**	**HDL-C**	**TC**	**TG**
Placebo	34	1.3	5.6	3.4	8.7
Lovastatin XL 10 mg	33	-23.8*	9.4	-17.9*	-17.3*
Lovastatin XL 20 mg	33	-29.6*	12.0*	-20.9*	-13.0*
Lovastatin XL 40 mg	33	-35.8*	13.1*	-25.4*	-9.9*
Lovastatin XL 60 mg	35	-40.8*	11.6*	-29.2*	-25.1*

*statistically significant vs placebo

When lovastatin XL was compared to Mevacor at the 20 mg and 60 mg doses (in Protocol 146-010):

1) Lovastatin XL 20 mg resulted in a significant greater (but clinically minor) decrease in LDL-C by 3% compared to Mevacor. Treatment with lovastatin XL 60 mg and Mevacor 60 mg resulted in no significant difference in LDL-C lowering between the two treatments.

2) With the exception of the lovastatin XL 20 mg group's TC result, there were no significant differences between the lovastatin XL and Mevacor treatment groups for any of the secondary endpoints.

The results are summarized in the following table

Table 65: Protocol 146-010 Efficacy Results, Summary

		Mean % Change From Baseline to Endpoint			
Treatment (Pooled)	**n**	**LDL-C**	**HDL-C**	**TC**	**TG**
Lovastatin XL 20 mg	149	-26.3*	3.7	-19.0*	-8.3
Mevacor 20 mg	149	-23.1	3.9	-17.1	-11.1
Lovastatin XL 60 mg	148	-34.7	5.0	-26.0	-17.5
Mevacor 60 mg	148	-33.0	5.2	-25.1	-18.6

*statistically significant vs Mevacor 20 mg

In the extension trial (Protocol 146-011), treatment with lovastatin XL 40 mg and 60 mg showed durable lipid-altering effects for up to 6 months of treatment. The results are summarized in the following table

Table 66: Protocol 146-011 Efficacy Results, Summary

		Mean % Change From Baseline to Endpoint			
Treatment	**n**	**LDL-C**	**HDL-C**	**TC**	**TG**
Lovastatin XL 40 mg	124	-33.3*	7.1*	-24.6*	-14.2*
Lovastatin XL 60 mg	232	-33.7*	7.1*	-24.8*	-14.7*

*statistically significant vs from baseline

When the studies are compared, there were some notable differences in the lipid-altering effects across the studies. The magnitude of LDL-C lowering was greater in the 146-009 study than in the 146-010 and 146-011 studies. For example, for the lovastatin XL 60 mg treatment groups, the mean percent decrease in LDL-C was –41% for protocol 146-009, -35% for 146-010, and –34% for 146-011. Greater lipid-altering effects were consistently seen for all lipid parameters measured in the 146-009 than for the other 2 studies. This Reviewer was unable to find any differences in the study populations, treatments, or protocol design to account for these differences. It is clear, however, that lovastatin XL produces significant decreases in LDL-C, TC, and TG, and increases in HDL-C that are similar to the results obtained for Mevacor in this clinical program and compared to historical data (see table EXCEL below).

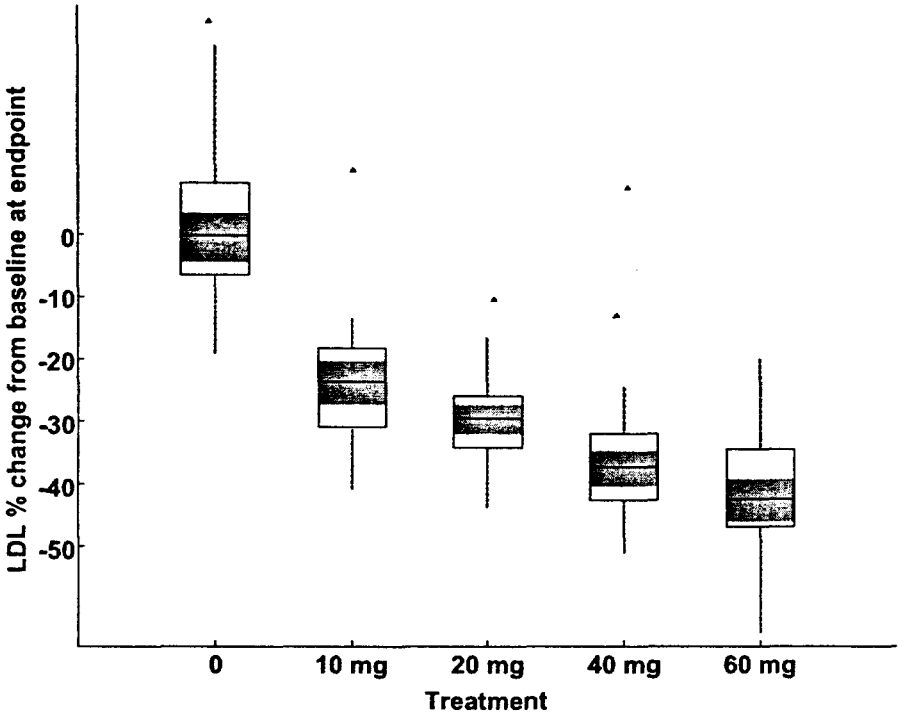
Table 67: EXCEL Study Mean % Change From Baseline in Lipids

Treatment	**n**	**LDL-C**	**HDL-C**	**TC**	**TG**
Placebo	1663	+0.4	+2	+0.7	+4
Mevacor 20 mg	1642	-24	+6.6	-17	-10
Mevacor 40 mg	1645	-30	+7.2	-22	-14
Mevacor 80 mg (40 mg BID)	1649	-40	+9.5	-29	-19

Therefore, to illustrate the variability in the results, it is recommended that labeling for lovastatin XL include the range of responses to lovastatin XL at each dose seen in the dose-response study (146-009), to guide the practicing physician in titrating patients to

goal with lovastatin XL. Ranges of responses for LDL-C (for Study 146-009) are summarized in the following figure (See also Appendix A Proposed Labeling comments for additional discussion).

Figure 29: 146-009 Boxplot of LDL-C Responses



Prepared by: Mele, Joy, M.S., Statistical Reviewer, Division of Biostatistics, CDER, FDA, 06-Nov-2001.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety testing was adequate to assess common AEs and treatment emergent laboratory abnormalities (TELAs) frequently seen with lovastatin, and in this regard, lovastatin XL was found to have a safety profile similar to Mevacor. The safety evaluation was too limited, however, to warrant any alteration in the less common safety warnings and precautions noted in the Mevacor label. The lovastatin XL label should therefore include the same warnings, precautions, and monitoring recommendations as are currently contained in the Mevacor label.

The lovastatin XL clinical program also did not include any drug-interaction testing. Given the delayed and extended-release properties of the extended-release formulation of lovastatin XL, assumptions on drug interactions with lovastatin XL cannot necessarily be made based on the 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.

B. Description of Patient Exposure

In the lovastatin XL clinical program, a total of 588 patients were exposed to lovastatin XL, 354 patients were exposed to Mevacor, and 34 patients were exposed to placebo [Note: This does not include patients in the single-dose Phase I studies]. There were 427 patients exposed to lovastatin XL for at least 12 weeks, and 233 patients exposed to lovastatin XL for 24 weeks or more. The majority of patients were exposed to lovastatin XL in the 2 large, controlled studies. For the controlled studies, mean exposure was similar across the treatment groups, with mean exposures of 11.6 weeks for the lovastatin XL groups, 12.0 weeks for the placebo group, and 11.7 weeks for the Mevacor groups. Exposures by clinical study are summarized in the following table

Table 68: Patient Exposure to Lovastatin XL, Mevacor, and Placebo in the Clinical Studies

		Treatment									
		Lovastatin XL					Mevacor				
Study	Placebo	10 mg	20 mg	40 mg	60 mg	All	20 mg	40 mg	60 mg	All	Total
Controlled Studies											
146-009	34	35	34	33	36	138	-	-	-	-	172
146-010	-	-	162	-	167	329	166	-	163	329	358
Total	34	35	196	33	203	467	166	-	163	329	530
Uncontrolled Studies											
146-008	-	-	-	68	-	68	-	-	-	-	68
146-011*	-	-	-	128	237	365	-	-	-	-	365
Total	-	-	-	196	237	433	-	-	-	-	433
Phase II PK/PD Study											
146-006	-	-	-	25	-	25	-	25	-	25	26
Overall Total	**34**	**35**	**196**	**223**	**302**	**588#**	**166**	**25**	**163**	**354**	**624**

*majority of patients exposed to lovastatin XL in studies 146-009 and 146-010
#includes additional 28 patients previously exposed to placebo in study 146-009, exposed to lovastatin XL in 146-011