CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-316

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 21-316	**Application Type: NDA 505(b)(2)**
Sponsor: Aura Laboratories, Inc.	**Proprietary Name: Altocor**
Investigator: Multiple (Not named)	**USAN Name: Lovastatin extended-release**
Category: Lipid-altering drug	**Route of Administration: Oral**
Reviewer: Anne R. Pariser, M.D.	**Review Date: 09-Jan-2001**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
30-Mar-2001	30-Mar-2001	3S	

RELATED APPLICATIONS (If applicable)

Document Date	Application Type	Comments

REVIEW SUMMARY: The NDA was submitted for the approval of Altocor (lovastatin extended-release) as a lipid-altering agent, a [redacted] to slow the progression of coronary atherosclerosis in established CHD, in hyperlipidemia to decrease the risk for atherosclerotic vascular disease due to hypercholesterolemia, and as an adjunct to diet for the reduction of elevated TC, LDL-C, apo B, and TG, and to increase HDL-C in patients with hypercholesterolemia types IIa and IIb. The Altocor clinical program sought to demonstrate the efficacy of Altocor on LDL-C, TC, TG, and HDL-C and to demonstrate Altocor's safety and efficacy for chronic administration. As this is a 505 (b)(2) application, references to clinical studies with Mevacor have also been submitted to the NDA. The sponsor submitted 13 studies to this application: 8 single-dose PK and bioequivalence studies, 1 multi-dose PK/PD study, and 4 clinical safety and efficacy studies.

The results of the review of the Altocor clinical program support the proposed indication:
1) as a treatment to lower TC, LDL-C, and TG, and to increase HDL-C.
2) as a treatment to slow the progression of coronary atherosclerosis in patients with CHD
It is recommended that Altocor receive approval for these indications pending changes to the sponsor's proposed labeling.

OUTSTANDING ISSUES: none

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies _____	**Clinical Hold**	_____ **Study May Proceed**
NDA, Efficacy/Label supplement:	XX **Approvable**	__ **Not Approvable**

SIGNATURES Medical Reviewer: Anne Pariser, M.D. **Date:** January 9, 2002

Medical Team Leader: **Date:**

Table of Contents

Executive Summary

I. Recommendations

A. Recommendations on Approvability

The data from the clinical safety and efficacy studies submitted to NDA 21-316 support the use of lovastatin extended-release (XL) as a treatment to lower total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), and triglyceride (TG), and to increase high density lipoprotein-cholesterol (HDL-C); and as a treatment to slow the progression of coronary atherosclerosis in patients with coronary heart disease (CHD). It is recommended that lovastatin XL receive approval for these indications pending changes to the sponsor's proposed labeling.

There were two controlled studies (146-009 and 146-010) and one uncontrolled study (146-011) that provided the majority of the clinical data for lovastatin XL. In study 146-009, lovastatin XL produced statistically significant decreases in LDL-C, TC and TG, and increases in HDL-C from baseline to endpoint. There were significant decreases in LDL-C, TC, and TG compared to placebo for all doses of lovastatin XL tested (10 to 60 mg a day), and statistically significant increases in HDL-C for all doses except for the 10 mg dose. There was a dose-response effect seen with progressive decreases in LDL-C and TC, with an approximately 6% further decrease in LDL-C with a doubling of the dose of lovastatin XL. Variable decreases in TG and variable increases in HDL-C were also seen, but there was no dose-response effect seen for TG or HDL-C.

Study 146-010, a comparative study of lovastatin XL vs Mevacor, produced similar lipid-altering effects for lovastatin XL as compared to Mevacor. Both lovastatin XL and Mevacor produced significant decreases in LDL-C and TC from baseline to endpoint, and both agents produced variable increases in HDL-C and variable decreases in TG.

The uncontrolled study 146-011 was an extension to studies 146-009 and 146-010. The results showed that lovastatin XL produced significant decreases in LDL-C, TC, and TG, and increases in HDL-C from baseline to endpoint that were maintained for up to 6 months of treatment.

The safety findings showed that, in general, lovastatin XL was well tolerated and had a side-effect profile similar to that of Mevacor. There were no meaningful differences in the frequencies and types of Adverse Events (AEs) between the lovastatin XL, Mevacor, and placebo groups, and the majority of AEs were not serious or severe. It is recommended that the lovastatin XL label contain the same precautions, warnings, and contraindications as are contained in the Mevacor label.

II. Summary of Clinical Findings

A. Overview of Clinical Program

Lovastatin extended-release (lovastatin XL) has been submitted under the proposed trade name of Altocor. Lovastatin XL is an extended-release formulation of lovastatin, an inhibitor of HMG-CoA reductase. Lovastatin XL is being proposed for the treatment of hypercholesterolemia and for use in patients with dyslipidemia who are at risk for atherosclerotic vascular disease. The sponsor plans to market lovastatin XL as 10 mg, 20 mg, 40 mg, and 60 mg tablets for once daily administration

Lovastatin immediate-release (IR), as Mevacor, has been clinically available since 1987 as a treatment to lower TC and LDL-C. Mevacor is approved for use as primary prevention of coronary heart disease (CHD) in patients with average to moderately elevated TC and LDL-C, and below average HDL-C. Specifically in this population, Mevacor is indicated to reduce the risk of myocardial infarction (MI), unstable angina, and coronary revascularization procedures. Mevacor has also been shown to slow the progression of coronary atherosclerosis in patients with established CHD. Mevacor has also been shown to be effective in reducing TC and LDL-C in familial and non-familial forms of primary hypercholesterolemia and mixed dyslipidemia (types IIa and IIb).

The lovastatin XL clinical program seeks to demonstrate the efficacy of lovastatin XL as a lipid-altering agent, particularly as a treatment to lower LDL-C, TC and triglyceride (TG), and to raise HDL-C. The clinical program also seeks to demonstrate the safety of lovastatin XL for chronic administration. The sponsor is proposing a number of clinical indications for lovastatin XL that it states are supported by the lovastatin XL clinical program and by previous clinical experience with lovastatin IR. The sponsor is proposing the following indications for lovastatin XL:

[

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- In established CHD, to slow the progression of coronary atherosclerosis and lower TC and LDL-C
- In hyperlipidemia, to decrease the risk for atherosclerotic vascular disease due to hypercholesterolemia, and as an adjunct to diet for the reduction of elevated TC, LDL-C, apolipoprotein B (apo B), and TG, and to increase HDL-C in patients with primary hypercholesterolemia Fredrickson types IIa and IIb

The sponsor submitted 13 studies in support of NDA 21-316. Eight of these studies were PK and bioavailability studies, 1 study was a multi-dose PK/PD study, and 4 studies were clinical safety and efficacy studies. Of the 8 PK and bioavailability studies, all were open-label, single-dose, cross-over studies designed to demonstrate the pharmacokinetic properties of lovastatin XL and its bioavailability under a variety of conditions. These studies are listed as follows:

1) Study 146-001: Randomized, single-dose, open-label, 2-way cross-over study, which evaluated the safety and PK profile of lovastatin XL 40 mg vs Mevacor 40 mg in 8 healthy male subjects.
2) Study 146-002: Randomized, single-dose, open-label, 3-way cross-over study, which evaluated the effect of food on the PK profiles of lovastatin XL 40 mg and Mevacor 40 mg in 9 healthy male subjects.
3) Study 146-003: Randomized, single-dose, open-label, 2-period cross-over study, which evaluated alternative formulations of extended-release lovastatin (lovastatin XL formulation A vs lovastatin XL ——————— in 6 healthy males.
4) Study 146-004: Randomized, single-dose, open-label, 3-period cross-over study, which evaluated alternative formulations of extended-release lovastatin (2 extended-release lovastatin XL formulations vs Mevacor) in 6 healthy males.
5) Study 146-007: Randomized, single-dose, open-label, 3-way cross-over study in 8 healthy males who received lovastatin XL 10 mg, 20 mg and 40 mg.
6) Study 146-012: Randomized, single-dose, open-label, 3-period, 6-sequence cross-over study in 24 subjects (12M, 12F), which evaluated the effect of dose (20 mg, 40 mg, and 60 mg) on the PK of lovastatin XL, and the effects of gender and body weight on PK.
7) Study 146-102: Randomized, single-dose, open-label, 2-way cross-over study in 24 healthy males, which compared lovastatin XL 60 mg tablets with lovastatin XL 20 mg + 40 mg tablets.
8) Study 146-103: Randomized, single-dose, open-label, 2-way cross-over study in 24 healthy males, which compared lovastatin XL 40 mg in am (fasting) vs Mevacor 40 mg in am (fasting).

The multi-dose PK/PD study is summarized as follows:

9) Study 146-006: Multi-dose, cross-over study comparing lovastatin XL 40 mg to Mevacor 40 mg in 26 subjects (12M, 14F) with hypercholesterolemia in two, 4-week treatment periods. This study evaluated the PK and PD of lovastatin XL and Mevacor after the first dose and at steady state after 28 days of treatment. Lipid parameters were compared from baseline to after 3-4 weeks of treatment for lovastatin XL vs Mevacor.

The above 9 studies have been reviewed in detail in the Biopharmaceutics Review.

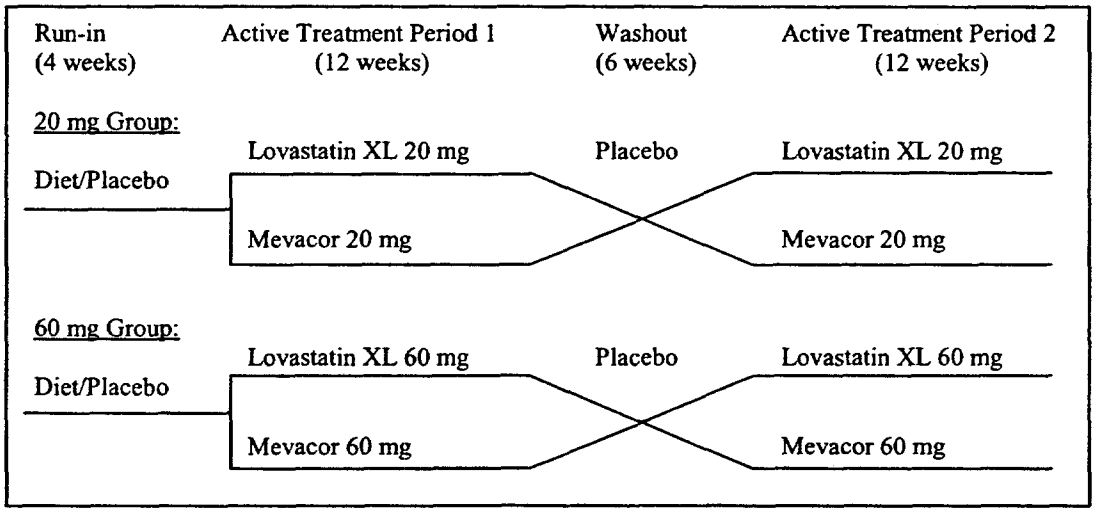
The 4 clinical safety and efficacy studies are summarized as follows:

1) Study 146-008 was a Phase II, multi-center, randomized, parallel group, placebo-controlled multi-dose, 4-week safety and efficacy study in 68 subjects with primary hypercholesterolemia, which evaluated lovastatin XL 40 mg administered before breakfast, after dinner, and before bedtime. This study evaluated mean changes in LDL-C, TC, HDL-C, and TG from baseline to endpoint, and compared the lipid changes across the treatment groups.

2) Study 146-009 was a 16-week, double-blind, randomized, placebo-controlled, parallel group, safety and efficacy study, which evaluated lovastatin XL 10 mg, 20 mg, 40 mg, and 60 mg vs placebo. The primary efficacy endpoint was mean percent change from baseline to endpoint in LDL-C. Secondary efficacy endpoints were mean percent change from baseline to endpoint in HDL-C, TC, and TG. Comparisons were also made between the placebo treatment group and each lovastatin XL treatment group for each lipid parameter. Lipid levels were assessed approximately every 4 weeks. Patients underwent a 4-week diet/placebo run-in followed by a 12-week active treatment phase. The study was conducted in 172 patients ≥21 years of age, with Type IIa or IIb hyperlipidemia, and there were 33-36 patients randomized to each of the 5 treatment groups.

3) Study 146-010 was a 34-week, double-blind, randomized, active-comparator, cross-over, safety and efficacy study. The study evaluated lovastatin XL 20 mg vs Mevacor 20 mg, and lovastatin XL 60 mg vs Mevacor 60 mg. The primary efficacy endpoint was mean percent change from baseline to endpoint in LDL-C compared between the lovastatin XL and Mevacor treatment groups. Secondary endpoints were mean percent changes from baseline to endpoint in HDL-C, TC, and TG between the lovastatin XL and Mevacor treatment groups. Lipids levels were assessed approximately every 4 weeks. Patients underwent a 4-week diet/placebo run-in, followed by a 12-week active-treatment period (Period 1), followed by a 6-week placebo/washout phase, and finally a 12-week active-treatment (cross-over treatment) period (Period 2). The treatment schedule is depicted schematically in the following figure

Figure 1: Study 146-010 Treatment Schedule



The study was conducted in 358 patients ≥21 years of age, with Type IIa or IIb hyperlipidemia, and there were 88-91 patients randomized to each of the 4 treatment groups.

4) Study 146-011 was a 12-week, double-blind, randomized, parallel group, safety and efficacy study. The study was an extension to the 146-009 and 146-010, which rolled-over patients who had successfully completed studies 146-009 and 146-010. All patients received lovastatin XL 40 mg or 60 mg. The primary efficacy endpoint was mean percent change from baseline to endpoint in LDL-C. Secondary efficacy endpoints were mean percent change from baseline to endpoint in HDL-C, TC, and TG. Lipid levels were assessed approximately every 4 weeks. The study was conducted in 356 patients ≥21 years of age, with Type IIa or IIb hyperlipidemia. There were 128 patients who received lovastatin XL 40 mg, and 237 patients who received lovastatin XL 60 mg.

An 120-day safety update was also submitted to the NDA in July-2001. The update contained the final results for Study 146-011 (interim results for Study 146-011 had been submitted with the original NDA submission).

B. Efficacy

The pivotal studies for the efficacy review that provided the majority of the efficacy data were the 2 controlled studies 146-009 and 146-010, and the large uncontrolled study 146-011. The results for these studies are summarized as follows.

The review of Study 146-009 efficacy data show that:

For the primary endpoint:

1) Lovastatin XL produced statistically significant 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 decreases in TC were 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 the mean TG decreases, and the results were variable from week to week.
4) The majority of the lipid-altering effects of lovastatin XL for TC, HDL-C and TG were seen after 4 weeks of treatment.

The efficacy results are summarized in the following table

Table 1: 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

The review of Study 146-010 efficacy data show that:

When lovastatin XL was compared to Mevacor at the 20 mg and 60 mg doses:

1) Lovastatin XL 20 mg resulted in a significantly 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 results, 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 2: 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

The review of Study 146-011 efficacy data show that:

In the extension trial, 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 3: 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 compared to 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

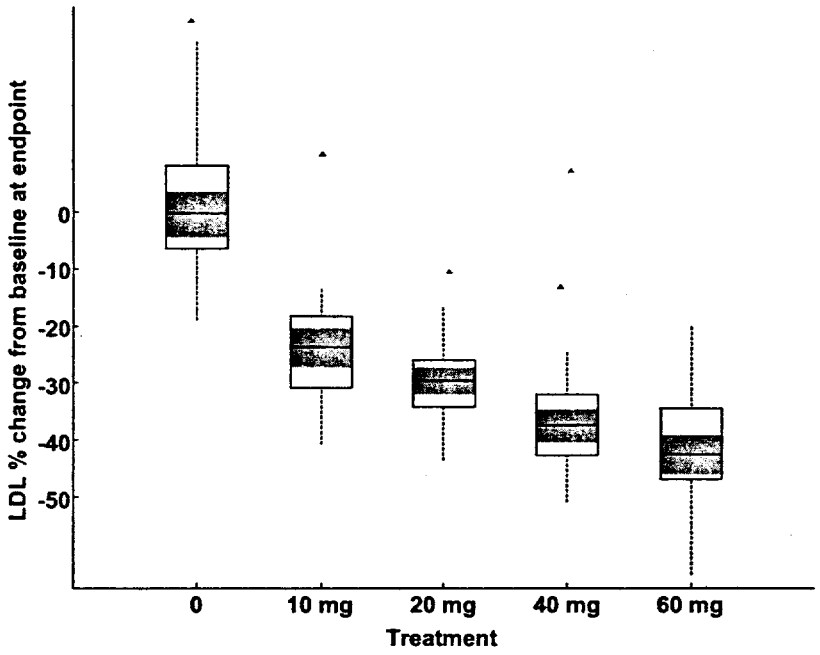
treatment groups, the mean percent decrease in LDL-C was –41% for protocol 146-009, -35% for 146-010, and –34% for 146-011. Greater lipid-altering effects were consistently seen for all lipid parameters measured in the 146-009 than for the other 2 studies. This Reviewer was unable to find any differences 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 4: EXCEL Study Mean % Change From Baseline in Lipids With Mevacor

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 graph

Figure 2: 146-009 Boxplot of LDL-C Responses



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

In summary, these findings support the use of lovastatin XL as treatment to lower LDL-C, TC, and TG, and increase HDL-C in patients with dyslipidemia who are at risk for atherosclerosis. In addition, data with immediate-release lovastatin support the use of lovastatin XL in established CHD to slow the progression of coronary atherosclerosis, and as a treatment to lower Apo B.

Indications not supported by the lovastatin XL clinical program include the [ ]

The sponsor's request for the proposed indications for [ ] are also not supported by the data submitted (in the form of clinical studies performed with Mevacor). In addition, no data on the interaction of lovastatin XL with other drugs were submitted, for either for safety or efficacy concerns. Given the delayed and extended-release properties of the extended-release formulation, assumptions on drug interactions cannot necessarily be made from lovastatin IR data.

Finally, the sponsor's request for the indications as a [ ] Therefore, approval for these indications is not recommended at this time.

C. Safety

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 uncommon 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 patients as it was in non-geriatric patients. Serious Adverse Events were infrequent, and were most commonly observed in the Cardiovascular system, which 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 occurred in one patient

(010-3094) receiving lovastatin XL 20 mg, and CPK elevations ≥10 X ULN occurred in 2 patients, both of whom were receiving lovastatin XL 20 mg (010-3062 and 010-3150).

The most common Treatment Emergent Signs and Symptoms (TESS) occurring in the pooled controlled studies safety analysis are as follows (similar results were obtained for studies 146-009, 146-010 and 146-011 when analyzed individually)

Table 5: 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)

The safety testing was adequate to assess common AEs and treatment emergent laboratory abnormalities 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 that were not adequately addressed by the sponsor's clinical program and by the data submitted. As no new data were presented to support these changes, it is recommended that the safety labeling for lovastatin XL contain the same warnings and precautions as for Mevacor.

Finally, 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.

D. Dosing

The efficacy and safety data from the Lovastatin XL clinical program support the use of lovastatin XL in patients with hypercholesterolemia who are at risk for atherosclerotic vascular disease, in a dosage range of 10-60 mg once daily at bedtime. 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 (ATP-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 in LDL-C and TC.

E. Special Populations

The efficacy and safety results for lovastatin XL were similar for male and female patients, and for geriatric and non-geriatric patients. There were too few non-Caucasian patients to evaluate by race. Lovastatin XL is contraindicated in women who are or may become pregnant and in lactating mothers. Lovastatin may cause fetal harm when administered to pregnant women. Pediatric studies have not yet been performed for lovastatin XL, but the sponsor has submitted a proposal for a pediatric safety and efficacy study. Lovastatin IR, however, has been studied in children (ages 10-16) for doses of lovastatin IR up to 40 mg a day, and the safety and efficacy profiles appear to be similar to those seen with adults. Studies have also not been performed in patients with renal and hepatic impairment.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication, Dose, Regimens, Age Groups

Lovastatin extended-release (lovastatin XL) has been submitted under NDA 21-316 under the proposed trade name of Altocor. Lovastatin XL is being proposed for use in patients with dyslipidemia who are at risk for atherosclerotic vascular disease.

Lovastatin XL is an extended-release formulation of lovastatin, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (a "statin"). Lovastatin is administered orally as an inactive lactone, which is hydrolyzed to its active form, the corresponding beta-hydroxyacid. The mechanism of action for the beta-hydroxyacid, which is common to all the statin medications, is as a competitive inhibitor of the HMG-CoA reductase enzyme. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the intracellular synthesis of cholesterol. The liver is the principal site of action for lovastatin. Preclinical and clinical data show that lovastatin can suppress cholesterol synthesis and up-regulate the number of hepatic LDL receptors[1]. This leads to increased uptake of LDL-C from the systemic circulation by hepatic cells and reduced plasma levels of LDL-C.

The sponsor is proposing lovastatin XL:

- [ ]
- In established CHD, to slow the progression of coronary atherosclerosis and lower TC and LDL-C
- In hyperlipidemia, to decrease the risk for atherosclerotic vascular disease due to hypercholesterolemia, and as an adjunct to diet for the reduction of elevated TC, LDL-C, apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia Fredrickson types IIa and IIb

Lovastatin XL is being proposed for once daily oral administration in a dosage range of 10-60 mg.

B. Historical Background

Hypercholesterolemia has been well established as a major risk factor for CHD. Large epidemiologic studies have shown that the relationship between serum cholesterol and CHD is continuous and graded over the entire range of serum cholesterol values, and that

[1] Bradford RH, Shear CL, Chremos AN, Dujovne C, Downton M, Franklin FA, Gould AL, Hesney M, Higgins J, Hurley DP, Langendorfer A, Nash DT, Pool JL, Schnaper H. Expanded clinical evaluation of lovastatin (EXCEL) study results. Arch Intern Med 1991;151:43-49.

the risk of CHD rises steadily with increasing serum cholesterol[2, 3]. Large clinical endpoint trials aimed at reducing TC or LDL-C have shown a reduction in the risk of CHD death and acute, major cardiovascular (CV) events with cholesterol-lowering therapy[4, 5]. These trials have demonstrated risk reductions in patients with established CHD (primary prevention)[6, 7], and without CHD (secondary prevention)[8, 9, 10] across a broad range of baseline cholesterol levels. Some of the strongest evidence for risk reduction in CHD with cholesterol-lowering therapy has been demonstrated in trials using HMG-CoA reductase inhibitors, however, risk reductions have also been shown with other cholesterol-lowering interventions, such as diet, fibrates, niacin, and bile-acid sequestrants.

Clinical trials have demonstrated that the treatment of risk factors for CHD, such as dyslipidemia with lipid-altering therapy, can reduce the risk of CHD by about 25-35%. In accordance with recent clinical trials evidence, the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults presented updated recommendations for cholesterol management in May, 2001[11]. The panel continued to identify LDL-C as the primary target of cholesterol-lowering therapy and to recommend

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[2] Stamler J, Wentworth D, Neaton JD, for the MRFIT Research Group. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356 222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 1986; 256 (20):2823-2828.

[3] Castelli WP, Anderson K, Wilson PWF, Levy D. Lipids and risk of coronary heart disease. The Framingham study. Ann Epidemiol 1992; 2:23-28.

[4] Lipid Research Clinics Program. The lipid research clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984; 251 (3):351-364.

[5] Frick MH, Elo O, Haapa K, Heinonen O, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Maenpaa J, Malkonen M, Manttari M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjoblom T, Nikkila E. Helsinki heart study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237-1245.

[6] Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333:1301-1307.

[7] Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. JAMA 1998;279 (20):1615-1622.

[8] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-1389.

[9] The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349-1357.

[10] Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun CC, Davis BR, Braunwald E for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001-1009.

[11] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285 (19):2486-2497.

the increased emphasis on CHD risk status as a guide to the type and intensity of cholesterol-lowering therapy. Current drug treatment guidelines recommend LDL-C treatment goals based on CHD risk as follows

Table 6: NCEP Guidelines for Cholesterol Reduction

Patient Category	LDL-C goal (mg/dL)	LDL-C Treatment Initiation Level (mg/dL)
Without CHD and with fewer than 2 risk factors (10-year risk of major coronary events <10%)	<160	≥190 (160-189: LDL-lowering optional)
Without CHD and with 2 or more risk factors (10-year risk ≤20%)	<130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
With CHD or CHD risk equivalents, e.g., diabetes (10-year risk >20%)	≤100	≥130 (100-129: drug optional)

Immediate-release lovastatin, as Mevacor, has been clinically available since 1987 as a cholesterol-lowering agent, and is indicated for the treatment of dyslipidemia in patients at risk for atherosclerotic vascular disease[12]. Mevacor is approved for use as primary prevention of CHD in patients with average to moderately elevated TC and LDL-C, and below average HDL-C. Specifically in this population, Mevacor is indicated to reduce the risk of MI, unstable angina, and coronary revascularization procedures. Mevacor has also been shown to slow the progression of coronary atherosclerosis in patients with CHD. Mevacor also has been shown to be effective in reducing TC and LDL-C in familial and non-familial forms of primary hypercholesterolemia and mixed dyslipidemia (types IIa and IIb).

C. Relevant Clinical Experience With Mevacor (lovastatin)

1. Efficacy

In a multi-center, double-blind, placebo-controlled clinical study in patients with primary hypercholesterolemia, Mevacor in doses ranging from 10-40 mg once a day was compared to placebo. Mevacor significantly reduced TC and LDL-C, modestly reduced TG, and modestly increased HDL-C after 6 weeks of treatment. Results from this study, per the Mevacor package insert, are summarized in the following table

Table 7: Mean % Change From Baseline in Lipids, Mevacor Package Insert

Treatment	n =	TC	LDL-C	HDL-C	TG
Placebo	33	-2	-1	-1	+9
Mevacor, dose					
10 mg qD	33	-16	-21	+5	-10
20 mg qD	33	-19	-27	+6	-9
10 mg BID	32	-19	-28	+8	-7
40 mg qD	33	-22	-31	+5	-8
20 mg BID	36	-24	-32	+2	-6

Mevacor was evaluated for long-term safety and efficacy in the Expanded Clinical Evaluation of Lovastatin (EXCEL) study[1]. EXCEL was a large (n = 8,245), multi-center,

[12] Medical Economics Company Inc. Mevacor Tablets (Merck) [2001]. In Physicians' Desk Reference PDR Electronic Library. [Online]. 2001 Physicians' Desk Reference. <http://www.pdrel.com/> ["Mevacor"] [2001, Feb. 08].

double-blind, randomized, placebo-controlled, clinical trial, which compared Mevacor in doses from 10-80 mg a day to placebo. Mevacor showed statistically significant decreases in TC and LDL-C, modest decreases in TG, and modest increases in HDL-C. These changes were sustained throughout 48 weeks of treatment, and similar results were obtained in the 2-year extension arm of the study[13]. Results for the EXCEL study (after 48 weeks of treatment) are summarized in the following table

Table 8: Mean % Change From Baseline in Lipids, EXCEL study

Dose	n	TC	LDL-C	HDL-C	TG
Placebo	1663	+0.7	+0.4	+2	+4
Mevacor 20 mg	1642	-17	-24	+6.6	-10
Mevacor 40 mg (20 mg BID)	1646	-24	-34	+8.6	-16
Mevacor 40 mg	1645	-22	-30	+7.2	-14
Mevacor 80 mg (40 mg BID)	1649	-29	-40	+9.5	-19

Mevacor has been evaluated in a large clinical endpoint study, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), for the primary prevention of major coronary events[6]. AFCAPS/TexCAPS was a multi-center, randomized, placebo-controlled trial in 6,605 patients with elevated TC and LDL-C, below average HDL-C, and no history of CV disease. Treatment with Mevacor compared to placebo resulted in statistically significant mean decreases in TC, LDL-C and TG, and increases in HDL-C, and was shown to decrease the rate of major coronary events compared to placebo by 37% over the course of 5.2 years. The relative risk of the secondary endpoint (unstable angina, MI, and cardiovascular revascularization procedures) was also reduced by 33%.

Mevacor has also been evaluated in smaller clinical angiographic endpoint trials for the treatment of atherosclerosis. Three of these studies are: the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT); the Monitored Atherosclerosis Regression Study (MARS); and the Asymptomatic Carotid Artery Progression Study (ACAPS). Two of these studies (CCAIT and MARS) investigated the effects of lovastatin on coronary atherosclerosis, and the other (ACAPS) investigated lovastatin's effects on carotid atherosclerosis.

CCAIT was a randomized, double-blind, placebo-controlled study in 331 patients with hypercholesterolemia and diffuse coronary atherosclerosis, who were treated with either placebo or lovastatin 20-80 mg daily[14]. Coronary arteriograms were assessed at baseline and after 2 years of treatment, and were assessed by visual estimation and computerized quantitative measurement. Lovastatin was shown to significantly slow the progression of lesions [measured by the mean change per-patient in minimum lumen diameter (primary

[13] Bradford RH, Shear CL, Chremos AN, Dujovne CA, Franklin FA, Grillo RB, Higgins J, Langendorfer A, Nash DT, Pool JL, Schnaper H. Expanded clinical evaluation of lovastatin (EXCEL) study results: Two-year efficacy and safety follow-up. Am J Cardiol 1994;74:667-673.

[14] Waters D, Higginson L, Gladstone P, Kimball B, Le May M, Boccuzzi SJ, Lesperance J, the CCAIT Study Group. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. Circulation 1994;89:959-968.

endpoint), and percent diameter stenosis], to significantly decrease the proportion of patients categorized with disease progression (lovastatin 33% vs placebo 50%), and to significantly decrease the proportion of patients with new lesions (lovastatin 16% vs placebo 32%). The clinical relevance of these findings is uncertain as the difference in coronary change of score between the treatments was small (0.04 mm). The findings were not associated with a reduction in coronary events during the trial.

MARS was a randomized, double-blind, placebo-controlled study in 270 patients with hypercholesterolemia and angiographically defined coronary artery disease (CAD)[15]. Patients were treated with either placebo or lovastatin 80 mg a day for 2 years. Coronary angiograms were assessed at baseline and after 2 years of treatment. There was no statistically significant difference between the groups in the primary end point (change in percent diameter stenosis). Treatment with lovastatin was found to slow the overall rate of progression (by global change score) [29% of lovastatin patients progressed vs 41% of placebo patients] and increased the overall rate of regression [23% of lovastatin patients vs 11% of placebo patients]. No statistical differences were observed between groups in the proportion of patients with clinical coronary events.

ACAPS was a randomized, double-blind, placebo-controlled study in 919 patients with moderately elevated LDL-C, early carotid atherosclerosis and no history of CHD[16]. Patients were randomized to four combination therapy groups: lovastatin/warfarin, lovastatin/warfarin placebo, lovastatin placebo/warfarin, or lovastatin placebo/warfarin placebo. Patients were assessed by carotid B-mode ultrasound at baseline and after 3 years of treatment. There was a statistically significant regression in carotid lesions [as measured by the maximum intimal-medial thickness (IMT)] in the lovastatin alone vs placebo alone groups (primary endpoint), and a reduction in the risk of major CV events (5 lovastatin patients experienced events vs 14 placebo patients), and all-cause mortality (1 lovastatin patient died vs 5 placebo patients).

One other study in the literature, the Familial Atherosclerosis Treatment Study (FATS), using combination therapy with Mevacor and colestipol will be briefly discussed.

FATS was a six-year randomized, double-blind, placebo-controlled study in 146 men with elevated apo B levels and a family history of CAD[14]. Patients had evidence of coronary atherosclerosis on a baseline arteriogram. Patients were randomized to treatment with colestipol + lovastatin, colestipol + niacin, or placebo. Combination therapy with either niacin or lovastatin with colestipol resulted in decreased progression of coronary atherosclerosis, an increased frequency of coronary atherosclerotic

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[15] Blankenhorn DH, Azen SP, Kramsch DM, Mack WJ, Cashin-Hemphill L, Hodis HN, DeBoer LWV, Mahrer PR, Masteller MJ, Vailas LI, Alaupovic P, Hirsch LJ, and the MARS Research Group. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). Ann Intern Med 1993;119:969-976.

[16] Furberg CD, Adams HP, Applegate WB, Byington RP, Espeland MA, Hartwell T, Hunninghake DB, Lefkowitz DS, Probstfield J, Riley WA, Young B for the Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. Circulation 1994;90:1679-1687.

regression, and a reduced incidence of CV events (death, MI, or the need for revascularization procedures).

Patients completing FATS were offered to continue indefinitely on triple therapy with niacin, lovastatin and colestipol after completion of the original study. Seventy-five (75) patients continued with a subsequent median follow-up of eight years[16]. The patients who declined further participation were returned to usual care (n = 101) and had a median follow-up of 10 years. Clinical event rates in the triple therapy group were significantly reduced compared to the usual care group (5.3% vs 18.8% respectively), and the event curves diverged steadily over 8-10 years. Triple therapy was not part of the original treatment plan, was added as an extension after the original study was completed, and was an open-label, uncontrolled design.

2. Safety

In clinical studies, Mevacor has been found to be generally well tolerated. In the EXCEL study, patients taking Mevacor experienced clinical adverse events of similar types and frequencies to those of placebo patients. In patients up to 48 weeks of treatment, 4.6% of patients treated were discontinued due to clinical or laboratory adverse events (AEs) [rated by the Investigator as at least possibly related to study medication] vs 2.5% of placebo patients. Mevacor and other HMG-CoA reductase inhibitors occasionally cause myopathy, and rarely, rhabdomyolysis. In EXCEL, there was one case of myopathy among 4,933 patients randomized to lovastatin 20-40 mg a day, and 4 cases of myopathy among 1649 patients randomized to 80 mg a day. The risk of myopathy is increased by concomitant therapy with certain drugs, including gemfibrozil and other fibrates, niacin, and CYP3A4 inhibitors, such as cyclosporine, azole antifungals, macrolide antibiotics, HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice. Persistent increases in serum transaminases occurred in up to 1.9% of adult patients who received lovastatin for at least one year in clinical trials. The incidence rates by dose are summarized in the following table:

Table 9: Mevacor, Incidence of Persistent Serum Transaminase Elevations, EXCEL Study

Treatment	Incidence of Persistent Serum Transaminase Increases
Placebo	0.1%
Mevacor 20 mg a day	0.1%
Mevacor 40 mg a day	0.9%
Mevacor 80 mg a day	1.5%

In AFCAPS/TexCAPS, the number of participants with consecutive elevations of ALT or AST was not significantly different between Mevacor and placebo over a median of 5.1 years of follow-up [Mevacor 0.6% vs placebo 0.3%]. Elevated transaminases resulted in the discontinuation of 6 patients (0.2%) from the Mevacor group (n=3,304) vs 4 patients (0.1%) from the placebo group (n=3,301). In post-marketing experience, symptomatic liver disease has been reported rarely at all doses.

D. Rationale for the Lovastatin XL Clinical Program

In the EXCEL clinical study reported in 1991, lovastatin 20 mg BID produced a significantly greater reduction in LDL-C than was seen with a 40 mg dose of lovastatin given once a day. Data in dogs by McClelland et al[17] also demonstrated that systemic concentrations of HMG-CoA reductase inhibitors could be minimized and the efficacy of the inhibitor enhanced by oral administration of an extended-release dosage form of simvastatin. The sponsor states that "*These observations suggested that an extended-release formulation of an HMG-CoA reductase inhibitor might provide a dose-sparing advantage for the treatment of hypercholesterolemia.*" [Italics mine. From: Aura Laboratories, NDA #21-316, Clinical Data Section 8, Volume 1.51, page 7]. The sponsor goes on further to state that lovastatin XL presents lovastatin to the liver in a more sustained manner compared to Mevacor. In PK studies, lovastatin XL demonstrated a more prolonged T_{max} and a lower C_{max} compared to Mevacor, and a greater bioavailability (as measured by AUC) of lovastatin with equivalent bioavailability of lovastatin acid (active drug) compared to Mevacor. However, as the plasma concentration of prodrug, but not active drug, was increased, the sponsor states that this will result in greater efficacy of lovastatin XL but would not be associated with greater safety risks.

Thus, the sponsor has hypothesized that lovastatin XL will provide greater efficacy (lipid-altering effects) than Mevacor, but without the greater safety risks associated with higher doses of lovastatin.

The sponsor is requesting the following indications for lovastatin XL:

Indications in the Mevacor package insert (PI) that are supported by this NDA, per the sponsor:

[ ]

- CHD – lovastatin XL is indicated
  - To slow the progression of atherosclerosis in patients with CHD as part of a treatment strategy to lower TC and LDL-C to target levels.
- Hypercholesterolemia – therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lovastatin XL is indicated
  - As an adjunct to diet for the reduction of elevated TC and LDL-C in patients with primary hypercholesterolemia (heterozygous familial and non-familial) and mixed

[17] McClelland GA, Stubbs RJ, Fix JA, Pogany SA Zentner GM. Enhancement of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor efficacy through administration of a controlled-porosity osmotic pump dosage form. Pharm Res 1991;8:873-876.

dyslipidemia (Fredrickson types IIa and IIb) when the response to diet restricted in saturated fat and cholesterol and to other non-pharmacological measures alone has been inadequate.

Indications NOT currently in the Mevacor package insert but are (per the sponsor) supported by this NDA for incorporation into the lovastatin XL package insert:

- In the section [redacted] the following are added:

[redacted]

- The section [redacted] changed to [redacted] and the following are added:
  - Reducing TG
  - Reducing Apo B
  - Increasing HDL-C
  - [redacted]

E. State of Armamentarium

Lovastatin immediate-release, as Mevacor, has been commercially available since 1987 for the treatment of hypercholesterolemia. Mevacor has been extensively studied in clinical trials, and there is considerable post-approval experience with Mevacor and other clinically available statin medications. Other statin medications currently available for clinical use include:
Mevacor (lovastatin)
Zocor (simvastatin)
Lipitor (atorvastatin)
Lescol (fluvastatin)
Pravachol (pravastatin)

In additional, there are several other classes of drugs currently available for the treatment of dyslipidemias. These medications include (but are not limited to): fibric acid derivatives [gemfibrozil (Lopid), fenofibrate (TriCor), clofibrate (Atromid-S)], bile acid sequestrants [cholestyramine (Questran, Questran Lite), colestipol (Colestid), colesevelam hydrochloride (WelChol)], niacin [prescription and non-prescription forms, immediate-release and sustained-release preparations], and others.

F. Important Milestones in Clinical Development

NDA- 21-316 is covered under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The following FDA guidance documents were referred to in the review of this NDA:

Guidance for Industry. Applications Covered by Section 505(b)(2)[18]; and

[18] U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry. Applications Covered by Section 505(b)(2), Draft Guidance 7/20/99. In U.S. Food and Drug Administration. Center for Drug Evaluation and Research

Guidelines for the Clinical Evaluation of Lipid-Altering Agents in Adults and Children[19]

The initial IND for lovastatin XL was submitted to the FDA on 11-June-1997 (IND —— Concerns were raised in the initial Pharmacology Review on 25-July-1997 about the potential for GI toxicity. In response to this concern, a 3-month GI toxicity study on beagle dogs was completed on 24-Nov-1998. No overt signs of toxicity were noted.

An end of Phase II meeting was held on 09-Dec-1998, at which time a Phase III clinical program was proposed and agreed to (See Aura Laboratories, NDA #21-316, Volume 1.51, Section 3 Dialogue and Agreements with the FDA, pages 10-14 for a complete discussion of the issues). There were no major disagreements or outstanding issues.

No significant protocol amendments were made to the clinical studies.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Please refer to the Chemistry, Animal Pharmacology and Toxicology, Biopharmaceutics, and Statistical reviews for this NDA.

Briefly, the Animal Pharmacology and Toxicology Reviewer has stated that "Since lovastatin is an approved drug, its safety profile has been well characterized, and is used at approved doses, the approval (AP) of the current application of Altocor is recommended, pending labeling changes." [Antonipillai, Indra, Ph.D., Pharmacotoxicology Reviewer, Division of Metabolic and Endocrine Drug Products, CDER. Review dated 17-Sep-2001].

III. Human Pharmacokinetics and Pharmacodynamics

Please refer to the Biopharmaceutics review.

Briefly, the sponsor's findings from the PK studies on lovastatin XL are:

- Lovastatin XL has delayed and extended-release properties relative to Mevacor. Lovastatin XL had a more prolonged T_{max} and a lower C_{max} compared to Mevacor.
- Lovastatin XL has a greater bioavailability of the prodrug lovastatin compared to Mevacor, but has equivalent bioavailability of the active drug lovastatin acid and the total and active inhibitors of HMG-CoA reductase.

[Online]. 2001 Regulatory Guidance. Guidance Documents Web page. <http://www.fda.gov/cder/guidance/2853dft.htm> ["505(b)(2)"] [2001,Nov. 07]

[19] U.S.Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidelines for the Clinical Evaluation of Lipid-Altering Agents in Adults and Children, September, 1990. In U.S. Food and Drug Administration. Center for Drug Evaluation and Research [Online]. 2001 Regulatory Guidance. Guidance Documents Web page. <http://www.fda.gov/cder/guidance/lipid.pdf > ["lipid-altering agents"] [2001,Nov. 07]

- Food decreases the bioavailability of lovastatin XL (food increases the bioavailability of Mevacor).
- Dose proportionality was established up to a dose of 60 mg.
- Gender and body weight did not affect the PK of lovastatin XL.

Briefly, findings from Phase II clinical trials show that:

- Lovastatin XL produces lipid changes that are at least as large as Mevacor
- The "before bedtime" dosing of lovastatin XL produced numerically greater, but not significantly greater, decreases in LDL-C, TC, TG, and increases in HDL-C.

IV. Description of Clinical Data and Sources

A. Overall Data

There were 13 clinical studies submitted to the NDA from the Aura Laboratories lovastatin XL clinical program. Data were submitted to the NDA in paper and electronic formats. As this is a 505(b)(2) application, the sponsor also refers to the Mevacor package insert and relevant medical literature on lovastatin, which were reviewed as appropriate.

B. Tables Listing the Clinical Trials

Thirteen (13) clinical studies were submitted to the NDA, including 8 Phase I studies, 2 Phase II studies, and 3 Phase III studies (2 controlled, 1 uncontrolled). These studies are summarized briefly in the following tables.

1. Phase I studies:

Table 10: NDA- 21-316 Summary of Phase I Clinical Trials

Phase I Studies		
Study Number	**Study Design/Description**	**Results**
146-001	Phase I PK Study Randomized, single-dose, open-label, 2-way cross-over study, which evaluated the safety and PK profile of lovastatin XL 40 mg vs Mevacor 40 mg in 8 healthy male subjects.	Lovastatin XL demonstrated delayed and extended-release properties, by a lower C_{max} and prolonged T_{max} relative to Mevacor. Lovastatin XL demonstrated enhanced bioavailability compared to Mevacor.
146-002	Phase I PK Study Randomized, single-dose, open-label, 3-way cross-over study, which evaluated the effect of food on the PK profiles of lovastatin XL 40 mg and Mevacor 40 mg in 9 healthy male subjects.	Confirmed the delayed and extended-release properties of lovastatin XL relative to Mevacor. Also demonstrated the greater bioavailability of lovastatin XL when given before a meal (fasting), and decreased bioavailability of lovastatin XL with food.
146-003	Phase I PK Study Randomized, single-dose, open-label, 2-period cross-over study, which evaluated alternative formulations of extended-release lovastatin (lovastatin XL formulation A vs lovastatin XL ———) in 6 healthy males.	Both formulations exhibited delayed-release characteristics. ——— had no merit over formulation A.
146-004	Phase I Safety and PK Study Randomized, single-dose, open-label, 3-period cross-over study, which evaluated alternative formulations of extended-release lovastatin (2 extended-release lovastatin XL formulations vs Mevacor) in 6 healthy males.	The 2 extended-release lovastatin XL formulations had the same degree of increased bioavailability compared with Mevacor as had the previous lovastatin XL formulation, and no further clinical development was undertaken with these 2 formulations.
146-007	Phase I PK Study Randomized, single-dose, open-label, 3-way cross-over study in 8 healthy males who received lovastatin XL 10 mg, 20 mg and 40 mg.	Dose proportionality suggested by mean dose-normalized C_{max} and AUC_{0-48hr}.
146-012	Phase I PK and Effects of Gender and Body Weight on PK Randomized, single-dose, open-label, 3-period, 6-sequence cross-over study in 24 subjects (12M, 12F), which evaluated the effect of dose (20 mg, 40 mg, and 60 mg) on the PK of lovastatin XL, and the effects of gender and body weight on PK.	Body weight and dose-normalized C_{max} and AUC_{0-72hr} were equivalent across the 3 lovastatin XL doses in both genders, indicating dose proportionality up to 60mg/day. There was no effect of gender on PK.
146-102	Phase I Bioavailability/Bioequivalence Study Randomized, single-dose, open-label, 2-way cross-over study in 24 healthy males, which compared lovastatin XL 60 mg tablets with lovastatin XL 20 mg + 40 mg tablets.	Lovastatin XL 60 mg was bioequivalent to lovastatin XL 20 mg + 40 mg tablets.
146-103	Phase I Bioavailability, Fasted Conditions Study Randomized, single-dose, open-label, 2-way cross-over study in 24 healthy males, which compared lovastatin XL 40 mg in am (fasting) vs Mevacor 40 mg in am (fasting)	Lovastatin XL 40 mg exhibited extended-release characteristics vs Mevacor 40 mg.

2. Phase II studies

Table 11: NDA 21-316 Summary of Phase II Clinical Trials

Phase II Studies		
Study Number	**Study Design/Description**	**Results**
146-006	Phase II PK/PD Study Multi-dose, cross-over study comparing lovastatin XL 40 mg to Mevacor 40 mg in 26 (12M, 14F) subjects with hypercholesterolemia (2, 4-week treatment periods). Evaluated PK and PD of lovastatin XL and Mevacor after the first dose and at steady state after 28 days of treatment. Lipid parameters were compared from baseline to after 3-4 weeks of treatment for lovastatin XL vs Mevacor.	Demonstrated accumulation of lovastatin and lovastatin acid, confirmed extended-release properties of lovastatin XL at Day 28, and increased bioavailability of inactive prodrug lovastatin relative to Mevacor. Bioavailability of lovastatin acid and active inhibitors of HMG-CoA reductase were equivalent to Mevacor at Day 28. LDL-C and TC reduction were greater with lovastatin XL compared to Mevacor (by 4% and 2% respectively, $p<.05$ for both), and TG reduction and HDL increase were equivalent to Mevacor.
146-008	Phase II Efficacy and Safety Study Multi-center, randomized, parallel group, placebo-controlled multi-dose (4 weeks) study in 68 subjects with primary hypercholesterolemia, which evaluated lovastatin XL 40 mg administered before breakfast, after dinner, and before bedtime.	Mean LDL-C was reduced from 32 to 37% across the 3 dosing time regimens. There was no statistically significant difference in the lipid changes seen, but the "before bedtime" treatment group had consistently greater numerical reductions in LDL-C, TC and TG, and greater increases in HDL-C. Based on these results, all subsequent trials administered lovastatin XL at bedtime.

3. Phase III

a) Controlled Studies

(Please refer to sections VII and VIII in this review for more detailed discussions of the efficacy and safety results of these studies):

Table 12: NDA 21-316 Summary of Phase III Controlled Clinical Trials

Controlled Studies		
Study Number	**Study Design/Description**	**Results**
146-009	Phase III Dose-Response Safety and Efficacy Study Multi-center, double-blind, randomized, parallel group, placebo-controlled study in 172 subjects with hypercholesterolemia, which evaluated lovastatin XL 10 mg, 20 mg, 40 mg, and 60 mg, vs placebo for 16-weeks (4-week single-blind/placebo run-in period followed by a 12-week double-blind treatment period).	Statistically significant decreases seen in all lovastatin XL treatment groups vs placebo for LDL-C, TC, and TG. Significant increases in HDL-C for all lovastatin XL groups (except 10 mg group) vs placebo. Dose-response was seen for LDL-C and TC. No notable or unexpected safety findings were seen.
146-010	Phase III Safety and Efficacy Study Multi-center, randomized, double-blind, cross-over study in 358 subjects with hypercholesterolemia, which evaluated lovastatin XL 20 mg vs Mevacor 20 mg, and lovastatin XL 60 mg vs Mevacor 60 mg for 34 weeks [4-week single-blind/placebo run-in period, 12-week double-blind treatment period, 6-week placebo/washout period, and 12-week double-blind treatment (cross-over) period].	Statistically significant decrease in LDL-C for lovastatin XL 20 mg vs Mevacor 20mg (by 3%). There were no other significant differences between the lovastatin XL and Mevacor treatment groups for efficacy. Safety results were comparable between lovastatin XL and Mevacor.

b) Uncontrolled Study

(Please refer to sections VII and VIII in this review for more detailed discussions of the efficacy and safety results of this study):

Table 13: NDA 21-316 Summary of Phase III Uncontrolled Clinical Trials

Uncontrolled Studies		
Study Number	**Study Design/Description**	**Results**
146-011	Phase III Extended Safety, Efficacy and Tolerability Study after Successful Completion of Protocol 146-009 or 146-010 Multi-center, double-blind, randomized, parallel-group extension study in 358 subjects with primary hypercholesterolemia rolled over after successfully completing either study 146-009 or 146-010. Evaluated the safety and efficacy of lovastatin XL 40 mg or 60 mg for an additional 12 weeks of treatment.	Demonstrated the durability of lipid-altering responses to lovastatin XL over an additional 12 weeks of treatment. There were no new notable or unexpected safety findings.

C. Literature Review

Relevant published literature on Mevacor was reviewed as appropriate. Please see summary of literature in section II, C

V. Clinical Review Methods

A. Describe How Review was Conducted

The pivotal studies for this review were the 2 Phase III, controlled clinical trials 146-009 and 146-010. These studies were reviewed in detail and provide the majority of the information on lovastatin XL available for the clinical review. In addition, protocol 146-011, the uncontrolled extension study, was also reviewed in detail, and provided additional safety and efficacy information. The sponsor's efficacy and safety data were confirmed or recalculated by this Reviewer using electronic data sets included with the submission. In addition, efficacy analyses of Studies 146-009 and 146-010 were performed by the Statistical Reviewer using data obtained from these trials, and will be referred to in this review. For a detailed discussion of the statistical findings, please refer to the statistical review [by: Mele, Joy M.S. Division of Biometrics, CDER, FDA, NDA #21-316, 14-Dec-2001]

B. Overview of Methods used to Evaluate Data Quality and Integrity

Audits of 4 clinical sites (2 each for studies 146-009 and 146-010) were completed by the Division of Special Investigations (DSI). The clinical sites audited include:
Study 146-009: Site 28, Dr. Margaret Drehobl and Site 29, Dr. Edward Gillie
Study 46-010: Site 8, Dr. Jon LeLevier, and Site 5, Dr. Larry Gilderman
There were no significant findings in these audits.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor states that "All clinical studies for —— (lovastatin USP) Extended-Release Tablets done by Aura Laboratories, Inc., a division of Andrx Pharmaceuticals, Inc. of Fort Lauderdale, Florida, were conducted in compliance with 21 CFR Part 50

(Protection of Human Subjects), Part 56 (Institutional Review Boards) and Part 312, Subpart D (Responsibilities of Sponsor and Investigators). " [From NDA 21-316 Section 8.99 subsection XIII. GCP Compliance Statement]. [Note: — was the originally proposed name for lovastatin XL, which has since been changed to Altocor.]

D. Evaluation of Financial Disclosure

A signed Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) was attached, that stated that the sponsor had not entered into any financial arrangement with any of the clinical investigators in the clinical studies.

VI. Integrated Review of Efficacy

A. Brief Conclusions

For the primary endpoint, lovastatin XL produced statistically significant and clinically important mean percent decreases in LDL-C from baseline to endpoint, and compared to placebo. There was a dose-response effect seen for LDL-lowering with increasing doses of lovastatin XL. The majority of the LDL-lowering response was seen after 4 weeks of treatment, and the response was durable over 6 months of treatment. Similar responses were seen when lovastatin XL 60 mg was compared to Mevacor 60 mg, and a significantly greater (by 3%), but clinically minor, response was seen when lovastatin XL 20 mg was compared to Mevacor 20 mg.

For the secondary endpoints, lovastatin XL produced significant decreases in TC and TG, and significant increases in HDL-C. The TC-lowering results were similar to those seen for LDL-C. There were significant decreases in TC from baseline to endpoint, and compared to placebo, and there were progressive decreases in TC with increasing doses of lovastatin XL. There were significant increases in HDL-C for all doses of lovastatin XL, except for the 10 mg dose; however, there was no dose-response effect seen. The HDL-C increases ranged from 4-13% with a plateauing of the HDL-raising effect at doses of lovastatin XL 20 mg or greater. Mean percent decreases in TG were highly variable, did not demonstrate a dose-response effect, and produced mean percent decreases from baseline of –8 to –25%. The HDL-C and TG results are similar to historical data for Mevacor.

For a detailed discussion regarding efficacy results and proposed labeling, please refer to Appendix A Proposed Labeling.

B. General Approach to Review of the Efficacy of the Drug

As stated in section VI, A., the pivotal studies for this review were the 2 Phase III controlled clinical trials 146-009 and 146-010. These studies were reviewed in detail as well as protocol 146-011, the uncontrolled extension study. The sponsor's efficacy and safety data were confirmed or recalculated by this Reviewer using electronic data sets included with the submission.

C. Detailed Review of Trials by Indication

The overall objectives of the clinical program for lovastatin XL were: to demonstrate statistically significant lipid-altering effects from baseline to endpoint for the primary (LDL-lowering) and secondary (HDL-raising, and TC and TG lowering) endpoints; to demonstrate dose-response lipid-altering effects; and to demonstrate that the lipid-altering effects would be durable over the 6 month of treatment. In addition, for Protocol 146-010, which compared lovastatin XL to Mevacor, the study sought to demonstrate that lovastatin XL would have lipid-altering effects at least as effective as Mevacor.
The 2 controlled clinical studies 146-009 and 146-010, and the uncontrolled study 146-011 have been reviewed in detail, as follows.

1. Protocol 146-009

a) Study Design for Protocol 146-009

(1) Study Design

Protocol 146-009 "A dose-response, safety and efficacy study of lovastatin XL in adult patients with hypercholesterolemia" was a multi-center, randomized, double-blind, placebo-controlled, parallel group, 16-week, study conducted at 12 clinical sites nationally. The study evaluated the efficacy and safety of four different doses (10 mg, 20 mg, 40 mg, and 60 mg) of lovastatin XL vs placebo in 172 patients with hypercholesterolemia.

(2) Study Objectives

The objectives of the study were to assess the dose response, efficacy and safety of lovastatin XL compared to placebo over 12 weeks of active treatment. The primary efficacy endpoint for each treatment group was the percent reduction in LDL-C after treatment compared to baseline. Secondary efficacy endpoints were the percent changes in TC, HDL-C, and TG after treatment compared to baseline.

(3) Eligibility Criteria

(a) Inclusion Criteria

1) Patient had signed the informed consent
2) Patients were cooperative male and female outpatients aged 21 to 70 years
3) Patient was willing to continue treatment in the 12-week Extension Period (Protocol 146-011)
4) Patients taking any lipid-modifying agent must have completed at least a 4-week washout of that agent prior to study entry (Visit 1). Lipid-modifying agents included statins (Mevacor, Zocor, Pravachol, Lescol, Lipitor, and Baycol), cholestyramine, fibrates (Lopid and Tricor), over-the-counter (OTC) fish oil, niacin, or food supplements that may have lipid-lowering effects. A stable dose of niacin <100 mg a day was permitted.
5) Patient must have followed an NCEP Step 1 diet for 4 weeks prior to Visit 1
6) Patient must have had a fasting plasma LDL-C level (based on Visit 1 laboratory data) with the following parameters:

a) For patients with CHD, peripheral vascular disease (PVD), or cerebrovascular disease (CVD) as determined by medical history: LDL-C > 100 mg/dL
b) For patients without CHD, PVD, or CVD and with ≥2 risk factors for heart disease (defined below): LDL-C ≥130 mg/dL
c) For patients without CHD, PVD, or CVD and with <2 risk factors for heart disease: LDL-C ≥160 mg/dL

Table 14: 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

7. Patient had a fasting plasma TG <350 mg/dL at Visit 1
8. CPK value was ≤3 X the upper limit of normal (ULN) [≤585 IU/L for male patients and ≤510 IU/L for female patients]

(b) Exclusion Criteria

1) Patient had received any lipid-modifying agent within 4 weeks prior to Visit 1
2) Premenopausal women, unless surgically sterile or using an effective method of contraception. Use of any oral contraceptives or any other hormonal methods of contraception was excluded.
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 a current diagnosis of malignancy, except for non-melanoma skin cancer
6) Patient had experienced acute MI, coronary revascularization procedure, or acute coronary insufficiency within the last 6 months
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 was taking 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 were 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 test for Hepatitis B or C
16) Patient had a 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 table. Study Visits 3 to 8 could occur within $\pm$3 days of the designated study day.

Table 15: 146-009 Study Visits and Procedures

	Screening	Diet/Placebo Run-in		Double-Blind Treatment				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Week (Study Day)	**-5 to -1 (-35 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		
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		X
Hepatitis B and C	X							

(a) Screening/Visit 1 (Weeks –5 to –1; Days –35 to –7)

Patients taking lipid-lowering drugs were seen on or before Day –35 to obtain informed consent and begin drug washout. Patients who were not following an NCEP Step I diet were seen on or before Day –35 to obtain informed consent and begin the NCEP diet. 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

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

(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:

- Diet and study instructions
- Concomitant medications record
- Vital signs (BP, pulse, and body temperature)
- Dispensing of study medication for Visits 2 and 3
- Adverse Event (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) and Visit 6 (Week 12; Day 84)

At Visits 5 and 6, 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)

(e) Visit 7 (Week 15; Day 105)

At Visit 7, 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

(f) End of Study/Visit 8 (Week 16; Day 112) or Early Termination

At Visit 8, 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 randomly assigned to one of 5 treatment groups, dosed once daily at bedtime, as follows:

Treatment A: Placebo once daily
Treatment B: Lovastatin XL 10 mg once daily
Treatment C: Lovastatin XL 20 mg once daily
Treatment D: Lovastatin XL 40 mg once daily
Treatment E: Lovastatin XL 60 mg once daily

Randomization occurred at the study sites using blocks of five dispensed sequentially by blinded study personnel. Study medication was supplied as 3 tablets within a sealed blister card containing one day's dose of medication, and dispensed for a 2-week period +

4 days extra medication. Placebo tablets were made to match the size and outside appearance of each strength of Lovastatin XL. 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 the percent change in LDL-C from baseline to endpoint. Baseline was defined as the average of the measurements taken after 3 and 4 weeks of placebo run-in treatments, at Visits 3 and 4 respectively. Endpoint was defined as the average of the measurements taken after 11 and 12 weeks of double-blind treatment, at Visits 7 and 8 respectively.

(b) Secondary

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

(c) Safety

Safety was assessed by the incidence and frequency of AEs, and by changes in vital signs, physical examinations, 12-lead 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 Intent-To-Treat (ITT) population included all randomized patients who received at least one dose of study medication and had at least one lipid measurement after taking study medication. The ITT population was the sponsor's primary efficacy analysis population. All Randomized patients was the primary safety population.

b) Results

Two-hundred eighty-seven (287) patients were screened at 12 study sites. One-hundred seventy-two (172) patients were randomized between 10-Jan-2000 and 05-May-2000. All Randomized and ITT patients by study treatment are summarized in the following table

Table 16: 146-009 Randomized and ITT Patients by Treatment Group

		Treatment				
	All	**Placebo**	**Lova 10**	**Lova 20**	**Lova 40**	**Lova 60**
All Randomized Patients, n =	172	34	35	34	33	36
ITT Patients, n =	169	34	33	34	33	35

(1) Baseline Characteristics and Demographics

Overall, 52% of ITT patients were male and 89% were Caucasian. Patient ages ranged from 29 to 70 years, with a mean age of 56.7 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 Lova 10 mg and Lova 60 mg groups compared to the other groups (Lova 10 mg: 48% male and 52% female; Lova 60 mg: 43% male and 57% female; All ITT patients 52% male and 48% female)
2) Baseline mean TG was higher in the Lova 20 mg group than in the other groups (Lova 20 mg mean TG 206 mg/dL vs 173.8-188.8 mg/dL for all other groups)

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

The baseline characteristics and demographics for the treatment groups are summarized in the following table:

Table 17: 146-009 Baseline Characteristics and Demographics

		Treatment				
	All	**Placebo**	**Lova 10**	**Lova 20**	**Lova 40**	**Lova 60**
ITT Patients, n =	169	34	33	34	33	35
Demographic Measure						
Gender, n (%)						
Male	90 (52)	18 (53)	16 (48)	19 (56)	19 (58)	15 (43)
Female	82 (48)	16 (47)	17 (52)	15 (44)	14 (42)	20 (57)
Age, years						
Mean	56.7	55.7	56.0	57.2	57.2	57.5
Median	58.0	55.5	57.0	58.5	59.0	58.0
min, max	29, 70	29, 70	38, 70	38, 70	38, 69	35, 68
Age ≥ 65 years, n (%)	33 (19)	9 (26)	5 (15)	5 (15)	5 (15)	9 (26)
Ethnicity, n(%)						
Caucasian	151 (89)	31 (91)	30 (91)	31 (91)	30 (91)	29 (83)
Black	9 (5)	0	2 (6)	2 (6)	2 (6)	3 (9)
Asian	0	0	0	0	0	0
Other	9 (5)	3 (9)	1 (3)	1 (3)	1 (3)	3 (9)
Risk Factors (RF)						
≥2 CAD RF or CHD, n (%)	93 (55)	20 (59)	15 (45)	20 (59)	20 (61)	18 (51)
<2 CAD RF, n (%)	76 (45)	14 (41)	18 (55)	14 (41)	13 (39)	17 (49)
Mean BMI, kg/M^2	27.7	28.0	28.3	26.8	27.2	28.1
Baseline Lipid Value						
Mean LDL-C, mg/dL		174.5	179.4	172.8	180.6	180.3
Mean HDL-C, mg/dL		43.5	45.1	45.1	44.0	48.9
Mean TC, mg/dL		252.5	259.3	261.4	262.8	263.8
Mean TG, mg/dL		174.8	174.6	206.0	188.8	173.8

(2) Patient Disposition

(a) Screening and Randomization

Of the 287 patients screened for the study, 115 (40% of total screened) were not randomized (screen failures). 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 40 screen failure patients (35% of all screen failures). Patients failing to meet eligibility criteria are summarized in the following table

Table 18: 146-009 Patients Failing to Meet Eligibility Criteria

Eligibility criteria not met, n = 115	n (%)
Failure to have appropriate lipid levels per inclusion criteria	40 (35)
Withdrawal of consent	34 (30)
Abnormal laboratory value	15 (13)
Lost to Follow-up	8 (7)
Other	18 (16)

(b) Dropouts

Of the 172 patients randomized to a treatment group, 160 patients completed treatment and 12 patients discontinued treatment prior to study completion. Of the 12 patients who discontinued, 6 discontinued for an AE, 3 withdrew consent, and 3 discontinued for other reasons. As the number of discontinuations that occurred during the study was small and was relatively evenly balanced across treatment groups, it is unlikely that dropouts significantly affected the overall study results. Patient discontinuations by treatment group are summarized in the following table

Table 19: 146-009 Patients Discontinued

		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)
Reason for Dropout						
Adverse event, n (%)	6 (3)	2 (6)	1 (3)	2 (6)	1 (3)	0
Withdrew consent, n (%)	3 (2)	0	1 (3)	1 (3)	0	1 (3)
Other, n (%)	3 (2)	0	1 (3)	0	0	2 (6)

(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, 169 of the 172 randomized patients (98%) 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 20: 146-009 Patients Reporting Any Concomitant Medication Use

		Treatment				
	All	**Placebo**	**Lova 10**	**Lova 20**	**Lova 40**	**Lova 60**
Randomized Patients, n =	172	34	35	34	33	36
Any conmed use, n (%)	169 (98)	34 (100)	33 (94)	34 (100)	32 (97)	36 (100)

A large number of different medications were used during the study (over 250 different medications were reported), with the majority of these medications used by a small number of patients (used by ≤ 2 patients per medication, or by $\leq 1\%$ of patients overall). The most commonly reported concomitant medications used during the study were multivitamins (by 39% of patients overall) and acetylsalicylic acid (35%). Only one patient, (Patient 2027) was reported as using a prohibited medication during the study. This patient resumed the lipid-altering medication Lipitor after deciding to withdraw from the study, but prior to actual study discontinuation. 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 in the following table

Table 21: 146-009 Concomitant Medications, Most Common (≥5%) Overall and by Treatment Group

		Treatment				
	All	**Placebo**	**Lova 10**	**Lova 20**	**Lova 40**	**Lova 60**
Randomized patients, n =	172	34	35	34	33	36
Medication						
Multivitamins	67 (39)	13 (38)	15 (43)	11 (32)	13 (39)	14 (39)
Acetylsalicylic Acid	60 (35)	9 (26)	11 (31)	14 (41)	15 (45)	11 (31)
Tocopherol	50 (29)	7 (21)	10 (29)	11 (32)	8 (24)	14 (39)
Ibuprofen	49 (28)	8 (24)	11 (31)	12 (35)	7 (21)	11 (31)
Ascorbic Acid	39 (23)	5 (15)	7 (20)	9 (26)	8 (24)	10 (28)
Calcium	36 (21)	8 (24)	8 (23)	4 (12)	7 (21)	9 (25)
Paracetamol	23 (13)	5 (15)	5 (14)	9 (26)	2 (6)	2 (6)
Levothyroxine	18 (10)	6 (18)	0	4 (12)	5 (15)	3 (8)
Estrogen	16 (9)	2 (6)	2 (6)	3 (9)	3 (9)	6 (17)
Pseudoephedrine	15 (9)	5 (15)	1 (3)	4 (12)	2 (6)	3 (8)
Hydrochlorothiazide	12 (7)	3 (9)	3 (9)	2 (6)	1 (3)	3 (8)
General Nutrients	11 (6)	0	3 (9)	5 (15)	0	3 (8)
Atenolol	9 (5)	3 (9)	2 (6)	0	3 (9)	1 (3)
Echinacea	9 (5)	1 (3)	2 (6)	2 (6)	2 (6)	2 (6)
Loratadine	9 (5)	5 (15)	2 (6)	0	1 (3)	1 (3)
Cyanocobalamin	8 (5)	2 (6)	1 (3)	2 (6)	1 (3)	2 (6)
Folic Acid	8 (5)	0	1 (3)	3 (9)	0	4 (11)
Naproxen	8 (5)	2 (6)	1 (3)	1 (3)	2 (6)	2 (6)
Omeprazole	8 (5)	3 (9)	2 (6)	2 (6)	0	1 (3)
Estrogen/Progestin	8 (5)	2 (6)	1 (3)	1 (3)	1 (3)	3 (8)

(4) Patient Compliance

Compliance was assessed by pill counts at each study visit. Patient compliance with study medication was ≥95% for all treatment groups during the double-blind portion of the study.

(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 in the ITT population. Comparisons were also made between the placebo treatment group and each lovastatin XL treatment group. The results show statistically significant mean percent decreases in LDL-C for all of the lovastatin XL treatment groups from baseline to endpoint, and in all the lovastatin XL treatment groups versus placebo. There was also a progressive mean percent decrease in LDL-C from baseline to endpoint with each increased dose of lovastatin XL. Mean percent change in LDL-C decreased from –23.8 % in the lovastatin XL 10 mg group to –29.6% in the lovastatin XL 20 mg group: a -5.8% decrease with a doubling of the lovastatin XL dose. A similar decrease was seen between the lovastatin XL 20 mg group (-29.6%) and the lovastatin XL 40 mg group (-35.8%): a –6.2% decrease with a doubling of the lovastatin XL dose. A decrease of –5% was seen with a 50% increase in dose from lovastatin XL 40 mg (-35.8%) to lovastatin XL 60 mg (-40.8%). The mean percent changes in LDL-C from baseline to endpoint by treatment group are summarized in the following table

Table 22: 146-009 Mean Percent Change in LDL-C Baseline to Endpoint

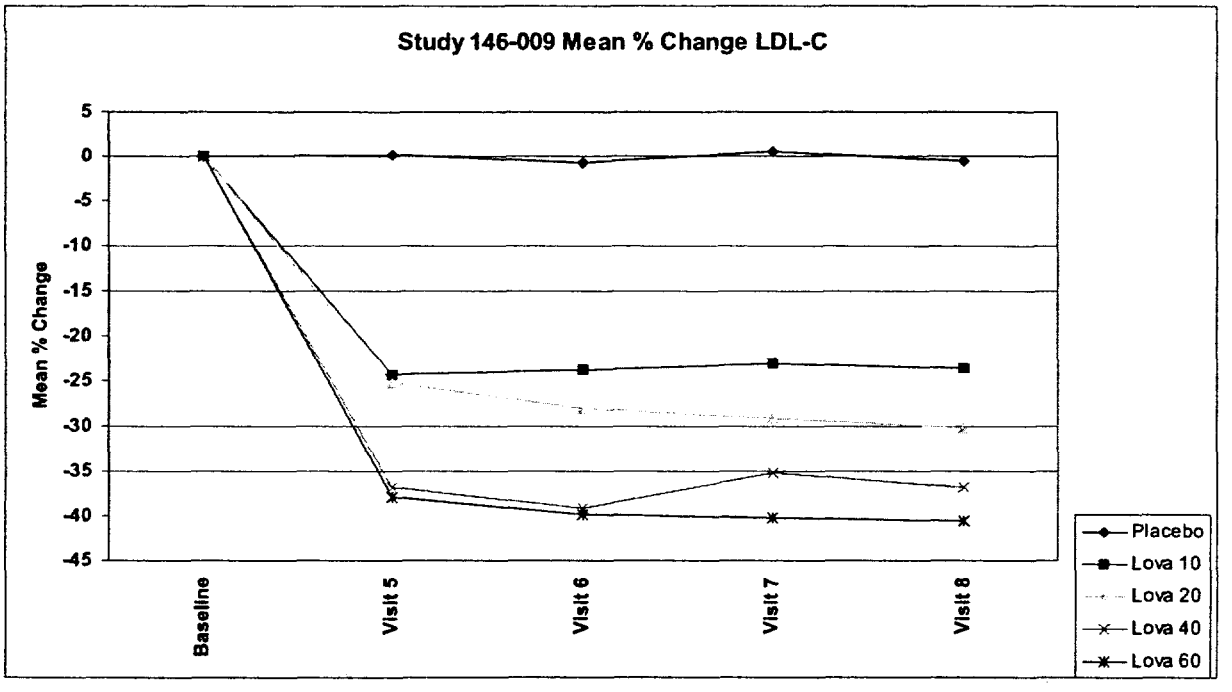
Treatment	n	Baseline mean LDL-C ± SD (mg/dL)	Endpoint mean LDL-C ±SD (mg/dL)	Mean Percent Change ± SD	% Change lova XL vs placebo p-value (95% CI)
Placebo	34	174.5 ± 28.3	174.8 ± 23.4	1.3 ± 12.6	N/A
Lovastatin XL 10 mg	33	179.4 ± 26.5	135.8 ± 21.5	-23.8 ± 9.8	-25.21 ± 2.53 ≤.0001 (-30.21, -20.21)
Lovastatin XL 20 mg	33	172.8 ± 20.1	121.3 ± 17.6	-29.6 ± 7.4	-30.96 ± 2.53 ≤.0001 (-35.95, -25.96)
Lovastatin XL 40 mg	33	180.6 ± 34.3	114.0 ± 19.8	-35.8 ± 11.0	-37.23 ± 2.53 ≤.0001 (-42.23, -32.24)
Lovastatin XL 60 mg	35	180.3 ± 34.5	105.6 ± 22.1	-40.8 ± 9.9	-42.05 ± 2.48 ≤.0001 (-46.96, -37.14)

Mean percent decrease in LDL-C is also shown by treatment visit. The results show that the maximum decrease in LDL-C is achieved in almost all treatment groups by Visit 5 (after 4 weeks of study drug treatment) with only minor percent changes at the subsequent treatment visits. The results are summarized in the following table and graph

Table 23: 146-009 Mean Percent Change from Baseline in LDL-C

Treatment	Baseline	Visit 5	Visit 6	Visit 7	Visit 8
Placebo, n =	34	34	33	31	31
Mean	174.5 mg/dL	0.1%	-0.7%	0.5%	-0.6%
Standard Deviation (SD)	13.8	1.95	12.6	12.5	12.7
Lovastatin XL 10 mg, n =	33	33	32	31	32
Mean	179.4 mg/dL	-24.3%	-23.7%	-23.0%	-23.6%
SD	4.6	10.2	12.4	9.2	12.5
Lovastatin XL 20 mg, n =	32	32	32	28	31
Mean	172.1 mg/dL	-25.1%	-28.0%	-29.1%	-30.1%
SD	3.4	11.8	7.0	8.3	8.3
Lovastatin XL 40 mg, n =	33	33	32	31	32
Mean	180.6 mg/dL	-36.7%	-39.1%	-35.1%	-36.8%
SD	6.0	9.2	9.3	12.3	12.4
Lovastatin XL 60 mg, n =	35	35	34	32	33
Mean	180.3 mg/dL	-37.8%	-39.7%	-40.1%	-40.6%
SD	5.8	10.9	10.7	10.8	10.5

Figure 3: 146-009 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. Comparisons were also made between the placebo treatment group and each lovastatin XL treatment group.

(i) Mean Percent Change HDL-C

The results show statistically significant mean percent increases in HDL-C for all of the lovastatin XL treatment groups from baseline to endpoint with the exception of the lovastatin XL 10 mg group. There were also significant increases in HDL-C versus placebo for all lovastatin XL treatment groups except for the lowest dosage group (10 mg). The HDL-C mean percent increases were also similar between the lovastatin XL 20 mg, 40 mg and 60 mg groups (12.0, 13.1, and 11.6% respectively), which suggests a maximum HDL-C response at the lovastatin XL 20 mg dose. The mean percent changes in HDL-C from baseline to endpoint by treatment group are summarized in the following table

Table 24: 146-009 Mean Percent Change in HDL-C Baseline to Endpoint

Treatment	n	Baseline mean HDL-C ± SD (mg/dL)	Endpoint mean HDL-C ±SD (mg/dL)	Mean Percent Change ± SD	% Change lova XL vs placebo p-value (95% CI)
Placebo	34	43.5 ± 10.0	46.1 ± 12.7	5.6 ± 13.1	N/A
Lovastatin XL 10 mg	33	45.1 ± 10.7	48.7 ± 10.6	9.4 ± 13.6	3.33 ± 2.88 .2494 (-2.36, 9.03)
Lovastatin XL 20 mg	34	45.1 ± 15.1	50.1 ± 15.8	12.0 ± 10.9	6.38 ± 2.86 .0271 (0.73, 12.02)
Lovastatin XL 40 mg	33	44.0 ± 9.3	49.5 ± 10.3	13.1 ± 10.9	7.62 ± 2.88 .0091 (1.92, 13.31)
Lovastatin XL 60 mg	35	48.9 ± 17.0	54.2 ± 18.3	11.6 ± 9.3	5.75 ± 2.83 .0441 (0.15, 11.34)

Mean percent increase in HDL-C is also shown by treatment visit. The results show that that most of the increase in HDL-C was achieved by Visit 5 (after 4 weeks of study drug treatment) with minor percent changes at the subsequent treatment visits. The results are summarized in the following table and graph

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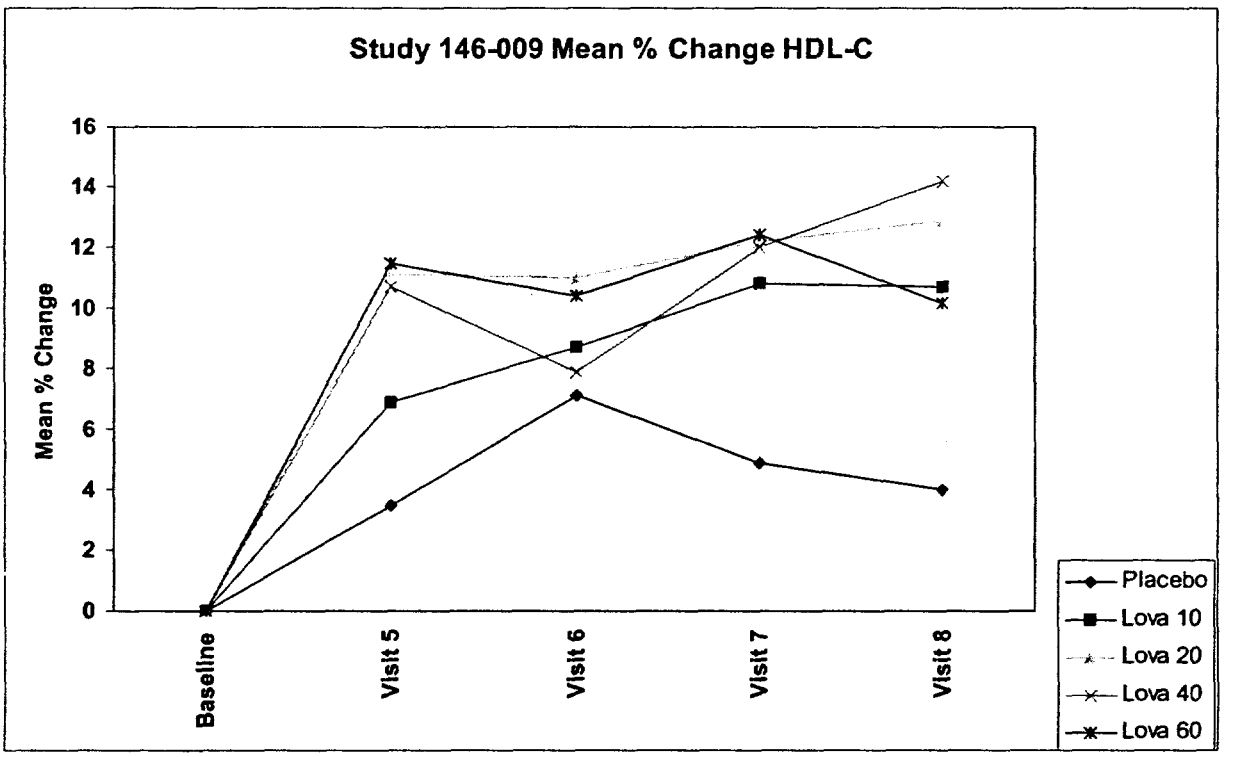
Table 25: 146-009 Mean Percent Change from Baseline in HDL-C

		Visit			
Treatment	**Baseline**	**5**	**6**	**7**	**8**
Placebo, n =	34	34	33	32	31
Mean	43.5 mg/dL	+3.5%	+7.1%	+4.9%	+4.0%
Standard Deviation (SD)	10.0	17.3	14.2	14.7	12.2
Lovastatin XL 10 mg, n =	33	33	32	31	32
Mean	45.1 mg/dL	+6.9%	+8.7%	+10.8%	+10.7%
SD	10.7	14.0	11.7	13.1	12.5
Lovastatin XL 20 mg, n =	34	34	32	29	31
Mean	45.1 mg/dL	+11.1%	+11.0%	+12.2%	+12.9%
SD	15.1	13.6	11.5	10.4	14.7
Lovastatin XL 40 mg, n =	33	33	32	31	32
Mean	44.0 mg/dL	+10.7%	+7.9%	+12.0%	+14.2%
SD	9.3	11.9	13.0	12.4	15.6
Lovastatin XL 60 mg, n =	35	35	34	32	33
Mean	48.9 mg/dL	+11.5%	+10.4%	+12.4%	+10.2%
SD	17.0	10.6	11.1	9.9	11.9

Figure 4: 146-009 Mean % Change HDL-C



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(ii) Mean Percent Change TC

The results show significant mean percent decreases in TC for all of the lovastatin XL treatment groups from baseline to endpoint, and in all the lovastatin XL treatment groups versus placebo. There was also a progressive mean percent decrease in TC from baseline to endpoint with each increased dose of lovastatin XL, from –17.9% in the lovastatin XL 10 mg group to –29.2% in the lovastatin XL 60 mg group. These findings for mean percent decrease in TC are similar to the findings for mean percent decrease in LDL-C. The mean percent changes in TC from baseline to endpoint by treatment group are summarized in the following table

Table 26: 146-009 Mean Percent Change in TC Baseline to Endpoint

Treatment	n	Baseline mean TC ± SD (mg/dL)	Endpoint mean TC ±SD (mg/dL)	Mean Percent Change ± SD	% Change lova XL vs placebo p-value (95% CI)
Placebo	34	252.5 ± 36.6	259.1 ± 30.3	3.4 ± 9.9	N/A
Lovastatin XL 10 mg	33	259.3 ± 29.8	212.6 ± 29.5	-17.9 ± 8.5	-21.22 ± 2.09 ≤.0001 (-25.35, -17.09)
Lovastatin XL 20 mg	34	261.4 ± 31.4	206.2 ± 26.8	-20.9 ± 7.1	-24.05 ± 2.07 ≤.0001 (-28.15, -19.96)
Lovastatin XL 40 mg	33	262.8 ± 35.9	194.8 ± 26.6	-25.4 ± 9.1	-28.65 ± 2.09 ≤.0001 (-32.78, -24.52)
Lovastatin XL 60 mg	35	263.8 ± 38.4	185.2 ± 25.3	-29.2 ± 8.3	-32.43 ± 2.05 ≤.0001 (-36.49, -28.37)

Mean percent decrease in TC is also shown by treatment visit. The results show that the maximum decrease in TC is achieved in almost all treatment groups by Visit 5 (after 4 weeks of study drug treatment) with only minor percent changes at the subsequent treatment visits. The results are summarized in the following table and graph

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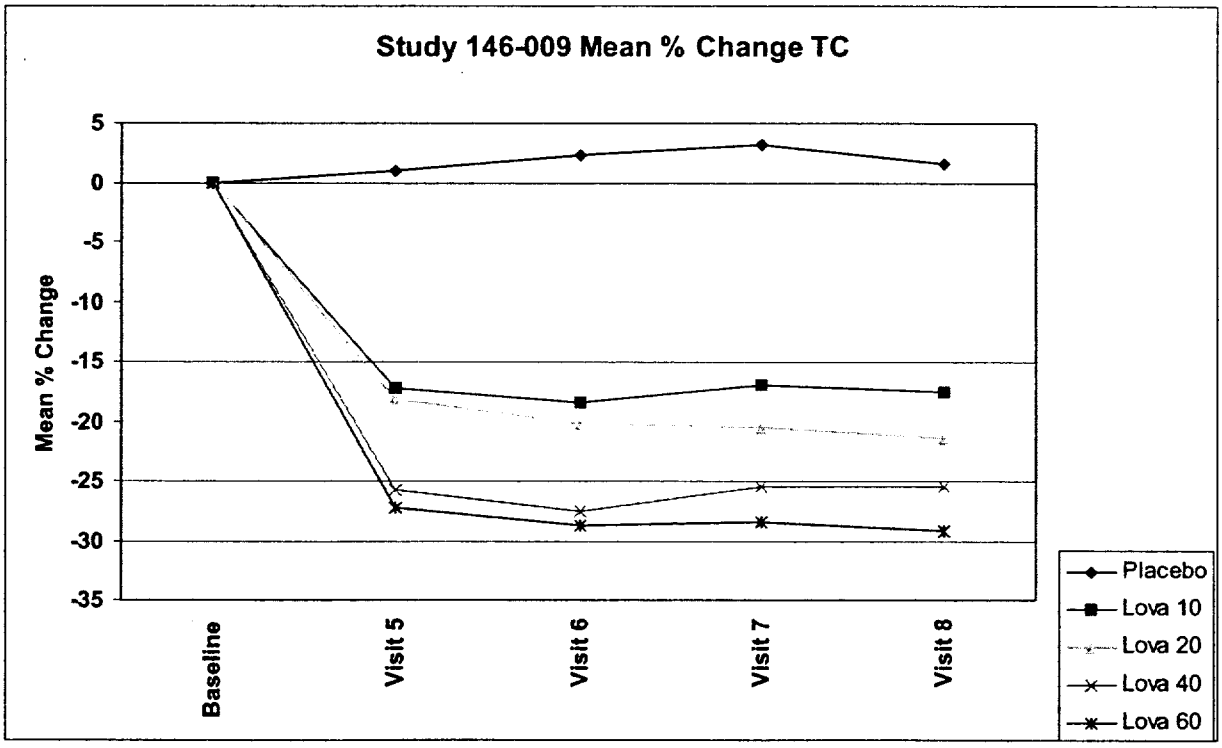
Table 27: 146-009 Mean Percent Change from Baseline in TC

Treatment	Baseline	Visit 5	Visit 6	Visit 7	Visit 8
Placebo, n =	34	34	34	32	31
Mean	252.5 mg/dL	0.9%	2.3%	3.2%	1.6%
Standard Deviation (SD)	36.6	10.8	10.5	10.5	9.3
Lovastatin XL 10 mg, n =	33	33	32	31	32
Mean	259.3 mg/dL	-17.2%	-18.5%	-17.0%	-17.6%
SD	29.8	9.2	7.9	8.1	9.7
Lovastatin XL 20 mg, n =	34	34	32	29	31
Mean	261.4 mg/dL	-18.1%	-20.2%	-20.5%	-21.4%
SD	31.4	8.7	5.1	7.7	7.9
Lovastatin XL 40 mg, n =	33	33	32	31	32
Mean	262.8 mg/dL	-25.7%	-27.5%	-25.5%	-25.4%
SD	35.9	7.7	7.4	9.4	10.3
Lovastatin XL 60 mg, n =	35	35	34	32	33
Mean	263.8 mg/dL	-27.3%	-28.8%	-28.4%	-29.2%
SD	38.4	7.8	8.3	8.5	9.8

Figure 5: 146-009 Men % Change TC



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(iii) Mean Percent Change in TG

The results show significant mean percent decreases in TG for all of the lovastatin XL treatment groups from baseline to endpoint, and in all the lovastatin XL treatment groups versus placebo. The mean percent decreases in TG were not progressive with increasing dose of lovastatin XL however, with the smallest decrease seen in the lovastatin XL 40 mg group, followed by the 20 mg group, 10 mg group, and the 60 mg group (-9.9%, -13.0%, -17.3%, and –25.1% respectively). The mean percent changes in TG from baseline to endpoint by treatment group are summarized in the following table

Table 28: 146-009 Mean Percent Change in TG Baseline to Endpoint

Treatment	n	Baseline mean TG ± SD (mg/dL)	Endpoint mean TG ±SD (mg/dL)	Mean Percent Change ± SD	% Change lova XL vs placebo p-value (95% CI)
Placebo	34	174.8 ± 72.6	192.1 ± 102.8	8.7 ± 23.5	N/A
Lovastatin XL 10 mg	33	174.6 ± 70.9	140.3 ± 63.3	-17.3 ± 26.7	-25.11 ± 6.70 .0003 (-38.35, -11.86)
Lovastatin XL 20 mg	34	206.0 ± 98.7	171.7 ± 100.1	-13.0 ± 33.4	-21.03 ± 6.65 .0019 (-34.17, -7.89)
Lovastatin XL 40 mg	33	188.8 ± 75.2	156.6 ± 50.6	-9.9 ± 34.1	-18.35 ± 6.70 .0069 (-31.59, -5.11)
Lovastatin XL 60 mg	35	173.8 ± 77.7	128.8 ± 57.6	-25.1 ± 18.4	-32.84 ± 6.59 .0001 (-45.86, -19.82)

Mean percent decrease in TG is also shown by treatment visit. The results show that that most of the decrease in TG was achieved by Visit 5 (after 4 weeks of study drug treatment) with variability in the percent changes at the subsequent treatment visits. The results are summarized in the following table and graph

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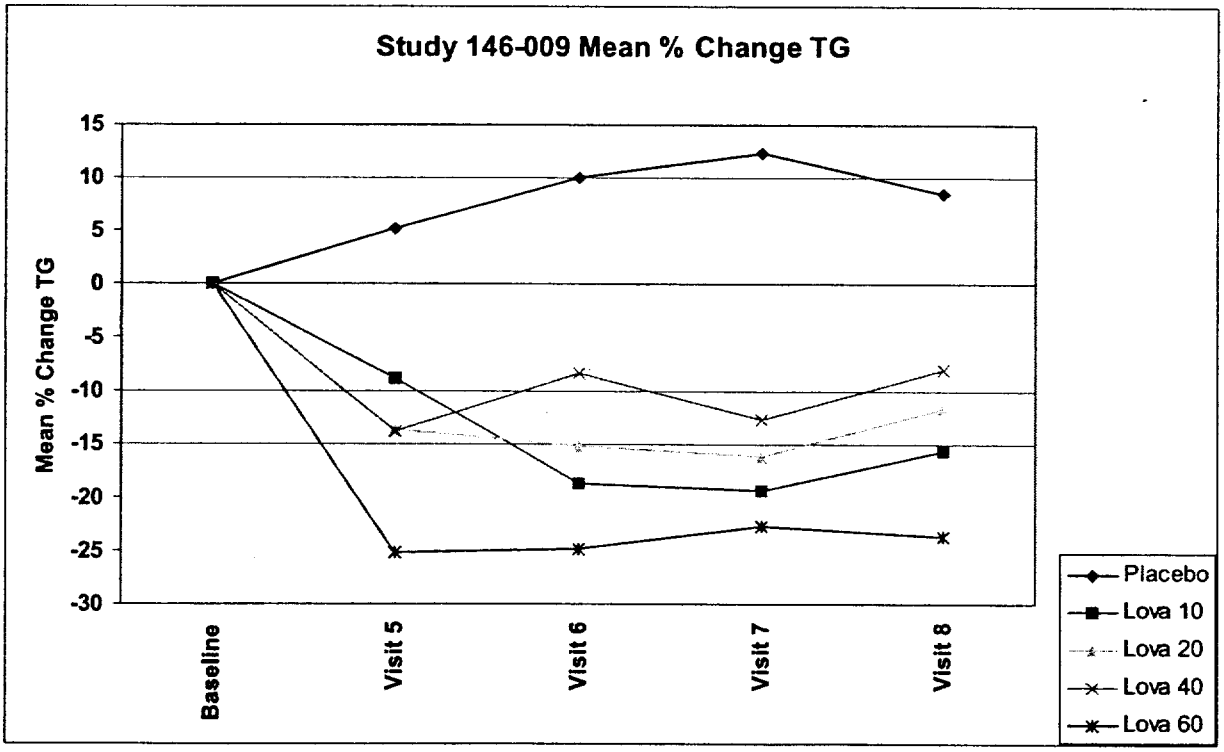
Table 29: 146-009 Mean Percent Change from Baseline in TG

		Visit			
Treatment	**Baseline**	**5**	**6**	**7**	**8**
Placebo, n =	34	34	34	32	31
Mean	174.8 mg/dL	5.1%	10.0%	12.4%	8.5%
Standard Deviation (SD)	72.6	38.8	48.9	30.8	25.6
Lovastatin XL 10 mg, n =	33	33	32	31	32
Mean	174.6 mg/dL	-8.8%	-18.6%	-19.4%	-15.6%
SD	70.9	33.7	26.6	30.5	32.2
Lovastatin XL 20 mg, n =	34	34	32	29	31
Mean	206.0 mg/dL	-13.7%	-15.2%	-16.1%	-11.6%
SD	98.7	27.7	30.4	33.4	40.4
Lovastatin XL 40 mg, n =	33	33	32	31	32
Mean	188.8 mg/dL	-13.8%	-8.4%	-12.7%	-8.0%
SD	75.2	23.3	34.0	41.8	37.4
Lovastatin XL 60 mg, n =	35	35	34	32	33
Mean	173.8 mg/dL	-25.2%	-24.9%	-22.6%	-23.6%
SD	77.7	19.4	20.8	19.3	24.1

Figure 6: Mean % Change TG



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(iv) Subgroup Analysis

Baseline TG ≥200 mg/dL vs TG <200 mg/dL
Within each treatment group, mean percent reductions in LDL-C were similar when the subgroup of patients with baseline TG <200 mg/dL was compared to the subgroup of patients with baseline TG ≥200 mg/dL. However, the mean percent increase in HDL-C was greater in the subgroup of patients with TG ≥200 mg/dL at baseline, with the exception of the lovastatin XL 60 mg group. Mean percent changes in TG were also greater in the subgroup of patients with baseline TG ≥200 mg/dL compared to the subgroup of patients with baseline TG <200 mg/dL. Although the subgroups were small, there appeared to be a greater reduction in TG in subgroups of patients with lower baseline HDL-C levels.

Baseline HDL
Although the subgroups were small, there were greater HDL-C elevations for the subgroups with lower baseline HDL-C levels compared to the subgroups with higher baseline HDL-C levels.

Age
No meaningful differences in LDL-C reductions were seen in patients <65 years of age compared to patients ≥65 years of age. There were also no differences seen for increases in HDL-C by age. The subgroups were small, but the subgroup of patients ≥65 years of age appeared to have greater TG reduction than subgroup of patients <65 years of age.

Male vs Female
No differences in LDL-C in males and females in the lovastatin XL 10 mg and 20 mg groups were seen; however, there were greater reductions in females for the lovastatin XL 40 mg and 60 mg groups than for males. HDL-C percent increases were greater in males compared to females in all groups with the exception of the lovastatin XL 20 mg group; however, males had lower baseline HDL-C compared to females and the difference may not have been related to gender, but rather to the baseline HDL-C. There was no differences in TG reduction in males compared to females.

Race
There were too few non-Caucasian patients to analyze by race.

(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. Subgroup analyses were also performed by gender, age, baseline LDL and baseline TG. The LDL results by subgroup were consistent with the overall results observed in the study. [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 146-009

The efficacy results for study 146-009 show that:

For the primary endpoint (mean percent change in LDL-C)

1) Lovastatin XL produced statistically significant decreases in LDL-C from baseline to endpoint, and significant decreases in LDL-C compared to placebo for all doses of lovastatin XL tested (10 to 60 mg a day). There was a dose-response effect with progressive decreases in LDL-C with increasing doses of lovastatin XL (from –23.8% at the 10 mg dose to –40.8% at the 60 mg dose), and about a -6% decrease in LDL-C was seen with a doubling of the lovastatin XL dose. Most of the LDL-C lowering was seen at Visit 5, after 4 weeks of study drug treatment.

For the secondary endpoints (mean percent changes in HDL-C, TC, and TG)

2) 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 the 10 mg dose. The increase in HDL-C plateaued at about 11-13% despite increasing doses of lovastatin XL from 20 to 60 mg. Most of the HDL-C increase was seen after 4 weeks of treatment.
3) Lovastatin XL produced significant decreases in TC from baseline to endpoint, and significant decreases in TC compared to placebo. The decrease in TC was progressive with increasing doses of lovastatin XL, and ranged from –17.9 at the 10 mg dose to –29.2 at the 60 mg dose. Most of the TC lowering was seen after 4 weeks of treatment.
4) 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 of –15.6% at the 10 mg dose, -11.6% at the 20 mg dose, -8.0% at the 40 mg dose, and –23.6% at the 60 mg dose. Most of the TG lowering effects of lovastatin XL were seen at after 4 weeks of treatment.

In subgroup analysis there were too few non-Caucasians patients to evaluate by race. There were no meaningful differences in LDL-C lowering for male vs female patients, and for geriatric vs non-geriatric patients.

2. Protocol 146-010

a) Study Design for Protocol 146-010

(1) Study Design

Protocol 146-010 "A comparative study of lovastatin XL with Mevacor in patients with hypercholesterolemia" was a 34-week, multi-center, randomized, double-blind, active-comparator, 2-way cross-over study conducted at 24 sites nationally. The study evaluated the efficacy and safety of 2 different doses of lovastatin XL (20 mg and 60 mg) vs the same doses of Mevacor in 358 patients with hypercholesterolemia.

(2) Study Objectives

The objectives of the study were to compare the efficacy and safety of lovastatin XL 20 mg per day with Mevacor 20 mg per day, and lovastatin XL 60 mg per day with Mevacor 60 mg per day in patients with hypercholesterolemia. The primary efficacy comparison was the mean percent change from baseline to endpoint in LDL-C between the lovastatin XL and Mevacor treatment groups. Secondary comparisons were mean percent changes from baseline to endpoint in HDL-C, TC, and TG between treatment groups.

(3) Eligibility Criteria

(a) Inclusion Criteria

1) Patient had signed the informed consent
2) Patients were cooperative male and female outpatients aged 21 to 70 years
3) Patient was willing to continue treatment in the 12-week Extension Period (Protocol 146-011)
4) Patients taking any lipid-modifying agent must have completed at least a 3-week washout of that agent prior to study entry (Visit 1). Lipid-modifying agents included statins (Mevacor, Zocor, Pravachol, Lescol, Lipitor, and Baycol), cholestyramine, fibrates (Lopid and Tricor), over-the-counter (OTC) fish oil, niacin, or food supplements that may have lipid-lowering effects. A stable dose of niacin <100 mg a day was permitted.
5) Patients must have had a fasting plasma LDL-C level (based on Visit 1 laboratory data) with the following parameters:
   a) For patients with CHD, PVD, or CVD as determined by medical history: LDL-C > 100 mg/dL
   b) For patients without CHD, PVD, or CVD and with ≥2 risk factors for heart disease (defined below): LDL-C ≥130 mg/dL
   c) For patients without CHD, PVD, or CVD and with <2 risk factors for heart disease: LDL-C ≥160 mg/dL