

**MEDICAL OFFICER'S DRAFT REVIEW OF
NEW DRUG APPLICATION**

NDA: 21-213

SPONSOR: Merck Research Laboratories

PRODUCT: Lovastatin (Mevacor) 10 mg tablets

INDICATION: Nonprescription use of Lovastatin 10 mg to treat mild-to-moderate hypercholesterolemia in men and postmenopausal women without clinical evidence of diabetes or cardiovascular disease

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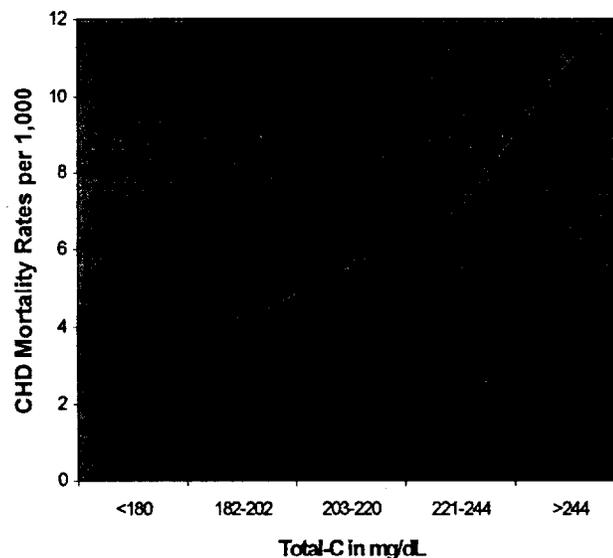
INTRODUCTION

CHOLESTEROL AS A RISK FACTOR FOR CARDIOVASCULAR DISEASE

The association between elevated serum cholesterol levels and risk of atherosclerotic cardiovascular disease has been established by data from animal models, large cohort studies, and clinical diseases of abnormal lipid metabolism. From epidemiologic observations, the direct relationship between cholesterol level and incidence of coronary heart disease (CHD) is continuous and graded with a 2% increase in incidence of coronary artery disease for each 1% increase in serum cholesterol.¹

The Multiple Risk Factor Intervention Trial (MRFIT) screenees were a group of 361,622 asymptomatic males who were observed over a 6-year period for the development of CHD.¹ In this cohort, the risk of CHD mortality increased with total-C levels greater than 180 mg/dL; this relationship was a curvilinear one with a dramatic escalation in event rates for total-C levels > 240 mg/dL (Figure 1).

Figure 1. Relationship Between Total-C Levels and CHD Mortality



Further support for the role of cholesterol in the development of atherosclerosis was derived from clinical trial data demonstrating that dietary and pharmacologic intervention aimed at lowering cholesterol reduces the risk of experiencing a cardiac event. Earlier trials involving a bile acid resin binder (the Lipid Research Clinics Coronary Primary Prevention Trial or LRC CPPT) or a fibric acid derivative (Helsinki Heart Study) demonstrated significant risk reductions in the incidence of fatal CHD events and in the composite endpoints of nonfatal MI and fatal CHD.^{2,3} The reduction in risk for CHD was, however, counterbalanced by increased deaths due to non-cardiovascular causes in the active treatment groups. At the time and for a number of years, this paradox resulted in debates over the risk versus benefits of cholesterol reduction.

Results from clinical trials involving several of the HMG-coA reductase inhibitors in the past decade have allayed many of the concerns arising out of the results of the LRC CPPT and similar studies. Unlike the non-statin trials, these more recent studies demonstrated reductions in fatal and nonfatal ischemic events without the offsetting increases in noncardiovascular deaths, lending stronger support for the pharmacologic treatment of hypercholesterolemia. This benefit has been documented in both primary and secondary prevention populations and across a broad range of cholesterol levels (Table 1).⁴⁻⁸

Table 1. Primary and Secondary Prevention Trials with HMG-coA Reductase Inhibitors Demonstrating Clinical Benefit

Clinical Trial and Primary Endpoint Measured	Mean Baseline Lipids (mg/dl)	Statin Event Rate	Placebo Event Rate	Relative Risk
Primary Prevention Trials				
WOSCOPS (n=6,595) NF-MI/fatal CHD	LDL-C 192 TC 272	174/3302 (5.3%)	248/3293 (7.5%)	0.69
AFCAPS/TexCAPS (n=6,605) NF-MI/fatal CHD/UAP	LDL-C 150 TC 221	116/3304 (3.5%)	183/3301 (5.5%)	0.63
Secondary Prevention Trials				
4S (n=4,444) Total Mortality	LDL-C 189 TC 260	182/2221 (8.2%)	256/2223 (11.5%)	0.70
CARE (n=4,159) NF-MI/fatal CHD	LDL-C 139 TC 209	212/2081 (10.2%)	274/2078 (13.2%)	0.76
LIPID (n=9,014) Total CHD Mortality	LDL-C 150 TC 219	287/4512 (6.4%)	373/4502 (8.3%)	0.76

NATIONAL GUIDELINES FOR THE TREATMENT OF HYPERCHOLESTEROLEMIA

Concurrent with the conduct of these large statin clinical trials, the National Cholesterol Education Program (NCEP) published the second report of the Expert Panel on Detection, Evaluation, and Treatment of hypercholesterolemia in adults in June 1993.⁹ The guidelines for treating hypercholesterolemia from this report are summarized in the table shown below.

Table 2. Treatment Recommendations Based on LDL-C levels

Patient Category	Initiation Level	LDL Goal
Dietary Therapy		
w/o CAD, < 2 risk factors	≥160 mg/dL (4.1 mmol/L)	<160 mg/dL (4.1 mmol/L)
w/o CAD, ≥ 2 risk factors	≥130 mg/dL (3.4 mmol/L)	<130 mg/dL (3.4 mmol/L)
w/ CAD	>100 mg/dL (2.6 mmol/L)	≤100 mg/dL (2.6 mmol/L)
Drug Treatment		
w/o CAD, < 2 risk factors	≥190 mg/dL (4.9 mmol/L)	<160 mg/dL (4.1 mmol/L)
w/o CAD, ≥ 2 risk factors	≥160 mg/dL (4.1 mmol/L)	<130 mg/dL (3.4 mmol/L)
w/ CAD	≥130 mg/dL (3.4 mmol/L)	≤100 mg/dL (2.6 mmol/L)

LDL-C level was the primary target of cholesterol reduction with different recommended treatment goals for different CHD risk populations. Positive risk factors for CHD included age (≥ 45 years for men; ≥ 55 years or early menopause without estrogen replacement for women), family history of premature CHD, current cigarette smoking, hypertension (HTN), HDL-C < 35 mg/dL, and diabetes mellitus (DM). An HDL-C ≥ 60 mg/dL was considered a negative risk factor for CHD.

Two approaches to achieving these goals were recommended in these guidelines. The first was a clinical approach in which the intensity of treatment was dictated by the CHD risk status of the individual. Those with the greatest risk as evidenced by the presence of established heart disease are initiated on drug therapy at a lower LDL-C level compared to the higher LDL-C threshold for pharmacologic intervention in those with no heart disease and few risk factors for CHD. The second approach was a population approach aimed at shifting the cholesterol distribution in the general population through dietary intervention and lifestyle changes.

Interestingly, the guidelines were published prior to the completion of many of the statin trials and hence included certain outdated comments and conclusions. For example, a statement regarding the lack of data demonstrating reduction of CHD risks associated with statin therapy has since been refuted by several clinical endpoint trials. Among these endpoint trials included the recent Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a primary prevention study involving individuals with mean LDL-C levels of 150 mg/dL and HDL-C levels of 37 mg/dL, which suggested that a significant proportion of the primary prevention population would benefit from initiating drug treatment at lower LDL-C levels than currently recommended.⁵

SPONSOR'S RATIONALE FOR NONPRESCRIPTION LOVASTATIN

Merck (sponsor of NDA) presented its rationale for the over-the-counter access to lovastatin 10 mg based on the demonstrated benefit of lovastatin treatment in a subgroup of the primary prevention population for which current guidelines do not recommend drug therapy as initial treatment. This subgroup consist of those individuals without CHD but whose total-C levels lie between 200 and 240 mg/dL and LDL-C levels are ≥ 130 mg/dL.

Although the risk of CHD mortality in the primary prevention population increases considerably above total-C levels of 240 mg/dL (Figure 1), there is a clear positive relationship between cholesterol levels of 200-240 mg/dL and the risk of dying from CHD. In the adult population without clinical evidence of CHD (primary prevention population) the initial step in managing high blood cholesterol is based on the nonfasting total-C and HDL-C level and the presence of CHD risk factors. For individuals with borderline-high blood cholesterol levels of 200 to 239 mg/dL, HDL-C ≥ 35 mg/dL, and fewer than 2 risk factors, the NCEP guidelines recommend dietary modification, exercise, and risk factor reduction. These individuals should have a repeat total and HDL-C measurement in 1 to 2 years. *Drug treatment is not recommended in this population unless the HDL-C is < 35 mg/dL OR there are ≥ 2 risk factors AND a fasting lipoprotein analysis reveals an LDL-C level of ≥ 160 mg/dL.*⁹

In AFCAPS, Merck targeted a primary prevention population consisting of men > 45 years of age and postmenopausal women with the following lipid profile at study enrollment:

- total-C 180-264 mg/dL
- LDL-C 130-190 mg/dL
- HDL-C < 45 mg/dL in men and <47 mg/dL in women
- triglycerides ≤ 400 mg/dL

Based on the CHD risk factors and baseline lipid profile of the 6,605 patients randomized in this trial, only 16.6% of the cohort would have qualified for drug treatment by NCEP guidelines.

In this trial of approximately 5 years duration, the incidence of an initial MI, unstable angina, or sudden cardiac death was 5.5% in those individuals randomized to treatment with placebo. In those individuals randomized to treatment with lovastatin 20 to 40 mg per day the incidence rate was lower at 3.5%. Thus, treatment with lovastatin reduced the relative risk of an initial ischemic event by 37% ($p < 0.0001$) in this study cohort in which the majority of the participants were not recommended to receive drug treatment by NCEP guidelines.

DEFINITION OF THE OTC POPULATION

The sponsor estimated the number of individuals in the U.S. population who are potentially eligible for nonprescription lovastatin by identifying a subset of the Third National Health and Nutrition Examination Survey (NHANES III) who had the following characteristics:

- males of age > 40 years old and postmenopausal females (surgical or natural) with
 - total-C levels of 200 to 240 mg/dL
 - LDL-C levels > 130 mg/dL
- (N.B. no HDL-C criterion was imposed)

Excluded from this group were those who had self-reported:

- the presence of cardiovascular disease (coronary, cerebrovascular, or peripheral vascular disease)
- the presence of diabetes
- the use of > 1 antihypertensive medication
- the use of lipid-lowering drugs

Using this approach, *the sponsor concluded that there are approximately 15.5 million men and women in the U.S. population who are potentially eligible for drug treatment.*

THE OTC CLINICAL PROGRAM

Clinical Studies

A total of seven studies were conducted to support the proposed indication for nonprescription lovastatin. The studies were designed and conducted to evaluate the following:

- the lipid-lowering efficacy of nonprescription lovastatin in a controlled clinical trial involving subjects with lipid profiles similar to the targeted OTC-population
- the ability of individuals to self-select and comply with the proposed drug label for nonprescription lovastatin

- the lipid-lowering efficacy of nonprescription lovastatin in an OTC-simulated study environment
- the tolerability of nonprescription lovastatin
- the pharmacokinetics of multiple daily dose lovastatin 10 to 40 mg
- the interaction of lovastatin 40 mg with CYP3A4 inhibitors and substrates

These studies are summarized in the following table.

Table 3. Studies Conducted to Support NDA 21-213

Study Protocol No.	Study Design
075 (Efficacy Study)	Double-blind, randomized, placebo-controlled (lovastatin 10 mg)
076 (Pharmacy Study)	Open-label, actual-use (lovastatin 10 mg)
077 (Nurse Worksite Study)	Open-label, actual-use (lovastatin 10 mg) (This study was terminated early due to poor enrollment)
078 (pK Study)	Open-label, single-dose, 4-period crossover with lovastatin 40 mg, midazolam 2 mg, or placebo
079 (Restricted Access Study)	Open-label, actual-use (lovastatin 10 mg)
081 (Red Arrow Study)	Label-comprehension study (lovastatin 10 mg)
082 (pK Study)	Randomized, 2-period crossover pharmacokinetic study of lovastatin 10 and 40 mg daily x 10 day in healthy subjects

Population Studied

The selection of study participants for Protocols 075, 076, 077, 079, and 081 was based on the proposed nonprescription lovastatin package label which underwent several revisions during the OTC clinical development program. The most recent version of the package label submitted to the NDA identified the following individuals as the ones “who should use MEVACOR CC” (proposed name for nonprescription lovastatin):

- men \geq 40 years of age and postmenopausal women defined as being at least 1 year past last menses
- individuals having total-C levels of 200 to 240 mg/dL and LDL-C \geq 130 mg/dL (N.B. no HDL-C criterion imposed)

The following group of individuals was excluded from the OTC Clinical Studies:

- individuals with CHD, diabetes, significant HTN (i.e. on more than 1 antihypertensive medication), history of stroke or peripheral vascular disease
- women who were pregnant, of childbearing potential, or breastfeeding
- individuals with hepatitis, active liver disease, or consume excessive amounts of alcohol
- individuals on selected medications which may potentiate skeletal muscle toxicity when used with lovastatin

Estimates of CHD Risk and Treatment Benefit in the OTC-targeted Population

Estimates of CHD risk and predictions of the potential benefit of nonprescription lovastatin in the proposed OTC population were provided from analyses of an OTC-eligible subpopulation of the AFCAPS cohort and modeling of epidemiologic data

derived from the Framingham Heart Study and Atherosclerosis Risk in Communities (ARIC) Study.

REVIEW OF NONPRESCRIPTION LOVASTATIN IN THE DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS

In considering the proposal to change lipid-altering drugs from a prescription to nonprescription status several issues need to be addressed. These issues pertain to the efficacy and safety of the drug product in the targeted population.

Efficacy

Historically, efficacy in the lipid-altering drug class refers to the ability of the drug to lower LDL-C levels at a minimum of 15% from baseline relative to placebo in individuals adhering to a low-fat diet.¹¹ This measure of efficacy has been proven to be a reliable surrogate marker for clinical benefit and remains the primary endpoint by which new drugs developed for lipid-altering are evaluated. In the absence of clinical cardiovascular benefit, the lipid-altering results from adequate and well-controlled studies are summarized in drug labeling accompanied by a disclaimer to that effect. In the nonprescription environment the evaluation of drug efficacy will focus on the following:

1. What is the expected mean % reduction in LDL-C for the targeted population?
2. Is there evidence that treatment with this drug to this degree of LDL-C lowering in this population will result in a clinical benefit?
3. Will the consumer adhere to taking the medication chronically to treat an asymptomatic condition whose deleterious effects may not be manifested until several years later?

Safety

Intuitively, one would not expect the inherent toxicities related to the prescription drug to differ from the nonprescription drug if the chemical structure and manufacturing remain unchanged. Provided that a formulation identical to the prescription drug will be marketed for nonprescription use, the safety profile from controlled clinical trials and postmarketing reports for the prescription formulation are adequate predictors of drug toxicity in the nonprescription environment. What may not be predictable in the nonprescription environment is consumer behavior hence the assessment of safety in this population will focus on the following:

4. Are consumers making appropriate decisions regarding the initiation of drug treatment?

These questions are not inclusive of all those that can be asked of this clinical development program. In addressing these questions, however, meaningful discussions may be generated regarding whether the OTC-availability of lovastatin 10 mg in the general population is a safe and effective method of reducing the risk for CHD.

The review of the nonprescription lovastatin clinical development program will be conducted separately but in consultation between reviewers from the Divisions of Metabolic and Endocrine Drug Products (DMEDP), Over-the-Counter Drug Products (DOTCDE), and Drug Marketing, Advertising, and Communication (DDMAC). Although the aforementioned issues will be addressed in this review, more detailed evaluations may be presented by reviewers in DOTCDE and DDMAC regarding consumer behavior and compliance.

The design, conduct, and results of the following protocols will be considered in this review:

- Protocol 075 (Efficacy Study)
- Protocol 076 (Pharmacy Study)
- Protocol 079 (Restricted Access Study)

The potential clinical benefit of nonprescription lovastatin in the targeted OTC population will only be addressed through analysis of a subset of patients from AFCAPS/TexCAPS with similar characteristics to the proposed OTC population. The findings from the sponsor's modeling of epidemiologic databases are only considered supportive of the positive relationship between serum cholesterol levels and CHD risk.

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PROTOCOL 075 (EFFICACY STUDY)

STUDY DESIGN

Protocol 075 was a 12-week, multi-center, randomized, double-blind, parallel-group clinical trial comparing lovastatin 10 mg per day to placebo for the treatment of mild-to-moderate hypercholesterolemia.

STUDY OBJECTIVES

Primary 1) to evaluate the LDL-C lowering efficacy of lovastatin 10 mg per day over a 12-week period, and 2) to compare the tolerability profile of lovastatin 10 mg per day with placebo over 12 weeks as measured by clinical adverse experiences

Secondary to evaluate the compliance with therapy by reduction in LDL-C, dietary recall, diary entries and tablet counts

ELIGIBILITY CRITERIA

Inclusion criteria

- Men \geq 45 years old and women \geq 55 years old or naturally postmenopausal for at least 1 year; general health was good
- LDL-C between 120-170 mg/dL at weeks -4 and -2 and the average of two consecutive LDL-C values between 125 and 165 mg/dL for randomization (Day 1)
- fasting triglycerides \leq 400 mg/dL at randomization (Day 1)
- compliant with AHA Step 1 diet at week -4
- demonstrated > 75% placebo compliance during dietary run-in period
- willing to participate in the study as evidenced by a signed informed consent
- considered by the study coordinator to be motivated to participate in the study

Exclusion criteria

- women of childbearing potential, pregnant, or breastfeeding
- any history of heart disease or peripheral vascular disease
- diabetes or fasting blood glucose > 140 mg/dL
- poorly controlled HTN (i.e. sitting DBP > 95 or SBP > 160 mm Hg)
- family history of premature heart disease
- currently taking cyclosporine, ketoconazole, itraconazole (or other systemic azole antifungals), erythromycin, clarithromycin, nefazodone, oral corticosteroids, or mibefradil dihydrochloride
- currently on another lipid-altering drug including over-the-counter fish oil or niacin > 500 mg daily within the 4 weeks prior to screening visit
- under regular physician's care for a medical condition and unable to obtain medical permission for study participation
- severe obesity \geq 30% ideal body weight
- history of more than 2 alcoholic drinks per day on a regular basis
- history of hepatitis or liver disease
- diagnosed as having thyroid disease, unless documented normal TSH available
- allergic to lovastatin
- participation in another clinical drug study within 2 months prior to this study, or at any time during this study
- recent history of substance abuse, psychosis, or any condition that was considered likely to make a patient noncompliant with the study protocol

SCREENING AND PRE-RANDOMIZATION

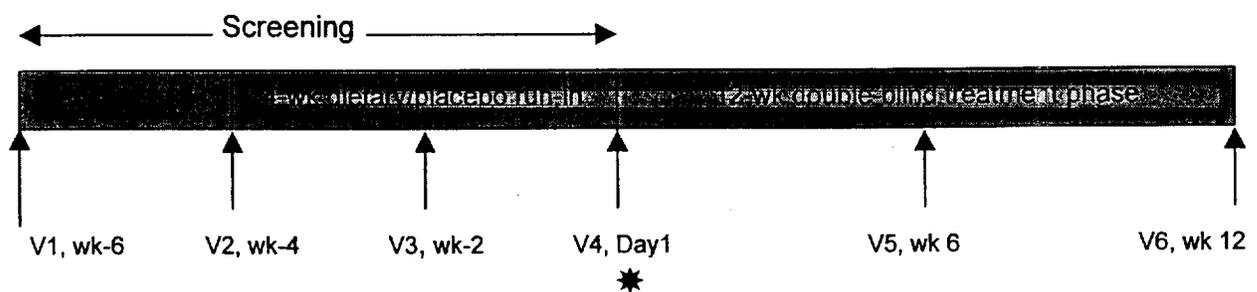
Participants were recruited from 12 study centers and screened for study eligibility at visit 1 (week -6) by physical examination, medical history, and a 12-hr fasting lipid determination. If the LDL-C level was between 140 and 175 mg/dL, the person was placed on an AHA step 1 diet in an effort to achieve an LDL-C level between 130-160 mg/dL. All participants meeting the eligibility criteria and adherent to an AHA step 1 or more restrictive diet were enrolled into a 4-week single-blind placebo run-in period at visit 2 (week -4).

Compliance with placebo and diet was assessed during the placebo run-in period. Bottles containing 35 placebo tablets were dispensed at the beginning of the placebo run-in period (week -4). Placebo compliance of $\geq 75\%$ during the 4-week single-blind placebo run-in period, and fasting lipid values at weeks -4 and -2 meeting the inclusion criteria were required for randomization into the double-blind treatment phase. Fasting blood glucose and TSH levels were also evaluated at week -4.

STUDY VISITS AND LABORATORY ASSESSMENTS AFTER RANDOMIZATION

A total of 6 clinic visits were scheduled during the 16 to 18 weeks of study duration. Visits 1 through 3 (see *Screening and Pre-Randomization*) took place before randomization and were scheduled at approximately 2 week intervals (weeks -6, -4, and -2). Visits 4 through 6 took place during the double-blind treatment phase and were scheduled at approximately 6 week intervals (Day 1, weeks 6 and 12). Randomization was at visit 4 (Day 1). Baseline lipid values were those obtained at visit 4 (Day 1/randomization) and consisted of total-C, HDL-C, and triglycerides levels. LDL-C levels were calculated using the Friedewald equation.[†] Fasting lipid values for efficacy were obtained at weeks +6 and +12.

Figure 2 illustrates the study visits for Protocol 075.



- Visits 1-3: lipid profile for study eligibility
- Visit 2: TSH and glucose for study eligibility
- Visit 4: Day 1 randomization and baseline lipid values
- Visit 5: 6-wk lipid profile for secondary endpoints
- Visit 6: 12-wk lipid profile for primary and secondary endpoints

[†] LDL-C = Total-C - [HDL-C + TG/5]

STUDY MEDICATION DISPENSING AND COMPLIANCE

At randomization, participants were issued a bottle containing either 50 tablets of placebo or lovastatin 10 mg (6-week supply) and a diary card on which they were to record the time and date of each dose taken. Another 6-week supply of medication was dispensed at visit 5 (week +6). Compliance to study medication was determined by pill counts and diary monitoring at visits 5 (week +6) and 6 (week +12).

CLINICAL EFFICACY AND ENDPOINT MEASURES

Primary The primary efficacy measure was a comparison of the mean of the percent changes in LDL-C, from baseline to week 12, for lovastatin compared to placebo.

Secondary Percent changes in LDL-C levels at 6 weeks and percent changes in total-C, HDL-C, total-C/HDL-C, and triglycerides levels at 6 and 12 weeks were also compared between the two treatment groups.

Compliance The relationship between efficacy and medication compliance at 6 and 12 weeks was explored.

Safety No laboratory assessments for safety were obtained during the treatment period. Safety was assessed by clinical adverse experiences reported and vital signs obtained during study visits.

STATISTICAL ANALYSIS

Primary Approach

This approach evaluated 12-week efficacy endpoints for all patients with baseline efficacy measurements and at least one measurement after 4 weeks on double-blind treatment. Missing data were estimated by carrying forward the last observed measure obtained after 4 weeks of treatment. The study was powered to detect a difference of ≥ 8 percent, between treatments, in the mean of the percent changes in LDL-C from baseline to 12 weeks. All statistical tests were two-sided and were performed at the 0.05 significance level. Missing data were not estimated for the week 6 assessment.

Per-Protocol Approach

This approach excluded data from patients with serious protocol deviations and missing data. Serious protocol violations were defined prior to unblinding of the study database and included the following:

1. not completing study diary cards
2. interrupting study drug for 3 or more consecutive days or having taken drug for less than 14 consecutive days prior to the week 12 measurement

RESULTS OF PROTOCOL 075/EFFICACY STUDY

Five hundred and eighty-two (582) participants were screened at 12 different study sites. Two hundred and ten (36.1%) were randomized to lovastatin 10 mg per day (n=104) or placebo (n=106).

Baseline Demographics and Patient Characteristics

Approximately 48% of the randomized population were male and > 90% were Caucasian. The nonrandomized population had slightly higher total-C and LDL-C levels than the randomized population, partly because of the exclusion criteria. Table 4

summarizes the baseline demographics and characteristics of the randomized and nonrandomized population.

Table 4. BASELINE DEMOGRAPHICS AND CHARACTERISTICS FOR ALL PARTICIPANTS SCREENED

Characteristic	Lovastatin (n=104)	Placebo (n=106)	Nonrandomized (n=372)
Gender, n (%)			
male	45 (43.3)	56 (52.8)	187 (50.3)
female	59 (56.7)	50 (47.2)	185 (49.7)
Age, yrs			
mean	60	58.8	59.6
range	45-82	44-83	44-92
Mean Age by Gender			
male	56.6	54.5	56.5
female	62.6	63.6	62.7
Ethnicity, n (%)			
Caucasian	95 (91.4)	96 (90.6)	340 (91.4)
Black	2 (1.9)	6 (5.7)	24 (6.5)
Hispanic American	5 (4.8)	1 (0.9)	4 (1.1)
Asian	1 (1.0)	1 (0.9)	3 (0.8)
Native American	1 (1.0)	1 (0.9)	0 (0)
Hispanic (Puerto Rican)	0 (0)	1 (0.9)	1 (0.3)
Mean Baseline Lipid Value; mg/dL (SD)			
total-C	233 (23.7)	230.5 (19.5)	244.5 (37.0)
LDL-C	143 (18.4)	144.8 (16.0)	154.2 (35.9)
HDL-C	56.6 (15.7)	53.9 (13.6)	55.7 (16.2)
TG	168.8 (94.2)	160.5 (77.8)	176.1 (90.3)
total-C/HDL-C	4.4 (1.3)	4.5 (1.0)	4.7 (1.4)

Patient Disposition

Of the 582 screenees, 372 (63.9%) were not randomized for the following reasons: failed to meet eligibility criteria (322); withdrew consent (30); lost to follow-up (7); laboratory AE (3); clinical AE (2); moved (2); protocol deviation (1); and other (5). Participants who were excluded because of failure to meet the eligibility criteria are accounted for in Table 5 below.

Table 5. PARTICIPANTS NOT RANDOMIZED BECAUSE OF FAILURE TO MEET ELIGIBILITY CRITERIA (n=322)

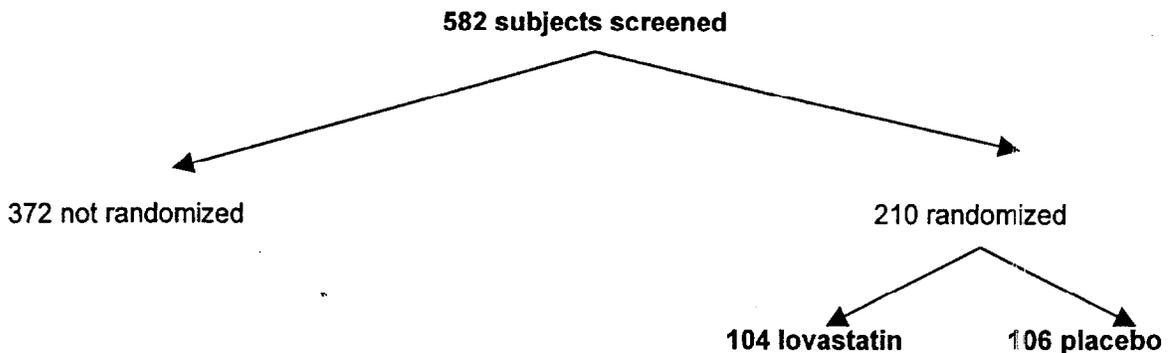
Eligibility Criteria not met	N	%
Cholesterol out of range	281	87.3
Severe obesity	12	3.7
TSH out of normal limits	6	1.9
Elevated BP	6	1.9
Family history of CHD/peripheral vascular disease	5	1.5
Reason not provided on CRF	3	0.9
Blood glucose	3	0.9
Unwilling/unable to participate	2	0.6
Out of age range	2	0.6
MD not approve	2	0.6
Not on AHA or equivalent diet	2	0.6
Alcohol use	1	0.3

Other cholesterol lowering medication	1	0.3
Liver function test abnormal	1	0.3
History of substance abuse/psychosis/other condition	1	0.3
Participation in another study	1	0.3
Placebo non-compliance	1	0.3

*Multiple reasons could be listed for a subject hence the total number of reasons for exclusion exceeds the number of subjects actually excluded

The following flow diagram depicts the subject disposition for the Efficacy Study.

Figure 3. DIAGRAM OF PARTICIPANT SELECTION FOR EFFICACY STUDY



Of those who were randomized to treatment (n=210), 95/104 (91.3%) participants in the lovastatin group and 101/106 (95.3%) in the placebo group completed the 12-week trial. The reasons for discontinuation are summarized in table 6 below.

Table 6. DISCONTINUATIONS IN EFFICACY STUDY

	Lovastatin (n=104)	Placebo (n=106)
Reason for Discontinuation		
Clinical AE	3 (2.9%)	3 (2.8%)
Investigator error	3 (2.9%)	0
Patient was on vacation	0	1 (<1%)
Withdrew consent	0	1 (<1%)
Lost to f/u	3 (2.9%)	0
Total Discontinued	9 (8.7%)	5 (4.7%)
Completed 12wks	95 (91.3%)	101 (95.3%)

Efficacy data were ascertained in all randomized participants at 12 weeks, except for 7 lovastatin-treated and 3 placebo-treated individuals due to lost to follow-up.

Concomitant Medications

The term 'concomitant medication' was used for any medication that was started during the study period or was started prior to the study and continued during the trial. There were 83 (79.8%) lovastatin subjects and 94 (88.7%) placebo subjects who reported concomitant use of medications during the trial.

The hormones and synthetic substitutes drug class included estrogens and progestagens that which could affect the lipid parameters. The numbers of participants in the two treatment groups who used estrogen alone or in combination with progestagen were similar (27 or 26% for lovastatin, 23 or 22% for placebo). The numbers of participants using progestational therapies alone were also similar (4 or 3.8% for lovastatin, 5 or 4.7% for placebo).

Other medications that could alter lipid profiles included beta-blockers, hydrochlorothiazide diuretics, and psyllium preparations. The use of psyllium preparations was similar between the 2 groups but use of anti-hypertensives, which may affect cholesterol levels, was slightly higher in the placebo group. The majority of these individuals were receiving treatment with these medications prior to randomization reducing the likelihood that there was a significant effect on the lipid-altering efficacy of this trial.

Patient Compliance

Compliance to study medication for the intervals between baseline and 6 weeks and 6 weeks and 12 weeks was defined as the number of tablets taken during the study period divided by the number of days in the study period. As defined in the sponsor's data analysis plan, the number of tablets taken was obtained from information recorded by the patient on the diary card. This number was verified by tablet counts at each study visit. The exclusion of participants from compliance determination in this trial was based primarily on the availability of diary cards regardless of pill counts. Seven lovastatin and 5 placebo participants at 6 weeks and 10 lovastatin and 7 placebo participants at 12 weeks were excluded from the assessment of compliance due to missing diary cards.

At 6 weeks the number of participants reporting a 75-100% compliance with study medication was 90/97 (92.8%) in the lovastatin group and 99/101 (98.0%) in the placebo group. At 12 weeks these numbers were 88/94 (93.6%) for the lovastatin group versus 95/99 (96.0%) for the placebo group.

Overall, the compliance with study medication appeared similar between the lovastatin and placebo groups.

Efficacy Results

Primary Efficacy Endpoint

The primary efficacy endpoint was the mean of the individual percent changes in LDL-C level from baseline to 12 weeks, for lovastatin compared to placebo. Using the primary approach for analysis, LDL-C values were available for 96 participants in the lovastatin group and 103 in the placebo group. Seven lovastatin-treated participants discontinued therapy without efficacy data at 12 weeks and 1 in the lovastatin group had no LDL-C value calculated due to TGs > 400 mg/dL. Three placebo-treated participants discontinued therapy without efficacy data available at the end of the trial.

Treatment with lovastatin for 12 weeks in this study population resulted in a mean reduction in LDL-C of 17.5% compared to an increase of 2.4% in the placebo group.

Table 7. 12-week LDL-C Results for by Treatment Groups in Protocol 075

	Lovastatin (n=96)	Placebo (n=103)
Baseline Mean LDL-C, mg/dL	143.0	144.8
Mean % Change (SD) at 12 wks*	-17.5 (15.7)	+2.4 (14.5)
Achieved LDL-C at 12 weeks, mg/dL		
Mean (SD)	116.8 (19.4)	147.2 (20.5)
25 th	103	132
50 th	117	146
75 th	129	160
Range	63-165	88-204

*p<0.001 compared to placebo

Secondary Efficacy Endpoints

Lipid changes were also evaluated at 6 and 12 weeks for total-C, HDL-C, TGs, and total-C/HDL-C ratios. Changes in LDL-C levels were assessed at 6 weeks as a secondary endpoint measure. Secondary efficacy measures were determined by the per-protocol approach and missing data were not estimated. The following tables summarize the secondary lipid efficacy results for each treatment group.

Table 8. Mean % Change in Secondary Lipid Parameters at 6 and 12 Weeks[‡]

Lipid Parameter	Lovastatin		Placebo	
	6 wks	12 wks	6 wks	12 wks
LDL-C				
n	95	96	101	103
baseline mean, mg/dL	143	143.0	145.0	144.8
mean % change (SD)	-19.3 (14.2)	-17.5 (15.7)	+1.1 (13.9)	+2.4 (14.5)
Total-C				
n	96	97	102	103
baseline mean, mg/dL	233.0	232.8	230.6	230.6
mean % change (SD)	-12.6 (9.2)	-11.4 (11.4)	+1.6 ()	+2.5 (10.0)
HDL-C				
n	96	97	102	103
baseline mean, mg/dL	56.5	56.5	54.0	53.9
mean % change (SD)	+5.7 (10.2)	+6.7 (11.3)	+2.0 (9.9)	+2.6 (11.5)
TGs				
n	96	97	102	103
baseline mean, mg/dL	168.4	167.3	160.7	161.0
mean % change (SD)	-8.6 (27.9)	-8.2 (34.7)	+9.4 (47.8)	+10.5 (31.4)
total-C/HDL-C				
n	96	97	102	103
baseline mean	4.4	4.4	4.5	4.5
mean % change (SD)	-16.8 (10.2)	-16.4 (11.8)	+0.3 (11.0)	+0.8 (11.6)

[‡] differences between treatment groups were statistically significant at p <0.001 for all lipid parameters measured

Conclusions on Efficacy Results

Treatment with lovastatin 10 mg for 12 weeks resulted in significant reductions in total-C, LDL-C, TGs, and total-C/HDL-C and increases in HDL-C values compared to placebo. These changes were achieved by 6 weeks and maintained after 12 weeks of treatment.

Safety Results

Overall Adverse Events and Serious AEs During Treatment Period

There were 76 participants [39/104 (37.5%) lovastatin; 37/106 (34.9%) placebo] who reported a total of 136 adverse events (AEs) during the double-blind treatment phase of Protocol 075. Two of these events were considered serious and occurred in lovastatin-treated individuals. The first was a 56-year old female with a prior history of a left ovarian cyst who had on ultrasound performed prior to randomization that revealed an enlarging cyst. This woman underwent laparoscopic removal of the cyst 26 days after randomization. The second person was a 56-year old white female who developed cholecystitis 56 days after randomization; she was hospitalized and gallstones were removed. Lovastatin therapy was interrupted and the woman recovered completely. Neither of these cases were considered drug-related by the investigators. There were no deaths reported in this 16 to 18-week study.

Table 9. SUMMARY OF REPORTED ADVERSE EVENTS BY BODY SYSTEMS

Body System	Lovastatin (n=104)	Placebo (n=106)
Body as a whole/site unspec.	10 (9.6%)	5 (4.7%)
Cardiovascular	3 (2.9%)	4 (3.8%)
Digestive	16 (15.4%)	7 (6.6%)
Metabolic/Immune	0	4 (3.8%)
Musculoskeletal	7 (6.7%)	13 (12.3%)
Nervous system/psychiatric	6 (5.8%)	11 (10.4%)
Respiratory	12 (11.5%)	16 (15.1%)
Skin	1 (<1%)	4 (3.8%)
Special senses	2 (1.9%)	4 (3.8%)
Urogenital	3 (2.9%)	8 (7.5%)

The most common AEs reported were diarrhea and nausea in the lovastatin group (4/104; 3.8%), and upper respiratory tract infection in the placebo group (6/106; 5.7%). One participant in the lovastatin group reported myalgias, whereas 6 in the placebo group reported arthralgias (3), muscle cramps (2), or myalgias (1). Since laboratory assessments were not done in this study, no information regarding CK levels were available.

The following table summarizes AEs by preferred terminology which were reported at incidence rates of > 1.0% in either treatment group.

Table 10. AEs REPORTED AT >1.0% INCIDENCE RATES

Lovastatin (n)	Placebo (n)
Diarrhea (4)	Respiratory infection (6)
Nausea (4)	Headache (4)
Bronchitis (3)	Arthralgia (3)
Upper Respiratory (3)	Insomnia (3)
Abdominal Pain (3)	Sinus Disorder (3)
Constipation (2)	Allergy (2)
Abdominal Distension (2)	Muscle Cramp (2)
Flatulence (2)	Diarrhea (2)
Flu-like Illness (2)	Edema/swelling (2)
Headaches (2)	Increased HTN (2)
Palpitations (2)	Myalgia (2)
Pharyngitis (2)	Tendon Disorder (2)
	Urinary Disorder (2)

Four (6.7%) of the AEs reported in the lovastatin group were considered probably related to drug compared to 2 (2.6%) in the placebo group. All 4 cases in the lovastatin group were GI-related complaints occurring in 2 patients.

Adverse Events Resulting in Study Discontinuation

A similar number of participants in each treatment group experienced an AE resulting in study discontinuation [3 lovastatin (2.9%); 3 placebo (2.8%)]. Table 11 summarizes these 6 subjects with respect AE, onset, and outcome.

Table 11. STUDY DISCONTINUATIONS DUE TO CLINICAL AE

Treatment Group	AE	Days from Randomization	Outcome
Lovastatin			
Pt 06087	diarrhea	16	recovered
Pt 08034	abdominal distention	22	recovered
Pt 12010	palpitations	27	recovered
Placebo			
Pt 08019	flatulence	7	recovered
Pt 08033	itchy eye, arthralgia, somnolence	2-4	recovered
Pt 09042	depression, headache, impotence, asthenia/fatigue, nausea	6 and 38	ongoing as of end of study

Conclusions on Safety Findings of Protocol 075

The numbers of AEs reported in this trial were similar for the lovastatin and placebo groups (37.5% vs. 34.9%, respectively). Patients tolerated study medication well with similar numbers of participants discontinuing lovastatin due to clinical AEs (2.9%) as compared to placebo (2.8%). The most common side effect reported with lovastatin was GI-related. Well-described serious side effects associated with lovastatin (myopathy with CK elevation and hepatic transaminitis) were not observed in this trial; however, this trial was not designed to monitor for these adverse events with routine laboratory assessments. Nonetheless, the tolerability findings of this study are not unexpected given the low dose of lovastatin, the careful selection of subjects, and the short duration of treatment. The effect of treatment duration on AEs experienced is best illustrated by the AE discontinuation rate of < 3% for both treatment groups compared to observed rates of 8-9% in other lovastatin trials of longer duration.

In conclusion, the safety findings in this trial did not reveal AEs that are not already described in the drug label. The findings from this trial, however, cannot provide reassurance of the safety of this drug in a general OTC-population because of the extensive inclusion and exclusion criteria used for the selection of the treatment population and the very short treatment duration.

CONCLUSIONS ON REVIEW OF PROTOCOL 075 (EFFICACY STUDY)

Treatment with lovastatin 10 mg per day in this study which enrolled patients with lipid profiles similar to the anticipated OTC population demonstrated a significant reduction in total-C, LDL-C, and TGs, and an increase in HDL-C, compared to placebo. The completion rate in this relatively short study was high (93%), and compliance with study medication in those who completed the trial was > 90%. The persistence and compliance findings in this trial are typical for controlled trials of short duration. The

selection of motivated individuals who are asked to return for scheduled visits reduces attrition, improves compliance, and increases drug effectiveness.

The lipid-lowering efficacy of lovastatin 10 mg per day observed in this study has already been established in previously conducted placebo-controlled trials with dietary restrictions (Table 12).

Table 12. MEAN % REDUCTIONS IN LDL-C FOR LOVASTATIN 10 MG OBSERVED IN 3 PLACEBO AND DIET-CONTROLLED CLINICAL TRIALS

Efficacy Study (075) at 12 weeks, n=96	Protocol 016 at 6 weeks, n=33	Protocol 061 at 12 weeks, n=82
-17.5%	-21.1%	-15.2%

The findings from the 075/Efficacy Study provide information on the expected cholesterol lowering of lovastatin 10 mg in the targeted OTC population. The results, however, do not establish the expected mean percent cholesterol reduction in an actual nonprescription-use setting since this trial was NOT an actual-use trial. Drug effectiveness in the actual-use population will require consideration of adherence to diet and drug therapy.

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PROTOCOL 076 (PHARMACY STUDY)

STUDY DESIGN

Protocol 076 was a 6-month, uncontrolled, multi-center, open-label clinical trial evaluating the treatment of mild-to-moderate hypercholesterolemia with lovastatin 10 mg per day. This was an actual-use study in which participants were not required to purchase study medication.

STUDY OBJECTIVES

Primary

1. to evaluate the mean of the individual percent reductions in LDL-C at the first follow-up visit (Visit 2, approximately 8 weeks of treatment)
2. to evaluate the mean of the individual percent reductions in LDL-C in patients remaining on lovastatin 10 mg per day at 6 months (Visit 4)

Secondary

1. to evaluate the ability of study participants to correctly self-select use/nonuse of lovastatin 10 mg per day as per labeling
2. to evaluate the ability of patients to remain on lovastatin 10 mg per day treatment in the OTC setting over the 6-month study period
3. to evaluate the tolerability of lovastatin 10 mg as measured by the incidence of clinical adverse experiences

This clinical review of Protocol 076 will specifically address the lipid-altering efficacy of lovastatin 10 mg per day and the safety of this product in the OTC population. Other endpoint measures such as compliance, persistence, and label comprehension, will be addressed by reviewers from DOTCDE and DDMAC.

ELIGIBILITY CRITERIA

(criteria denoted by an asterisk were not part of the prototype market package label but were required for determining eligibility in this study)

Inclusion criteria:

- men \geq 45 years old and women \geq 55 years old without heart disease (e.g. heart attack or angina)
- total-C between 200-240 mg/dL and LDL-C \geq 130 mg/dL on Day 1 of protocol
- patients have tried a low-fat diet to lower cholesterol within the year prior to study entry
- patients in general good health who demonstrated a willingness to participate in the study as evidenced by written informed consent
- patients had to be able to comprehend and comply with the study requirements

Exclusion criteria:

- patients currently taking cyclosporine, itraconazole, (or other systemic azole antifungal medications), erythromycin, clarithromycin, or nefazodone
- patients currently taking ketoconazole, mibefradil dihydrochloride, and oral corticosteroids
- patients currently on other cholesterol-lowering medications (including OTC niacin in doses $>$ 500 mg qd) within 4 weeks prior to screening
- women who were of childbearing potential, pregnant, or breastfeeding
- history of heart disease or peripheral vascular disease

- family history of premature heart disease (MI before age 55 in parents or siblings)
- consumption of 3 or more alcohol-containing beverages per day on most days of the week
- any contraindication to the use of lovastatin, including allergy to lovastatin, diagnosis of hepatitis, or a past history of liver disease
- participation in another drug study within 2 months prior to visit 1

STUDY SITES AND INVESTIGATORS

Fifty-nine retail pharmacies staffed by registered pharmacists or PharmD co-investigators participated in this clinical trial. One physician co-investigator was available for consultation but was not involved in the enrollment of study participants. Study sites were located in 23 states located in different regions of the United States.

The study site co-investigators were responsible for taking all measurements, assessing study eligibility, and collecting and recording all study data. The study physician co-investigator was available at a toll-free number for patient-initiated and pharmacist-initiated telephone consultations and to receive reports of adverse experiences.

RECRUITMENT AND SCREENING

Study participants were recruited through print advertisements and television and radio announcements. A toll-free telephone number was provided where interested individuals could call and be scheduled for a screening visit at a nearby pharmacy study-site. At the study sites, potential study participants were shown a prototype market package label. Participants self-selected to continue in the study after review of the materials and provided answers to the following 2 questions:

1. After reading all of the information on the product carton label, and knowing your current health situation, do you feel this product is right for you? Answer choices:
 - a) yes
 - b) no
 - c) I need more information
2. If this product were available for you to use right now, what would you decide to do next? Answer choices:
 - a) obtain this product and use it
 - b) get my cholesterol checked before deciding to use this product
 - c) talk to a doctor before deciding to use this product
 - d) get my cholesterol checked and talk to a doctor
 - e) would not be interested in using this product

Participants also completed a self-administered medical history questionnaire which included questions pertaining to the study eligibility criteria. The questionnaire was then reviewed by the pharmacist to determine if the individual was **potentially qualified** to proceed with the lipid profile determination. To be potentially qualified an individual must have met the inclusion/exclusion criteria, provided answer 'a' or 'c' to question 1 above, and signed an informed consent. The fingerstick lipid profile determination was performed at the study site; subjects who recently ate (within 2 hrs prior to lipid testing) were asked to return to the site after a minimum 2 hr fast. If the lipid results fell within the acceptable range, subjects were considered **qualified** and given study medication (8 wk supply), informational brochure, compliance program enrollment card, information

cards, and the toll-free study physician phone number. Individuals enrolling in the compliance program were provided with a cookbook, monthly educational and compliance promoting newsletters.

Individuals interested in participating in Protocol 076 underwent several phases of screening before being considered eligible for drug treatment. As a consequence, several groups of study participants were generated after they completed the medical history screening questionnaire. These groups are listed and defined in the following section.

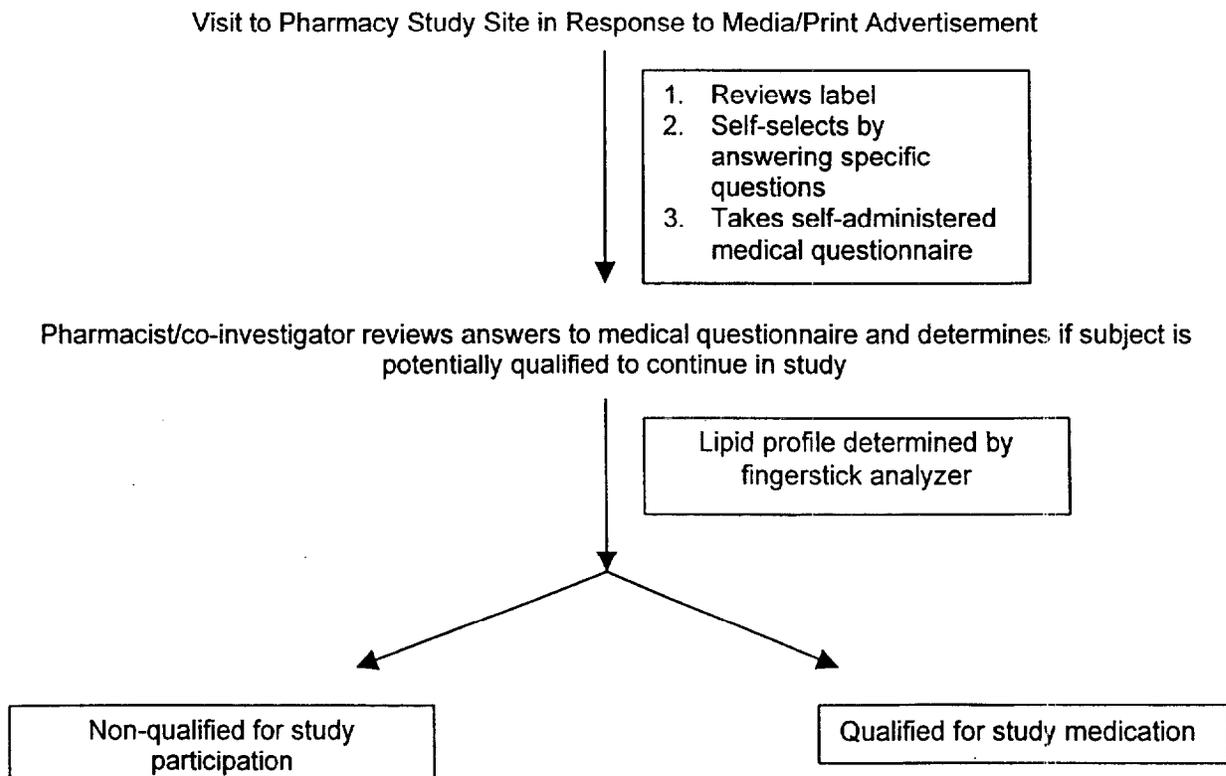
All Study Participants: this group included all individuals visiting the study sites who were assigned a patient identification number. These individuals reviewed the proposed product label, answered the self-selection questions, and completed the medical history questionnaire.

Potential Purchasers: this group referred to individuals who stated that they would either obtain the product and use it or get their cholesterol checked before deciding to use this product without seeking medical advice. This population was considered the population at-risk for making a self-selection error.

Nonqualified Participants: this group included all individuals disqualified by the pharmacist from receiving lovastatin for either medical history reasons, cholesterol test results, other inclusion/exclusion criteria, or the participant selected not to use the product.

Qualified Participants: those individuals who were potentially qualified based on their medical history, signed an informed consent, and had a cholesterol test with values within the ranges specified by the eligibility criteria. These individuals were dispensed study drug.

Figure 4. Diagram of Screening and Selection for Pharmacy Study



STUDY VISITS AND LABORATORY ASSESSMENTS AFTER STUDY ENROLLMENT

There was a total of 4 pharmacy study-site visits; except for the final visit (visit 4 at 24 weeks), none of the study visits was scheduled. Since only an 8-week supply of study medication was dispensed at each study visit, it was estimated that the interval between visits would be approximately 8 weeks. Fingertstick lipid profiles (total-C, HDL-C, TG, and calculated LDL-C) were determined at each visit for efficacy analyses. Lipid values were considered invalid for efficacy determination if they were not obtained during specified day ranges (Table 13).

Table 13. Day Ranges for Post-Baseline Visits

	Day Ranges
Visit 1 (baseline)	Visit date ≤ dispensed date
Visit 2 (approximately 8 wks)	28 days < visit date ≤ 84 days
Visit 3 (approximately 16 wks)	84 days < visit date ≤ 140 days
Visit 4 (approximately 24 wks)	140 days < visit date ≤ 196 days

Pill counts and collection of clinical adverse experiences took place at each study visit post-baseline. A new 8-week supply of study medication was dispensed at each visit except Visit 4.

EFFICACY AND ENDPOINT MEASURES REVIEWED IN DMEDP

Primary Efficacy: two co-primary endpoints were defined as:

1. the mean of the individual percent changes in LDL-C from baseline to visit 2 (~8 wks of therapy) in all subjects dispensed drug. Those with missing data at 8 weeks had lipid values estimated by carrying forward their baseline values.
2. the mean of the individual percent changes in LDL-C from baseline to visit 4 (~6 mos of therapy) in only those subjects remaining on drug; missing data were not estimated.

Secondary Endpoints:

1. to evaluate tolerability of nonprescription lovastatin in those subjects dispensed study medication. These secondary endpoints were obtained through adverse experience reports provided at study visits or through calls to the study physician. No laboratory assessments for safety were scheduled in this trial.

RESULTS OF PHARMACY STUDY

Patient Disposition

Fifty-nine (59) pharmacies located throughout the United States screened 6,095 subjects. Of these, only 722 (11.8%) qualified for study medication use while 5,373 (88.2%) were not qualified based on pharmacist-reviewed medical questionnaire (n=2,320), cholesterol not within acceptable range or invalid results (n=2,812), consent withdrawal or other reasons (n=241[†]).

[†] this number includes 2 subjects not evaluated by the pharmacist/co-investigator; these 2 subjects were counted separately in the Clinical Study Report (CSR)

Reasons for Study Exclusion

Individuals Excluded Based on Medical History Questionnaire

The self-administered questionnaire consisted of 16 questions pertaining to the study eligibility criteria which allowed the pharmacist to determine if the subject qualified for a lipid profile determination. A total of 2,320 subjects were ineligible for study participation because of answers provided in this questionnaire. Table 14 summarizes the patient exclusions as determined by the medical history questionnaire. Because an individual could be disqualified for more than one reason, the number of subjects listed in this table exceeds the 2,320 subjects disqualified based on the questionnaire.

Table 14. Reasons for Exclusion of the 2,320 Subjects Not Potentially Qualified Through Self-Administered Medical Questionnaire

Reasons for Exclusion	Number of Subjects
Familial heart disease	870 (37.5%)
Not following low-fat diet	670 (28.9%)
Heart disease	445 (19.2%)
Prohibited meds	395 (17.0%)
Age (males < 45, females < 55)	351 (15.1%)
Poor/fair health status	210 (9.1%)
Heavy alcohol use	214 (9.2%)
History of liver disease/hepatitis	227 (9.8%)
Another drug study	99 (4.3%)
Allergy to lovastatin	59 (2.5%)
Potential for pregnancy	10 (0.4%)

Although self-reported cholesterol levels were obtained from the questionnaire, participants were not excluded based on these responses. Exclusions due to lipid values were applied only after the individuals underwent fingerstick cholesterol testing (see below). The most common reason for study exclusion based on the medical questionnaire was family history of heart disease followed by in adherence to a low-fat diet within the past year.

Individuals Excluded Based on Lipid Profile

In the population of individuals not qualified to receive study medication, 2,826 underwent cholesterol testing (14 were not qualified based on medical questionnaire but were inadvertently allowed to proceed with cholesterol testing). The median total-C level in these individuals was 266 mg/dL suggesting that the majority of people excluded for cholesterol values outside the eligibility range had values exceeding this range (total-C 200-240 mg/dL). Overall, baseline cholesterol values not within the 200-240 mg/dL range was the most common reason an individual was not allowed to participate in Protocol 076.

Individuals Excluded for Other Reasons

A smaller number of the study participants (n=241) were excluded secondary to inability to comply with study protocol or rejected the drug product (200), inability to obtain lipid profile (11), withdrawal of study consent (7), or other reasons (23).

Note: There were 11 participants who were screened twice at separate times and assigned different identification numbers. Nine of these participants did not qualify for study drug and 2 received study drug. The total number of participants (n=6,095) includes these 11 individuals who were screened twice but the number unique

individuals contributing data to this study was 6,084. This study report summarized the duplicate data from these 11 individuals as separate individuals.

Study Discontinuation

Of the 722 individuals dispensed study drug, 200 discontinued from the study and 522 (72.3%) completed the trial. The term, 'study completer', was assigned to any subject who returned to the study site after 20 weeks in the study, had a lipid profile determination and adverse experience ascertainment, and completed study close-out forms. All other subjects were considered 'discontinued'.

By 6 months after initiating drug therapy, 27.7% of the qualified population had discontinued treatment with clinical AEs being the most common reason for drug discontinuation (Table 15).

Table 15. Patient Disposition and Reasons for Discontinuation in Pharmacy Study

Number of Subjects Qualified for Study Drug	722
Reasons for Discontinuation, n (%)	
Clinical AEs	68 (9.4)
Withdrew consent	44 (6.1)
Lost to F/U	29 (4.0)
Personal MD	20 (2.8)
Patient did not come in for final visit	15 (2.1)
Investigator error	9 (1.2)
Moved	5 (<1)
Lack of response	4 (<1)
Patient failed to complete final visit procedures	3 (<1)
Study MD medical reason	1 (<1)
Physician administered medical history	1 (<1)
Protocol deviation	1 (<1)
Total non-completers, n (%)	200 (27.7)
Completers, n (%)	522 (72.3)

The term, 'time in study', referred to that period between the day study drug was first dispensed to the last day in the study. The term, 'last day in the study', was defined as the latest day on which one of the following occurred:

- a site visit that included a lipid evaluation
- an adverse experience occurred (if the study medication was returned prior to resolution of the AE, the date that the AE resolved was considered the last day in the study)

Based on this definition of 'time in study', the rate of study discontinuation was calculated and depicted in Figure 5. The rate of discontinuation was highest within 1 month after study drug initiation and appeared to stabilize for the duration of this trial of 6 months. Predictions of persistence beyond this time period, however, cannot be made with any degree of accuracy.

Figure 5. Rate of Study Discontinuation

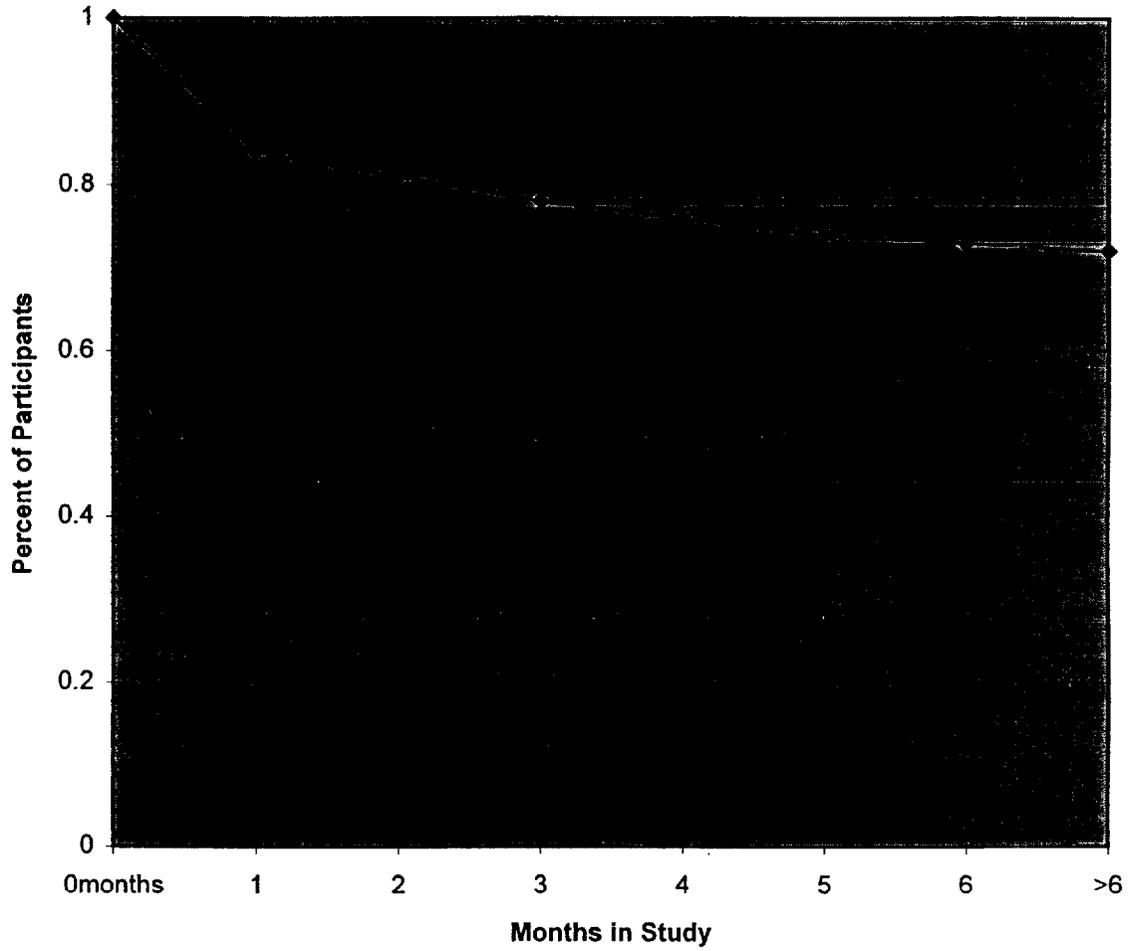
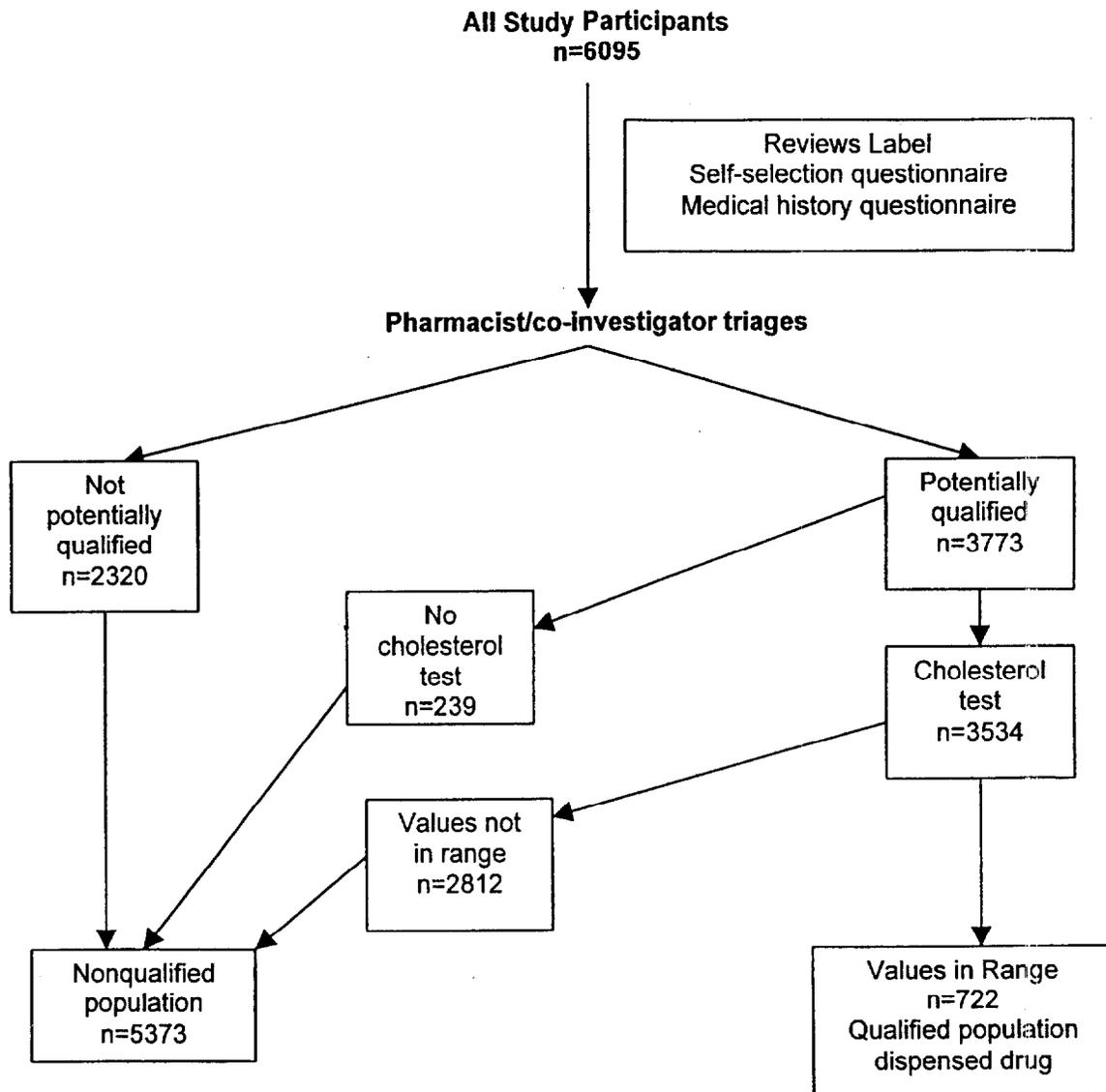


Figure 6 summarizes the disposition of study participants in Protocol 076.



BASELINE DEMOGRAPHICS AND PATIENT CHARACTERISTICS

The baseline characteristics of individuals enrolled in Protocol 076 are presented by those who qualified for study medication (n=722) and those who were disqualified (n=5,373).

Table 16. Baseline Demographics and Patient Characteristics for All Subjects Screened

Characteristic	Qualified Subjects (n=722)	Non-qualified Subjects (n=5373)
Gender (%)		
male	533 (73.8%)	2883 (53.7%)
female	189 (26.2%)	2460 (45.8%)
not provided	0	30 (0.6%)

Characteristic	Qualified Subjects (n=722)	Non-qualified Subjects (n=5373)
Age (yrs)		
mean	60	59.9
range	42-83	21-95
Mean Age By Gender		
male	58.7	57.4
female	63.8	62.9
Ethnicity (%)		
Caucasian	665 (92.1%)	4888 (91.0%)
Black	21 (2.9%)	160 (3.0%)
Hispanic	14 (1.9%)	120 (2.2%)
Asian	9 (1.2%)	38 (0.7%)
Native American	4 (0.6%)	20 (0.4%)
Mean Baseline Lipid Value (SD)		
total-C (mg/dL)	226 (10.5)	267.7 (48.4)
LDL-C (mg/dL)	148.2 (13.1)	167.6 (45.5)
HDL-C (mg/dL)	43.6 (13.3)	52.5 (18.4)
TG (mg/dL)	172.6 (68.7)	246 (131.5)
total-C/HDL-C	5.7 (1.9)	5.8 (2.8)

* mean baseline lipid values in the nonqualified population obtained in only 2,826 subjects who had a baseline lipid profile
NA = not applicable

More men (73.8%) qualified for treatment than women (26.2%) and more than 90% of the screened and treated population were Caucasian. Although the mean age was similar in both qualified and nonqualified subjects, the range was greater in those disqualified from study participation. As expected, in the non-qualified subjects who had a baseline lipid profile (n=2,826), the mean total-C, LDL-C, TGs, and HDL-C levels were higher than observed in the qualified population. The higher HDL-C level seen in the non-qualified population may be due to a higher proportion of women contributing to this group compared to the qualified group (Table 17).

Table 17. Mean HDL-C Levels by Gender in Qualified and Nonqualified Population

Gender	Qualified N=719*		Nonqualified N=2,716	
	N (%)	Mean HDL (SD)	N (%)	Mean HDL (SD)
Females	189 (26.3)	52 (14.8)	1301 (47.9)	61.4 (18)
Males	530 (73.7)	40.8 (11.5)	1415 (52.1)	44.3 (14.6)

*3 subjects did not have available baseline HDL-C values

EFFICACY RESULTS

Primary Efficacy Endpoints

LDL-C Change at Visit 2 (8 weeks)

The efficacy of lovastatin 10 mg per day after 8 weeks was summarized as the mean of the individual percent changes in LDL-C level from baseline to visit 2 in all subjects dispensed study medication. Of the 722 individuals dispensed study drug, 2 people were excluded from efficacy analysis due to an invalid baseline LDL-C values secondary to elevated TGs. Efficacy data were available at 8 weeks in only 568 participants (78.7%); values were carried forward for the remaining 152 (21%) individuals.

Treatment with lovastatin 10 mg for 8 weeks in this actual-use study resulted in a mean reduction of 17.1% (SD 16.8) in LDL-C levels compared to baseline. Excluding the subjects with missing values at Visit 2 resulted in 21.7% (SD 16.1) reduction in LDL-C.

LDL-C Change at Visit 4 (6 months)

Of the 722 treated subjects only 494 (68.4%, 494/722) were included in the efficacy analysis at 6 months. Subjects were excluded due to unavailable LDL-C data at 6 months or had a value obtained outside the visit range (n=226) and invalid baseline LDL-C values (n=2).

Persistence with nonprescription lovastatin at 6 months resulted in a mean reduction of 23.9% (SD 17.1) in LDL-C values compared to baseline.

Table 18. LDL-C Results at 8 Weeks and 6 Months in Protocol 076

	n		(95% CI)
Visit 2 (8 weeks)			
mean % change (SD)	720	-17.1 (16.8)	(-18.3, -15.9)
baseline mean value, mg/dL		148.2	
mean achieved value, mg/dL (SD)		122.5 (25.8)	
Visit 2 (8 weeks)*			
mean % change (SD)	568	-21.7 (16.1)	(-23.0, -20.4)
baseline mean value, mg/dL		148.7	
mean achieved value, mg/dL (SD)		116.1 (24.7)	
Visit 4 (6 months)*			
mean % reduction (SD)	494	-23.9 (17.1)	(-25.4, -22.4)
baseline mean value, mg/dL		149.1	
mean achieved value, mg/dL (SD)		113.3 (26.4)	

*missing data were not estimated

Other parameters of the lipid profile were summarized only in those individuals with efficacy data at visits 2 and 4. Table 19 summarizes the mean percent changes for total-C, HDL-C, and triglycerides at 8 and 24 weeks.

Table 19. Summary of Secondary Lipid Changes in Individuals with Valid Data*

	8 weeks	24 weeks
Total-C		
N	571	500
mean baseline value, mg/dL	226.5	226.7
mean % change (SD)	-12.9 (11.1)	-15.7 (12.2)
HDL-C		
N	571	499
mean baseline value, mg/dL	43.4	43.3
mean % change (SD)	+6.9 (22.4)	+6.0 (23.0)
Triglycerides		
N	571	499
mean baseline value, mg/dL	172.8	171.4
median baseline value, mg/dL	162.0	160.0
mean % change (SD)	+9.2 (43.6)	+2.2 (43.5)

*missing data were not estimate

SAFETY RESULTS

Of the 722 participants dispensed study medication, 42 reported not consuming any amount of drug. The incidence rates of adverse experiences in this trial were presented by the sponsor as proportions of those dispensed medication. This reviewer will present AE incidence rates in only those who consumed any amount of study drug since the risk of experiencing an AE should only be determined in those who took lovastatin (n=680). Comparison of the two rate calculations will be presented at the conclusion of the safety review.

Overall Adverse Events Reported

There were a 228 subjects (33.5%) who reported a total of 398 AEs while receiving treatment with nonprescription lovastatin. The most common body system for which AEs were reported involved the digestive system followed by the nervous system/psychiatric body system. Table 20 lists the overall AEs reported by body system and the specific AEs (by preferred terminology) that occurred at an incidence rate > 1.0%. An individual could experience more than 1 AE but was only counted once in each body system.

Table 20. Overall Incidence of AEs by Body System and

	No. of Persons Exposed to Drug (n=680)
Body as a whole/site unspecified	42 (6.2%)
asthenia/fatigue	7
pain, abdominal	17
pain, chest	12
Cardiovascular	13 (1.9%)
Digestive	102 (15%)
acid regurgitation	8
constipation	17
diarrhea	15
dyspepsia	9
flatulence	40
nausea	7
Endocrine	1 (<1%)
Metabolic/Immune	6 (<1%)
Musculoskeletal	42 (6.2%)
myalgias	14
pain, back	8
Nervous system/Psychiatric	55 (8.1%)
headache	19
dizziness	9
Respiratory	28 (4.1%)
infection, upper respiratory	8
sinusitis	8
influenza	7
Skin	27 (4.0%)
rash	8
Special senses	3 (<1%)
Urogenital	15 (2.2%)

Serious AEs

Thirteen serious AEs were reported by 7 (1.0%) subjects, none of which were considered drug-related by the study investigators. There were no fatalities during this

study period. Table 21 summarizes the SAEs reported by preferred terminology during Protocol 076.

Table 21. Serious AEs by Preferred Terminology Reported During Treatment with Nonprescription Lovastatin in Protocol 076

PID	SAE	Onset	Drug Discontinued?
6110024	esophagalgia	17 days	yes
	esophageal obstruction	17 days	yes
	reflux esophagitis	17 days	yes
6130130	chest pain	13 days	yes
	coronary atherosclerosis	13 days	yes
6340028	dyspnea	86 days	yes
	chest pain	86 days	yes
	blood pressure increased	86 days	yes
6400010	costochondritis	6 days	yes
6520033	postoperative pain	135 days	no
	intestinal diverticulitis	135 days	no
6520095	neoplasm, skin, malignant	8 days	no
6600069	cholecystitis	103 days	no

Source: NDA 21-213 case report tabulations for Protocol 076 (allaes.xpt)

Drug-Related AEs

One hundred fifty seven (157) individuals experienced a total of 218 AEs that were considered drug-related. The most commonly reported drug-related AEs were flatulence and constipation. There were 60 participants who had drug-related AEs resulting in study discontinuation.

AEs Resulting in Study Drug Discontinuations

Sixty-eight (10%) of the participants exposed to study drug discontinued therapy due to AEs reported during the 6 months treatment period (4 subjects discontinued during the extension study period); GI-related symptoms accounted for the majority of these AEs with flatulence being the most commonly reported AE resulting in study discontinuation. Eight subjects (1.2%) discontinued therapy due to complaints of myalgias, the second most common AE reported that resulted in discontinuation of treatment. In all cases of myalgias, the investigator considered this AE to be drug-related. CK levels were not routinely obtained during this trial to associate symptoms with laboratory abnormalities but one patient (ID 6450069) had CK levels drawn after reporting symptoms of myalgias to his personal physician. The symptoms started 90 days after study initiation and CK levels were reported elevated at 284. Normal ranges from the laboratory from which this value was obtained was not available; however, reference to several other laboratories suggest this elevation to be < than 10x upper limit of normal. Study drug was stopped by the personal physician and the patient recovered 45 days after drug discontinuation.

AEs Involving the Musculoskeletal System

Thirteen people reported 14 cases of myalgias during this study. There were no cases of rhabdomyolysis or myoglobinuria reported and other than the CK elevation presented in the previous section, no clinical laboratories were available in these individuals. The incidence of myalgias in this trial (1.9%) is slightly higher than that observed in the lovastatin-treated group in the Efficacy Study (<1%) but not exceeding other trials involving lovastatin at higher doses. For example, in the Expanded Clinical Evaluation of

Lovastatin (EXCEL) study the incidence of muscle-related symptoms without CK elevations was 6.2, 5.7, and 5.8% for lovastatin 20 mg q pm, 40 mg q pm, and 40 mg bid, respectively.

Summary of Safety and Tolerability Findings of Protocol 076

The clinical adverse experiences observed in this study are summarized in the following table with both incidence rates determined by the sponsor and this reviewer.

Table 22. Summary of Clinical AEs Reported by Individuals in Protocol 076

	Number of Individuals	Sponsor's Rates N=722	Reviewer's Rates N=680
Overall AEs reported	228	31.6%	33.5%
Drug-related AEs	157	21.7%	23.1%
Serious AEs	7	<1%	1%
Serious drug-related AEs	0	0	0
Deaths	0	0	0
Discontinued due to AE	68	9.4%	10%
Discontinued due to drug-related AE	60	8.3%	8.8%
Discontinued due to serious AE	4	<1%	<1%
Discontinued due to serious drug-related AE	0	0	0
Myalgias reported	13	1.8%	1.9%

The most common body system for which AEs were reported involved the digestive system with flatulence being the most commonly reported AE (40; 5.9%), drug-related AE, and AE resulting in study drug discontinuation. The incidence of musculoskeletal-related AEs without associated CK elevations was lower in this 6-month actual use trial (1.9%) compared to another lovastatin trial of similar duration (EXCEL study) with incidence rates of 5.7 to 6.2% across different dose ranges.

There were no reports of hepatic injury, myoglobinuria, or rhabdomyolysis associated with lovastatin use in this study; however, no routine laboratories were obtained to determine if significant elevations in hepatic transaminases or creatinine kinase levels occurred.

The tolerability for lovastatin in this trial appeared to be lower than observed in other short-term placebo-controlled clinical trials. The percentage of subjects discontinuing treatment due to clinical AEs in this study (9.4%) was higher than observed in 2 other controlled clinical trials involving lovastatin 10 mg per day [study 016 (6 weeks)] and 061 (12 weeks)]. In those trials the AE drop-out rate was 2.9% and 1.2%, respectively. Similarly, the AE drop-out rate in the placebo-controlled Efficacy Study (protocol 075) was 2.9% after 12 weeks of treatment.

SUMMARY OF PROTOCOL 076 (PHARMACY STUDY)

The Pharmacy Study was designed to evaluate:

- the consumer's ability to self-select treatment of mild-to-moderate hypercholesterolemia with lovastatin 10 mg per day based on review of the proposed package label
- the adherence to study drug consumption
- the lipid-altering effects, safety, and tolerability of lovastatin

This trial was advertised in many different regions of the United States with the goal of attracting a diverse socioeconomic and ethnic study population that would be representative of the general population potentially benefiting from nonprescription lovastatin therapy. More than 90% of the population recruited and started on treatment were Caucasians and the majority of the treated population were male. Despite several thousand responses to the study recruitment, the number of individuals eventually qualifying for drug treatment only accounted for 11.8% of the response population. Among those who were dispensed drug (n=722), only 522 (72.3%) completed the study after 6 months of initiating treatment. Of the total screenees (n=6,095), the percentage of participants taking drug and completing 6 months of therapy was 8.6%.

The LDL-C reduction observed with 8 weeks of lovastatin 10 mg per day in the population dispensed medication (qualified population) was 17.1%. Since efficacy data were available in only 78.7% of the qualified population by 8 weeks of treatment and 68.4% by 24 weeks, the sponsor also summarized efficacy among the completers only. This resulted in a greater LDL-C reduction at 8 and 24 weeks of 21.7% and 23.9%, respectively. Given the high number individuals discontinuing drug treatment with unavailable efficacy data by the end of 6 months, estimates of the mean percent change in cholesterol in this population is unknown.

The most commonly reported adverse experience during this trial was flatulence followed by headaches. Although a significant number of these events resulted in study drug discontinuation, none of them were considered serious. There were no cases of rhabdomyolysis or hepatic toxicity in this study. This is not an unexpected finding given the relatively short duration of treatment, the careful selection of study participants, and perhaps, the low dose of lovastatin studied. The tolerability to some of the adverse experiences reported was low which may have accounted for the higher study discontinuation rate due to AEs reported compared to other clinical trials involving the same dose of lovastatin.

The clinical outcome of interest in a lipid-lowering program is the reduction in morbidity and mortality due to cardiovascular events. Protocol 076 does not provide evidence that treating the targeted OTC population with lovastatin 10 mg per day will result in a clinical benefit and predictions of such benefit will be discussed in a subsequent section of this review.

PROTOCOL 079 (RESTRICTED ACCESS STUDY)

STUDY DESIGN

Protocol 079 was an 8-week, open-label, uncontrolled clinical trial evaluating the treatment of mild-to-moderate hypercholesterolemia in a population of individuals who qualified for treatment after being screened by an initial telephone label reinforcement service followed by a storefront study site. This was an actual-use study in which participants were not required to purchase study medication.

STUDY OBJECTIVES

Primary

- to evaluate the mean of the individual reductions in LDL-C at the 8-week follow-up visit

Secondary

- to evaluate the ability of study participants to remain on lovastatin 10 mg per day over the 8-week study period
- to evaluate the tolerability of lovastatin 10 mg per day as measured by the incidence of clinical adverse experiences reported

The clinical review of Protocol 079 in DMEDP will specifically address the lipid-altering efficacy of lovastatin 10 mg per day and the safety of its use in this study population. Other endpoints will be addressed by DOTCDE and DDMAC.

ELIGIBILITY CRITERIA

The eligibility criteria differed for the telephone and study site qualification.

Inclusion criteria for telephone qualification:

- men \geq 40 years old and women \geq 55 years old

Exclusion criteria for telephone qualification:

- individuals currently taking mibefradil dihydrochloride, cyclosporine, itraconazole, ketoconazole (or other systemic azole antifungal medications), erythromycin, clarithromycin, nefazadone
- individuals ever taken any other prescription or OTC cholesterol-lowering medications including niacin at doses $>$ 500 mg qd and CholestinTM or oral corticosteroids within 4 weeks prior to screening visit
- women who were of childbearing potential, pregnant, or breastfeeding
- history of heart disease, angina, stroke, PTCA, CABG, or peripheral vascular disease
- history of diabetes mellitus
- individuals taking more than 1 antihypertensive medication
- consumption of 3 or more alcohol-containing drinks per day on 4 or more days in a week
- any contraindication to the use of lovastatin including allergy to lovastatin, diagnosis of hepatitis, or past history of liver disease
- individuals who knew their total-C level was $<$ 190 mg/dL or $>$ 250 mg/dL
- participation in any drug study within 2 months prior to enrolling or during this study
- individuals were also excluded if they were not able to read or understand English, were associated with a company that manufactured pharmaceutical, medical, or healthcare products (these exclusion criteria were not listed in the study protocol)

If individuals qualified for further evaluation based on fulfilling the above telephone eligibility criteria, an appointment was scheduled for a storefront study visit. Further study eligibility was determined at this site visit.

Inclusion criteria at storefront study site:

- total-C \leq 240 mg/dL and LDL-C \geq 130 mg/dL obtained by a desktop fingerstick cholesterol analyzer (these values were obtained by nurse co-investigators at storefront study site) on D1
- individuals must comprehend and comply with study requirements and have demonstrated a willingness to participate in the study as provided by a written informed consent

Exclusion criteria at storefront study site:

- individuals not currently taking an antihypertensive agent with a sitting diastolic BP \geq 100 mmHg (obtained by nurse co-investigator at storefront study site)
- isolated systolic hypertension was also excluded and defined as sitting SBP \geq 180 mmHg with a DBP \leq 90 mmHg.

STUDY SITES AND INVESTIGATORS

Seven storefront study sites located in leased office or retail space of shopping malls were staffed by registered nurses who conducted interviews and screening. One physician co-investigator was available for consultation by a toll-free telephone number. Study visits were by appointment only but participants were provided a toll-free number for inquiries or reports of adverse experiences.

RECRUITMENT AND SCREENING

Study participants in Protocol 079 underwent 2 separate screening periods. Participants were recruited through media advertisements and directed to a toll-free telephone label reinforcement service. Interested individuals who called this number were interviewed by trained personnel provided with a written script which included questions pertaining to the inclusion/exclusion criteria. Those who potentially qualified for study participation by telephone interview were scheduled for a storefront study visit for further screening.

STUDY VISITS AND LABORATORY ASSESSMENTS AFTER STUDY ENROLLMENT

There were only 2 planned study visits in this protocol. The first study visit (Day 1) was the initial storefront visit where subjects obtained additional study information, signed the informed consent for study participation, underwent cholesterol testing and blood pressure measurement. If qualified, subjects were provided with an 8-week supply (56 tablets) of study medication and instructed to take 1 tablet with food in the evening. The second study visit (~8 weeks) was not scheduled by the co-investigator nor were reminders sent to participants. If the participant decided to return to the study site, he/she would have to call the toll-free number to schedule a study visit. During this visit pill counts were conducted, adverse events were documented, and lipid profile was measured. If after 16 weeks a study participant had not returned, the site investigator attempted to contact the subject for a follow-up visit.

Total-C, LDL-C, HDL-C, and TGs levels were obtained from a desktop analyzer using fingerstick blood samples. LDL-C was calculated by the Friedewald equation. Subjects with marginal total-C (241-250 mg/dL) or LDL-C (120-129 mg/dL) values or whose TGs

were > 400 mg/dL were permitted to return for repeat lipid testing. The maximum number of retests allowed were 2 for each reason cited. Subjects were advised not to eat any food within 6 hours prior to the study visit.

STATISTICAL ANALYSES

Primary Endpoint

The primary endpoint in this trial was the mean of the individual percent changes in LDL-C level from baseline to Visit 2 (approximately 8 weeks) in all subjects dispensed drug. The baseline cholesterol value was the last available visit 1 cholesterol test (i.e. the initial test on Day 1 or the last retest value). Missing values or out of prespecified day range (see Table 23) values at visit 2 were estimated by carrying forward the baseline cholesterol value.

Table 23. Day Ranges for Lipid Data to be Considered Valid

	Day Ranges
Visit 1 (baseline)	Visit date ≤ dispensed drug date
Visit 2 (approx. 8 weeks)	23 days < visit date ≤ 84 days

In a secondary approach to analyzing the lipid changes, participants with missing data or values obtained outside of specified day ranges at Visit 2 were excluded from analysis. All other lipid parameters (total-C, HDL-C, and TGs) were summarized using only data from study completers.

Two-sided 95% confidence intervals were calculated for the mean percent change from baseline for each of the lipid parameters at 8 weeks. A meaningful reduction in LDL-C was defined as being at least 14.7% for the mean of the individual percent changes from baseline to approximately 8 weeks.

Secondary Endpoints

Persistence to study drug was evaluated in all subjects dispensed drug and defined as the number of subjects who returned for the second visit having taken any amount of tablets.

Compliance was calculated in those subjects who were persistent and defined as the number of tablets taken (determined by pill counts) by the number of days the subject had study drug.

Tolerability to study medication was assessed by collection of reported adverse experiences and assigning severity code and relation to drug. No laboratory assessments for safety were obtained.

RESULTS OF RESTRICTED ACCESS STUDY

Patient Disposition

Given the multiple screening process in this protocol (i.e. telephone interview and storefront), different subject populations were generated at each screening stage and are defined in the following section.

All Study Participants: this population included all people who responded to the study advertising campaign and answered a questionnaire administered by the telephone label reinforcement service.

Nonqualifiers, Telephone Interview: this population refers to the subset of screened participants who were not eligible for drug based on the telephone interview. This group was comprised of those people who did not complete the telephone interview or did not meet study inclusion/exclusion criteria.

Potentially Eligible Population: these individuals represented the subset of screened participants who were eligible for study drug based on the telephone interview and were offered an appointment at the storefront study site.

Lost Participants: these individuals were those potentially eligible participants who did not keep an appointment at the storefront study site.

Refused Participation: these were the potentially eligible participants who refused to make an appointment for a storefront visit.

Nonqualifiers, Storefront: these individuals qualified by telephone interview, were offered a storefront appointment, kept the appointment, and were disqualified from receiving study drug for any of the following reasons:

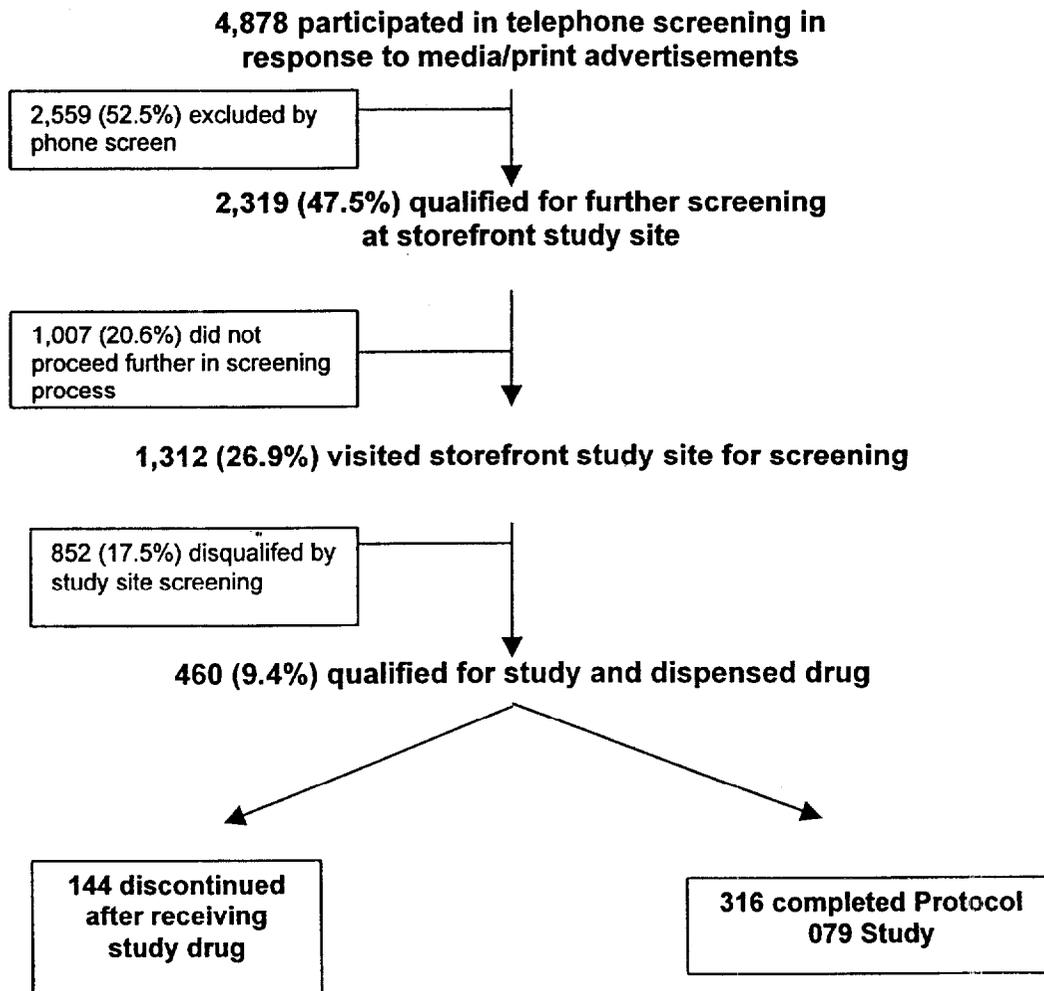
- cholesterol outside study eligibility range
- blood pressure outside of study eligibility range
- other (not willing to sign informed consent, could not comply with study procedures, did not meet study inclusion/exclusion criteria because this was missed during telephone interview or information was not provided at that time)

Qualifiers: these were the potentially eligible participants who met all the inclusion/exclusion criteria and were dispensed study medication

Figure 7 illustrates the screening process for the Restricted Access Study and the different subgroups generated at each stage of screening.

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Figure 7. Schematic of Protocol 079/Restricted Access Study and Subject Disposition



Of the 4,878 subjects who responded to the media and print advertisements, 460 (9.4%) were eventually qualified and dispensed study medication. The reasons for study disqualification are summarized in the table 24. The majority of subjects were excluded during the telephone screening phase (52.5%). Overall, the most common reason individuals were excluded from receiving study medication was having cholesterol levels outside of the study range.

Table 24. Disposition of Study Participants in Protocol 079*

All Study Participants	N=4,878
Nonqualifiers, telephone interview	2,559 (52.5%)**
self-reported total-C >250 mg/dL	888
prior or current lipid-lowering medication	727
age not in eligibility range (male < 40; female < 55)	320
excessive alcohol use	256
history of liver disease	251
use of prohibited medications	199
>1 antihypertensive medication	196
did not complete telephone interview	145
history of heart disease	117
stroke	109
associated with pharmaceutical/healthcare industry	105
self-reported total-C < 190 mg/dL	98
in another drug study	83
history of diabetes	81
could not read/understand English	15
Nonqualifiers, storefront	852 (17.5%)
total-C > 240 mg/dL	461
LDL-C < 130 mg/dL	367
blood pressure	13
no informed consent	25
withdrew consent	16
advice of personal MD	3
unable to obtain lipid profile	1
not able to comprehend/comply	4
medical history	7
Lost participants	554 (11.4%)
Refused participation	453 (9.3%)
Qualified and dispensed study medication	460 (9.4%)

*An individual could have more than 1 reason for study disqualification

**percentages provided are of all study participants

Of the 460 individuals who qualified for treatment and were dispensed with study medication, 316 (68.7%) completed the 8 week trial. The most common reason for study drug discontinuation was clinical adverse experience (see Table 25).

Table 25. Reasons for Study Discontinuation After Initiating Treatment

Number Dispensed Study Drug, N	460
Reasons for Discontinuation, n (% of N)	
Clinical AE	39 (8.5%)
Withdrew consent	29 (6.3%)
Lost to follow-up	29 (6.3%)
Did not come in for final visit	25 (5.4%)
Did not complete final visit	6 (1.3%)
Advice of personal MD	14 (3.0%)
Advice of study MD	2 (<1%)
Total discontinuing study medication	144 (31.3%)

Baseline Demographics and Patient Characteristics

The baseline characteristics of participants in Protocol 079 are presented by the qualified and nonqualified populations. Among the nonqualified population, these data

are summarized for those who were disqualified during the telephone screening and those disqualified after their visit to the storefront study site.

Table 26. Baseline Characteristics of Participants in Protocol 079

	Qualified, N=460 N (%)	Nonqualified, n=4,418	
		Storefront, N=852	Telephone, N=3566
		N (%)	N (%)
Gender			
Female	89 (19.3)	305 (35.8)	1646 (46.4)
Male	371 (80.7)	547 (64.2)	1900 (53.6)
Missing	0	0	20
Age (yrs)			
mean	57.7	58.0	57.7
range	40-88	39-85	22-87
Mean age (SD) by gender			
Males	56.5 (9.5)	54.5 (9.2)	54.3 (10.5)
Females	62.7 (6.1)	64 (7.0)	61.6 (10.3)
Race			
Caucasian	412 (89.6)	717 (84.2)	Not determined during telephone interview
Hispanic	16 (3.5)	32 (3.8)	
Asian	16 (3.5)	23 (2.7)	
African-American	14 (3.0)	49 (5.8)	
Other	2 (0.4)	4 (0.5)	
Unknown	0	27	
Family History of CHD			
any parent/sibling	74 (16.1)	140 (16.4)	615 (17.3)
mother/sister	28 (6.1)	53 (6.2)	266 (7.5)
father/brother	54 (11.7)	103 (12.1)	425 (12.0)
Current Smoker			
yes	45 (9.8)	77 (9.0)	445 (12.5)

The qualified and nonqualified individuals were similar with respect to familial history of CHD and smoking status. The telephone screening process did not obtain ethnic background therefore this information is incomplete in all study participants; however, from the available data, the eventual treated population was comprised of mostly Caucasians (89.6%).

The proportion of men contributing to the study population increased during the progression of the screening process with males accounting for approximately 54% and 64% of the 2 nonqualified populations but eventually comprising 80.7% of the population dispensed drug (qualified population). The different age eligibility-criteria applied to the men and women and differences in the baseline lipid profile between sexes may have contributed to the exclusion of more women from receiving study medication.

Baseline Lipid Profile

Of the 1,312 potentially eligible participants who went to the storefront study site, all of the qualified individuals had baseline lipid profile measurements (n=460) and 821 of the nonqualified individuals had lipid determination. Table 27 presents the baseline lipid profile for the qualified and nonqualified population.

Table 27. Baseline Lipid Profile in Subjects Who Had Lipid Determinations

		Qualified (n=460)	Nonqualified (n=821)
LDL-C (mg/dL)	N	460	759
	mean (SD)	147.2 (11.8)	150.5 (40.8)
	median	146.0	152.0
	range	130-192	47-302
total-C (mg/dL)	N	460	821
	mean (SD)	223.3 (11.7)	241.2 (42.9)
	median	225.0	251.0
	range	185-240	102-470
HDL-C (mg/dL)	N	460	805
	mean (SD)	46.1 (13.2)	52.6 (17.7)
	median	45.0	50.0
	range	17-86	17-134*
total-C/HDL-C	N	460	805
	mean (SD)	5.3 (1.7)	5.1 (2.0)
	median	4.9	4.8
	range	2.8-14	0.6-17
TGs	N	460	821
	mean (SD)	150.1 (62.8)	204.1 (120.9)
	median	140.0	176.0
	range	45-386	45-650

Source: NDA 21-213 lipdiet.xpt

*one HDL-C value of 453 mg/dL was excluded due to extreme outlying result

The mean total-C, LDL-C, and TG values were lower in the qualified versus the nonqualified population with greater variability in the lipid levels observed in the nonqualified group. The mean HDL-C level was lower in the qualified group compared to the nonqualified individuals; this difference resulted in a total-C/HDL-C ratio that was similar between the two populations.

The lower HDL-C levels observed in the qualified group is a result of the higher proportion of men with lower baseline HDL-C levels contributing to this population's lipid profile as summarized in table 28.

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Table 28. Baseline Lipid Profile in Qualified and Nonqualified Population by Gender

	Qualified (n=460)		Nonqualified (n=821)	
	Males (n=371)	Females (n=89)	Males (n=522)	Females (n=299)
Total-C				
n	371	89	522	299
mean (SD) mg/dL	221.9 (12.5)	228.3 (8.5)	239.9 (45.8)	243.5 (37.3)
range	183-242	204-240	102-470	143-368
LDL-C				
n	371	89	474	285
mean (SD) mg/dL	147.6 (12.4)	144.4 (11.3)	153.7 (42.1)	145.0 (38.2)
range	94-192	130-183	47-302	61-267
HDL-C				
n	371	89	507	297
mean (SD) mg/dL	43.5 (11.8)	56.7 (13.4)	47.1 (23.2)	63.3 (16.9)
range	17-76	22-86	18-453	17-100
TGs				
n	371	89	522	299
mean (SD) mg/dL	153.8 (63.8)	136.1 (57.3)	216.9 (133.6)	181.7 (90.8)
range	45-386	48-343	45-650	49-650

Source: NDA 21-213, data generated from lipidiet.xpt file for Protocol 079

Efficacy Results

Primary Endpoint

The primary endpoint was the mean of the individual percent reductions in LDL-C at visit 2 (8 wks) from baseline. LDL-C values were valid if they were obtained within predefined day ranges (>28 days and ≤ 84 days) and if the TGs were ≤ 400 mg/dL. Of the 460 participants dispensed study medication, primary efficacy measures of LDL-C values were available in only 288 individuals (62.6%). LDL-C values were carried forward from baseline in 172 persons (37.4%). Approximately 75% of those individuals missing efficacy data did not have a final visit.

A secondary analysis of the primary endpoint was performed by the sponsor with all subjects missing visit 2 lipid data excluded from analysis.

Table 29 summarizes the LDL-C changes for all participants dispensed study medication and in those who had valid efficacy data.

Table 29. Reduction in LDL-C in Restricted Access Study after 8 weeks

	N	Mean % reduction (SD)	(95% CI)	Mean Achieved Value, mg/dL (SD)
Primary Analysis	460	-11.5 (15.1)	(-12.9, -10.2)	129.9 (22.7)
Secondary Analysis	288	-18.4 (15.3)	(-20.2, -16.7)	119.9 (21.9)

*3 subjects did not have LDL-C data due to elevated TGs (>400 mg/dL)

Other Lipid Parameters

The sponsor summarized mean percent changes in total-C, HDL-C, and TGs using only those subjects with available data at visit 2 and did not estimate the missing values. The following table summarizes these results.

Table 30. Changes in Other Lipid Parameters

	N	Mean % Change (SD)	(95% CI)	Mean Achieved Value, mg/dL (SD)
Total-C	293	-10.4 (11.5)	(-11.7, -9.1)	203.3 (28.3)
HDL-C	293	+5.4 (19.9)	(3.2, 7.7)	47.3 (13.3)
TGs	293	+12.9 (51.0)	(7.0, 18.8)	167.8 (89.2)

Safety Results

Of the 460 participants who were dispensed study medication, 28 reported not consuming any amount of drug and no information was available in 69 individuals. This safety review will report incidence rates excluding those individuals who did not consume any drug since they would not be at risk of experiencing any adverse event from lovastatin.

Overall Assessment of Clinical Adverse Experiences

A total of 177 AEs were reported by 115 individuals in the Restricted Access Study. The most common body system for which AEs were reported involved the digestive system followed by the nervous system/psychiatric body system. Table 31 lists the overall AEs reported by body system and the specific AEs (by preferred terminology) that occurred at an incidence rate > 1.0%. An individual could experience more than 1 AE but was only counted once in each body system.

Table 31. Adverse Events Reported by Body System

	No. of Persons Exposed to Drug (n= 432)
Body as a whole/site unspecified	24 (5.6%)
pain, abdominal	9
asthenia/fatigue	6
chest pain	4
Cardiovascular	10 (2.3%)
blood pressure increased	5
Digestive	36 (8.3%)
flatulence	18
constipation	4
diarrhea	4
Metabolic/immune	2 (<1%)
Musculoskeletal	23 (5.3%)
myalgia	6
Nervous system/psychiatric	30 (6.9%)
headache	16
dizziness	5
Respiratory	9 (2.1%)
upper respiratory infection	4
Skin	11 (2.5%)
rash	5
Special senses	1 (<1%)
Urogenital	10 (2.3%)
urinary frequency	5

Flatulence (digestive body system) and headache (nervous system/psychiatric) accounted for the most commonly reported AEs in this study with headaches resulting in many study drug discontinuations.

Serious AEs

Seven serious AEs were reported by 4 subjects (<1%); none were considered drug-related (Table 32). There were no fatalities in Protocol 079.

Table 32. Serious AEs Reported for Protocol 079

Patient	Adverse Event	Action Taken
0203187	non-Q wave MI coronary atherosclerosis syncope	interrupted interrupted interrupted
0304888	coronary atherosclerosis postoperative infection	discontinued
0502981	myocardial infarction	discontinued
0704862	malignant prostate neoplasm	none

Drug-Related AEs

Seventy-nine individuals reported 107 AEs that were considered drug-related. The most common drug-related AE reported was flatulence followed by headaches. None of the drug-related AEs were considered serious. Thirty-two individuals discontinued study medication as a result of an AE reported to be drug-related.

AEs Resulting in Study Drug Discontinuation

Forty-two (9.7%) individuals discontinued study medication due to AEs experienced while receiving treatment with lovastatin 10 mg per day; 3 of these subjects discontinued treatment during the extension period. The most common body system for which AEs leading to discontinuation were reported occurred in the musculoskeletal system followed by the nervous system/psychiatric system. Headaches accounted for the most commonly reported AE (by preferred terminology) resulting in study drug discontinuation.

AEs Involving the Musculoskeletal System

There were 30 AEs reported by 23 participants which were categorized in the musculoskeletal body system. The most common AE (by preferred terminology) was myalgias with 6 cases being reported in 6 individuals (1.4%). No cases of rhabdomyolysis or myoglobinuria were reported in this trial.

Summary of Safety and Tolerability Findings of Protocol 079

The clinical adverse experiences observed in this study are summarized in the following table with both incidence rates determined by the sponsor and this reviewer.

Table 33. Summary of Clinical AEs Reported by Individuals in Protocol 076

	Number of Individuals	Sponsor's Rates N= 460	Reviewer's Rates N= 432
Overall AEs reported	115	25%	26.6%
Drug-related AEs	79	17.2%	18.3%
Serious AEs	4	<1%	<1%
Serious drug-related AEs	0	0	0
Deaths	0	0	0
Discontinued due to AE	42	9.1%	9.7%
Discontinued due to drug-related AE	32	7.0%	7.4%
Discontinued due to serious AE	2	<1%	<1%
Discontinued due to serious drug-	0	0	0

related AE Myalgias reported	6	1.3%	1.4%
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Treatment with lovastatin 10 mg per day in this actual-use trial resulted in similar safety and tolerability findings observed in Protocol 076. The most commonly reported AEs were, again, flatulence and headaches. The incidence of myalgias was similar in both trials and there were no cases of rhabdomyolysis, myoglobinuria, or hepatic toxicity reported in this study.

Individuals initiated on treatment with lovastatin 10 mg per day discontinued medication due to reported AEs at a rate of 8.5%. This is similar to Protocol 076 and higher than the placebo-controlled studies involving lovastatin 10 mg.

SUMMARY OF PROTOCOL 079 (RESTRICTED ACCESS STUDY)

Protocol 079 was designed to evaluate efficacy, safety, and tolerability of lovastatin 10 mg per day in a population with similar baseline characteristics as targeted in the proposed package label. Adherence to taking study medication during this 8-week study was also evaluated. This trial differed from the Protocol 076 in that participants were selected for treatment based on a telephone interview and further storefront screening. Interested individuals were not provided a package label and asked to self-select treatment based on their comprehension of the label.

Of the 4,878 individuals screened by telephone operators, 52.5% were excluded primarily on a self-reported total-C level > 250 mg/dL followed by current or past use of a lipid-altering agent. Further storefront screening revealed the primary reasons for study exclusion to be, again, cholesterol levels outside of the range targeted for nonprescription lovastatin therapy.

During the telephone screening process, 2,319 (47.5%) of the all study participants were told they qualified for a storefront visit. Of these, almost half were either not interested in continuing, never kept or cancelled their study visit appointment (1,007; 43.4%).

Of the 1,312 participants who took part in the storefront screen, the eventual number of individuals dispensed study medication was 460 with only 316 (68.7%) of this group completing the 8-week treatment period.

Treatment with lovastatin 10 mg per day for 8 weeks resulted in an average 11.5% LDL-C reduction in all individuals dispensed study medication. Since efficacy data were available in only 62.6% of the population dispensed drug, the sponsor also summarized efficacy among the completers only. This resulted in a greater LDL-C reduction at 8 weeks of 18.4%. Since lipid-altering efficacy data was not available in more than one-third of the population considered qualified for drug treatment and dispensed medication, estimates of the lipid-response to drug treatment in the OTC population can not be determined.

The safety profile of lovastatin 10 mg in this actual-use study did not suggest a more toxic drug profile than observed in placebo-controlled clinical trials. The tolerability appeared less in this trial, however, with 8.5% of the qualified population discontinuing due to adverse experiences compared to < 3.0% in the controlled studies.

COMMENTS ON NONPRESCRIPTION LOVASTATIN CLINICAL DEVELOPMENT PROGRAM

Merck has submitted results of 7 clinical studies to support an indication for nonprescription availability of lovastatin 10 mg. These studies were conducted to demonstrate efficacy and safety in the target population. In addition, consumer behavior in the use of nonprescription lovastatin was evaluated in several actual-use trials and label comprehension studies.

The review of this application by the Division of Metabolic and Endocrine Drug Products (DMEDP) focused on efficacy and safety results from Protocols 075, 076, and 079. As outlined in the *Introduction* section of this review, several issues need consideration during the evaluation of this NDA. The following questions pertaining to efficacy and safety of lovastatin 10 mg in the targeted population are addressed in this section of the review:

1. What is the expected mean percent reduction in LDL-C levels for the targeted population?
2. Is there evidence that treatment with this drug to this degree of LDL-C lowering in this population will result in a clinical benefit?
3. Will the consumer adhere to taking the medication chronically to treat an asymptomatic condition whose deleterious effects may not be manifested until several years later?
4. Are consumers appropriately making decisions regarding the initiation and of drug treatment?

EFFICACY

1. What is the expected mean percent reduction in LDL-C for the targeted population?

The target population was defined by sponsor and discussed under the section, *Definition of the OTC Population*, of this review. In brief, Merck proposes to target the following individuals for nonprescription lovastatin treatment:

- men 40 years or older or women past menopause (at least 1 year past menopause) without evidence of CVD, diabetes mellitus, or significant HTN (on > 1 antihypertensive medication) AND
- those individuals with total-C between 200 and 240 mg/dL AND LDL-C > 130 mg/dL

The expected mean percent reduction in LDL-C in this targeted OTC population was determined in the Efficacy Study (Protocol 075). The baseline characteristics of this study population approximated those of the targeted population. Mean baseline total and LDL-cholesterol levels in this study population were 233 and 143 mg/dL, respectively. The study participants were also excluded for the presence of CHD, diabetes, HTN, or stroke, and other characteristics not suited for nonprescription lovastatin use.

In the Efficacy Study, the individuals randomized to treatment with lovastatin 10 mg per day had an average LDL-C reduction of -17.5% compared to a mean increase of +2.4% in the placebo-treated group.

Lipid-altering data were also summarized in the uncontrolled studies, Protocols 076 and 079, for study participants with similar lipid profiles as the target population. These trials evaluated the cholesterol-lowering effect of lovastatin 10 mg in a simulated OTC-environment. Lipid-response data were available in only 68.4% of the study population after 6 months (Protocol 076) and 62.6% after 8 weeks (Protocol 079). Thus, any estimate of LDL-C reduction based on these actual-use studies is biased by the large number of study discontinuations.

The Efficacy Study summarized lipid-response data in 93% of those who took lovastatin 10 mg and suggested that ***in the population eligible for nonprescription lovastatin treatment, the expected lipid-altering benefit associated with lovastatin 10 mg per day is similar to that observed in other clinical trials using lovastatin 10 mg as a prescription drug. The expected mean percent LDL-C reduction is approximately 17.5% in the targeted population adhering to drug treatment and a diet restricted in saturated fats.***

2. Is there evidence that treatment with this drug to this degree of LDL-C lowering in this population will result in a clinical benefit?

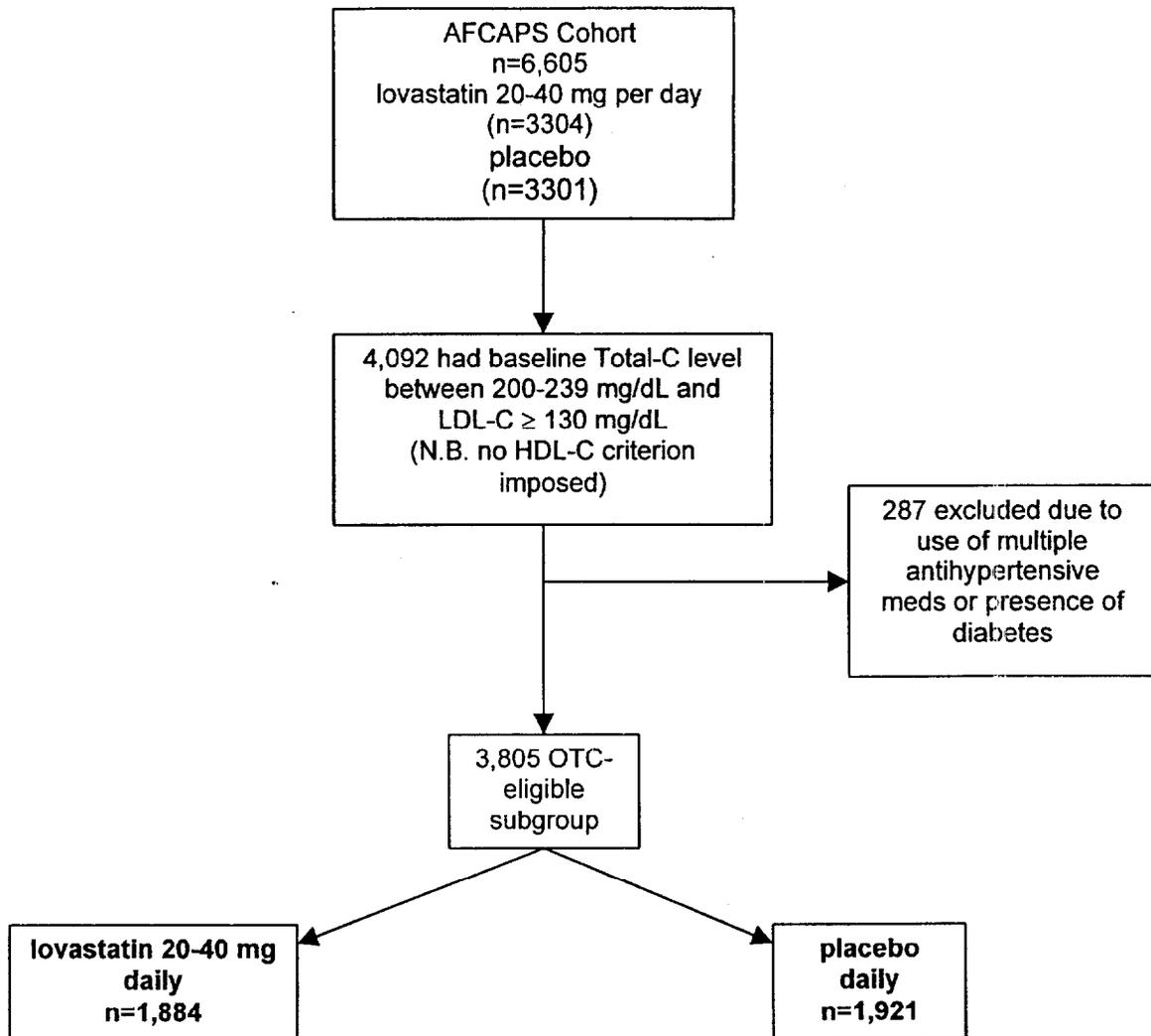
The CHD risk in the nonprescription-eligible population and the clinical benefit of treating this population with an over-the-counter lipid-altering drug has never been studied in a controlled clinical trial. The CHD risks and benefits of drug therapy, however, were estimated by the sponsor based on analyses of a 5-year placebo-controlled clinical outcome trial (AFCAPS/TexCAPS) in a population similar to the targeted OTC population.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was a randomized, double-blind, placebo-controlled clinical trial designed to demonstrate that treatment with lovastatin 20 to 40 mg qd in 6,605 patients without clinical evidence of CHD and moderately elevated TC and LDL-C and low HDL-C levels would reduce the incidence of a first acute coronary event (composite endpoint consisting of: fatal CHD; nonfatal MI; and unstable angina). After a mean follow-up duration of 5 years, treatment with lovastatin 20 to 40 mg daily in conjunction with a low saturated fat diet resulted in a 37% risk reduction ($p < .0001$) in experiencing an acute coronary event compared to placebo. †

A subgroup (n=4,092) of the AFCAPS/TexCAPS cohort was selected for baseline lipid levels which matched those of the OTC-eligible population (i.e. total-C 200-239 mg/dL and LDL-C \geq 130 mg/dL). After excluding for the presence of diabetes and/or use of multiple antihypertensive medications, there were 3,805 patients (57.6%) remaining in the AFCAPS/TexCAPS cohort meeting the eligibility criteria for treatment with nonprescription lovastatin. Of these, 1,884 (49.5%) were treated with lovastatin 20-40 mg daily and 1,921 (50.5%) were treated with placebo (see Figure 8).

† see FDA Joint Medical and Statistical Review of AFCAPS/TexCAPS (NDA 19-643/S055)

Figure 8. Diagram of AFCAPS/TexCAPS OTC-Eligible Subgroup Selection



The risk of developing CHD in the targeted OTC population was estimated from the incidence of having an initial MI, unstable angina, or sudden cardiac death in the placebo-treated group of the AFCAPS OTC-eligible population. In these patients the incidence rate of an initial ischemic event was 108/1,921 or 5.6% over 5 years.

To determine if treatment with lovastatin in this population could reduce this risk, the sponsor evaluated the incidence of an initial MI, unstable angina, or sudden cardiac death in the lovastatin-treated group of the AFCAPS OTC-eligible population. In these patients, the treatment with lovastatin 20 to 40 mg per day for a mean follow-up period of 5 years resulted in an incidence rate of 60/1,884 or 3.2%. The following table summarizes the incidence rates for the 2 treatment groups as estimated by the Kaplan-Meier survival method.

Table 34. Incidence Rates for Experiencing an Initial Acute Coronary Event in the AFCAPS/TexCAPS OTC-Eligible Subgroup Treated with Lovastatin or Placebo

Lovastatin 20-40 mg n=1,884	Placebo n=1,921	Risk Reduction (95% CI)	p-value
Events/Patients (%)	Events/Patients (%)	0.44 (0.23, 0.59)	0.001
60/1,884 (3.0%)	108/1,921 (5.3%)		

Based on analyses of the AFCAPS OTC-eligible subgroup, treatment with lovastatin 20-40 mg per day for an average of 5 years resulted in a 44% reduction in risk of experiencing either an MI, unstable angina, or sudden cardiac death compared to placebo.

From the results summarized in Tables 34, the sponsor concluded that treatment with nonprescription lovastatin in the targeted OTC-population can reduce the risk of CHD. This conclusion may not be valid based on the following:

- The lovastatin dose for which a clinical benefit was demonstrated is 2 to 4 times higher than the proposed nonprescription dose. The LDL-C lowering results associated with the 20 to 40 mg per day dose are not comparable to the nonprescription dose.
- The average duration of treatment in AFCAPS/TexCAPS exceeds the treatment duration observed in any trial conducted in the OTC clinical development program
- The benefit of lovastatin treatment in the AFCAPS/TexCAPS OTC-eligible subgroup was greatest in those with HDL-C levels < 40 mg/dL. In the targeted OTC population, the majority of individuals had HDL-C levels exceeding this value, suggesting that any potential benefit will apply to a much smaller proportion of the U.S. population than estimated by the sponsor.

Lovastatin Dose in AFCAPS/TexCAPS OTC-Eligible Subgroup

All patients in AFCAPS/TexCAPS randomized to the lovastatin group were initiated on the 20 mg per day dose. As per protocol, if study participants had not reached an LDL-C goal of 110 mg/dL or less, based on the average values obtained at Weeks 6 and 12, their dose of lovastatin was doubled to 40 mg per day at the Week 18 visit.

In the AFCAPS/TexCAPS OTC-eligible subgroup, 971 (51.5%) of the 1,884 patients randomized to lovastatin required treatment with lovastatin 40 mg per day in order to achieve an LDL-C level < 110 mg/dL.

LDL-C Changes From Baseline in the AFCAPS/TexCAPS OTC-Eligible Subgroup

Since the Efficacy Study assessed the LDL-C lowering effects of the nonprescription lovastatin dose after 12 weeks of treatment as the primary efficacy measure, the Agency requested the lipid changes in the AFCAPS/TexCAPS OTC-eligible subgroup prior to one year. The following table summarizes the LDL-C changes for the AFCAPS OTC-eligible subgroup at weeks 6, 12, and 18. All data in the lovastatin group presented in the table below are pre-titration results and are therefore reflective of the expected changes for lovastatin 20 mg per day.

Table 35. LDL-C Changes in Lovastatin and Placebo Treatment Groups in AFCAPS/TexCAPS OTC-Eligible Subgroup Prior to Dose Titration

Study Week	Treatment Group	N	Baseline Value		Post-Tx Value		%Chg from Baseline	
			Mean	SD	Mean	SD	Mean	SD
WK 6	lovastatin	1357	150.7	10.6	113.8	18.7	-24.4	11.9
	placebo	1374	151.1	11.2	152.8	20.2	+1.2	11.8
Wk 12	lovastatin	1325	150.8	10.6	114.4	19.0	-24.1	12.3
	placebo	1346	151.1	11.2	153.2	20.6	+1.55	12.5
Wk 18	lovastatin	1292	150.9	10.6	114.1	18.8	-24.3	12.1
	placebo	1306	151.1	11.2	152.3	20.7	+0.89	12.2

Treatment with lovastatin 20 mg per day resulted in an average LDL-C reduction of approximately -24.0% after 6 to 18 weeks. These results exceeded the expected mean percent reduction in LDL-C levels (-17.5%) observed with the proposed nonprescription lovastatin dose studied in the Efficacy Study. Since the clinical benefits observed in the AFCAPS OTC-eligible subgroup were associated with the cholesterol reduction from lovastatin 20-40 mg treatment, the markedly lower percent LDL-C reduction associated with nonprescription lovastatin dose precludes any extrapolation of clinical benefit from AFCAPS to the nonprescription lovastatin dose.

Comparability of the AFCAPS OTC-Eligible Population to the Targeted Population

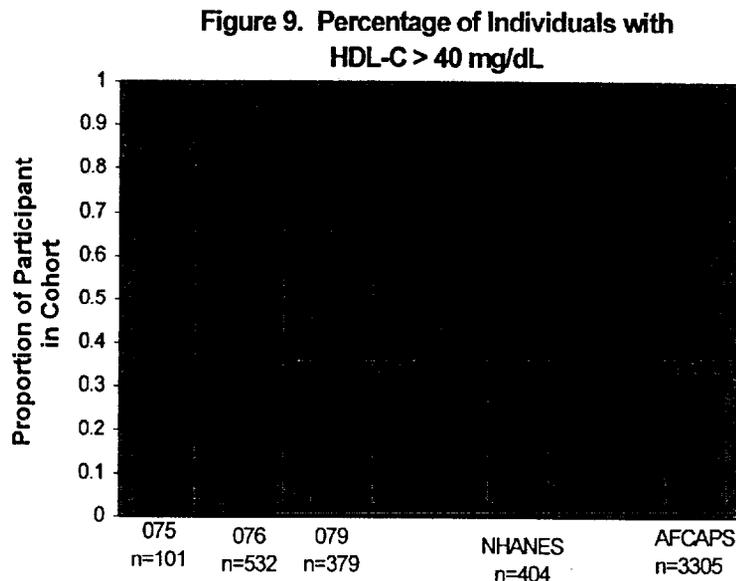
The sponsor defined the OTC-eligible population as those individuals with a total-C level between 200 and 240 mg/dL and LDL-C level \geq 130 mg/dL and no evidence of CVD or diabetes. Based on this definition, an estimate of those in the U.S. population who are eligible for nonprescription lovastatin treatment was determined from NHANES III. Furthermore, the selection of study subjects for Protocols 075, 076, and 079 was also based on this definition. ***HDL-C level was never specified as a criterion for selecting those individuals from the primary prevention population who would be eligible for treatment with lovastatin.***

AFCAPS specifically enrolled individuals with below average HDL-C levels based on an exclusion criterion specifying that HDL-C levels be $<$ 45 mg/dL in males and $<$ 47 mg/dL in females. ***When the estimates of CHD risk and treatment benefit were summarized in the OTC-eligible subgroup of AFCAPS based on baseline HDL-C levels of $<$ 35, 35 to $<$ 40, and \geq 40 mg/dL, the risk reductions were greatest in those with HDL-C levels $<$ 40 mg/dL (see Table 36). There was no treatment difference seen in those individuals with HDL-C levels \geq 40 mg/dL who otherwise met the sponsor's definition of being eligible for nonprescription lovastatin treatment.***

Table 36. 5-Year Kaplan-Meier Event Rates in AFCAPS OTC-Eligible Subgroups by HDL Strata

	Lovastatin 20-40 mg daily	Placebo	Risk Reduction (95% CI)	p-value
HDL $<$ 35 mg/dL	22/637 (3.4%)	48/641 (7.5%)	0.55 (0.26, 0.73)	0.002
HDL 35 to $<$ 40 mg/dL	17/655 (2.2%)	37/637 (5.4%)	0.44 (0.21, 0.75)	0.006
HDL \geq 40 mg/dL	21/592 (3.6%)	23/643 (3.1%)	0.02 (-0.78, 0.46)	0.957

Comparing the study cohorts in the OTC clinical development program and the OTC-eligible NHANES population revealed that the majority of individuals in the targeted population had HDL-C values exceeding 40 mg/dL (Figure 9).



Notably, 78% of the OTC-eligible NHANES population for which the sponsor estimated the number of Americans eligible for nonprescription lovastatin treatment had HDL-C levels > 40 mg/dL. In contrast, individuals in the AFCAPS OTC-eligible cohort with HDL-C levels exceeding this value accounted for only about one-third of the study group. The marked difference in HDL-C distribution between the targeted population and the AFCAPS cohort make any predictions of clinical benefit problematic.

3. Will the consumer adhere to taking the medication chronically to treat an asymptomatic condition whose deleterious effects may not be manifested until several years later?

As stated above, the clinical benefits of lovastatin treatment observed in the AFCAPS OTC-eligible cohort may not be appropriately extrapolated to the targeted OTC population due to the significant differences in treatment duration. In AFCAPS, approximately 71% of the lovastatin group and 63% of the placebo group completed the study. The mean duration of follow-up for the entire cohort was 5.2 years (median of 5.1) and was similar in the two treatment groups.

In contrast, results from the actual-use studies (Protocols 076 and 079) suggested that in an OTC-simulated environment with little physician oversight, the adherence to taking study medication was much lower. Both trials reported study discontinuation rates of approximately 30% after 8 or 24 weeks of treatment with the primary reason for discontinuation being clinical adverse experience. The greater proportion of individuals discontinuing treatment due to reported AEs in the actual-use trials compared to controlled clinical studies may suggest unwillingness to tolerate apparent side-effects (Table 37).

Table 37. Discontinuations Due to Clinical AEs Reported in Actual-Use vs. Controlled Clinical Trials

Actual-Use Trials		Placebo-Controlled Trials		
Protocol 076 24 weeks	Protocol 079 8 weeks	Protocol 075 12 weeks	Study 016 6 weeks	Study 061 12 weeks
9.4%	8.5%	2.9%	2.9%	1.2%

The sponsor argues that despite the seemingly high discontinuation rate in these actual-use trials, in those individuals who adhere to treatment, the LDL-C lowering (18.4 to 23.9% reduction) was higher than observed in the Efficacy Study (17.5% reduction). These results suggest that in those who persist with chronic lovastatin use, the LDL-C lowering effect is similar to that observed in the AFCAPS OTC-eligible cohort (25.3% reduction at 1 year) and therefore, a reduction in CHD risk will be realized. Such a statement is not supported by any data since predictions of persistence to treatment cannot be made with any degree of accuracy beyond the periods of observation in the actual-use trials.

The Restricted Access Study (Protocol 079) also suggested that a large proportion of individuals in the population who may qualify for treatment may not self-select treatment. In this study, 2,319 interested individuals were told after a telephone screen that they were qualified for further screening at the storefront clinic. One thousand and seven (1,007) or 43.4% of these individuals either refused further participation, made but cancelled their study visit, or never kept their appointment.

The population approach to treating an asymptomatic chronic disease such as hypercholesterolemia, requires lifelong drug intervention. ***The high discontinuation rates in these actual-use studies of relatively short duration may foretell an unsuccessful population approach to treating hypercholesterolemia. The early discontinuation of lipid-lowering drug treatment undermines both the lipid-altering efficacy of the drug and the potential reduction in cardiovascular morbidity and mortality in the population.***

4. Are consumers appropriately making decisions regarding the initiation of drug treatment?

This question addresses both the potential efficacy and safety of nonprescription lovastatin in the targeted OTC population. Efficacy can be summarized as the persistent use of this product in the population most likely to benefit from its availability. In the previous section this reviewer has raised concerns about the adherence to taking lovastatin as demonstrated in the actual-use trials. Issues regarding the actual at-risk population were raised with respect to HDL-C levels. ***Since the proposed package***

label included only total-C and LDL-C levels as the lipid parameters necessary for appropriate self-selection by the consumer, it is evident that the ability of the consumer to self-select based on his/her HDL-C has not been studied.

SAFETY

The safety results of the lovastatin 10 mg daily use from Protocols 075, 076, and 079 suggest a similar clinical adverse experience profile for the regulated (prescription) and unrestricted (nonprescription) use of this product. The most common body system for which clinical adverse experiences (AEs) were reported in the lovastatin group involved the digestive system in all three trials. The most common lovastatin-associated AEs reported were diarrhea in Protocol 075 and flatulence in 076 and 079. The incidence of myalgias experienced by individuals was similar between lovastatin and placebo groups (<1% for both) in Protocol 075 and <2% for the actual-use trials. The incidence of myalgias associated with lovastatin 10 mg did not exceed those rates observed in the 6-month Expanded Clinical Experience with Lovastatin (EXCEL) study evaluating the safety of lovastatin 20 to 80 mg daily. These findings are not unexpected since the inherent toxicity of lovastatin 10 mg should not be different whether the patient takes the drug prescribed by his/her physician or the consumer takes the drug over-the-counter. Table 38 summarizes the clinical adverse experiences for Protocols 075, 076, and 079.

Table 38. Number of Individuals and Incidence of Clinical AEs Reported in Protocols 075, 076, and 079

Clinical AEs	Protocol 075		Protocol 076	Protocol 079
	Placebo n=106	Lovastatin n=104	Lovastatin n=680*	Lovastatin n=432*
overall AEs	37 (34.9%)	39 (37.5%)	228 (33.5%)	115 (26.6%)
drug-related AEs	11 (10.4%)	6 (5.8%)	157 (23.1%)	79 (18.3%)
serious AEs	0	2 (1.9%)	7 (1%)	4 (<1%)
deaths	0	0	0	0
discontinued due to AE	3 (2.8%)	3 (2.9%)	68 (10%)	42 (9.7%)
discontinued due to drug-related AE	3 (2.8%)	2 (1.9%)	60 (8.8%)	32 (7.4%)
discontinued due to serious AE	0	0	4 (<1%)	2 (<1%)
discontinued due to serious drug-related AE	0	0	0	0
myalgias reported	1 (<1%)	1 (<1%)	13 (1.9%)	6 (1.4%)

*incidence rates calculated based on number of individuals consuming any amount of drug

Adverse events of concern which have been reported in association with lovastatin use include hepatic toxicity and myopathy. None of these events was observed in the nonprescription lovastatin clinical trials. The absence of these events, however, may reflect the limitations associated with the safety assessment in these three protocols. These limitations include the lack of laboratory assessments for safety, particularly hepatic enzyme and CK level determination, the relatively short duration of exposure, and the exclusion of high-risk individuals.

Experience from controlled clinical trials involving lovastatin across the entire dose spectrum suggest that frequent laboratory monitoring for hepatic and skeletal muscle toxicity are seldom predictive of these events given the infrequency of their occurrence. In the case of muscle toxicity associated with lovastatin, with the exception of one case, all reported cases of rhabdomyolysis have only been observed in the uncontrolled postmarketing environment.

Defining rhabdomyolysis as reported cases with CPK > 10,000 IU/L, signs and symptoms (myalgia, myopathy, gait disturbances), and clinical diagnosis of rhabdomyolysis, a search of the Adverse Event Reporting System (AERS) revealed 115 cases involving lovastatin (dose range 20-100 mg/day). There were no cases reported for lovastatin 10 mg. The limitations of this database, however, preclude any conclusions that lovastatin 10 mg is not associated with rhabdomyolysis. The limitations include an unknown degree of underreporting of cases through the voluntary reporting system and the unknown number of individuals using lovastatin 10 mg.

Rhabdomyolysis is a rare but serious side-effect associated with lovastatin use. Because of this rarity, the incidence of this event cannot be determined from controlled studies; however, the incidence of myalgias in association with elevated CK levels has been reported at < 1.0% in several statin trials. Although the mechanism of muscle toxicity is not known, numerous reports suggest an increased risk in the setting of drug interactions involving inhibitors of CYP3A4 thereby interfering with the metabolism of lovastatin. From the Agency's analysis of postmarketing cases, the onset of rhabdomyolysis in cases involving lovastatin-drug interactions appears more rapid (median 32 days) than in cases of lovastatin monotherapy (median 120 days).

The proposed package label for nonprescription lovastatin advises consumers NOT to take nonprescription lovastatin if they are on any of the following medications:

- erythromycin or clarithromycin-Biaxin
- ketoconazole-Nizoral, itraconazol-Sporanox
- nefazadone-Serzone
- cyclosporine
- protease inhibitors
- other cholesterol-reducing drugs such as niacin at daily doses of 500 mg or more, gemfibrozil, or prescription statins including simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, or lovastatin

Although the consumer's ability to appropriately reject nonprescription lovastatin therapy based on concomitant use of the above drugs will be evaluated by DOTCDE and DDMAC, the results of their review will be limited by the incompleteness of this list. The current list is not inclusive of all known CYP3A4 inhibitors including grapefruit juice. Furthermore, the number of drugs capable of potentiating the skeletal muscle toxicity associated with lovastatin will likely expand with future approvals of new drugs. Keeping current with these newly approved drugs will be challenging to the consumer.

The safety results from controlled and actual-use clinical trials involving lovastatin 10 mg do not suggest that this dose of lovastatin poses an increased risk to the population as a nonprescription drug. These studies, however, do not provide reassurance that

self-titration to higher doses or use in combination with drugs, food, or co-morbid medical conditions which may increase the risk of serious adverse events will not occur in the 'real world' use of this product.

CONCLUSIONS ON THE REVIEW OF PROTOCOLS 075, 076, 079, AND AFCAPS/TexCAPS OTC-ELIGIBLE SUBGROUP

Based on AFCAPS/TexCAPS, the sponsor demonstrated that a subgroup of the primary prevention population, for which current NCEP guidelines do not recommend pharmacologic treatment for dyslipidemia, has a risk of developing CHD that can be reduced with drug treatment. These individuals are characterized by total-C levels between 200 and 240 mg/dL, LDL-C over 130 mg/dL AND low HDL-C levels. Merck proposes to make lovastatin 10 mg available to the public as a nonprescription drug to allow the estimated 15.5 million Americans eligible for drug treatment access to an effective and safe alternative for cholesterol lowering.

The data reviewed from selected studies in the OTC Clinical Development Program and the OTC-eligible AFCAPS cohort do not support the sponsor's proposal for the following reasons:

1. The clinical benefit of lovastatin treatment observed in AFCAPS was associated with the 20 to 40 mg dose whereas the proposed nonprescription dose is 10 mg. The LDL-lowering effect of 20 mg in AFCAPS exceeds that of the 10 mg dose observed in the Efficacy Study.
2. The risk reductions associated with lovastatin therapy in AFCAPS was over an average 5-year treatment duration with approximately 70% of those randomized to lovastatin treatment remaining on therapy for this duration. In contrast, the actual-use studies suggest that any potential benefit associated with nonprescription lovastatin use will be limited by the high number of individuals discontinuing treatment after a few months of treatment.
3. The potential clinical benefit of nonprescription lovastatin relies on the ability of the consumer to appropriately initiate treatment based on his/her CHD risk profile. The individuals in the primary prevention population most likely to benefit from drug treatment are those with low HDL-C levels. The sponsor did not evaluate whether a consumer could appropriately initiate drug treatment based on his/her HDL-C level since this criterion was not on the proposed package label.

The aforementioned reasons add significant uncertainty to any estimates of benefit associated with lovastatin 10 mg use in the nonprescription setting. Given the unknown clinical cardiovascular benefits of treating the primary prevention population with the unrestricted availability of lovastatin 10 mg, the benefit-to-risk relationship of this drug in this population cannot be adequately assessed.

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