Consumer Behavior and Safety Data for the Non-Prescription Mevacor® 20 mg Joint Advsiory Committee Meeting

Application Type	NDA
Submission Number	21-213
Letter Date	August 24, 2004
Review Completion Date	December 13, 2004
Established Name	Lovastatin
(Proposed) Trade Name	Mevacor™ Daily
Therapeutic Class	Cholesterol reducer
Applicant	Merck & Co., Inc.
Formulation	20 mg Tablet
Dosing Regimen	One tablet daily
Indication	Cholesterol reducer
Intended Population	Men 45 years or older Women 55 years or older

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1 EXECUTIVE SUMMARY

1.1 Brief Overview of Clinical Program

The sponsor is seeking to market MEVACOR™ Daily 20 mg tablet as a cholesterol reducer for men (45 years of age and over) and women (55 years of age and over) with low density lipoprotein cholesterol (LDL-C) between 130 and 170 mg/dL, who also have one or more additional risk factors for coronary heart disease (CHD).

This is the sponsor's second attempt to switch Mevacor from Rx to OTC status. The original NDA 21-213 sought to switch lovastatin 10 mg from Rx to OTC status and was submitted on December 10, 1999. In support of the Rx-to-OTC switch, the sponsor submitted the results of seven clinical studies: four in-home "Use" studies, one placebo-controlled double-blind efficacy study, two pharmacokinetic studies, and three label comprehension studies. The data were presented at the Advisory Committee on July 13, 2000. The NDA was found to be non-approvable, based on the data reviewed. Several deficiencies were raised by the Agency in the October 6, 2000 not approvable (NA) letter:

1. Neither the rationale for treating the proposed target population with Mevacor 10 mg in the OTC setting, nor a favorable benefit/risk ratio for such treatment has been adequately established.
2. The data did not demonstrate that consumers can understand and adequately implement treatment to a defined goal or that there is an identifiable population of consumers for whom treatment with a fixed dose of Mevacor, without titration to reach a treatment goal, would represent an acceptable standard of care.
3. Consumers' ability to self-select and adequately comply/adhere with chronic therapy, as well as recognize the risks of therapy, was not demonstrated.
4. The sponsor did not provide adequate justification for deleting the recommendation for hepatic transaminase monitoring for Mevacor 10 mg when used in the OTC setting.
5. The data did not adequately demonstrate the ability of consumers to comprehend the risks associated with concomitant use of Mevacor with numerous interacting drugs.
6. The sponsor has not adequately addressed the risks to the fetus of potential Mevacor use by women who are pregnant or of childbearing potential in the OTC setting.
7. The product name, Mevacor CC, was not acceptable.

The current submission is the sponsor's complete response to the October 6, 2000 NA letter. In support of this new proposal, the sponsor has submitted the following for the Agency review:

1. Revised target population
2. Revised dosing directions
3. Actual Use Study (Protocol #084)
4. Label Comprehension Study (Protocol #90-NG)
5. Proposed labeling and other marketing tools
6. Reanalysis of data from the AFCAPS/TexCAPS study.
7. To support revising the liver function test recommendations in the prescription lovastatin label, information was submitted to the prescription MEVACOR™ NDA 19-643.

8. The sponsor requested to change lovastatin's Pregnancy Category from X to C. The data to support this request was submitted to the prescription MEVACOR™ NDA 19-643. The request was subsequently denied by the Agency.
9. In addition to the new information, the sponsor has resubmitted information from several other previously submitted and reviewed studies.

1.2 Consumer Behavior Data

The sponsor conducted one actual use study entitled: **A Consumer Use Study of OTC MEVACOR™ (CUSTOM): A 6-Month Consumer Behavior Study of the MEVACOR™ OTC Self-Management System (# 084).**

The objective of the actual use study was "to determine, if the MEVACOR™ OTC (MOTC) Self-Management System enables consumers to appropriately manage elevated cholesterol levels, and to assess the safety and tolerability of MEVACOR™ OTC in a population who chooses to self-medicate." This was an open-label, uncontrolled, "all-comers," multi-center 6-month duration actual use study in a simulated OTC setting. Participants were recruited by using an advertisement targeted to consumers who knew their cholesterol numbers. All participants were pre-screened by phone prior to enrollment at the study site. The study sites were in a pharmacy setting. At the site consumers had access to cholesterol testing and a nurse investigator to assist at the time of purchase.

Study Results

A total of 3316 subjects participated in the purchase-decision part of the study. Of those, 1205 (36.3%) made a decision to purchase the product. The most common reason for not purchasing the study medication was that participants needed more information (62.5%) or to talk to their physician (46.2%). Three subjects were excluded because they had ALT values >3x ULN.

Self-selection is a consumer decision to use the drug product. De-selection is a consumer decision not to use the drug after the treatment already started. The sponsor did post-hoc analysis to assess the correctness of the self-selection.

One thousand sixty one (1061) subjects used the study medication. Two subjects, who purchased and used the drug, were subsequently found to be protocol violators and therefore were excluded. The remaining 1059 participants were considered as the population of Users. Seven hundred and one (66.1%) Users completed the study.

Self-Selection Assessment

According to the proposed label, there are 4 conditions that determine correctness of the self-selection, and the hierarchy of a thought process that consumers have to go through when looking at the label is as follows:

1. Age: **only** for men 45 years or older or women 55 years or older,
plus

2. LDL-C level **only** between 130 and 170 mg/dL,
plus
3. One or more of the following risk factors for CHD:
Smoking
High blood pressure
Family history of CHD
HDL-C 1 to 39 mg/dL
plus
4. Absence of conditions that may put users at increased risk of an adverse experience from using the product.

The number of study participants fitting the first three criteria is very low: only 206 (19.5%) out of the 1059 Users. The majority of these (66.5%, N = 137) were men. Only 69 of the female Users in the study met these criteria. The flow chart below gives a summary of the self-selection according to the proposed OTC label data.

Total Users (N=**1059**: 430 women and 629 men)		
↓	→	Did not meet age criteria:
Met age criteria		161 women
269 women (≥ 45 years)		101 men
528 men (≥ 55 years)		
↓	→	LDL-C not within 130-170 mg/dL
LDL-C within 130-170 mg/dL		169 women
100 women		349 men
179 men		
↓	→	≤ 1 risk factor for CHD
> 1 risk factor for CHD		31 women
69 women		42 men
137 men		
↓	→	+ liver disease
No Liver disease		2 women
67 women		1 man
136 men		
↓	→	+ history of muscle weakness
No history of muscle weakness		7 women
60 women		10 men
126 men		
↓	→	1 CHD risk factor and HDL-C > 60 mg/dL
HDL-C < 60 mg/dL		11 women
49 women		9 men
117 men		

Among the 1061 subjects who purchased and used the study drug, 430 (40.5%) were females and 631 (59.5%) were males. Of the 430 women, 161 (37.4%) were less than 55 years of age (below the targeted age). Breakdown of women Users by age is as follows:

- 23 (5.4%) women < 40 years

- 24 (5.6%) women 40-44 years
- 45(10.5%) women 45-49 years
- 69 (16.1%) women 50-54 years

A low literacy population comprised 12.8% of all Users.

Of the 269 (62.9%) women that met the age criteria (≥ 55 years), 100 had a baseline LDL-C between 130 and 170 mg/dL. Of these women only 69 had one or more additional risk factors for CHD. Excluding 2 women with underlying liver disease and 7 women with a history of muscle weakness from taking a statin reduces this to 60 women. Finally, there were 11 out of 60 women, who had a high level (> 60 mg/dL) of HDL-C and only one risk factor for CHD in addition to the age, which would not qualify them for treatment according to the NCEP guidelines (HDL-C above 60 mg/dL is a "negative" risk factor for CHD, i.e., one other factor can be negated by a high HDL-C level).

Out of the 629 male Users, 528 met the age criteria (≥ 45 years). Of those, 179 had a baseline LDL-C between 130 and 170 mg/dL, and 137 had one or more additional CHD risk factor. Excluding one subject with underlying liver disease and 10 subjects with a history of muscle weakness from taking a statin, reduces this to 126. Nine out of 126 men had a high level (> 60 mg/dL) of HDL-C and only one risk factor for CHD in addition to the age.

Therefore, the final numbers of correct self-selectors according to the label is 163 with a gender demographic of 49 women and 117 men. The sponsor could not provide which of these subjects consulted with a health care provider prior to self-selection.

The sponsor estimates prior to study initiation that > 80% of subjects would make a correct self-selection decision, > 75% would correctly continue to use the drug by Week 6, and > 75% would correctly continue to use the drug by Week 26. Results of the study, **based on the sponsor's primary analyses**, show that those percentages were 55.1% (n = 571), 41.3% (n = 409), and 50.1% (n = 494), respectively.

The most common reason for failure in self-selection was that participants did not know their cholesterol levels. Of those subjects who stated that they knew their cholesterol levels, only half identified their LDL-C level correctly. Even though 188 (18%) did not know their complete lipid profile, they chose to use the drug. Elevated triglycerides (> 200 mg/dL), one of the "do not use" conditions on the label, were present in 170 participants (16% of all Users).

Of the 1061 Users, 589 (55.5%) had one or more medical risks specified on the label. In addition, 23 (2.2%) subjects' self-selection status was not known due to missing information. Therefore, 449 (42.3%) Users did not have medical risks to justify use of MOTC 20 mg.

There was a notable difference between men and women in the distribution of CHD risk. A total of 51.2% of the women had a 10-year risk for myocardial infarction and/or coronary death that was less than 5% compared to 11.0% of the men. In contrast, 59.5% of the men fell in the 5% to 25% range compared to 28.1% of the women falling in this range.

The sponsor included several post-hoc analysis to determine if consumers that chose this product were appropriate for cholesterol reeducation therapy. One such analysis was the "closely adhered to label benefit criteria". This category included individuals who did not meet the label defined ranges for age, LDL-C, HDL-C or number of CHD risk factors, but who knew their lipid profile, had a self-reported TG < 200 mg/dL, did not substitute MOTC for their prescription cholesterol lowering medication, and did not have diabetes, heart disease, or stroke. It is important to note that consumers fitting these profiles would not be appropriate self-selectors based on the current label.

Compliance with the Follow-up Cholesterol Test
Compliance with the follow-up cholesterol testing was relatively low: 666 (63%) of the 1059 Users had a follow-up test during the 6 months of the study. Only 346 (32.7%) had it within the specified time interval of 4 to 12 weeks.

There were numerical differences among the analyzed demographic subgroups; none of them were statistically significant. With respect to the initial use decision and follow-up cholesterol test, greater percentages of elderly Users compared to those < 65 years of age, and normal literacy compared to low literacy Users, adhered to label criteria. More Caucasians compared to non-Caucasian Users adhered to the label criteria in respect to follow-up cholesterol testing.

Consumer Decision with Respect to Continuation of Treatment
The median reduction in LDL-C achieved in the population who used MOTC was 20.6%. A total of 282 (26.6%) Users achieved the LDL-C goal of < 130 mg/dL within 4 to 12 weeks (of the 346 that correctly tested at this timepoint. According to the sponsor's definition, of the 878 Users with a known LDL-C value at the end of the study and who had a known LDL-C value at baseline, 548 (62.4%) achieved the LDL-C goal (< 130 mg/dL) by the end of the 6-month study. This number includes 160 Users whose LDL-C level at baseline was < 130 mg/dL and 39 Users whose LDL-C level at baseline was unknown. If we deduct these 199 (160+39) Users, the percentage of Users achieving benefit by the end of the study decreases to 39.7% (349/878).

1.5 Drug-Drug Interactions

Several drugs (cyclosporine, clarithromycin, itraconazole, ketoconazole, nefazodone, erythromycin, and HIV protease inhibitors) have the potential to interact with lovastatin when administered concomitantly. These drugs and grapefruit juice, are strong CYP3A4 inhibitors, and may increase plasma HMG-CoA inhibitory activity levels, and therefore may increase the individual's risk of myopathy. In addition, gemfibrozil and niacin may also increase the risk of myopathy through a different mechanism.

1.6 Special Populations

Presently lovastatin has Pregnancy Category X labeling.

Of particular concern is the fact that 50% of women enrolled in the actual use study were less than 55 years of age, and 37.4% of the women Users were less than 55 years. These data demonstrate poor understanding of the product use and failure in self-selection.

The issue of liver toxicity also remains unresolved. It is unclear how asymptomatic consumers with LFTs 3x ULN would properly self-select not to use Mevacor.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Mevacor™ (lovastatin), is a cholesterol lowering agent isolated from a strain of Aspergillus terreus. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding (beta)-hydroxyacid form. This is the principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

The sponsor is proposing to market Mevacor™ 20 mg tablet in the OTC setting for men 45 years and older and women 55 years of age and older, with LDL-C level between 130 mg/dL and 170 mg/dL, and additional one or more risk factors for CHD.

2.2 Currently Available Treatment for Indications

There are no OTC drugs currently available for the treatment of hypercholesterolemia. Current medical practice is such, that elevated serum cholesterol is treated based on the latest National Cholesterol Education Program (NCEP) Adult Panel Treatment Panel (ATP) III guidelines (Table 1, References 1 and 2).

Table 1. NCEP LDL-C Cholesterol Treatment Guidelines based on Risk for CHD Categorization

Levels of LDL-C at which to consider Drug Therapy (mg/dL)			
Risk Categories	**TLC***	**Drugs**	**Goal**
High risk: CHD or CHD risk equivalents (10 year risk >20%)	≥ 100	≥ 100	< 100
Moderately high risk: 2 or more risk factors (10-year risk 10-20%)	**≥ 130**	**≥ 130**	**< 130****
Moderate risk: 2 or more risk (10-year risk < 10%)	**≥ 130**	**≥ 160**	**< 130**
Lower risk: 0-1 risk factors	≥ 160	≥ 190	< 160

* TLC: therapeutic lifestyle changes; ** for moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available trial results.

According to the ATP III guidelines, elevated LDL cholesterol is the primary target of cholesterol-lowering therapy. Therapeutic lifestyle changes (TLC) are the essential initial step of therapy in all the risk categories. When LDL-lowering drug therapy is employed, the guidelines

advise that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

Risk factors include:

- family history of premature coronary heart disease (below age of 55 years in a male parent or sibling or below 65 in female relative)
- hypertension (BP $\geq$ 140/90 mmHg or an antihypertensive medication)
- cigarette smoking
- diabetes mellitus
- low high density lipoprotein cholesterol (HDL-C) (< 40 mg/dL), and
- age (men $\geq$ 45 years, women $\geq$ 55 years).

HDL-C $\geq$ 60 mg/dl is a negative risk factor, i.e., one other factor can be negated by a high HDL-C level.

Comment:
The sponsor's proposed targeted OTC population falls into a category eligible for drug therapy, and therefore, meets the ATP III guidelines for the treatment of hypercholesterolemia. It includes people in the moderate and moderately high risk for CHD category.

2.3 Availability of Proposed Active Ingredient in the United States

There are several HMG-CoA reductase inhibitors available as prescription drugs for the treatment of elevated serum cholesterol in the United States. This class of drugs is not currently approved for over-the-counter marketing.

2.4 Presubmission Regulatory Activity

NDA 21-213 originally was submitted on December 10, 1999 by Merck & Co, Inc. and Johnson & Johnson Consumer Pharmaceuticals Co. requesting the Agency's approval to market 10 mg strength tablets of lovastatin as an OTC drug product. In support of the Rx to OTC switch, the sponsor submitted the results of seven clinical studies: four in-home "Use" studies (Protocols 076, 077, 079, and 081); one placebo-controlled double-blind efficacy study (Protocol 075); two pharmacokinetic studies (Protocols 078 and 082); and three label comprehension studies. The data were presented at the Advisory Committee on July 13, 2000. The NDA was considered not-approvable, based on the data reviewed. Several deficiency issues were raised by the Agency in the October 6, 2000 not approvable (NA) letter:

1. Neither the rationale for treating the proposed target population with Mevacor 10 mg in the over-the-counter (OTC) setting, nor a favorable benefit/risk ratio for such treatment has been adequately established.
2. The data did not demonstrate that consumers can understand and adequately implement treatment to a defined goal or that there is an identifiable population of consumers for whom treatment with a fixed dose of Mevacor, without titration to reach a treatment goal, would represent an acceptable standard of care.

3. Consumers' ability to self-select and adequately comply/adhere with chronic therapy, as well as recognize the risks of therapy, were not demonstrated.
4. The sponsor did not provide adequate justification for deleting the recommendation for hepatic transaminase monitoring for Mevacor 10 mg when used in the OTC setting.
5. Data did not adequately demonstrate the ability of consumers to comprehend the risks associated with concomitant use of Mevacor with numerous interacting drugs.
6. The sponsor has not adequately addressed the risks to the fetus of potential Mevacor use by women who are pregnant or of childbearing potential in the OTC setting.
7. The product name, Mevacor CC, was not acceptable.

Since the NA letter, there have been a series of communications between FDA and the sponsor on different aspects of the Mevacor Rx-to-OTC switch development program.

The current submission is the sponsor's complete response to the October 6, 2000 NA letter. In support of this new proposal, the sponsor has submitted the following for the Agency review:

1. Revised target population
2. Revised dosing directions
3. Actual Use Study (Protocol #084)
4. Label Comprehension Study (Protocol #90-NG)
5. Proposed labeling and other marketing tools
6. Reanalysis of AFCAPS/TexCaps data.
7. In support of revising the liver function test recommendations in the prescription lovastatin label, information was submitted to the prescription MEVACOR™ NDA 19-643.
8. The sponsor also requested to change the lovastatin's pregnancy Category from X to C. The data to support this request was submitted to the prescription MEVACOR™ NDA 19-643.
9. In addition to the new information, the sponsor has resubmitted information from several other previously submitted and reviewed studies.

2.5 Other Relevant Background Information

As of March 26, 2004, lovastatin has received marketing approval in 59 countries. It has been withdrawn from the market in 13 countries. None of the withdrawals were for safety reasons.

The only country where statins are available without a prescription is the United Kingdom. Simvastatin (Zocor Heart Pro) 10 mg tablets were reclassified from prescription to over-the-counter status (for sale in pharmacies) in May, 2004. Simvastatin 10 mg is indicated for men 45 years and over and women 55 years and over with one or more risk factors for CHD.

3 DATA SOURCES AND REVIEW STRATEGY

In support of the current resubmission, requesting to switch Mevacor™ 20 mg from Rx-to-OTC status, the sponsor provided results of one actual use study, an integrated summary of safety, and proposed OTC labeling which are being considered in this review. The label comprehension

study is under review by Laura Shay, RN, MS, C-ANP in HFD-560. The reanalysis of AFCAPS/TexCAPS and LFT data are being reviewed by the Division of Endocrine and Metabolic Drug products. The pregnancy risk data submitted in March was already reviewed.

This review covers the results of the Consumer Use Study of OTC MEVACOR™ (CUSTOM): A 6-Month Consumer Behavior Study of the MEVACOR™ OTC Self-Management System (#084).

The study description (design, methodology, and results) in an abbreviated form were taken from the sponsor's submission of the NDA. The reviewer's comments are written in an italic font.

4 REVIEW OF CONSUMER BEHAVIOR STUDIES

Title of the Study: A Consumer Use Study of OTC MEVACOR™ (CUSTOM): A 6-Month Consumer Behavior Study of the MEVACOR™ OTC Self-Management System (# 084)

4.1 General Discussion of Endpoints

Objectives

- To determine if the MEVACOR™ OTC Self-Management System enables consumers to appropriately manage elevated cholesterol levels.
- To assess the safety and tolerability of MEVACOR™ OTC in a population who chooses to self-medicate.

This study was primarily designed to evaluate the effectiveness of the MEVACOR™ OTC Self-Management System in guiding consumer behavior. The sponsor states that two facets concerning consumer behavior were of primary interest in this study:

- The initial self-selection decision to use the product, and
- The ongoing decision process regarding continued use (de-selection).

Based on the information collected from the participants, decisions were assessed on the day of first dose and at Weeks 6 and 26 (initial self-selection and de-selection decisions jointly), and were classified into ordinal categories. The sponsor revised the pre-specified categories after the study results were available. According to the initial protocol, those categories were:
Based on this information, decisions will be classified into 1 of the following
3 categories:

- According to Label (AL) – this category represents a decision that is entirely consistent with the product label.
- Not According to Label, Medically Acceptable for Self-Management (NALMASM) - this category represents a decision that is not entirely consistent with the product label, but still results in a favorable benefit to risk ratio for the participant

- Not According to Label, Medically Unacceptable for Self-Management (NALMUSM) – this category represents a decision that is not consistent with the product label and would result in an unfavorable benefit to risk ratio for the participant.

After the study was completed the sponsor redefined these categories. The major difference that was introduced is the "physician override" concept. The categories used by the sponsor for the final analysis of data are as follows.

1. Medically Acceptable for Self-Management (MASM):
   - According to Label, Medically Acceptable for Self-Management (AL-MASM). This category represents a decision that is entirely consistent with the product label. Participants were also considered AL-MASM if their behavior was not entirely consistent with the label but they consulted with a doctor about their use of Mevacor OTC (MOTC) (a physician override).
   - Adequate Benefit, Medically Acceptable for Self-Management (AB-MASM). This category represents a decision that is not entirely consistent with the product label but use of the product still provides some benefit (i.e., lowering cholesterol) to the individual.
2. Medically Unacceptable for Self- Management (MUSM):
   - Not Adequate Benefit, Medically Unacceptable for Self-Management (NAB-MUSM). This category represents a decision that is not consistent with the product label and that deviates sufficiently that it allows potentially inadequate therapeutic benefit but without imparting undue potential safety risk. Some participants were placed in this category to self-manage their cholesterol levels either because their CHD risk was too low or too high.
   - Not Adequate Safety, Medically Unacceptable for Self-Management (NAS-MUSM). This category represents a decision that significantly deviates from the label directions, creating potential safety risks despite potential therapeutic benefit. It would be medically unacceptable for participants in this category to self-manage their cholesterol levels because of inappropriate safety decisions.

Primary Hypotheses

The sponsor states that the hypotheses of this study were constructed to evaluate whether a sufficient number of participants, while using the MEVACOR™ OTC Self-Management System, would make initial MASM self-selection and de-selection decisions. Of those who make an initial self-selection decision to use MEVACOR™ OTC:

- ≥ 80% will make an initial self-selection decision that is medically acceptable for self-management,
- ≥ 75% will make a final de-selection decision that is medically acceptable for self-management between the day of first dose and Week 6, and
- ≥ 75% will make a final de-selection decision that is medically acceptable for self-management between the day of first dose and Week 26.

Comment:
The sponsor states that the above mentioned benchmarks of ≥ 80%, ≥ 75%, and ≥ 75% were primarily based on the results of pilot label comprehension studies of the CUSTOM product

label. However, the questionnaires, correct/acceptable answers, and the results of these pilot studies were not submitted with the application.

Secondary Hypotheses
The secondary hypotheses serve to further assess other aspects of the primary objective and also the safety and tolerability of MEVACOR™ OTC in a population who chooses to self-medicate:

- Of the users who take the End-of-Study Questionnaire, the proportion of responses that are medically acceptable for self-management will be ≥ 80% for each individual situation that should prompt a user to discontinue therapy or consult with a physician.
- MEVACOR™ OTC is well tolerated as measured by the incidence of adverse experiences in all users regardless of whether or not they made an appropriate self-selection decision.

Comment:
The End-of-Study Questionnaire was a group of consumer behavior questions administered at Week 26 or when a consumer chose not to repurchase Mevacor. It included a list of questions about the diagnostic material use, de-selection, adverse event, and reasons for inappropriate self-selection and de-selection.

4.2 Study Design

This was an open-label, uncontrolled, "all-comers," multi-center actual use study in a naturalistic OTC setting.

Recruitment
Participants were recruited by mass media advertising. The advertisement included a toll-free number for interested individuals to call for an appointment. The advertisements did not include any of the specific label inclusion/exclusion criteria. However, the advertisements stated that potential participants should know all 4 of their cholesterol numbers (i.e., Total-C, HDL-C, LDL-C, and triglycerides), even though knowledge of Total-C is not a criterion for product eligibility.

When they made the phone call, participants provided personal and demographic information (e.g., date of birth, gender, race, name, address) and were asked administrative exclusion questions. The telephone operator did not provide a reminder to bring cholesterol values; however, if a participant inquired about cholesterol testing at the site, they were told that they could purchase a test for $10 and that a fast of 9 to 12 hours prior to the test was advisable.

The operator advised interested participants that this study was designed to simulate a retail setting. Therefore, they were required to purchase study medication, but would be compensated for time and travel expenses.

Signs were posted in the storefront windows to attract potential participants as walk-ins. In order to track all participants in the database, walk-ins were required to call the toll-free study advertisement number from the site to be asked the administrative exclusion questions, and

assigned a Participant Identification Number (PIN) even if the site had time for them to complete their first visit that day. If there was an immediate opening in the schedule, the participant provided requested information to the toll-free operator and then passed the phone to the investigator who recorded the PIN and demographic information on the site study record. The investigator then used the date-of-birth and gender information for the eligibility assessment if performed at the first visit. The eligibility assessment is discussed in detail below.

Inclusion Criteria
When participants called to make an appointment, they were included only if they said they could read and understand English without assistance.

Administrative Exclusion Criteria
1. Telephone Appointment Stage Exclusion Criteria
- Participant was currently or has recently (within 30 days of study start) participated in any clinical trial of an investigational or approved drug.
- Participant or household member was a physician or pharmacist, or was employed by a pharmaceutical company.
- Participant had participated in a clinical trial in which cholesterol medication was available only by purchase.

2. Storefront Visit (Following Purchase Decision), Exclusion Criteria
- Participant was a woman who indicated she was pregnant or breast-feeding.
- Participant had been told she/he had an allergy to prescription MEVACOR™.
- Participant had a baseline ALT value > 3 x ULN (only for purchasers who signed consent).

Overall Eligibility Assessment Based on Product Label
Eligibility for MEVACOR™ OTC was assessed using a scripted questionnaire and results were used for the analysis of self-selection and de-selection. The eligibility assessment was collected only one time, but could have been collected in one of three places (i.e., at the study site, through the toll-free product specialist/interactive voice response system (IVRS), or on the website). Participants who opted to use the toll-free product specialist/IVRS or website were informed if MEVACOR™ OTC was not right for them. They also learned their eligibility from the nurse investigator (acting as a pharmacist) if they asked for assistance at the first visit to the study site. Participants who did not avail themselves of these aspects of the MEVACOR™ OTC Self-Management System were administered the eligibility assessment at the end-of-study visit.

The following criteria had to be met in order for a participant to be considered eligible by the box label for MEVACOR™ OTC. An eligible participant:
- was a male ≥ 45 years (derived from date-of-birth given at initial phone contact; was not asked again on script),
- was a female ≥ 55 years (derived from date-of-birth given at initial phone contact; was not asked again on script),
- knew his/her LDL cholesterol was 130 mg/dL to 170 mg/dL,

- had one or more of the following risks for heart disease: hypertension, a family history of heart disease (heart disease in father or brother before 55 years of age or in mother or sister before 65 years), HDL ≤ 39 mg/dL, or was a smoker,
- was not currently taking one of the following prescription medications known to potentially interact with lovastatin: cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, nefazodone, gemfibrozil, or an HIV protease inhibitor,
- was not currently taking any prescription cholesterol-lowering medication, or prescription or nonprescription niacin (≥ 1000 mg/day),
- did not have active liver disease,
- had no history of heart disease (heart attack or angina), diabetes, or stroke,
- did not have triglycerides ≥ 200 mg/dL,
- did not have HDL ≥ 60 mg/dL, and
- had no history of muscle pain, weakness, or tenderness from taking a cholesterol-lowering medication.

Since this was an "all comers" study, ineligible participants (who did not meet the exclusion criteria) were not excluded from purchasing and using MEVACOR™ OTC for up to 6 months.

Figure 1 shows the general study procedures and procedures specific to visits. Table 2 lists a schedule of events specific to each visit. In addition, Figures 2 through 5 (Appendix I) taken directly from the sponsor's submission show study procedures for participants specific to:

- Storefront Visit (Figure 2)
- Follow-up visits to the Storefront for Purchasing Drug (Figure 3)
- Follow-up visits to the Storefront for Cholesterol Testing (Figure 4)
- Final Visit at the Storefront (Figure 5)

Figure 1. Overall Study Flow Chart

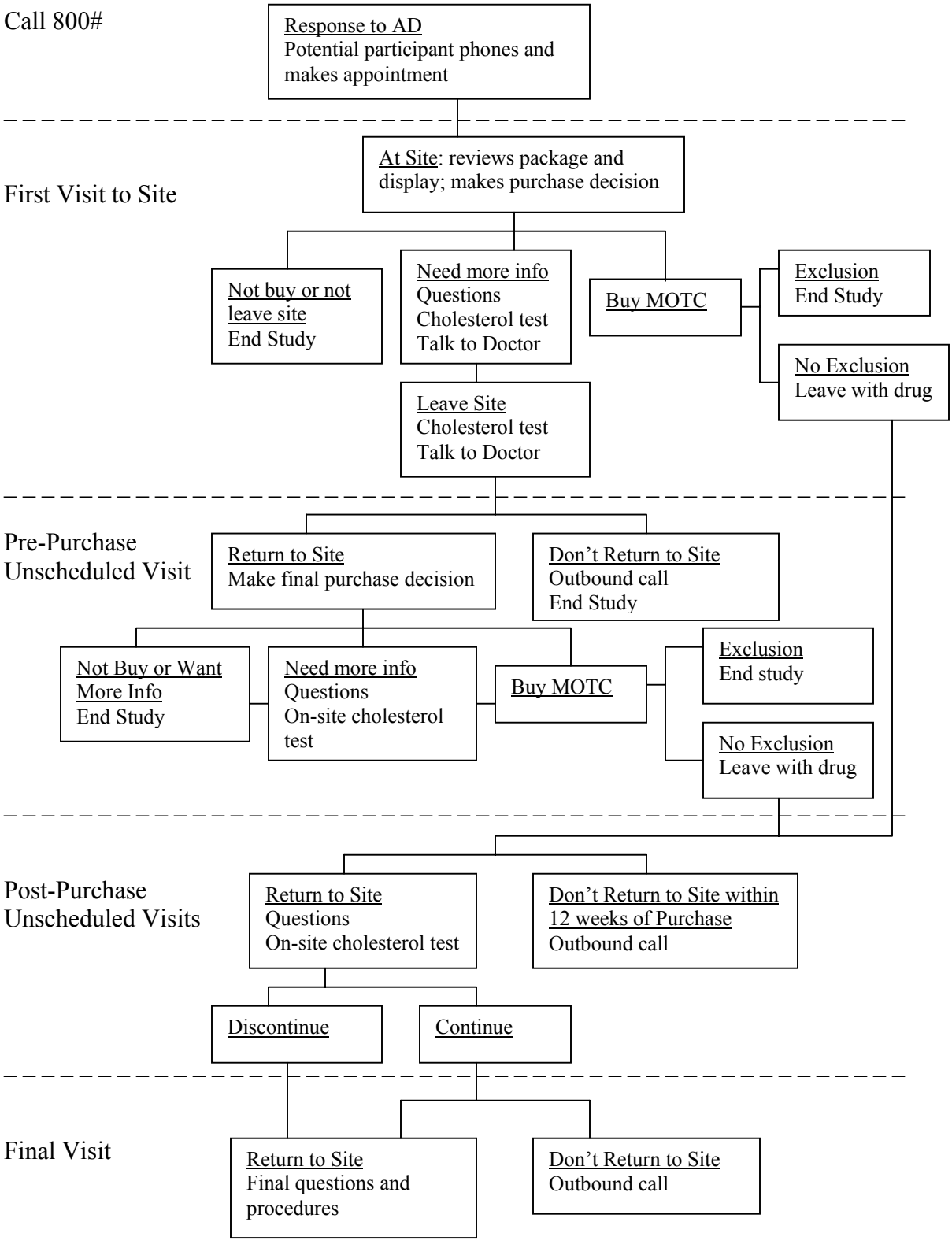


Table 2. Schedule of Clinical Observations and Laboratory Measurements

Activity	Pre-study	Day 1 Site Visit	Between Visits*	Follow-up Visits**	Final Visit
Demographics (collected by phone)	✓				
Participants read proposed OTC carton label and shelf signage		✓			
Participants made self-selection and purchase decision		✓		✓	
Participants who needed more information asked questions to investigator, left to talk to physician/get a cholesterol test and returned to make a decision		✓			
Collected lipid profile and ALT by Cholestech L·D·X™ fingerstick		✓		✓	✓
Collected systolic and diastolic blood pressure		✓			
Excluded participants who indicated they were pregnant/breast-feeding or who were told they were allergic to lovastatin		✓			
Collected eligibility assessment on participants who did not purchase or requested assistance at the first visit; discontinued early; or completed the study		✓		✓	✓
Participants who purchased study drug provided written consent		✓			
Administered MEDFICTS dietary assessment questionnaire		✓			✓
Participants were dispensed drug and study information card		✓		✓	
Consulted with personal or study physician			✓		
Participants/users may have called product specialist (IVRS) or visited the website			✓		
Participants/users may have purchased a home cholesterol test via mail or purchased a "referral kit" to have their cholesterol tested at a local participating lab			✓		
Collected returned drug packaging and tablets					✓
Recorded new medical conditions and new prescription medications				✓	✓
Recorded adverse experiences				✓	✓
If new condition or medication was present, asked user if she/he consulted with personal or study physician regarding continued use of MEVACOR™ OTC				✓	✓
If follow-up cholesterol test not done at site, asked users if they received a test outside of the site and if they consulted with a physician regarding results				✓	✓
Users asked if their eating and exercise habits changed					✓
Users were compensated for time and travel expenses					✓
End of study questionnaires					✓

* Between visits included consumer behavior outside the study site; ** All follow-up visits were optional.

Initial Storefront Visit

Participants were given a brief, general explanation of the self-selection and purchase part of the study. Using a standardized Introductory Script, participants were told to imagine they were in an actual pharmacy, and to do what they would normally do if they came across the MEVACOR™ OTC product display while shopping in the pharmacy.

Participants were asked to make a decision about purchasing study drug, and were able to purchase 1 to 4 cartons (45-day supply per carton) of study drug (lovastatin 20 mg). Enrollment was to be stopped when about 1000 subjects had purchased drug in order to achieve the planned sample size of 1000 Users. Only the initial visit to the study site and the final visit were scheduled. Purchasers were informed that they could return to the storefront at any time during the 26-week period to purchase additional medication or a cholesterol test.

A MEVACOR™ OTC Self-Management System (SMS) was available to guide consumer behavior. This system included shelf display signage, product carton and bottle, package insert, a Quick Start Guide and brochure, video, product website, toll-free call center, and cholesterol testing referral service. A Consumer Assistance Program, which is a component of the MEVACOR™ OTC Self-Management System, provided compliance and appropriate de-selection support for participants/users choosing to enroll. This program consisted of postcard reminders, e-mails, and newsletters. Participants were offered the opportunity to enroll through the toll free phone number, the website, or with the pharmacist at the study site.

All participants had the opportunity to read the proposed outer carton label or interact with the in-store materials (e.g., shelf display), and indicate if they were interested in purchasing a carton of 45 tablets (which included support materials) for $15 (i.e., yes, no, or need more information before purchasing). Participants were allowed to purchase a total of 4 cartons (a total of 180 tablets) during the study either as single or multiple carton purchases. The initial payment was made prior to obtaining informed consent. Participants who indicated that they were not interested in an initial purchase or a repurchase during the study were asked the reason(s) why, completed an eligibility assessment (if not already done), and discontinued from the study.

To determine the reading ability of all participants, the Rapid Estimate of Adult Literacy in Medicine (REALM) test was completed during the initial storefront visit.

If participants needed cholesterol values and asked about the Cholesterol Testing sign in the storefront, they were allowed to purchase a test for $10. Although fasting for 9 to 12 hours before the test was recommended, it was not required. If participants had not fasted prior to their appointment, they were allowed to return to the site at a later date to receive the test. All participants who took advantage of cholesterol testing at the study site were asked to sign an abbreviated consent form for a pre-purchase cholesterol test. The test was a fingerstick lipid profile using the Cholestech L·D·X™ (Cholestech Corporation) desktop analyzer.

Comments:

The study design was not reflective of the naturalistic environment. The availability of a cholesterol screening test and a nurse investigator to assist at the time of purchase is not reflective of the current marketplace in the U.S.

Participants of the study could only purchase four cartons during entire study, which is not reflective of naturalistic OTC access to medications.

At the first site visit, prospective users who had not purchased a cholesterol test prior to making a purchase decision were given a cholesterol test. However, since this test was not purchased, they were not given their values or told their cholesterol was being measured. This test was performed after full informed consent was obtained, so ultimately, all Users had a First Visit cholesterol test. All users received a complimentary test at the final visit which they were not told about until they received a reminder call ~1 week before their scheduled visit. Cholesterol results from the first and last visits were used to evaluate compliance during the 26-Week study. For all cholesterol tests, the investigator recorded whether or not the participant fasted for 9 to 12 hours.

Participants had their ALT measured when the cholesterol test was given. ALT was also measured using a fingerstick test. Participants with an ALT value of > 3 x ULN were excluded. If ALT was > 3 x ULN, the participant was asked to return to the site in ~2 weeks for a follow-up test. If ALT remained > 3 x ULN, the participant was given a letter to take to his/her personal physician. The study physician followed up with the participant until resolution.

Information regarding these options was available via the website and on the toll-free number. Participants who enrolled in the Consumer Assistance Program were also mailed information on these options.

The nurse-investigators were allowed to function as pharmacists, and could answer questions initiated by the participant relating to the study or study drug. If participants asked the investigator for help regarding a specific eligibility item (e.g., was not sure if they should take MEVACOR™ OTC because they have diabetes or are taking a prescription medication), the investigator answered their question. Acting as a pharmacist, the investigator then asked participants if they would like further assistance to determine if MEVACOR™ OTC is right for them. If participants had questions about results of their 6-week follow-up cholesterol test, the investigator directed them to the shelf signage for guidance about the 6-week test and what to do if LDL-C goal was not achieved. If there were questions which the investigator could not answer, the participant was advised to call the study physician, in order to simulate the physician consultation urged by the MOTC SMS.

Comment:
The availability of a health care professional, acting as a pharmacist, to assist in guiding consumers to buy the product may not be reflective of the actual use conditions, but is possible.

A study Information Card was provided at purchase. It included the days/times when the study site was open; the study site phone number to report side effects; the toll-free telephone number to consult with the study physician (to ask questions or for after hour emergencies); information

needed to access the MEVACOR™ OTC website; and space for the user to write the date of first dose of study medication. Participants/users were asked to return this card at their next visit. A new Study Information Card was given at each visit; there was a different card for follow-up visits which did not capture the first dose.

Comment:
It is unclear if or how the sponsor could provide the expansive support system (offered to study participants) to the true OTC consumer if Mevacor was switched from Rx to OTC. If the system were not available, then the ability of the study results to predict true OTC behavior is limited.

Participants could also have chosen to consult with their personal physician or, likewise, the study personnel to initially determine if MEVACOR™ OTC was right for them. Following purchase, all study related procedural questions were to be directed to the study physician or study personnel.

Prior to receiving study medication and to being assigned an allocation number (AN), participants who purchased MEVACOR™ OTC provided written informed consent. Participants who purchased MEVACOR™ OTC were asked the first 2 exclusion questions. Those who met either of the exclusion criteria were given the eligibility assessment and were discontinued from the study.

Following consent at the first site visit, all purchasers had their sitting blood pressure measured. One reading for systolic and diastolic blood pressure was recorded on a worksheet.

The nurse-investigator explained that a study physician was available in lieu of a personal physician at a toll-free number (1-800-MEVACOR), for participant/user-initiated telephone consultation. The informed consent form also reminded users to contact the study physician for medical questions and after-hour emergencies.

The MEDFICTS dietary assessment questionnaire was administered only to those who decided to purchase.

At the time of study drug purchase, an appointment for the final visit (Week 26) was scheduled.

Pre-purchase Unscheduled Visit
A participant may have wanted to consult a personal physician, obtain a new cholesterol test, fast, or obtain test values on file at their physician's office prior to making a purchase decision. These participants were allowed to leave the study site (one time only) and return once the information was obtained to make a repeat purchase decision. If the participants did not return to the site (or schedule another appointment) within 2 weeks, the investigator called them to ask if they were continuing in the study. If the participants did not want to continue, the investigator administered the eligibility assessment over the phone if it had not already been collected, and compensated the participant for time required to complete the phone interview.

Between Visits

All users who were deemed eligible according to label criteria for MEVACOR™ OTC via website, IVRS or outbound call were invited to enroll in the Consumer Assistance Program. Users who were found to be ineligible were not allowed to enroll in the program. They were advised to stop taking study medication and return their unused drug and packaging to the storefront site where they were given a full refund and completed the end-of-study procedures.

Users received incentives for joining the Consumer Assistance Program. For this study, incentives included a coupon for a complementary bottle of MEVACOR™ OTC to be redeemed at their next visit to the study site, a coupon for $5 off a cholesterol test, an "American Heart Association" cookbook, and newsletters about cholesterol and healthy living reminders. In addition, participants always had the option of consulting the study physician to determine if MEVACOR™ OTC was right for them.

As a tool to confirm correct self-selection, and to direct those who made an incorrect initial use decision to discontinue, participants/users who called 1-800- MEVACOR™ to join the Consumer Assistance Program were administered the eligibility assessment (eligibility/ineligibility criteria per label), if not previously completed at the study site. Likewise, anyone who used the website to join completed the eligibility assessment on the website. Participants/users who mailed the business reply card to join were contacted by a product specialist to complete the eligibility assessment.

Post-purchase Unscheduled Visits

Users returned to the storefront at their own initiative when they needed to purchase additional supplies of study medication or to purchase a follow-up cholesterol test. For regulatory compliance purposes, each purchaser received a study-specific bag to keep all empty/unused drug supplies and study materials and was instructed to return the bag at the final visit.

At each follow-up visit, users who returned their drug supplies bag were instructed to keep the bag (with all supplies) and return it at the final follow-up visit at which time worksheets were completed:

- Users were asked, if they experienced any discomfort since the last visit.
- Information on new prescription medications and adverse experiences (including new medical conditions) was collected. Serious adverse experiences were reported to the study physician at the toll-free physician service.
- Any users who were prescribed a new medication or developed a new medical condition were asked if a physician was consulted about continued use of MEVACOR™ OTC.

Users who did not purchase a follow-up cholesterol test at the study site were asked if they received a cholesterol test elsewhere. Results from the follow-up test and where it was performed were recorded. Users were also asked if a physician was contacted regarding any follow-up cholesterol results.

The nurse-investigator contacted all users who had purchased only 1 box and had not returned to the storefront for follow-up by Week 12, to ask if they were still participating in the study.

For follow-up cholesterol tests, there were 3 additional options. Participants could have:

- received a $10 test at a local participating laboratory (via referral from the study site),
- mailed a business reply card with a $10 check to receive a home test kit, or
- received a test through their doctor's office or elsewhere.

Final Visit

At the user's last follow-up visit, the nurse-investigator:
(1) administered the MEDFICTS dietary assessment questionnaire,
(2) performed an ALT and cholesterol test,
(3) asked about any change in eating and exercise habits during the study,
(4) administered the End of Study questionnaires, and
(5) provided compensation (for time and travel expenses).

If a user had not returned for the Week 26 visit, the nurse-investigator immediately attempted contact to emphasize the importance of a return visit. If the user refused to return to the study site, she/he was asked the reason why and a mailer was sent for return of all study-related materials including study medication. During this telephone contact, the nurse-investigator administered the eligibility assessment (if not previously obtained), queried the user about new prescription medications, new medical conditions, adverse experiences, and if appropriate, administered the reasons for inappropriate self-selection/de-selection portion of the End of Study questionnaire. The user was compensated for the time required to complete the phone interview.

The End-of-Study Questionnaire was administered at the last visit (Week 26) or at any point when the user decided not to repurchase. It included a list of questions about the diagnostic material use, de-selection, adverse event, and reasons for inappropriate self-selection and de-selection.

At the last visit to the study site participants were given the opportunity to read and sign an IRB-approved "Permission Form for Post-Study Contact." The post-study follow-up questions were comprised of the two groupings described below.

1. Post CUSTOM Study Clarification Questions

The subgroups identified were users of MEVACOR™ OTC who, as part of the eligibility assessment, reported previous muscle pain from cholesterol-lowering medicine, concomitant use of prescription lipid-lowering medication with MEVACOR™ OTC, or current liver disease, and had not consulted with a physician prior to use of MEVACOR™ OTC. A study coordinator contacted the identified individuals and collected the follow-up question data.

2. Post-CUSTOM Survey

The Post-CUSTOM (telephone) Survey was intended to include a substantial portion of all product users who signed the permission form (~400). The objective was to obtain a more complete characterization of the users, how users interacted with the drug package and internal materials, and how the MEVACOR™ OTC Self-Management System impacted their attitudes and behaviors with regard to cholesterol lowering and heart health. The survey commenced three months after the last participant finished in CUSTOM. For many, six months or more

could have elapsed between the time that they completed or discontinued from CUSTOM and the survey.

Efficacy Measurements
Lipid measurements (total, HDL, LDL, and triglycerides) were collected at the first and last visits. The baseline and final LDL values were used to assess compliance and lipid lowering efficacy at Week 26.

For participants who obtained a lipid measurement at the Week 6 time interval (defined by the range of Weeks 4-12), this measurement was used to evaluate whether or not the user reached goal of LDL-C < 130 mg/dL.

Safety Assessment
Clinical adverse experience information was collected at all follow-up visits by asking the user if they experienced any discomfort since the last visit.

Serious adverse experiences were reported to the study physician at the 1-800- MEVACOR™ toll-free physician service.

4.3 Study Results

Subject Disposition
There were a total of 18692 calls to the Call Center from December 2002 through March 15, 2003 (end of the appointment-scheduling phase of the study). There were 11252 callers who provided at least some of demographic data in the Merck database. Of these callers, 3346 participants came to the study site. The other 7906 participants did not come to the study site. The following are the Merck Exclusion Reasons why the 7906 callers were excluded before coming to the study site:

- 377 did not meet telephone appointment stage eligibility criteria (i.e., Administrative Exclusion Criteria)
- 2372 were lost to follow-up (did not come to the study site)
- 4 participants were inadvertently assigned two baseline numbers
- 5153 callers were uncooperative (refused to complete the telephone interview, hang ups, inquiries, prank calls, cancelled appointments)

Of the 3346 subjects that came to the study site, 30 left the site without making a purchase decision. Table 3 depicts the number of unique calls received, assigned to each site by the callers zip code, and the purchase decision participants made during their appointment.

Table 3. Number of Participants by Study Site

Site No. and Name	Calls N (%)	Appointm. Kept N (%)	Made a Purchase Decision				No Purchase Decision N (%)
			Purchaser			Non-Purchaser N (%)	
			User N (%)	Non-User N (%)	Unknown N (%)		
1. Springfield	642 (5.7)	115 (3.4)	48 (4.5)	2 (2.1)	3 (6.0)	62 (2.9)	0 (0.0)
2. Fairfax	924 (8.2)	165 (4.9)	61 (5.7)	10 (10.6)	7 (14.0)	85 (4.0)	2 (6.7)
3. Dallas	964 (8.6)	285 (8.5)	122 (11.5)	8 (8.5)	2 (4.0)	150 (7.1)	3 (10.0)
4. Fort Worth	882 (7.8)	264 (7.9)	123 (11.6)	6 (6.4)	4 (8.0)	129 (6.1)	2 (6.7)
5. Westheimer	847 (7.5)	289 (8.6)	83 (7.8)	7 (7.4)	3 (6.0)	195 (9.2)	1 (3.3)
6. Inwood Forest	953 (8.5)	294 (8.8)	77 (7.3)	8 (8.5)	2 (4.0)	206 (9.8)	1 (3.3)
7. Willoughby	508 (4.5)	132 (3.9)	47 (4.4)	2 (2.1)	1 (2.0)	80 (3.8)	2 (6.7)
8. Brunswick	734 (6.5)	159 (4.8)	52 (4.9)	4 (4.3)	3 (6.0)	100 (4.7)	0 (0.0)
9. Pontiac	1068 (9.5)	386 (11.5)	47 (4.4)	2 (2.1)	5 (10.0)	325 (15.4)	7 (23.3)
10. Clinton Township	681 (6.1)	151 (4.5)	45 (4.2)	4 (4.3)	4 (8.0)	98 (4.6)	0 (0.0)
11. Bloomington	716 (6.4)	303 (9.1)	85 (8.0)	12 (12.8)	2 (4.0)	198 (9.4)	6 (20.0)
12. Mounds View	673 (6.0)	208 (6.2)	73 (6.9)	6 (6.4)	7 (14.0)	121 (5.7)	1 (3.3)
13. Phoenix	711 (6.3)	250 (7.5)	81 (7.6)	7 (7.4)	1 (2.0)	159 (7.5)	2 (6.7)
14. Glendale	949 (8.4)	345 (10.3)	117 (11.0)	16 (17.0)	6 (12.0)	203 (9.6)	3 (10.0)
Total	11252	3346	1061	94	50	2111	30

The Pontiac, Michigan site (Site Number 9) received the largest proportion of calls and appointments kept, and also had the largest proportion of Non-Purchasers and participants not making a purchase decision. According to the sponsor, this was a result of a unique situation that developed in this study site region, where a church located across the street from a half-way house posted unauthorized signs indicating that anyone could call the toll-free study appointment line and would receive monetary compensation for visiting the study site. According to the sponsor, a large number of individuals who had no intention of purchasing study drug were motivated to visit the study site solely to obtain the monetary compensation.

Participant disposition is summarized in Table 4. Of the 3316 participants who made a purchase decision, 1205 (36.3%) made a decision to purchase. A total of 94 purchasers did not use the product either because they were not dispensed drug (30) at the end of the visit or they returned the drug before using it (64). The two most common reasons participants returned drug before using it were that they were advised not to use it by their doctor (n=26) or they learned MEVACOR OTC was not appropriate for them (n=17). Three of these Purchaser Non-Users had elevated ALT values > 3x ULN (ALT Values: 135, 154, and 189 IU/L) and were excluded from the study and not dispensed drug. Fifty of the 1205 purchasers were lost to follow-up and their decision to use drug is unknown. The remaining 1061 purchasers are known to have used the drug.

Comment:
In the initial submission, the sponsor stated that there were 58 subjects among the 1205 purchasers with elevated ALT values greater than the upper limit of normal, but ≤ 3 x ULN who purchased but did not use the drug. Upon further request by the FDA to clarify the behavior of these subjects (why they did not use the study drug), the sponsor stated that the original data was not accurate. In the subsequent amendment to the NDA submitted on December 2, 2004, the sponsor states that 58 of the 1205 Purchasers had baseline ALT value in the > 1 x ULN to

≤ 3 x ULN range. Most of them (49 of 58) were Users, 3 were among the 50 in the Unknown Use subset, and only 6 were Purchaser Non-Users. Of the 6 Purchaser Non-Users who had a baseline ALT value in the > 1 x ULN to ≤ 3 x ULN range, 5 left the study site with drug and 1 did not. The reasons why these 6 subjects did not take Mevacor OTC are as follows: one reached cholesterol goal, two were advised by a doctor not to continue, two did not give a reason, and one learned that MOTC is not right for him.

Users were considered to have completed the study if they took at least one dose of drug, and completed all final study visit procedures. Two-thirds (66.1%) of the Users (701/1061) completed the study, and 398 Users responded to the post-CUSTOM Survey.

Table 4. Participant Disposition

Efficacy Populations	Counts (%)
Purchasers	1205 (36.3)
• Use Decision: Non-User	94 (7.7)
Not dispensed drug	30 (31.9)
Ineligible	8 (26.7)
ALT > 3 x ULN	3 (37.5)
Other	5 (62.5)
Withdrew consent	2 (6.7)
Refused therapy	3 (10.0)
Moved	2 (6.7)
Trial enrollment closed at site	5 (16.7)
Complete not continuing	10 (33.3)
Returned drug before using	64 (68.1)
• User Decision: User	1061 (88.0)
Completed Study*	701 (66.1)
Discontinued Study	360 (33.9)
Adverse clinical experience	108 (30.0)
Deviation from protocol occurred	2 (0.6)
Patient was lost to follow-up	13 (3.6)
Patient moved	18 (5.0)
Patient withdrew consent	157 (43.6)
Patient discontinued for other reason	53 (14.7)
Uncooperative	9 (2.5)
• User Decision: Unknown (Lost to follow-up)	50 (4.1)
Non-purchasers	2111 (63.7)
• Did not want to buy	1673 (79.3)
• Needed more info	438 (10.7)
Total who made a purchase decision	3316

* includes participants who made decision to purchase, received and used the drug, and completed all final study visit procedures.

There were 2111 participants who did not purchase MOTC. The Non-Purchasers were composed of participants who either indicated they did not want to buy (1673) or needed more information and were considered Non-Purchasers by default (438).

There were 1061 participants who initially decided to purchase and use the product (Users). Two Users were identified as protocol violators: one subject was a physician, and the second

participant took his wife's medication before visiting and signing consent. Therefore, they were excluded and the sponsor considered the remaining 1059 as the population of Users for all summaries and analyses except for analyses pertaining to adverse experiences. The original population of 1061 is considered the population of Users for adverse experiences. Purchasers who did not use any Mevacor (Non-Users) were not included in the evaluation of the primary hypotheses. Fifty participants who purchased drug and were lost to follow-up (Unknowns) were not considered in the evaluation of the hypotheses.

How many purchasers needed more information outside of the label instructions?
The reasons purchasers and non-purchasers needed more information are listed in Table 5. The majority 826/1205 purchasers needed more information. The most common reason among purchasers needing more information was to obtain their cholesterol numbers (37.0%, 446/1205). The second most common reason was related to information such as the cost, study duration or general product information (32.0%, 386/1205). Non-Purchasers commonly cited a need for personal health information (62.5%, 1319/2111) or to talk to a doctor (46.2%, 975/2111).

Table 5. Prevalence of Specific Reasons for Participants Who Needed More Information

	Purchasers (N)	Non-Purchasers (N)	Total (N)
Did not need more information	379	10	389
Reasons for Participants Who Needed More* Information	826	2101	2927
• Study related information	386	546	932
• General information on side effect	285	377	662
• Personal health information	188	1319	1507
• To obtain cholesterol numbers	446	847	1293
• To talk to a doctor	261	975	1236
• Other information	10	95	105
Total	1205	2111	3316

* Some participants gave more than one reason for needing more information.

Comment:
The vast majority of purchasers (826/1205) and non-purchasers (2101/2111) needed more information. This underscores the need for health care provider involvement in the self-selection process.

Missing Data for the Endpoint Assessment
In total, 92 of the 1059 Users had some unknown data; only 3 Users had unknown data at all three time points relevant to the study primary hypotheses (initial self-selection, de-selection through Week-6, and de-selection through Week-26). Due to missing responses the population of Users is further reduced from 1059 for the self-selection decisions and the two de-selection decision intervals:

Decision Time Point	# of Users with Complete Data	# of Users with Missing Data
Self-Selection	1037	22
De-selection through Week 6	990	69
De-selection through Week 26	986	73

Demographic and Other Baseline Characteristics

The participants' baseline characteristics are summarized in Table 6. (Appendix II). Of the 11,252 consumers who called in response to study advertising, 20.4% were Black and 5.6% were Hispanic. The majority of Users were Caucasians (82%). The percentages of Users who were Black and Hispanic were 8.5% and 5.5%, respectively.

Among the 1061 subjects who purchased and used the study drug, 430 (40.5%) were females and 631 (59.5%) were males. Of the 430 women, 161 (37.4%) were less than 55 years of age (below the targeted age). Breakdown of women Users by age is as follows:

- 23 (5.4%) women < 40 years
- 24 (5.6%) women 40-44 years
- 45(10.5%) women 45-49 years
- 69 (16.1%) women 50-54 years

A low literacy population comprised 12.8% of all Users.

Comment:
Mevacor is a pregnancy Category X drug. The fact that a high percentage of women of child bearing age chose to use Mevacor is an important safety concern.

Correct Self-Selection According to Label Criteria

For the purposes of this discussion, self-selection refers the decision to use the product at the initial visit. This analysis includes only purchasers of the product. It is not entirely clear from the design of the protocol that non-purchasers made a selection decision (based on the eligibility criteria). According to the proposed label, there are 4 conditions that determine correctness of their self-selection. The order that consumers have to go through in their thought process when looking at the label is as follows:

1. Age: **only** for men 45 years or older or women 55 years or older,
   plus
2. LDL-C level **only** between 130 and 170 mg/dL,
   plus
3. One or more of the following risk factors for CHD:
   Smoking
   High blood pressure
   Family history of CHD
   HDL-C 1 to 39 mg/dL
   plus
4. Absence of conditions that may put users at increased risk of an adverse experience from using the product.

The number of study participants fitting the first three criteria is very low: only 206 (19.5%) out of the 1059 Users. The majority of these (66.5%, N = 137) were men. Only 69 of the women Users in the study met these criteria. The flow chart (Figure 6) below gives a summary of the self-selection data based on these 4 label criteria.

Figure 6. Correctness of the Self-Selection

Total Users (N=**1059**: 430 women and 629 men)		
↓	→	Did not meet age criteria:
Met age criteria		161 women
269 women (≥ 45 years)		101 men
528 men (≥ 55 years)		
↓	→	LDL-C not within 130-170 mg/dL
LDL-C within 130-170 mg/dL		169 women
100 women		349 men
179 men		
↓	→	≤ 1 risk factor for CHD
> 1 risk factor for CHD		31 women
69 women		42 men
137 men		
↓	→	+ liver disease
No Liver disease		2 women
67 women		1 man
136 men		
↓	→	+ history of muscle weakness
No history of muscle weakness		7 women
60 women		10 men
126 men		
↓	→	1 CHD risk factor and HDL-C > 60 mg/dL
HDL-C < 60 mg/dL		11 women
49 women		9 men
117 men		

Out of the 430 women who purchased and used the study drug, 269 met the age criteria (≥ 55 years), of those only 100 had a baseline LDL-C between 130 and 170 mg/dL, and only 69 had one or more risk factors for CHD.

Male Users were older and had a higher number of risk factors for CHD. Out of the 629 male Users, 528 met the age criteria (≥ 45 years), of those 179 had a baseline LDL-C between 130 and 170 mg/dL, and 137 had one or more CHD risk factors. Furthermore, if we exclude 3 subjects with underlying liver disease (1 man and 2 women) and 17 (10 men and 7 women) subjects with a history of muscle weakness from taking statin, the numbers are 60 women and 126 men. Finally, there were 11 women and 9 men, who had only one risk factor for CHD in addition to the age and a high level (> 60 mg/dL) of HDL-C. According to NCEP guidelines, HDL-C above 60 mg/dL is a "negative" risk factor for CHD, i.e., one other factor can be negated by a high HDL-C level, and therefore, these 20 Users are not in the target population for Mevacor OTC therapy. The final numbers of correct self-selectors according to the label becomes 49 women and 117 men. It is unclear which of them consulted a physician prior to the use of Mevacor.

Additional Analysis Conducted by the Sponsor

The sponsor conducted additional analysis that included:

- Calculated 10-Year Risk for Myocardial Infarction or Coronary Death;
- Off Label Risk Subsets: high lipids subset, preexisting atherosclerotic cardiovascular disease or diabetes, contraindicated underlying conditions (e.g. allergy to lovastatin).

These analyses are not included in this summary of the study. Please refer to the sponsor's background package for information related to these analyses. FDA will provide comments on these analyses during the FDA presentation at the advisory committee.

Can Consumers Self-Select Based on Their Knowledge of Their Cholesterol?

A finger stick blood evaluation was performed using a desktop analyzer for all participants choosing to purchase study drug. The mean and median values for LDL-C were lower, and for triglycerides were higher, in the non-fasted group compared with the fasted group. There were relatively high values of HDL-C in the study population (mean of 47 and median of 45 mg/dL). None of the Users had ALT value greater than 3 x ULN (normal range 20-40 IU/L) at baseline.

At the initial visit, subjects were asked their LDL-C levels. Baseline LDL-C levels were measure in most users (128 of 1059 did not have measurements). The agreement between self-reported and measured LDL-C values is displayed in Table 8.

Table 8. Number of Users by Self-Reported and Measured LDL-C Values (Baseline)

	Measured LDL-C (mg/dL)				
Self-Reported LDL-C	Missing	< 130	130 to 170	> 170	Total
Missing	15	0	10	2	27
Unknown	66	55	103	94	318
< 130 mg/dL	10	87	16	9	122
130-170 mg/dL	19	54	250	44	367
> 170 mg/dL	18	13	26	168	225
Total	128	209	405	317	1059

For LDL-C, 667 (63%) of the user population had both a known self-reported LDL-C value and a non-missing measured LDL-C from the Cholestech L·D·X™ evaluation. Sixty-nine Users over-reported (self-reported greater than measured) and 93 Users under-reported (self-reported less than measured) their LDL-C.

Four hundred and thirty-six Users reported unknown or LDL-C less than 130 and 225 reported LDL-C greater than 170. Based on the labeled directions, none of these should have entered the study. Further analysis is needed to determine the percentage who may have purchased a cholesterol level at the site or received physician override to participate.

For Total-C, 855 of the user population had both a known self-reported Total-C value and a non-missing measured Total-C from the Cholestech L·D·X™ evaluation. A total of 663 (77.5%) of the 855 had a self-reported Total-C that agreed with the measured Total-C value. Ninety-one User (91) over-reported and 101 Users under-reported their Total-C.

Comments
A significant number of participants in the study did not correctly identify their LDL-C level. A total of 505 (47.7%) participants correctly identified their LDL cholesterol level. Out of a total of 317 participants with measured high (> 170 mg/dL) LDL-C levels, 168 (53%) self reported their LDL-C level correctly, 53 (16.7%) underreported, and 96 (30%) did not know or their self-reported LDL-C levels were missing. For the other subgroups, the correct self-reporting LDL-C level rates were:

- *42% for the group with a measured LDL-C level < 130 mg/dL*
- *62% for the group with a measured LDL-C level of 130 to 170 mg/dL*

The knowledge of cholesterol levels becomes important in OTC setting, if there is no access to testing.

Can Consumers Self-Select Based on Their Risk for CHD Factors?
Table 9 presents the distribution of study participants by the number of CHD risk factors for several of the study populations. A higher percentage of Users had 2 or more CHD risk factors compared to the Non-Purchasers (57.3% vs. 42.8%) and were thereby statin eligible by ATP III.

Table 9. Self-Reported CHD Risk Factors

		Purchaser		
		User (N=1061)	Non-User (N=94)	Unknown (N=50)
No. of CHD Risk Factors	0	93 (8.8)	9 (9.6)	16 (32.0)
	1	360 (33.9)	37 (39.4)	29 (58.0)
	2	381 (35.9)	33 (35.1)	3 (6.0)
	3	178 (16.8)	13 (13.8)	1 (2.0)
	4	46 (4.3)	2 (2.1)	1 (2.0)
	5	3 (0.3)	0 (0.0)	0 (0.0)
Age (Years)	Male: < 45	101 (16.0)	8 (15.4)	12 (35.3)
	≥ 45	530 (84.0)	44 (84.6)	22 (64.7)
	Female: < 55	161 (37.4)	15 (35.7)	7 (43.8)
	≥ 55	269 (62.6)	27 (64.3)	9 (56.3)
Smoking Status	Yes	120 (11.5)	14 (16.7)	1 (8.3)
	No	926 (88.5)	70 (83.3)	11 (91.7)
Family History of CHD	Yes	372 (35.6)	23 (27.4)	2 (16.7)
	No	674 (64.4)	61 (72.6)	10 (83.3)
Hypertension	Yes	349 (33.5)	25 (29.8)	3 (25.0)
	No	694 (66.5)	59 (70.2)	9 (75.0)
HDL-C	Male: < 40 mg/dL	173 (27.9)	11 (23.9)	5 (55.6)
	≥ 40 mg/dL	289 (46.7)	19 (41.3)	2 (22.2)
	Don't know	157 (25.4)	16 (34.8)	2 (22.2)
	Female: < 40 mg/dL	42 (9.9)	6 (15.8)	0 (0.0)
	≥ 40 mg/dL	254 (59.8)	25 (65.8)	1 (33.3)
	Don't know	129 (30.4)	7 (18.4)	2 (66.7)

Comment:
According to the NCEP ATP III treatment guidelines, for people with 0 to 1 risk factor for CHD to qualify for drug therapy, their LDL-C level has to be ≥ 190 mg/dL. It is of concern that 42.7% of Users did not have at least 2 risk factors and used the product. They fall outside the

NCEP ATP III treatment guidelines and the label eligibility criteria (age plus 1 or more additional risk factors) for the treatment with statins.

Duration of Use

The Users whose duration of treatment was > 24 weeks (168 days) were considered by the sponsor to have remained in the study for 26 weeks. The sponsor determined that a total of 61.8% (656/1061) of the Users had treatment duration of at least 169 days. Data on duration of treatment are presented in the Safety Section of the review.

The sponsor acknowledges that the above assessment of duration of use is confounded by several factors:

- The MEVACOR™ OTC Self-Management System contained prominent and pervasive messages encouraging appropriate discontinuation of therapy.
- Study drug stop date was not collected from Users. The date of last drug return (or last contact with the User if drug was not returned) was used as a surrogate for therapy stop date. This is illustrated by the single death in the study. The data for this subject indicates continued use of Mevacor after the date of death.
- Some Users "remained in the trial" until their scheduled last visit even if they had discontinued study drug long before their final visit, or had never taken any drug.

Related information on duration of use is available from the Post-CUSTOM Survey. Of the 398 Users who responded to the survey, 266 reported that they "generally used" MEVACOR™ OTC throughout the 6-month study period. When these 266 Users were asked about the likelihood of their continuing with MEVACOR™ OTC had it been available after the study, 77% (205/266) responded that they would have been "very likely" to continue to use the product, and another 9% (25/266) said they would have been "somewhat likely" to continue use.

Compliance

The sponsor states that compliance was calculated as the number of tablets taken divided by the number of days users had access to medication in all 1059 Users. The percent compliance can be more than 100% for several reasons, including:

- User actually took more than 1 tablet per day
- Artifacts created by data handling and entry guidelines
- Error in data collection or entry (discovered after database lock)

Comments:
The methodology of the study to assess compliance is flawed. The study was open label, uncontrolled, and diaries on drug use were not given to participants. In addition, participants were not asked if they were taking MEVACOR OTC daily, and when they stopped taking the study drug. Rather the duration of treatment was estimated based on the time participants had the drug in their possession even if they were not using Mevacor. As noted earlier, there was one subject in the study who died while participating in the study. Since the study medication was not returned to the study personnel immediately, he was considered to be on drug therapy for 9 days after his death.

The sponsor states that the data support the conclusion that there is no evidence of excessive dosing on a chronic basis in the User population. However, consumers were restricted to purchasing no more than 4 cartons of Mevacor during the study. The data collection was insufficient to make this conclusion.

Effectiveness of the MEVACOR™ OTC Self-Management System in Guiding Appropriate Behavior

The sponsor is submitting with this plan a self-management guiding program. The main part of this program that was evaluated was the physician override of label criteria. It is important to note in the actual use study that consumers should have had to leave from their initial visit to consult with their physi8cian and then return for an unscheduled visit. However, even though there was a high number of reported physician overrides, there were few unscheduled visits. The sponsor has not yet explained this discrepancy.

Physician override of label criteria for selection.

For this determination the sponsor defined 2 categories: 1) medically acceptable for self management (MASM) and 2) Medically unacceptable for self-management (MUSM). These were further subdivided into AL-MASM and AB-MASM as below:

1. Medically Acceptable for Self-Management (MASM):
    - According to Label, Medically Acceptable for Self-Management (AL-MASM). This category represents a decision that is entirely consistent with the product label. Participants were also considered AL-MASM if their behavior was not entirely consistent with the label but they consulted with a doctor about their use of Mevacor OTC (MOTC) (a physician override).
    - Adequate Benefit, Medically Acceptable for Self-Management (AB-MASM). This category represents a decision that is not entirely consistent with the product label but use of the product still provides some benefit (i.e., lowering cholesterol) to the individual.
2. Medically Unacceptable for Self- Management (MUSM):
    - Not Adequate Benefit, Medically Unacceptable for Self-Management (NAB-MUSM). This category represents a decision that is not consistent with the product label and that deviates sufficiently that it allows potentially inadequate therapeutic benefit but without imparting undue potential safety risk. Some participants were placed in this category to self-manage their cholesterol levels either because their CHD risk was too low or too high.
    - Not Adequate Safety, Medically Unacceptable for Self-Management (NAS-MUSM). This category represents a decision that significantly deviates from the label directions, creating potential safety risks despite potential therapeutic benefit. It would be medically unacceptable for participants in this category to self-manage their cholesterol levels because of inappropriate safety decisions.

The results of this analysis are in Table 10 below.

Table 10. Assessment of Participant Behavior by Decision Time Interval (Users)

	MASM			MUSM		
Decision	AL	AB	Total	NAB	NAS	Total
Self-Selection	484	87	571	357	109	466
De-Selection through Week 6	366	43	409	483	98	581
De-Selection through Week 26	348	146	494	391	101	492

AL=According to label; AB=Adequate benefit; NAB=Not adequate benefit; NAS=Not adequate safety; MASM=Medically acceptable for self-management; MUSM=Medically unacceptable for self-management.

Around 10% of User behavior was classified as MUSM-NAS at each interval.

From these redefined subsets, we see that 484 subjects were reclassified as appropriate users. This is further detailed in Table 11 below.

Table 11. Number of Participants by Adherence to Label Benefit Criteria for Initial Use Decision

Adherence to Label Benefit Criteria	AL	AB	NAB	NAS	Unknown	Total
Adhered to label Benefit Criteria	484	0	0	1	0	485
• Without physician override	68	0	0	1	0	69
• With physician override	416	0	0	0	0	416
Closely adhered to label benefit criteria*	0	87	81	27	7	202
• Outside of age criteria	0	9	50	3	2	64
• Absence of label risk factors	0	45	47	11	3	106
• LDL-C < 130 mg/dL	0	8	4	5	1	19
• LDL-C > 170 mg/dL	0	49	31	11	4	95
• HDL-C ≥ 60 mg/dL	0	21	40	9	1	71
Did not adhere to label benefit criteria	0	0	276	81	0	357
• Did not know lipid profile	0	0	145	43	0	188
Did not know LDL-C	0	0	134	40	0	174
Did not know HDL-C	0	0	115	37	0	152
Did not know TG	0	0	116	37	0	153
• Self-reported TG ≥ 200 mg/dL	0	0	136	34	0	170
• Subs MOTC for lipid-lowering meds	0	0	10	1	0	11
• High CHD risk	0	0	38	32	0	70
Diabetes	0	0	18	12	0	30
CHD	0	0	18	18	0	36
Stroke	0	0	7	9	0	16
Missing eligibility assessment	0	0	0	0	15	15
Total	484	87	357	109	22	1059

* Participants may be counted in more than one subgroup

A total of 485 Users adhered to all of the label benefit criteria. Four hundred eighty-four (484) also had a DAP self-selection classification of According to Label (AL) implying that they had none of the specific conditions or situations identified in the label ineligibility criteria or that they consulted with a physician, plus one subject who was classified as NAS (not adequate safety) due to previous muscle pain, weakness, or tenderness from taking a cholesterol-lowering medication.

An additional 202 Users closely adhered to the label benefit criteria. The distribution of individuals in this subset by their calculated 10-year risk for myocardial infarction and/or coronary death (based on measured lipid values) was as follows:

- 4 participants had a 10-year risk for myocardial infarction and/or coronary death exceeding 20%
- 101 had a 10-year risk for myocardial infarction and/or coronary death in the 5 to 20% range
- 90 had a 10-year risk for myocardial infarction and/or coronary death that was less than 5% (20 men and 70 women)

The sponsor combined users that adhered and those who closely adhered to the label benefit criteria. This analysis brought the sponsor's new number of appropriate self-selectors to a total of 686 of the 1059 Users.

A total of 357 Users did not adhere to the label benefit criteria for one or more of the following reasons:

- 188 did not know their complete lipid profile (LDL-C, HDL-C and triglycerides) when making their decision to use MEVACOR™ OTC.
- 170 had a self-reported triglyceride ≥ 200 mg/dL. This was based on a non-fasted triglyceride evaluation in 95 of the 170 individuals. The majority (125 of 170; 74%) had reported triglyceride values below 400 mg/dL, but 26% (45 of 170), had triglycerides ≥ 400 mg/dL.
- 11 indicated that they substituted MEVACOR™ OTC for a prescription cholesterol-lowering medication.
- 70 indicated that they had diabetes, heart disease, or stroke (high CHD risk subset). Forty-six (46) of the 70 did not report being on a prescription cholesterol-lowering medication and 26 of the 70 reported a physician interaction during the course of this study.

Comments:
One of the conditions for the drug to be safely used in the over-the-counter setting is appropriate self-selection based on the labeling. Data from this study show that significant number of participants did not know their lipid profile, which is the basis for the treatment of hypercholesterolemia with statins.

The most common reason for failure in self-selection was that participants did not know their cholesterol levels. A total of 188 did not know their complete lipid profile and chose to use the drug. This comprises 18% of all 1059 Users. Even though the subsequent testing showed that 175 of the 188 participants had elevated values of LDL-C or Total-C, this still does not justify their self-selection. Additionally, it is unclear from the submission how many of those participants had LDL-C levels that fell within the acceptable treatment range. Elevated triglycerides (> 200 mg/dL), one of the "do not use" conditions on the label were present in 170 participants; they comprised 16% of all Users.

The sponsor states that although 357 Users did not adhere to the label benefit criteria, at least 72% (n=258) of this cohort was eligible for statin therapy by ATP III guidelines, and thus, raising the initial appropriate self-selection rate from 55.1% to 89% (944 of 1059 users). These post-hoc analyses are not based on the subject's self-selection decision but rather on the retrospective analyses of their baseline characteristics.

There were 109 Users (Table 11) identified as making an initial decision to use MEVACOR™ OTC that potentially put them at increased risk of an adverse experience.

The specific label ineligibility criteria used to identify these 109 Users were the following:
• allergy to lovastatin
• pregnant or breast-feeding
• liver disease
• previous muscle pain, weakness or tenderness from taking a cholesterol lowering medication
• taking (or unsure if they are taking) potentially interacting medications
• concomitant use with a prescription cholesterol-lowering medication

Sixty-three (63) of the 109 completed the study, although one reported that a doctor advised him/her not to continue. Thirty (30) of the 109 discontinued from the study on or before Study Day 84 of which 23 reported either that they learned MEVACOR™ OTC was not right for them (n=17) or that a doctor advised them not to continue (n=3) or both (n=3). An additional 16 of the 109 discontinued from the study after Study Day 84 of which 6 reported either that they learned MEVACOR™ OTC was not right for them (n=5) or that a doctor advised them not to continue (n=1).

Comment:
A total of 10.3% of Users made a self-selection error to take MOTC that could put them at risk. Given the incorporated study pre-purchase screening procedures (telephone screening prior to enrollment, the availability of Cholestech analyzer, and the interactions with a study physician and a nurse investigator), the risk may increase significantly if the drug becomes available to a large unscreened OTC population of consumers.

Also, as noted in Table 7 (Appendix III), even if we assume that some participants, in fact, discussed a particular risk condition with their personal physician, a significant proportion of users with each individual risk factors remain who did not get physician clearance. If we compare the categories, a listing of these non clearance users follows:

- *37.5% (62 out of 165) of Users were taking prescription lipid lowering medication Without physician override (wpo),*
- *64.5% (281/435) of Users had high LDL-C or TG WPO,*
- *37.5% (12/32) of Users took potentially interacting drugs WPO,*
- *41% (30/73) of Users had diabetes WPO,*
- *41.5% (37/89) of Users had CHD WPO,*
- *51.6% (16/31) of Users had a history of stroke WPO,*
- *61.6% (53/86) of Users had a history of previous muscle pain while on statin WPO.*

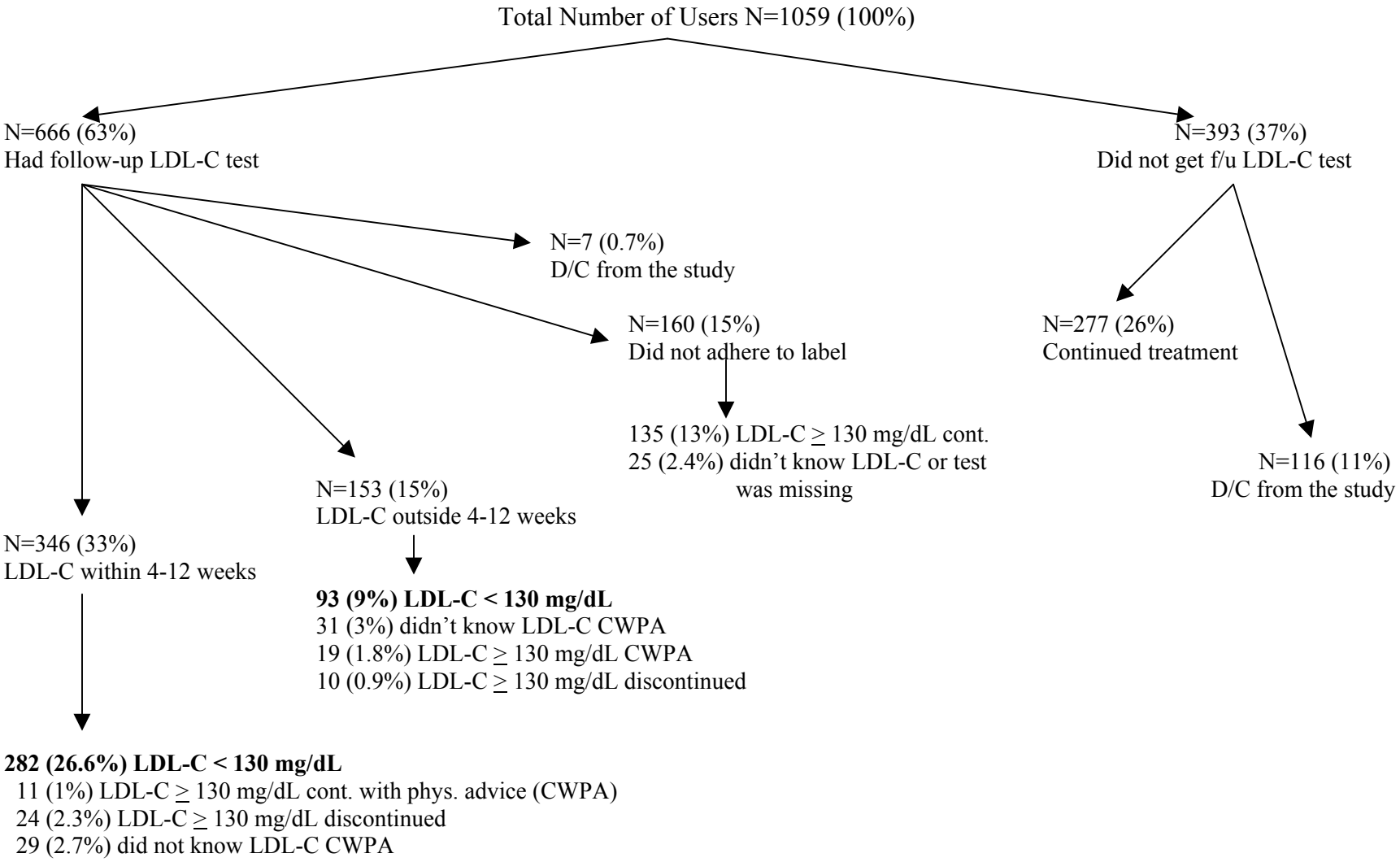
How many Users obtained a follow-up cholesterol test, how did they use that information and did they achieve goal?

The label instructed users to test their cholesterol after 6 weeks of treatment. Table 12 (Appendix IV) presents details on the decision for continuing use of MEVACOR™ OTC with regard to follow up cholesterol testing for all 1059 Users: getting a follow-up cholesterol test within a specific time frame after starting to use MEVACOR™ OTC, and whether to continue or stop using the product based on the test results. The flow chart below (Figure 7) gives a summary of the same data.

A total of 666 (346+153+160+7, Table 12) of the 1059 Users obtained at least one follow-up cholesterol test prior to the mandatory end-of-study test. This includes 406 individuals who had one follow-up test and 260 individuals who had more than one follow-up test (up to six tests). The remaining 393 (37%) individuals did not get a follow-up cholesterol test. One hundred sixteen of the 393 discontinued from the study on or before Study Day 84. This leaves 277 (26%) individuals who did not get a follow-up cholesterol test and continued in the study past Day 84 (91 discontinued from the study after study Day 84 and 186 completed the study).

A total of 123 (11.6%) out of 1059 individuals discontinued from the study and were considered missing for the assessment of adherence to label criteria regarding the follow-up cholesterol test. This includes the 116 participants described in the preceding paragraph as well as 7 individuals who did get a follow-up cholesterol test, but who discontinued and did not report that the results of the cholesterol test were a factor in their decision. Therefore, 936 Users were available for the assessment of adherence to label criteria regarding the follow-up cholesterol test.

Figure 7. Decisions with Respect to Continuation of Therapy



Three hundred forty-six (346, 36.5%) Users obtained a follow-up cholesterol test within the pre-defined interval for Week 6 (within 4-12 weeks) and exhibited behavior that adhered to the label directions. This included 282 individuals who achieved an LDL-C goal level of < 130 mg/dL and continued with the product, 24 individuals who did not achieve the LDL-C goal level of < 130 mg/dL and discontinued use of the product and 40 individuals who continued use of the product following a physician interaction.

An additional 153 Users obtained a follow-up cholesterol test and exhibited behavior that adhered to the label directions for LDL-C goal except that the follow-up test was obtained outside of the pre-defined interval for Week 6.

Four hundred thirty-seven Users exhibited behavior that did not adhere to label criteria regarding the follow-up cholesterol test. This includes the 277 Users who did not get a follow-up cholesterol test and continued in the study past Day 84 (described earlier) and 160 Users who got a follow-up cholesterol test and exhibited behavior that did not adhere to the label directions for LDL-C goal. Of the 277 Users who did not get a cholesterol test and continued without a physician override (Table 18), an end of study LDL-C value was available for 201 of these and 55% (111 of 201) achieved LDL-C target goal. One hundred-thirty (130) of the 270 provided a reason for their behavior:

- 51 indicated that it "was not convenient to get a test"
- 18 of the 64 Users who were categorized as 'other' had discontinued MOTC treatment, therefore it was unnecessary for these individuals to get a test
- 78 of the 147 Users who did not provide a reason indicated that they were not aware of the label directive

Of the 160 Users who got a follow up cholesterol test but who did not adhere to label criteria regarding that test, 135 Users had an LDL-C ≥ 130 and continued with treatment. Additionally, only 14 of 97 Users who did not provide a reason indicated that they were not aware of the label directive and the remaining 83 of 97 were not asked the question.

Comment:
Even though a physician's advise to continue or discontinue the drug therapy is a valid justification for deviation from the label use directions, this is not always possible in the over-the-counter setting. We cannot estimate the real rate of consumer contact with a health care provider during this study, because the contact itself and the information discussed with a health care provider were not verified by the study personnel. Compliance with the follow-up cholesterol testing was relatively low: 666 (63%) of the 1059 Users obtained a follow-up test during the 6 months of the study. Only 346 (32.7%) obtained it within the specified time interval of 4 to 12 weeks. A total of 282 (26.6%) Users achieved the LDL-C goal of < 130 mg/dL within 4 to 12 weeks, and an additional 93 (9%) Users had their LDL-C test outside the 4 to 12 week period and achieved LDL-C goal.

For the group of 484 Users who self-selected according to the label criteria (includes physician override), 297 achieved LDL-C goal (< 130 mg/dL) at the end of the study. Thirty-nine of these

297 participants discontinued the study for various reasons. Twenty-three of these participants gave reasons that were directed by the label. These reasons were:

- *Did not reach cholesterol goal*
- *Adverse experience that was judged to be muscle pain related*
- *Doctor advised not to continue*
- *Learned MEVACOR OTC is not right for me*

Sixty-eight of the 484 Users self-selected correctly according to the label criteria without a physician interaction. Of these 68 Users, 41 achieved their LDL-C goal (< 130 mg/dL) at the end of the study. Three of these 41 participants discontinued the study for various reasons; two of these had reasons that were directed by the label. Table 13 below summarizes these data.

Table 13. Participants That Self-Selected Correctly According to Label: Goal Status & Discontinued Study Counts

	Achieved Goal at the End of the study	Discontinued Study	Discontinued Study Due to Reasons on Label
Initially self-selected Correctly According to Label (N=484)	297	39	23
Initially self-selected Correctly According to Label Without Physician Interaction (N=68)	41	3	2

Of the 398 users who responded to the Post-CUSTOM survey, 139 (35%) felt that they did not attain the LDL-C goal. Seventy-five (75) of the 139 reported that they subsequently spoke to their physician about cholesterol, and an additional 28 of the 139 said that they had made an appointment to talk with their physician. Of the 75 people who said they saw their physician, 56 were put on a new treatment plan, and prescription cholesterol-lowering medication was part of the treatment plan for 55 of the 56.

User Decisions Related to Emergent Medical Conditions, New Prescription Medications, and Occurrence of Unexplained Muscle Pain

Table 14 (Appendix V) presents the decision for continuing use of MEVACOR™ OTC for all 1059 Users. Three hundred sixty six (366, 35%) of the 1059 Users reported an emergent medical condition or new prescription:

- One hundred sixty-one (105+53+3) reported an emergent medical condition other then an unexplained muscle pain:
  - 6 newly diagnosed cases of diabetes,
  - 1 stroke, and
  - 4 cases of coronary artery disease.

  One hundred five (105) of the 161 informed a physician about taking MEVACOR™ OTC including five of the six diabetes cases and three of the four coronary artery disease cases.

Examples of other commonly reported new medical conditions included sinus infection (13 cases), hypertension (11 cases), and urinary tract infection (8 cases).

- Two hundred seventy reported a new prescription during the period they were in the study. Only two of the 270 reported a specific interacting medication and failed to inform a physician about taking MEVACOR™ OTC. Both individuals were taking clarithromycin, one stopped study medication and the second interrupted study medication.
- Sixty-three reported unexplained muscle pain during their time in the study. Sixteen (16) of the 63 participants who reported unexplained muscle pain did not discontinue drug or inform a physician, although one did discontinue from the study at some point. Of the remaining 15, 8 provided a reason for not discontinuing or informing a physician. The reasons included two Users who said that they, in fact, did talk to a doctor and 2 who knew what was causing the problem. One individual stated that the problem stopped after a short time, one participant said the problem was minor, and 2 provided a reason categorized as "other."

Level of Assistance and Physician Interaction

Of the 1048 users for which the level of assistance was known, 791 (75%) received some assistance, and 58% of the 791 talked to a physician about MEVACOR™ OTC before initiating use. Assistance may have included interactions with a study coordinator acting as a pharmacist, or the Heart Health System personnel administering eligibility assessment questions, or a physician, or all of the above.

Of the 360 participants in the Post-CUSTOM survey who used other OTC products, 82% (296) believed that MEVACOR™ OTC treated a more serious health problem than the other OTC products they used.

Comments:
The data from the study show that the majority of consumers needed a health care provider's advice when making a decision to use lovastatin. It is clear from the data that those who talked to their physicians achieved more accurate self-selection than those who did not. This is of concern if this product were to become available OTC.

Subgroup Analysis of User Decisions

The following demographic groups were evaluated:

- Males versus Females
- Caucasians versus Non-Caucasians
- Younger users (age < 65 years) versus Older users (age ≥ 65 years)
- Low Literacy Users versus Literate Users

Although behavior was generally similar across all demographic groups, the sample sizes of some subgroups were small. Therefore, these data may not be generalizable to non-CUSTOM-related groups. Table 15 below summarizes adherence to label benefit criteria by demographic subgroups, based on the sponsor's DAP analyses.

Table 15. Adherence to Label Benefit Criteria by Demographic Subgroups

Demographic Subgroups	Adherence to Label Benefit Criteria (AL†)		
	Initial Use Decision % (N)*	Follow-up Cholesterol Test % (N)*	De-selection due Emergent Events for 26 Weeks % (N)**
Males	42.8% (269/629)	32.8% (206/629)	61.1% (121/198)
Females	50.2% (216/430)	32.6% (140/430)	63.3% (107/168)
Caucasians	46.7% (405/867)	35.2% (305/867)	62.5% (193/309)
Non-Caucasians	42.4% (78/184)	20.6% (38/184)	60.0% (33/55)
Age ≥ 65 years	56.8% (154/271)	43.9% (119/271)	62.7% (64/102)
Age < 65 years	42.0% (331/788)	28.8% (227/788)	62.1% (164/264)
Low Literacy	41.2% (56/136)	29.4% (40/136)	60.5% (26/43)
Non Low Literacy	46.6% (428/918)	33.2% (306/923)	62.5% (200/320)
Total	45.8% (485/1059)	32.7% (275/1059)	62.3% (228/366)

* Number of subjects for each category may differ depending on the number of subjects with missing data
** Denominator for the subgroups is a total number of subjects in a subgroup experiencing emergent event
† AL: According to label, includes those designated as physician override

Comments:
There were some differences among the analyzed demographic subgroups; however, none of them were statistically significant. With respect to initial use decision and follow-up cholesterol test, greater percentages of elderly Users compared to those < 65 years of age, and normal literacy compared to low literacy Users adhered to label benefit criteria. More Caucasians compared to non-Caucasian Users adhered to the label benefit criteria with respect to the follow-up cholesterol test. The overall adherence to the label was of concern, ranging from 45.7% for the initial self-selection to 32.9% by the end of the study (de-selection by Week-26) (see Table 16).

Were the ancillary materials available to the Users helpful?
In addition to the self-selection and compliance with treatment, the sponsor assessed usefulness of additional materials used in the study. A total of 967 Users responded to questions about what materials they looked at, and their assessment of the usefulness of the items. Most Users reported that the shelf display materials were very or somewhat useful (893/967, 92.3%). The most viewed product package materials were the drug package (903/967, 93.4%) and the Quick Start Guide (828/967, 85.6%), followed by the booklet (727/967, 75.2%) and package insert (542/967, 56%).

All of the package materials were rated as very or somewhat useful by almost all Users who read them (93.5%-98.5%). Only 124 (12.8%) of the 967 Users looked at the product website, but most of those that went on the website felt it was very or somewhat useful (103/124, 83.1%). Most of the 258 Users who reported joining the Heart Health Program looked at the newsletters (186/258, 72.1%), and 88.7% (165/186) of those that looked at the newsletters reported that the newsletters were very or somewhat useful. Of the 241 Users who reported receiving the video; 166 viewed it, and 87.3% (145/166) of those who viewed the video believed it was very or somewhat useful.

Users in this study were concerned about their cholesterol. Eighty-one percent of the 1030 Users who completed the end-of study behavior questions said they had discussed their cholesterol

concerns with a physician at some time: 62% within the year before starting the study, and 74% within two years of starting the study. More than half (56.4%) of the 1030 Users reported that they talked to a physician about their taking MEVACOR™ OTC while they were participating in the study.

Of the 2111 non-purchasers 22% (471) reportedly talked with their physician about using the product before deciding not to purchase, and of the 1205 purchasers 42% (504) said they talked with their physician about using the product before deciding to take the first dose.

A total of 31% (359/1146) of participants who had high LDL-C or high triglycerides and responded to the question about physician interaction reported that they interacted with a physician regarding MEVACOR™ OTC.

Comments:
Even though the majority of participants liked additional study materials, their behavior did not translate into good decision making. Data show that consumers had difficulty making a decision themselves to use MOTC. Out of the 485 subjects who self-selected appropriately (the sponsor's definition "according to label") 86% stated that they consulted with a physician, and only 68 (14%) made a correct decision on their own. Forty-two percent (42%) of the participants in the study did not take the first dose until they obtained advice from their physician. The sponsor states that these data suggest that the MEVACOR™ OTC Self-Management System motivated participants to interact with their physician regarding cholesterol management. This may be true for those subjects who have a personal physician, but it is not clear what consumers without health insurance or those who do not have a personal physician would do. Data on how consumer behavior was influenced by having access to a learned intermediary was not collected. It is unclear how the sponsor would implement this OTC Self-Management System outside the boundaries of this clinical study.

Physician Referral Follow-Up Cohort

A total of 127 participants received the advice and follow-up letter recommending that they contact their physician because they had LDL-C > 170 mg/dL or triglycerides > 200 mg/dL, and had either sought assistance at the point of initial purchase, or incorrectly purchased the product but sought post-purchase assistance. Fifty-eight (58) of the 127 provided follow-up information. Nearly two-thirds (36/58) of them reported they had visited or called their physician since their visit to the study site, and most of those (32/36) discussed cholesterol management with their physician. Of the 32 participants who discussed cholesterol management with their physician, 20 reported that they did so because of the advice/letter they received from the Physician Referral portion of the MEVACOR™ OTC Self-Management System in the study. About four-fifths (25/32) of the participants who discussed cholesterol management with their physician were placed on a new treatment plan, and about three-quarters (19/25) of those placed on a new treatment plan were prescribed a lipid-lowering drug. The drug was a statin in 18 of the 19 participants who received a prescription for a lipid-lowering drug.

Other Behavior Assessments

At the final study site visit, Users of MEVACOR™ OTC were asked if they ever made an effort to lower their cholesterol by eating healthy foods or exercising. Ninety-seven percent of Users

(1030/1061) provided a response to this question, and 79.6% (820/1030) had previously tried to lower their cholesterol by eating healthy foods or exercising.

When the Users were asked if they changed their diet and exercise habits while taking MEVACOR™ OTC, the majority responded that they did not change their eating (57.6%) or exercise (70.7%) habits; 40.3% reported eating healthier foods, and 23.7% reported exercising more. A total of 2.1% reported eating less healthy foods, and 5.6% reported exercising less.

The MEDFICTS Dietary Assessment scores at pre-treatment and post-treatment collected to determine if Users maintained a healthy diet confirmed the above observations:

- At baseline, 82% (677/820) of Users were already following a Step 1 (cholesterol intake < 300 mg/day) or Step 2 diet (cholesterol intake < 200 mg/day).
- 56% (80/143) of Users who had not been on either a Step 1 or Step 2 diet prior to the study had MEDFICTS scores that indicated they were following a Step 1 or 2 diet by the end of the study.
- 48% (140/292) of Users who were following a Step 1 diet at baseline were following a Step 2 diet by the end of the study.
- 83% (318/385) of Users who were following a Step 2 diet at baseline maintained their Step 2 diet throughout the study

Comment:
The data suggests that participants of the study were relatively highly motivated to follow a healthy lifestyle prior to and during the study.

What was the change in cholesterol with lovastatin 20 mg?
Data summarizing available information about percent change from baseline in cholesterol values is summarized in Table 16. Additional details concerning the data for LDL-C are presented in Table 17. The median reduction in LDL-C achieved in the population who used MOTC was 20.6%. Further reduction, 25.2%, was observed in the cohort of 243 Users that fasted at the baseline and the end of study.

Table 16. Summary of LDL-C, HDL-C, and Total Cholesterol

		Baseline	End of Study	% Change from Baseline
LDL-C	N	931	878	811
	Median (mg/dL)	155	120	-20.6
	25th, 75th Percentiles	132, 180	100, 144	-34.4, -5.0
HDL-C	N	1015	932	906
	Median (mg/dL)	45	45	0
	25th, 75th Percentiles	37, 55	37, 54	-9.5, 10.0
Total-C	N	1053	962	957
	Median (mg/dL)	243	204	-14.6
	25th, 75th Percentiles	218, 271	179, 232	-24.9, -4.6

Table 17. Summary of LDL Cholesterol by Fasting Status

	Fasting Status*	N	Median (mg/dL)	25th, 75th Percentiles
Baseline (n=931)	Fasted	378	165	142, 188
	Not fasted	551	146	126, 173
	Unknown	2	198	NA
End of Study (n=878)	Fasted	608	118	100, 142
	Not fasted	267	122	102, 148
	Unknown	3	133	NA
% Change from Baseline (n=811)	FF	243	-25.2	-38.4, -9.0
	NF	324	-19.7	-32.4, -3.3
	FN	83	-20.7	-37.7, -8.8
	NN	156	-16.5	-32.2, -2.2
	Unknown	5	-25.8	NA

* FF: fasted both at baseline and End of Study; NF: did not fast at baseline and fasted at End of Study; FN: fasted at baseline and did not fast at End of Study; NN: did not fast at either time point.

The distribution of the 1059 Users by baseline and end of study LDL-C is presented in Table 18. Of the 878 Users with a known LDL-C value at the end of the study and who had known LDL-C value at baseline, 548 (62.4%) were at the LDL-C goal level of < 130 mg/dL.

Table 18. Counts of LDL-C Results: Baseline vs. End of Study (Users)

	End of Study						
Baseline	< 100	100-129	130-159	160-170	>170	Unknown	**Total**
< 100	38	17	3	0	1	6	65
100-129	47	58	26	1	2	10	144
130-159	69	123	54	10	10	44	310
160-170	10	31	22	10	7	15	95
> 170	28	88	84	22	50	45	317
Unknown	16	23	16	6	6	61	128
Total	208	340	205	49	76	181	1059

Comments:
The efficacy information gathered during the study has to be interpreted with caution because there was no control group and compliance with the treatment was not enforced or monitored. There was a higher proportion of people at baseline with non-fasting cholesterol values than at the end of the study.

The study results show that the majority of the enrolled subjects had lowered their LDL cholesterol level. According to the sponsor's definition, a total of 548 (62.4%) Users with known LDL-C levels at the end of the study achieved the LDL-C goal (< 130 mg/dL) by the end of the study. This number includes 160 Users whose LDL-C level at baseline was < 130 mg/dL and 39 Users whose LDL-C level at baseline was unknown. We do not know what benefit, if any this subpopulation derived from the treatment. If we deduct these 199 (160+39) Users, the percentage of Users achieving benefit by the end of the study decreases to 39.7% (349/878).

4.4 Conclusions

The majority of Users of Mevacor in the study lowered their cholesterol.

With respect to behavior end-points of the study, the study results show poor consumer understanding of self-treatment of hypercholesterolemia. The majority (69%) of participants who made a decision to purchase Mevacor needed more information; 37% of purchasers did not know their cholesterol and 18% chose to use it. Of those who stated that they knew their cholesterol level, half could not identify it correctly. The most disturbing results are in self-selection. Over 80% of subjects in the study did not self-select appropriately, as defined by the label. Only 484 Users initially self-selected correctly according to the label and of those only 68 were able to do this without a physician's input. Nearly 1/3 of all Users (51% of women and 11% of men) had a 10-year risk for CHD < 5%. The pre-purchase screening measures may have enhanced the appearance of appropriate self-selection.

There was a relatively low compliance with follow-up cholesterol test rate; 63% of Users obtained at least one follow-up test during 6 months of the study, but only 33% obtained it within the specified time interval of 4 to 12 weeks. Only 26.6% of Users achieved the target LDL-C goal of < 130 mg/dL within 4 to 12 weeks of the study, and an additional 9% achieved the goal outside the 4 to 12 week time period. Consumers were restricted to only 4 cartons of Mevacor purchase, which may have also influenced the efficacy results.

Of the 484 participants, who based on the sponsor's DAP analysis self-selected according to the label, 297 achieved the LDL-C goal (< 130 mg/dL) at the end of the study. Of the 68 participants, who initially self-selected correctly according to the label criteria without a physician interaction, 41 achieved the target LDL-C goal (< 130 mg/dL) at the end of the study. Thus, of the 1059 Users, 41 (4%) correctly, independently achieved the target LDL-C < 130 mg/dL.

5 INTEGRATED REVIEW OF SAFETY

This section of review will focus on safety data gathered during the Actual Use Study #084.

5.1 Methods and Findings

All 1061 Users who reported taking at least one dose of study medication were included in the assessment of safety.

Table 19 displays the number of participants on study drug, by dose and duration of treatment. The range of days on drug displayed in Table 25 does not actually mean that subjects were on drug all of that time; rather, it indicates that subjects had drug in their possession for the specific number of days. The study drug therapy stop date was not recorded by or asked of the participant. The last date the participant returned drug to the study site was used in lieu of a study drug therapy stop date in the calculation of duration of treatment. If a participant's final study drug was returned via the mail, then their therapy stop date was the date that drug was received by the investigator. For those participants that were lost to follow-up, their therapy stop date was equal to the last date of contact (i.e., last study site visit or phone call). In addition, participants did not record the number of 20 mg tablets they took each day. The mean duration of exposure to lovastatin 20 mg "based on the therapy stop date" was 148.3 days (range 1 to 290 days).

Table 19. Number of Patients on Study Drug and Duration of Treatment

	1 to 28 days	29 to 56 days	57 to 84 days	85 to 112 days	113 to 140 days	141 to 168 days	≥ 169 days	Total
Lovastatin 20 mg	53	79	50	100	43	80	656	1061

Comments:
The methodology to assess drug exposure is flawed. The study duration was relatively short considering that the drug is to be used indefinitely. It is not clear when the stop treatment date was relative to the user's last dose of the study drug; this information was not collected. There were no diaries used in the study. Data on drug accountability was not provided by the sponsor. Therefore, the extent of exposure to the study drug may be overestimated and not reliable. This makes any safety signals even more relevant and also means that the study may not have been able to provide as much information on safety in actual use as it may appear to do.

At the agency's request, the sponsor submitted additional data on the number of tablets participants purchased during the study. The extent of exposure by the number of tablets dispensed to participants is much lower than the sponsor's initial calculations. The mean duration of exposure "based on the number of tablets dispensed" becomes 122 days assuming no more than one tablet was used per day. When the calculation takes into account the number of tablets participants returned at their last visit, the mean duration of exposure becomes 112.9 days. Distribution of subjects by the number of tablets dispensed is as follows:

- *294 (28%) - 45 tablets,*
- *176 (17%) - 90 tablets,*
- *132 (13%) - 135 tablets,*
- *454 (43%) - 180 tablets,*
- *3 (0.3%) - 225 tablets.*

Table 20 summarizes the number (%) of subjects with clinical adverse experiences, drug-related adverse experiences, serious adverse experiences, serious drug-related adverse experiences, and adverse experiences that caused discontinuation from the study.

Table 20. Adverse Experience Summary

Number (%) of subjects	Lovastatin 20 mg (N=1061)	
	N	(%)
With one or more adverse experiences	452	42.6
With no adverse experience	609	57.4
With drug-related adverse experiences	180	17.0
With serious adverse experiences	28	2.6
With serious drug-related adverse experiences	1	0.1
Who died	1	0.1
Discontinued due to adverse experiences	125	11.8
Discontinued due drug-related experiences	102	9.6
Discontinued due to serious adverse experiences	7	0.7
Discontinued due to serious drug-related experiences	1	0.1

Overall, 452 (42.6%) subjects had at least one adverse experience; of these, 180 had drug-related experiences as determined by an investigator. Twenty-eight reported serious adverse experiences, one of which was drug-related. Seven of the 28 discontinued from the study due to the serious adverse experiences, one of which was drug related.

One of the non drug-related serious adverse experiences resulted in death. One hundred twenty-five (11.8%) patients discontinued drug therapy due to an adverse experience. Of these, 102 discontinued drug therapy due to a drug-related adverse experience.

5.1.1 Deaths

One death occurred in the study. This was a 50-year-old male with a history of atrial fibrillation and high blood pressure who developed a massive stroke. The patient began a regimen of lovastatin 20 mg, once daily on 07-DEC- 2002. Concomitant therapy included Coumadin. On 06-APR-2003 (Day 121 of treatment) the patient experienced a stroke and was hospitalized. Upon hospitalization the patient was administered alteplase, recombinant tissue plasminogen activator, and his lovastatin therapy was discontinued. Subsequently, the patient experienced massive bleeding into the brain and was placed on life support. On 08-APR-2003 the patient was declared brain dead by his attending physician. The patient was taken off all life support and died within minutes. The reported cause of death was a massive stroke. The reporting physician determined that the massive stroke and subsequent death were probably not related to study drug therapy.

5.1.2 Other Serious Adverse Events

There were 30 participants who experienced at least one serious clinical adverse event while on lovastatin 20 mg, of which 2 were reported as pre-study adverse experiences. Seven of the 28 participants, had serious adverse experiences that led to discontinuation of drug therapy; however only 1 of these events (Hypersensitivity NOS), was assessed as being drug related.

5.1.3 Dropouts and Other Significant Adverse Events

A total of 360 (33.9%) subjects out of 1061 Users discontinued prior to the end of the study. One hundred twenty-five (11.8%) reported that they discontinued therapy due to a clinical adverse experience (see Table 26). Of these, 102 (9.6 %) adverse experiences that resulted in

discontinuation were considered by the study investigator to be drug related. Seven (0.7%) subjects discontinued study therapy due to serious adverse experiences. Fifteen participants reporting discontinuation of therapy due to a clinical adverse experience continued in the study to completion. These participants were counted as "completers" of the study because they returned for their final scheduled visit. As mentioned earlier, the date of the last dose taken was not recorded.

5.1.3.1 Overall profile of dropouts

The following is a disposition of the 360 User dropouts from the study:

Adverse clinical experience	108 (30.0%)
Deviation from protocol occurred	2 (0.6%)
Lost to follow-up	13 (3.6%)
Moved	18 (5.0%)
Withdrew consent	157 (43.6%)
Discontinued for other reasons	53 (14.7%)
Uncooperative	9 (2.5%)

In addition to 360 discontinued subjects, there were 50 subjects with no known use decision who were lost to follow-up after the initial purchase of the study drug.

5.1.3.2 Adverse events associated with dropouts

Adverse experiences resulting in discontinuation of therapy are summarized by body system in Table 21.

Adverse experiences resulting in study therapy discontinuation most often occurred in the categories of Musculoskeletal and Connective Tissue Disorders (6.3%) and Gastrointestinal Disorders (2.8%). The most frequently reported adverse experiences resulting in study therapy discontinuation were Myalgia (3.7%) and Arthralgia (1.2%). Thirty-nine subjects discontinued because of myalgias. Of these, 30 (77%), reported that they recovered by the time the trial concluded. Of the 9 participants with unresolved muscle symptoms, 1 reported 2 events of myalgia (1 event resolved by the end of the study and the other did not). This participant was counted among 9 participants that did not recover from their symptoms by the end of the study. Eight (21%) of the 39 who discontinued due to myalgias also had a previous history of muscle pain and of these participants, 6 had resolution of their muscle symptoms by the end of the study.

Table 21. Number (%) of Subjects Discontinued Therapy due to Clinical Adverse Experience by Body System

	Users (N=1061) N (%)
Subjects with one or more adverse experience	125 (11.8)
Subjects with no adverse experience	936 (88.2)
Cardiac Disorders	2 (0.2)
Ear and Labyrinth Disorders	1 (0.1)
Gastrointestinal Disorders	30 (2.8)
General Disorders and Administration Site Conditions	14 (1.3)
Immune System Disorders	1 (0.1)
Infections and Infestations	1 (0.1)
Investigations	4 (0.4)
Metabolism and Nutrition Disorders	1 (0.1)
Musculoskeletal and Connective Tissue Disorders	67 (6.3)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	1 (0.1)
Nervous System Disorders	15 (1.4)
Psychiatric Disorders	4 (0.4)
Reproductive System and Breast Disorders	3 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	5 (0.5)
Skin And Subcutaneous Tissue Disorders	8 (0.8)
Vascular Disorders	4 (0.4)

5.1.3.3 Other significant adverse events

There were no other safety issues associated with dropouts.

5.1.4 Common Adverse Events

Table 22 summarizes clinical adverse experiences by body system that occurred at an observed incidence of ≥ 2%. Although the same subject may have had 2 or more adverse experiences in a body system, the subject is counted only once within a body system category total.

Table 22. Number (%) of Subjects with Adverse Experiences by Body System (Incidence ≥ 2%)

	Lovastatin 20 mg N=1061	
	n	%
Subjects with one or more adverse experiences	452	42.6
Subjects with no adverse experience	609	57.4
Gastrointestinal Disorders	94	8.9
General Disorders and Administration Site Conditions	40	3.8
Infections and Infestations	89	8.4
Injury, Poisoning and Procedural Complications	24	2.3
Musculoskeletal and Connective Tissue Disorders	184	17.3
• Arthralgia	41	3.9
• Myalgia	74	7.0
• Pain in extremity	21	2.0
Nervous System Disorders	44	4.1
Psychiatric Disorders	22	2.1
Respiratory, Thoracic, and Mediastinal Disorders	37	3.5
Skin and Subcutaneous Tissue Disorders	27	2.5
Vascular Disorders	22	2.1

The most common types of adverse experiences were those occurring in the Musculoskeletal System (17.3%). The most frequently reported adverse experiences were myalgia, arthralgia, and pain in extremity.

5.1.4.1 Eliciting adverse events data in the development program

Adverse event information during the actual use study was collected in several ways:

- Subjects who purchased only one box of the study medication and did not return to the study site by Week-12, and those users that did not return for the Week-26 visit, were contacted by the nurse-investigator.
- Participants had an opportunity to return to the study site for repurchase of medication at which time they were asked by the study investigator if they experienced any discomfort since the last visit.
- At the last visit (Week-26) all participants were given a questionnaire which included questions about the adverse experiences.

All serious adverse events were reported to the study physician at the toll-free physician services.

5.1.4.3 Incidence of common adverse events

The most frequently reported adverse experiences were myalgia, arthralgia, and pain in extremity.

5.1.4.4 Common adverse event tables

There were a total of 890 adverse events reported during the study. The most common adverse events by frequency (>1%) irrespective to relationship to the study drug in decreasing incidence are listed in Table 23 below.

Table 23. Most Common Adverse Events (>1%) Reported During the Course of the Study

Adverse Event by Preferred Term	Number of AEs (N = 1061) N (%)
Myalgia	95 (9.0%)
Arthralgia	52 (4.9%)
Pain in extremity	27 (2.6%)
Flatulence	21 (2.0%)
Diarrhea NOS	19 (1.8%)
Headache	18 (1.7%)
Back pain	17 (1.6%)
Sinusitis NOS	15 (1.4%)
Muscle weakness NOS	15 (1.4%)
Hypertension NOS	15 (1.4%)
Dizziness	15 (1.4%)
Rash NOS	14 (1.3%)
Dyspepsia	13 (1.2%)
Cough	13 (1.2%)
Abdominal pain upper	13 (1.2%)
Chest pain	11 (1.0%)
Bronchitis	11 (1.0%)

5.1.4.5 Identifying common and drug-related adverse events

Table 24 (Appendix VI) displays clinical adverse experiences determined by the investigator to be possibly, probably, or definitely related to study medication. Although the subject may have had 2 or more adverse experiences in a body system, the subject is counted only once within a body system category total.

There was a relatively low incidence of drug-related clinical adverse experiences in each body system category except for "Musculoskeletal and Connective Tissue Disorders (8.8%)," and "Gastrointestinal Disorders (5.4%)." The most frequently reported drug-related clinical adverse experiences were myalgia (5.4%), flatulence (1.7%), arthralgia (1.5%), headache (1.2%), and muscle weakness (1.1%).

Comment:
CPK levels were not measured in subjects developing muscle weakness or pain. This is one of the deficiencies of the study.

5.1.4.6 Additional analyses and explorations

The sponsor analyzed the overall distribution of subjects who reported an adverse experience and those with specific drug-related clinical adverse experiences by the subject's self-selection and

de-selection behavior classifications. There were some numerical differences in the incidence of subjects with drug-related clinical adverse experiences in the Musculoskeletal and Connective Tissue Disorder body system category. There were higher proportions of Users with drug-related musculoskeletal adverse events in the MUSM NAS (not acceptable safety) subgroup compared to the MASM AL (according to label) subgroup based on their self-selection and de-selection behavior. However, no conclusions can be drawn from the observed differences since there were no placebo or control groups, and the number of events in each subgroup was relatively small.

5.1.5 Less Common Adverse Events

An assessment of the incidence of less common adverse events in the actual use study is not possible because:

- the number of subjects treated in the actual use trial is relatively small to detect infrequent adverse events
- there was no control group, and
- methodology for assessment of extent of exposure and compliance with the treatment were not reliable.

5.1.6 Laboratory Findings

There were no serious laboratory adverse experiences.

The only laboratory safety test required by the protocol was ALT measurements.

Of the 1061 subjects that took at least 1 dose of study medication, 986 subjects were included in the population that had a laboratory test post-baseline. Five (0.5%) of the subjects had one or more laboratory adverse experiences during the study. The laboratory adverse experience profile is summarized in Table 25.

Table 25. Laboratory Adverse Experience Summary

	Users (N=1061)	
Number (%) of subjects	N	%
With at least one laboratory test post baseline	986	
With one or more adverse experiences	5	0.5
With no adverse experience	981	99.5
With drug-related adverse experiences	4	0.4
With serious adverse experiences	0	0.0
With serious drug-related adverse experiences	0	0.0
Who died	0	0.0
Discontinued due to adverse experiences	1	0.1
Discontinued due to drug-related adverse experiences	1	0.1
Discontinued due to serious adverse experiences	0	0.0
Discontinued due to serious drug-related adverse experiences	0	0.0

Drug-related increased ALT (Normal Range 10-40 U/L) occurred in 4 out of 986 (0.4%) subjects (Table 31). One of them discontinued due to an ALT of 59 U/L (ULN = 40 U/L), and an AST of 53 U/L (ULN = 40 U/L). No follow-up was required as per protocol. Three subjects had an ALT that was > 3 x ULN at the end of the study. All 3 had a repeat ALT: 2 on the repeat test had values below 1 x ULN and the third had a value of 43 U/L.

Comment:
Although follow up was not required, it appears that it was done for the 3 subjects who did not discontinue.

Table 26 summarizes the ALT values for all users in the study.

Table 26. Summary of Serum Alanine Aminotransferase (ALT) Values

	End of Study					
Baseline	ALT≤1xULN	1xULN<ALT ≤2xULN	1xULN<ALT ≤2xULN	ALT>3xULN	Unknown	Total
ALT≤1xULN	860	46	3	2	96	1007
1xULN<ALT≤2xULN	20	19	3	1	6	49
Unknown	5	0	0	0	0	5
Total	885	65	6	3	102	1061

At baseline testing, 1007 of 1061 (94.9%) subjects had an ALT test result less than or equal to 1 x ULN (40 U/L). Forty-nine (4.6%) had ALT elevations above 1 x ULN at baseline, but were less than or equal to 2 x ULN. There were no Users in the study with a baseline ALT > 3xULN, as this was an exclusion criterion. Of those that entered the study, there were 5 subjects who did not have a baseline ALT value due to investigator or Cholestech machine error. All 5 of them had an End of Study ALT ≤ 1 x ULN.

There were 3 subjects that self-selected to purchase MEVACOR™ OTC, but they were prohibited from leaving the study site with drug as their ALT was > 3 x ULN (135, 154, and 189 U/L). As already discussed, three subjects had an ALT > 3 x ULN for the End of Study ALT (121, 151, and 134 U/L). When re-tested at their next visit, all the ALTs had decreased (22, 29, 43 U/L).

Comment:
Since people with ALT > 3 x ULN were excluded, this study could not provide safety data on this cohort if they had chosen to self-select. This is a concern since there are people with asymptomatic LFT elevations who may choose to take Mevacor if it were sold OTC.

The mean ALT change from baseline was 3.9 U/L (±10.5 S.D.). As shown in Table 27, 952 subjects were included in both the baseline and end of study calculations. Change from baseline is calculated using the end of study value which was collected between 1 and 290 days.

Table 27. Serum Alanine Aminotransferase (ALT) Change from Baseline

	ALT (U/L)		
	N	Mean (U/L)	Standard Deviation (U/L)
Baseline	1054	23.2	8.9
End of study	957	26.9	12.3
Mean change from baseline	952	3.9	10.5

No predefined limit of change was established for laboratory adverse experiences.

5.1.7 Withdrawal Phenomena and/or Abuse Potential

There are no published reports on the recreational use of lovastatin. Furthermore, there are no reports to the Worldwide Adverse Experience System (WAES) Database where lovastatin was the primary suspect agent that could be construed as evidence of drug abuse. Based on the drug's pharmacological properties and the extensive knowledge of the drug's clinical adverse experience profile, there is no information to suggest that the drug has the potential to be abused.

Comment:
There are no data that the use of lovastatin has a potential for abuse or withdrawal phenomena.

5.1.8 Human Reproduction and Pregnancy Data

No new data on human reproduction and pregnancy were submitted to this application. Lovastatin is a Pregnancy Category X drug. In a submission to the prescription lovastatin NDA 19-643/S-061 dated March 31, 2004 the sponsor requested to change lovastatin's Pregnancy Category from X to C. The request was denied due to insufficient data to support the change. Even though the proposed OTC label targets women at least 55 years of age, the results of actual use study #084 show that 37.4% of women below this age chose to use the drug.

5.1.9 Overdose Experience

Overdose information on lovastatin is summarized from three sources:

1. exposure and/or overdose reports received at regional poison control centers and summarized in the Toxic Exposure Surveillance System (TESS) by the American Association of Poison Control Centers (AAPCC);

2. cases of deliberate or accidental overdose reported to Merck through the Worldwide Adverse Experience System (WAES) Database; and
3. published literature.

The term "exposure" is used throughout this section to identify calls or reports to poison control centers or to the WAES. Not all of these exposure reports were actually true cases of overdosage.

The sponsor states, that from all sources, including the published literature, there have been no known reports of overdosage with a fatal outcome involving lovastatin as the sole agent. There are 4 known cases with fatal outcome involving potential overdose with lovastatin and concomitant agents.

There were 4 deaths reported to AAPCC from 1988 through 2002 involving lovastatin taken with other agents. There have been no fatal overdose exposure cases reported to AAPCC involving lovastatin as the sole agent.

The first fatal exposure occurred in a 28-year-old male patient with a history of paranoid schizophrenia and polysubstance abuse. The patient presented to the clinic with hematemesis, mild abdominal pain, nausea and vomiting following 4 days of anorexia. His medications included lovastatin 20 mg, niacin 1000 mg 3 times a day, aspirin 325 mg 3 times a day, and NAVANE™ (thiothixene) 40 mg at nighttime and 10 mg as needed for agitation. He also took COGENTIN™12 mg at bedtime and 150 mg of desipramine. The patient was known to hoard all his medicines, especially niacin. A serum screen showed desipramine and acetaminophen at a concentration of 2 mcg/mL. Laboratory data showed elevation in AST (6700 units) and ALT (7900 units) with a bilirubin of 6.4 mg/dL. The patient's hospital course was that of fulminant hepatic failure with coma, seizures, renal failure, and coagulopathy. He expired 36 hours after admission. Postmortem examination showed massive acute hepatic necrosis with acute renal tubular necrosis. AAPCC identified nicotinic acid as the primary agent and lovastatin as the secondary agent and categorized the exposures as an adverse drug reaction.

The second fatal exposure was that of a suicide in a 42-year-old male who ingested ~80 pills identified as controlled-release diltiazem and lovastatin (dose not specified) 7 hours prior to hospitalization. The patient's initial vital signs included a blood pressure of 50 to 60 mm Hg and a pulse of 61 beats/minute. Serum chemistries were normal except for hypokalemia (3.2 mEg/L). Following calcium gluconate, glucagon, external pacing, and initiation of a 20-mcg drip of dopamine, blood pressure improved to 110 mm Hg and pulse to 71 beats per minute. The patient was transferred to a critical care unit where he went into asystole and died shortly after arriving. Toxicology laboratory tests for drugs of abuse, acetaminophen, and aspirin were negative. AAPCC identified diltiazem as the primary agent in the exposure and lovastatin as the secondary agent.

The third fatal exposure was that of a suicide in a 75-year-old male with a recent diagnosis of Alzheimer's disease. He ingested the following agents in a suspected suicide attempt: lorazepam, hydroxyzine hydrochloride, cimetidine, lovastatin (dose not specified), hydrochlorothiazide, and ethanol. The patient was found pulseless and apneic by paramedics.

Emergency treatment included vasopressors, fluids and electrolytes, and anti-arrhythmic therapy. QRS was 0.04 seconds, potassium was 1.6 mmol/L, and bicarbonate was 19 mmol/L. Acetaminophen and salicylate were not detected and blood alcohol was 95 mg/dL. Despite maximal support, he developed renal failure with elevated CPK (2033 IU/L). Two days following admission he became hypotensive and a decision was made to withdraw life support. AAPCC identified lorazepam as the primary agent in the exposure and lovastatin as a secondary agent.

The fourth fatal exposure occurred in a 78-year-old male patient with a history of cerebrovascular accident (CVA) with left hemiparesis, diabetes mellitus, and depression. In an apparent suicide attempt, the patient ingested unknown quantities of the following agents: metformin, glipizide, acarbose, terazosin hydrochloride, lisinopril, gabapentin, hydroxyzine hydrochloride, dipyridamole, lovastatin (dose not specified), and finasteride. He was intubated by EMS and transferred to a critical care unit. His family confirmed that the patient's medicine bottles had been emptied. The patient was acidotic (blood pH = 6.9; bicarbonate = 3 mEq/L) and sodium bicarbonate therapy was administered. Despite treatment, the patient's acidosis worsened. He became more hypotensive, bradycardic, and hypothermic and was treated with multiple vasopressors. The patient subsequently became hypoglycemic (blood glucose <20 mg/dL) and developed lactic acidosis (26 mmol/L). His family declined hemodialysis and treatment for low blood sugar and the patient expired. AAPCC identified metformin as the primary agent and lovastatin as a secondary agent.

Considering all exposure categories (lovastatin single and multiple agents), accidental (unintentional) events represented the largest category for reason for exposure according to data collected by AAPCC for the 1988 through 2002 time period. The inappropriate use of lovastatin with other agents for suicide attempts or other misuse or abuse was very uncommon for the years 1988 through 2002, representing ~7% of the total exposures (4612) reported to regional poison control centers.

With single-agent exposures of lovastatin, accidental exposures also represented the largest category for reason for exposure. Of the total exposures for the years 1988 through 2002, ~95% were listed as accidental (unintentional). The misuse of lovastatin (single agent) as a drug involved in suicide attempts or other misuse or abuse was very uncommon, representing < 3% of the total single-agent exposures (3254) reported to poison control centers.

AAPCC defines a medical outcome as a clinical effect in a patient that resulted in one of the following: no effect, minor effect, moderate effect, major effect, death, and an "other" category. During the 1988 through 2002 time period, the largest category of outcomes (54.8% of total exposures) was "other," which includes in part the sub-classifications of "not followed, nontoxic" and "not followed, minimal clinical effects." The combined categories of "no effect" or "minor effect" represent ~43.2% of the total reports for the years 1988 through 2002. There were 17 reports with a "major" effect (0.4% of the total reports).

For lovastatin single-agent exposures, the largest category of outcomes (59.1% of total exposures) for the 15-year period 1988 through 2002 was the category "other". The largest subcategories in this group were "not followed, nontoxic" and "not followed, minimal clinical

effects". The combined categories "no effect" or "minor effect" accounted for ~40.5% (1319 patients) of the total outcomes. There were 11 patients who had moderate effects (0.9%).

There was 1 patient who had major effects that were considered life threatening or produced disability as a result of lovastatin exposure. This patient was a 64-year-old male who presented to the hospital with an adverse reaction of rhabdomyolysis while on lovastatin. The duration of clinical effects was not reported. Following treatment with intravenous fluids, the patient's symptoms resolved. Lovastatin was discontinued and the patient was released from the hospital. There have been no reports in the Toxic Exposure Surveillance System from 1988 through 2002 that identified an overdose fatality with lovastatin as the sole agent.

AAPCC began to tabulate the duration of clinical effects in overdose exposures beginning in 1993. The largest category within medical outcomes was identified as "other," which is a broad category designation that included predominately "not followed, nontoxic" and "not followed, minimal clinical effects." The second most common category of classification was "no effect."

With the lovastatin "all exposures" cases for the 1993 through 2002 time frame, the clinical effects considered moderate resolved in 1 month or less in the 51 cases where a duration was specified. In addition, 1 case with moderate outcome had a duration recorded as "anticipated permanent." The remaining 7 moderate cases had a duration of "unknown," "missing," or "invalid." A large majority of the moderate cases resolved in ≤ 3 days. Twelve of the 14 cases classified as "major" were evaluated for duration and resolved in ≤ 1 week.

With the single-agent lovastatin exposures for the 1993 through 2002 time frame, the clinical effects for those exposures identified as moderate resolved in ≤ 3 days in 6 cases and ≤ 1 week in 1 case, out of 7 cases where a specific duration was evaluated. In addition, 1 case with moderate outcome had a duration recorded as "anticipated permanent." The remaining 2 moderate cases had a duration of "unknown," "missing," or "invalid." There was 1 case where the clinical outcome was classified as "major" for the 1993 through 2002 time frame; the duration of clinical effect was not reported in this case.

AAPCC Tabulations of Specific Symptoms Associated With Lovastatin Exposures
The AAPCC began to tabulate specific symptoms associated with overdose exposures in 1993. In their tabulations and reports, the AAPCC refers to these symptoms as "clinical effects." The TESS database lists symptoms in 8 major body system categories (cardiovascular, dermal, gastrointestinal, heme/hepatic, neurological, ocular, renal, respiratory) and a miscellaneous category. The miscellaneous group identifies 18 additional symptoms, including "other." In total, the AAPCC database contains 118 separate symptom terms.

A patient with 2 symptoms (for example nausea and drowsiness) for a single exposure would have been counted under 2 different symptom terms. It is assumed that any one particular symptom (for example, tachycardia or vomiting) was tabulated only once for a particular patient for an overdose incident. Therefore, for purposes of calculating an estimate of the proportion of patients with a given symptom/sign, the assumption has been made that the count for a given symptom term equates reasonably well with the number of patients who reported to have had or were observed to have had that particular symptom. Finally, the data from AAPCC does not

identify patients who had more than one exposure in the same year or in multiple years. It is assumed that such a patient would be treated in the database as any other exposure case and counted again. All symptoms associated with lovastatin all exposures and lovastatin single-agent exposures, whether or not related to the exposure, were examined. There were 686 symptoms reported in association with 3285 all-exposures cases (single-agent plus lovastatin with other agents) and 216 symptoms associated with 2251 lovastatin single-agent exposures during the 10-year period 1993 through 2002. From an examination of all 8 major body symptom categories, there was no specific clustering of symptoms within a category associated with lovastatin single agent or lovastatin all exposures.

Based on the all-exposure category for the period 1993 through 2002, a reporting cutoff (number reported for a specific symptom ÷ number of exposures) of ≥ 0.4 % was selected for inclusion by the sponsor. All symptoms that were reported at a frequency of ≥ 0.4% among the "all exposures" and single-agent exposures are presented in Table 28. The denominator used in constructing this proportion was the total patients with an outcome over the 10-year period. In the miscellaneous effects category, the designation of "other" symptoms was tabulated because it had the greatest number of symptoms counts. Selected symptoms related to the potential of lovastatin to cause muscle toxicity (muscle weakness, rhabdomyolysis, CPK elevated) or hepatic dysfunction ("AST/ALT increase > 100 units < 1000 units" term and "AST/ALT >1000 units" term combined) were also tabulated under the heading of "selected symptoms." These selected symptoms are displayed regardless of the reporting rate (i.e., symptom included if there was at least one occurrence in the TESS database from 1993 through 2002).

Table 28. Number of Symptoms Associated with Lovastatin: All Exposures and Single Agent Exposures (Reporting Rate of ≥ 0.4%)

Symptom category	Symptoms	Total for 1993 through 2002 All Exposures N=3285		Total for 1993 through 2002 Single-Agent Exposures	
		N	%	N	%
Cardiovascular Effects	Bradycardia	15	0.5	0	0
	Hypotension	19	0.6	0	0
	Tachycardia	29	0.9	5	0.2
Dermal	Erythema/flushed	18	0.5	6	0.3
Gastrointestinal Effects	Abdominal pain	16	0.5	8	0.4
	Diarrhea	27	0.8	15	0.7
	Nausea	36	1.1	16	0.7
	Vomiting	54	1.6	19	0.8
Neurological effects	Agitation/irritable	17	0.5	6	0.3
	Confusion	17	0.5	5	0.2
	Dizziness/vertigo	28	0.9	8	0.4
	Drowsiness/lethargy	77	2.3	17	0.8
	Headache	10	0.3	4	0.2
Miscellaneous effects	Other	70	2.1	36	1.6
Selected signs and symptoms	AST/ALT increase	5	0.2	4	0.2
	CPK elevated	2	0.1	0	0
	Muscle weakness	9	0.3	3	0.1
	Rhabdomyolysis	3	0.1	2	0.1
Total symptoms		686	10.9	216	9.6

There were 3285 exposures involving either lovastatin as a single agent or lovastatin with other agents during 1993 through 2002. The symptom with the greatest number of reports was drowsiness/lethargy (2.3% reporting rate), followed by miscellaneous/other (2.1%). Other than drowsiness/lethargy, the most common CNS symptom was dizziness/vertigo (0.9%). The most common cardiovascular symptom was tachycardia at 0.9%. In the GI category, the proportions of patients with nausea, vomiting, and diarrhea were 1.1, 1.6, and 0.8%, respectively. During the time frame 1993 through 2002, there were 5 cases (0.2%) out of 3285 exposures of abnormal liver function tests (AST/ALT increased), 9 cases (0.3%) of muscle weakness, 3 cases (0.1%) of rhabdomyolysis, and 2 cases (0.1%) of CPK elevations. In general, the proportion of symptoms observed with all exposures (multiple- and single-agent) was somewhat higher than that observed with single-agent lovastatin exposures.

During the time frame 1993 through 2002, there were 4 cases of abnormal liver function tests (AST/ALT increased) reported out of 2251 exposures, as well as 3 cases of muscle weakness, and 2 cases of rhabdomyolysis.

Exposure of Lovastatin in Children < 6 Years of Age
From 1988 through 2002, there were 3001 accidental (unintentional) ingestions involving lovastatin (all exposures) in children < 6 years of age, of which 2342 were reports on lovastatin as a single agent. There were 5 additional exposures in this age group involving lovastatin (all exposures) for reasons other than accidental ingestion; 2 of these were reports on lovastatin as a single agent.

There were no deaths in children < 6 years old associated with overdose exposures due to lovastatin as a single agent or when ingested with other drugs. The largest category of medical outcome was "other," representing 49.6% of the total exposures for the years 1988 through 2002. After the "other" category, the next 2 largest categories of outcomes were the "no effect" category with 1422 cases (47.3%) of lovastatin ingestion (all exposures) and the "minor effect" category with 82 cases (2.7%) that were judged to have produced minor clinical effects. There were no cases judged to have a major clinical outcome, although there were 10 cases assessed to have moderate clinical outcome over the 15-year period beginning in 1988.

For the lovastatin single-agent exposures in children <6 years, the largest category of clinical outcomes was the "other" category, which represented 53.5% of all clinical outcomes for the years 1988 through 2002. The second largest category of clinical outcomes was "no effect" and this was 44.6% of all effects. There was 1 case in which the clinical outcome was moderate. No cases had major clinical effects and there were no deaths reported in children < 6 years of age as a result of lovastatin single-agent exposures.

2. WAES Data Review of Overdoses

The Worldwide Adverse Experience System is a Merck Research Laboratories database that compiles adverse experiences on Merck products including overdoses from around the world.

The sponsor searched the WAES database for reports of potential overdose with lovastatin by querying for the following preferred terms: accidental exposure, accidental overdose, accidental overdose (non-therapeutic agent or chemical), accidental overdose (therapeutic agent), accidental poisoning, alcohol poisoning, anticonvulsant toxicity, drug toxicity, drug toxicity NOS, ergot poisoning, exposure to toxic agent, exposure to toxic agent (non-occupational), gas poisoning, non-accidental overdose, overdose, overdose NOS, poisoning deliberate, prescribed overdose, or therapeutic agent toxicity. Since lovastatin was approved for prescription use in 1987 through 01-Nov-2003, there have been 41 spontaneous reports with one or more of these terms reported to Merck from health care professionals and entered into WAES. It should be noted that not all of these cases document actual instances of lovastatin overdose. Two of these reports involved overdoses of other drugs with lovastatin as a concomitant therapy taken at the therapeutic dose. Another report documents "possible acetaminophen toxicity," but does not include any indication that the patient was exposed to an overdose of lovastatin. A fourth report describes a patient who took a glyburide tablet rather than her customary lovastatin dose.

Among these 41 WAES reports are 6 cases with fatal outcome. Five of the 6 fatal outcome reports involved lovastatin exposure with concomitant drugs:
(1) an overdose of lovastatin and diltiazem in a suicide attempt;
(2) an overdose of warfarin with lovastatin taken at a therapeutic dose;
(3) an exposure to lovastatin (dose unknown) with possible acetaminophen toxicity;
(4) an overdose of lovastatin and other suspected therapies in an apparent suicide attempt, and
(5) an overdose of lovastatin and other suspected therapies in a suspected suicide attempt.
In the sixth case with fatal outcome, a 36-year-old female experienced 4 miscarriages while her husband was on treatment with lovastatin.

Three of the 6 cases were reported to AAPCC and were documented in the published literature. These 3 cases also have been discussed previously in the previous section of the review.

There is one additional case with fatal outcome that is not included among the 41 WAES reports discussed above, but was reported to AAPCC and published in the clinical literature. Information received in the published article has been entered into the WAES database, but the report was not identified by the overdose query since it did not contain any of the preferred terms defined by the search strategy. AAPCC identified nicotinic acid as the primary agent and lovastatin as the secondary agent and categorized the exposures as an adverse drug reaction.

Therefore, a total of 7 unique cases with fatal outcome have been identified that were either classified as "overdose" in the WAES query or reported to AAPCC (or both). In 3 of these cases, it appears that the patient was not actually exposed to an overdose of lovastatin. None of these 7 cases suggest a cause for concern with lovastatin OTC.

The remaining 35 cases identified as overdose in WAES were nonfatal reports. The amount of lovastatin involved in 11 exposure cases was unknown, and among the remaining cases, the reported amount of lovastatin taken varied from 10 mg to as much as 1040 mg in 2 cases, one of which reported no symptoms. The second case was a 3 year old female who accidentally ingested 1040 mg of lovastatin; back pain was the only symptom reported but the final outcome is unknown.

With regard to symptoms associated with lovastatin overdoses, there were no symptoms reported in 12 of the 35 cases. Symptoms related to skeletal muscle such as myositis, muscle pain, rhabdomyolysis, and laboratory findings of an elevated creatine phosphokinase were observed in 7 listed individuals, all of which involved lovastatin with other agents. The outcome of the exposure has also been tabulated and these data show that at the time of the report, 16 individuals had recovered/improved from the exposure and 17 individuals had the outcome listed as "unknown." Two patients had not recovered; other agents were involved in their overdose exposure.

Published Reports of Lovastatin Overdoses
Since lovastatin has been marketed through 01-Nov-2003, there have been 4 reports in the published literature of overdose in patients exposed to lovastatin. All 4 cases involved individuals who attempted suicide by ingesting lovastatin with concomitant drugs and were published in the Annual Reports of the AAPCC and are summarized in the previous section of the review.

Comments:
Data on overdose with lovastatin's supports its wide margin of safety. To date, there are no deaths reported due to a single overdose of lovastatin.

5.1.10 Postmarketing Experience

Postmarketing safety data will be reviewed by reviewers in the Division of Metabolic and Endocrine Drug Products.

5.2 Adequacy of Patient Exposure and Safety Assessments

The safety profile of lovastatin was extensively studied and characterized during its approval as prescription product, and since, in the post-marketing period. No new signals have appeared in the course of the Rx-to-OTC switch development program. The proposed OTC label contains all appropriate drug interaction warnings. However, use in OTC setting has the potential to result in unexpected adverse events in the future. Of great concern, is the potential use of lovastatin by women of childbearing age, particularly since many were Users in the CUSTOM study.

Use of lovastatin by consumers with LDL-C levels outside the range specified in the label, is also a safety issue. The risk/benefit ratio of this therapy for those with LDL-C below 130 mg/dL may be unfavorable. On the other hand, even though some benefit may be achieved for consumers with LDL-C above 170 mg/dL, the risk of treatment with a sub-therapeutic OTC dose of lovastatin is also unclear. Finally, consumers with underlying liver disease and those taking interacting medications also may be at risk. It is unclear how a consumer with asymptomatic liver disease would know not to use Mevacor.

5.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Safety data gathered from the Actual Use study is consistent with the safety profile of lovastatin as a prescription drug.

6 ADDITIONAL CLINICAL ISSUES

6.1 Dosing Regimen and Administration

The proposed nonprescription dose of lovastatin is 20 mg once daily with the evening meal. The usual recommended prescription starting dose is 20 mg daily with the evening meal. Single daily doses of lovastatin given with the evening meal are more effective than the same dose given in the morning.

In order to assess the cholesterol-lowering effect of MEVACOR™ OTC, consumers are instructed by the proposed nonprescription label to have a cholesterol test after 6 weeks of treatment. If the LDL-C target goal of < 130 mg/dL has been achieved, consumers are further instructed to continue using drug along with diet and exercise. If they do not reach the LDL-C target goal, users are instructed to stop taking MEVACOR™ OTC and talk to their physician.

Comment:

The proposed 20 mg dose of lovastatin has been shown to be efficacious in lowering serum cholesterol. However, whether the untitrated 20 mg is the appropriate dose for the target OTC population, remains a topic for the Advisory Committee discussion.

6.2 Drug-Drug Interactions

Several drugs (cyclosporine, clarithromycin, itraconazole, ketoconazole, nefazodone, erythromycin, and HIV protease inhibitors) have the potential to interact with lovastatin when administered concomitantly. These drugs and grapefruit juice, are strong CYP3A4 inhibitors, and may increase plasma HMG-CoA inhibitory activity levels, and therefore may increase the individual's risk of myopathy. In addition, gemfibrozil and niacin may also increase the risk of myopathy through a different mechanism.

6.3 Special Populations

Lovastatin is a pregnancy Category X drug. The sponsor has requested to change this classification to Category C. The data to support this request was submitted to the lovastatin prescription NDA 19-643. The only new data presented in support of the change was a limited postnatal neurodevelopment assessment following direct dosing of neonatal rats. FDA reviewed the data and found that information presented was inadequate to support a labeling change from pregnancy Category X to Category C.

Of particular concern is the fact that 50% of women enrolled in the actual use study were less than 55 years of age; 37.4% of women users were less than 55 years and 11% were under 45 years. These data demonstrate that women of childbearing age erroneously chose to take Mevacor OTC and is a cause for concern.

The appropriateness of availability of this Category X drug over-the-counter remains an unresolved issue and warrants further discussion at the Advisory Committee.

6.4 Pediatrics

The sponsor requested a waiver to the pediatric requirement because the product does not represent a meaningful benefit to pediatric patients.

The proposed OTC label directs that this product is for men 45 years of age and older and women 55 years of age or older. It is clear from the results of the study that the package label poorly communicates the message not to use the drug if the consumer is under these ages. Lovastatin use in adolescent population (10 to 17 years of age) will remain under the prescription label. Lovastatin use in the prepubertal pediatric population has not been studied.

6.5 Advisory Committee Meeting

Advisory Committee Meeting to discuss the appropriateness of lovastatin Rx-to-OTC switch is warranted.

6.6 Literature Review

There were no literature reports submitted to support this application.

6.7 Postmarketing Risk Management Plan

The sponsor is proposing to market lovastatin OTC under the conditions similar to the actual use study:

- Sales restricted to the pharmacies only,
- Pharmacist acting in a role of a health care provider, advising consumers how to self-select and use the product, as well as providing access to serum cholesterol testing.

Currently, FDA has no control over the practice of pharmacies, and has no regulatory authority to enforce over-the-counter drug sales to pharmacy outlets only. The sponsor states that the Self Management System used in the actual use study will also be implemented upon the approval of Mevacor for OTC marketing. It is unclear how the sponsor will guarantee the presence of a medical staff and functional Cholestech machine in pharmacies where this product would be sold if approved.

7 OVERALL ASSESSMENT

7.1 Conclusions

The current paradigm for the treatment of hypercholesterolemia is individualized, based on serum cholesterol levels and the presence of certain number of risk factors for CHD. The results of the Actual Use study show that the majority of consumers cannot correctly self-select to use lovastatin without an input of a health care provider. It is not clear, whether this difficulty is related to the label used in the study, the complexity of the treatment guidelines, or both.

The study as conducted gave unreliable information about consumer compliance with the daily dosing regimen.

Unresolved issues related to OTC marketing of lovastatin remain:

- Poor appropriate consumer self-selection rates based on the label alone,
- Poor compliance with the follow-up cholesterol test and the issue of treatment to an LDL-C goal,
- Pregnancy Category X and potential use of the drug by women of childbearing age (a risk demonstrated by errors in self-selection),
- The need for monitoring of liver function tests,
- A realistic assessment of how consumers would dose themselves and for how long a duration,
- Risk/benefit for people with < 5% 10-year risk for CHD.

Thus, the potential benefit/risk ratio for this drug if it is switched from Rx to OTC becomes difficult to characterize based upon the "Use" data.

7.2 Labeling Review

The proposed labeling is being reviewed in detail by an interdisciplinary scientist in the Division of Over-the-Counter Drug Products. In addition, a Label Comprehension study to assess comprehension of the proposed label is being reviewed by Laura Shay, RN, MS, C-ANP.

The proposed label is not in conformance with the format and content requirements for over the counter drug product labeling as specified in 21 CFR 201.66.

The same label was used in the Actual Use Study CUSTOM. It is clear from the study results that the majority of consumers were not able to follow directions when selecting the product for their own use. Consequently, the proposed label will need major revisions and retesting to assure better consumer understanding.

8 APPENDICES

Appendix I.

Figure 2

Flow Chart of Study Procedures—Initial Storefront Visit

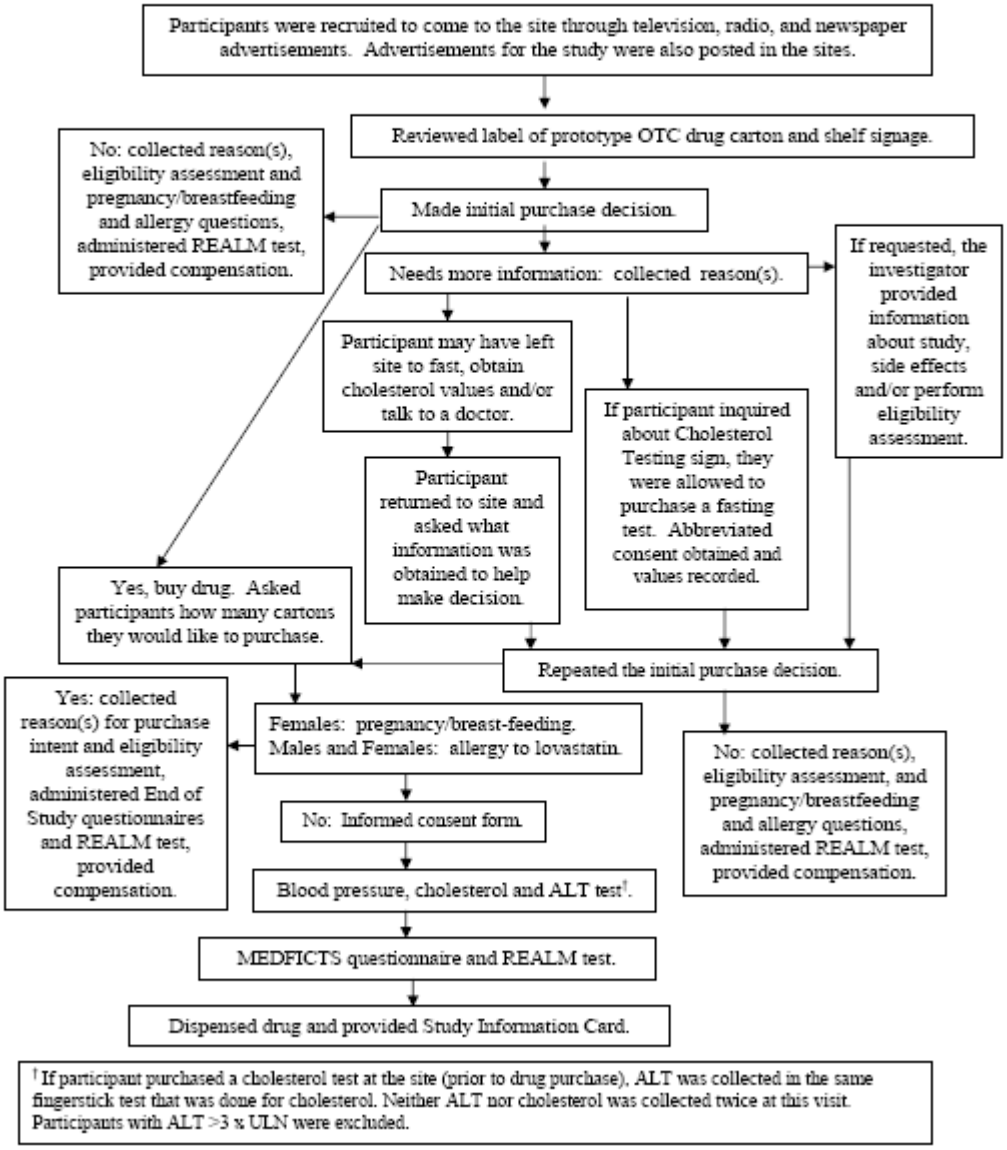
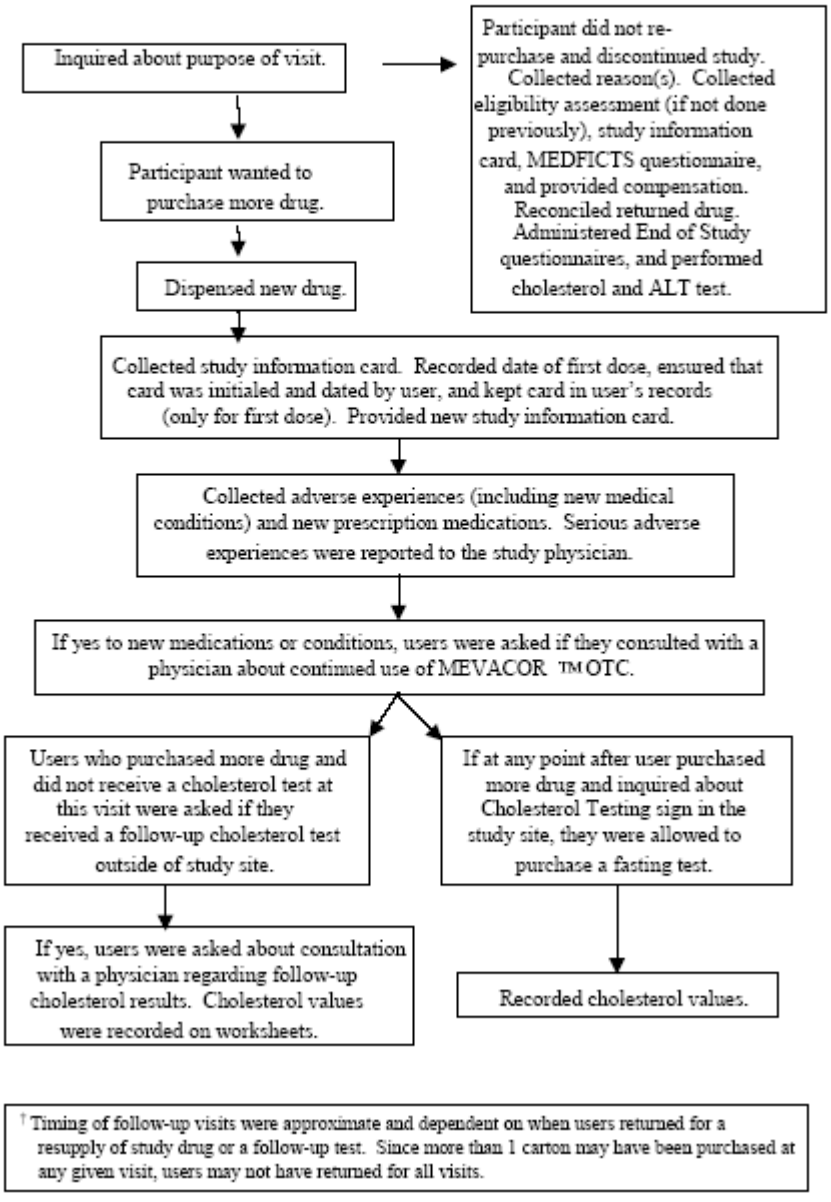


Figure 3

Flow Chart of Study Procedures—
Follow-Up Storefront Visits for Purchasing Drug†



† Timing of follow-up visits were approximate and dependent on when users returned for a resupply of study drug or a follow-up test. Since more than 1 carton may have been purchased at any given visit, users may not have returned for all visits.

Figure 4

Flow Chart of Study Procedures—Follow-Up Storefront Visits for Cholesterol Te

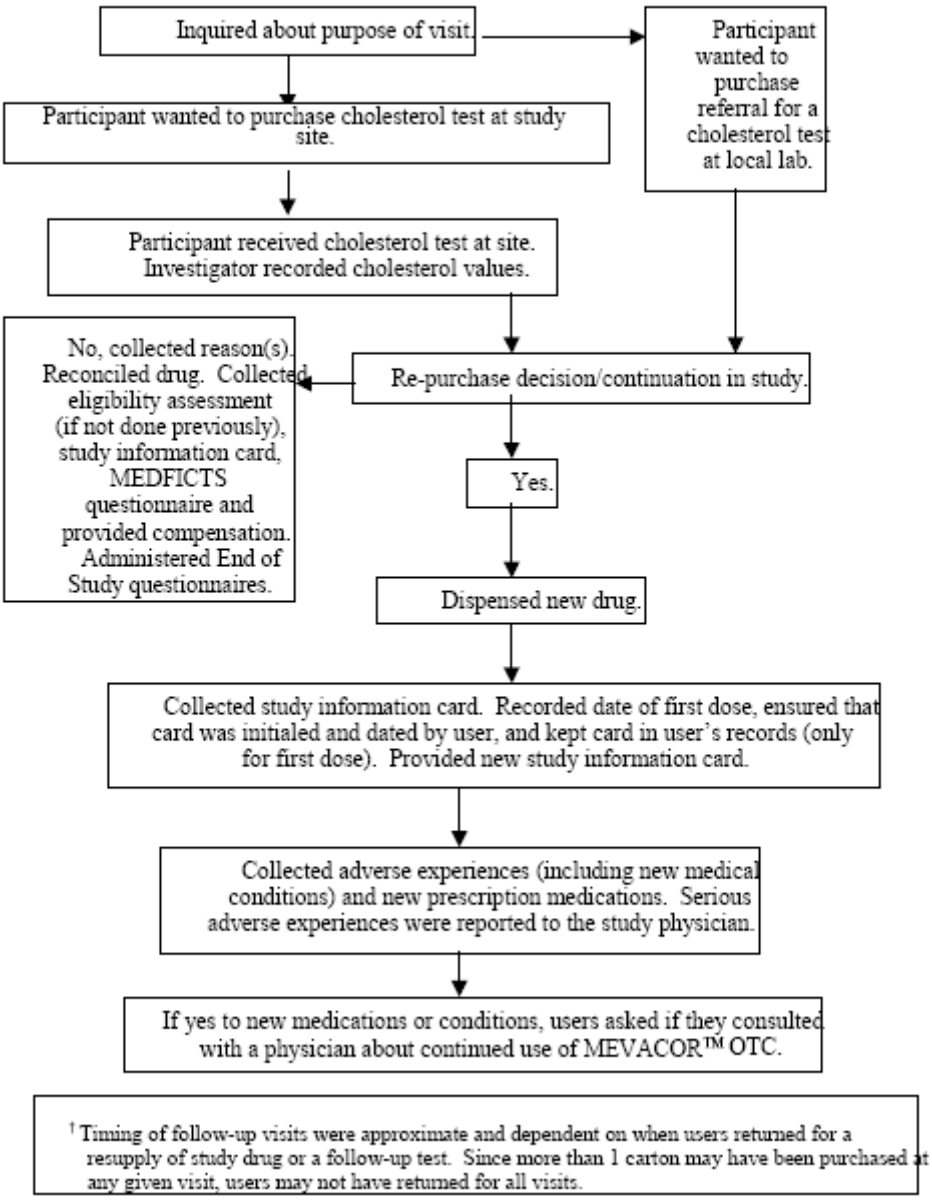
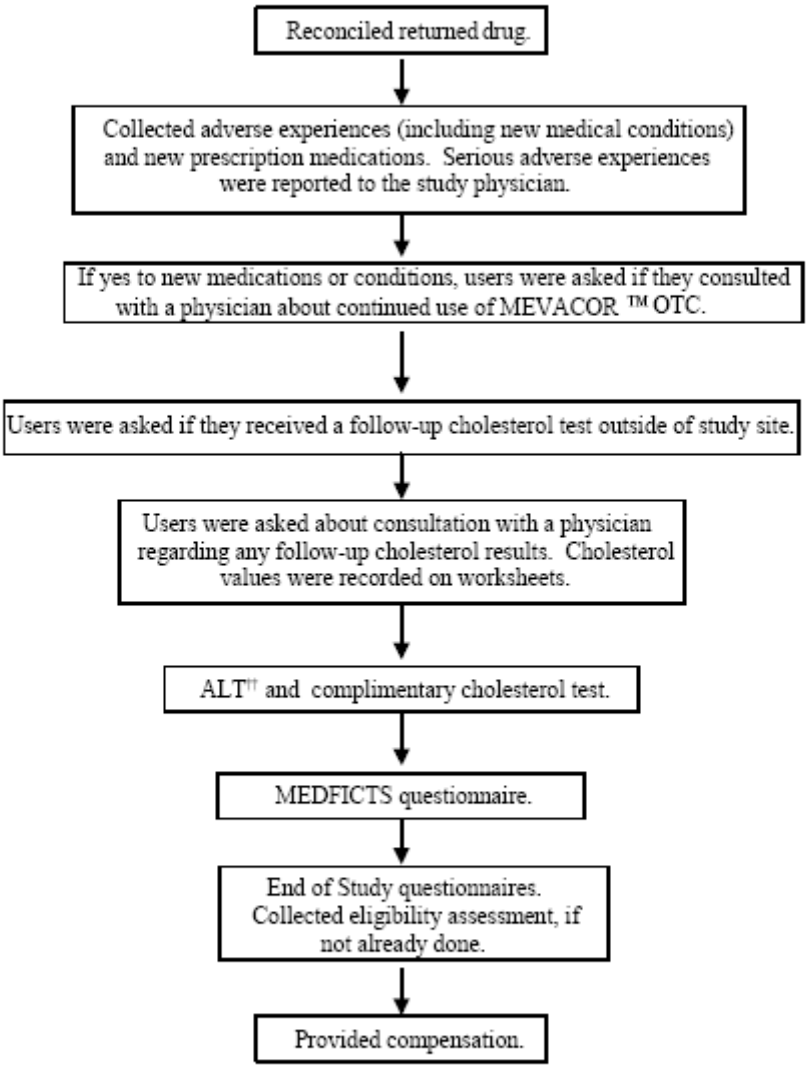


Figure 5

Flowchart of Study Procedures—
Final Storefront Visit†



† If a user completed the study, the final visit occured at approximately 26 weeks after the first visit to the study site.
†† Participants with ALT > 3xULN returned in approximately 2 weeks for follow-up test.

Appendix II.

Table 6. Baseline Participant Characteristics

		Calls (N=11252)	Appointments Kept (N=3346)	Purchase Decision (N=3316)				No Purchase Decision (N=30)
				Purchaser				
				User (N=1061)	Non-User (N=94)	Unknown (N=50)	Non-Purchaser (N=2111)	
Gender	Male	5872 (52.2)	1962 (58.6)	631 (59.5)	52 (55.3)	34 (68.0)	1226 (58.1)	19 (63.3)
	Female	5380 (47.8)	1384 (41.4)	430 (40.5)	42 (44.7)	16 (32.0)	885 (41.9)	11 (36.7)
Age (years)	< 40	1703 (15.1)	457 (13.7)	68 (6.4)	8 (8.5)	9 (18.0)	367 (17.4)	5 (16.7)
	40-44	1291 (11.5)	377 (11.3)	80 (7.5)	5 (5.3)	4 (8.0)	281 (13.3)	7 (23.3)
	45 to 49	1514 (13.5)	461 (13.8)	132 (12.4)	13 (13.8)	5 (10.0)	310 (14.7)	1 (3.3)
	50 to 54	1656 (14.7)	509 (15.2)	179 (16.9)	13 (13.8)	16 (32.0)	297 (14.1)	4 (13.3)
	55 to 59	1399 (12.4)	445 (13.3)	174 (16.4)	8 (8.5)	6 (12.0)	256 (12.1)	1 (3.3)
	60 to 64	1231 (10.9)	413 (12.3)	156 (14.7)	17 (18.1)	6 (12.0)	232 (11.0)	2 (6.7)
	65 to 69	952 (8.5)	303 (9.1)	148 (13.9)	10 (10.6)	2 (4.0)	138 (6.5)	5 (16.7)
	70 to 75	804 (7.1)	234 (7.0)	78 (7.4)	10 (10.6)	2 (4.0)	144 (6.8)	0 (0.0)
	≥ 76	609 (5.4)	145 (4.3)	46 (4.3)	10 (10.6)	0 (0.0)	84 (4.0)	5 (16.7)
	Unknown	93 (0.8)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Racial Origin	Asian	235 (2.1)	68 (2.0)	21 (2.0)	2 (2.1)	2 (4.0)	43 (2.0)	0 (0.0)
	Black	2298 (20.4)	632 (18.9)	90 (8.5)	13 (13.8)	10 (20.0)	513 (24.3)	6 (20.0)
	Hispanic American	632 (5.6)	171 (5.1)	58 (5.5)	5 (5.3)	4 (8.0)	102 (4.8)	2 (6.7)
	Native American	108 (1.0)	23 (0.7)	9 (0.8)	1 (1.1)	1 (2.0)	12 (0.6)	0 (0.0)
	White	7674 (68.2)	2393 (71.5)	869 (81.9)	70 (74.5)	33 (66.0)	1401 (66.4)	20 (66.7)
	Other	120 (1.1)	29 (0.9)	6 (0.6)	3 (3.2)	0 (0.0)	20 (0.9)	0 (0.0)
	Unknown	185 (1.6)	30 (0.9)	8 (0.8)	0 (0.0)	0 (0.0)	20 (0.9)	2 (6.7)
Literacy	Low	NA	NA	136 (12.8)	10 (10.6)	9 (18.0)	255 (12.1)	NA
	Normal	NA	NA	920 (86.7)	64 (68.1)	41 (82.0)	982 (46.5)	NA
	Unknown	NA	NA	5 (0.5)	20 (21.3)	0 (0.0)	874 (41.4)	NA

Appendix III.

Table 7. Prevalence of Specific Label Ineligibility Criteria

Ineligibility Criteria[†]	Made a purchase decision (N=3316)		Non-Purchasers (N=2111)		Purchasers Use Decision (N=1205)						
					User (N=1061)			Non-User (N=94)		Unknown (N=50)	
	N	M[‡]	n	M	**n**[§]	**n**[‖]	M[#]	n	M	n	M
Too young	1194	3314	890	2109	**147**	**115**	1061	23	94	19	50
Did not know LDL-C cholesterol numbers	1078	2913	732	1783	**174**	**144**	1034	24	84	4	12
LDL-C was too low	567	2913	432	1783	**60**	**62**	1034	11	84	2	12
LDL-C was too high	551	2913	299	1783	**150**	**75**	1034	26	84	1	12
Did not know HDL-C cholesterol numbers	992	2939	679	1799	**152**	**134**	1044	23	84	4	12
HDL-C was too high	436	2939	282	1799	**83**	**56**	1044	15	84	0	12
Didn't know triglycerides	967	2935	659	1795	**153**	**129**	1044	23	84	3	12
Triglycerides were too high	768	2935	468	1795	**170**	**98**	1044	25	84	7	12
Taking any Rx medication	1735	2945	1049	1805	**313**	**317**	1044	48	84	8	12
Taking potentially interacting drugs[¶]	152	2947	116	1806	**12**	**20**	1046	4	84	0	11
Don't know if taking other potentially interacting drugs	44	2947	29	1806	**6**	**7**	1046	2	84	0	11
Taking other Rx cholesterol medication	609	2933	424	1801	**62**	**103**	1037	19	84	1	11
Don't know if taking other Rx cholesterol medication	3	2933	3	1801	**0**	**0**	1037	0	84	0	11
Medical condition: stroke	135	2947	100	1806	**16**	**15**	1046	2	84	2	11
Medical condition: heart disease	285	2947	186	1805	**37**[††]	**52**	1046	9	84	1	12
Medical condition: liver disease	80	2949	70	1807	**3**	**6**	1046	1	84	0	12
Medical condition: diabetes	275	2949	196	1807	**30**	**43**	1046	5	84	1	12
Don't have one of the risk factors	1178	2949	712	1807	**269**	**153**	1046	36	84	8	12
Have had muscle problem from previous use of cholesterol medication	300	2932	200	1791	**53**	**33**	1046	13	84	1	11
Allergic to lovastatin	13	3026	13	1825	**0**	**0**	1061	0	90	0	50
Pregnant or breastfeeding	12	3029	12	1828	**0**	**0**	2061	0	90	0	50

[†] Participants can be counted in more than one ineligible criteria. [‡] M represents the number of Evaluators, Non-Purchasers, Users, etc. who provided a response on the eligibility assessment. [§] Without Physician Override. [‖] With Physician Override. [¶] Potentially interacting drugs are Nefazodone, Cyclosporine, Erythromycin or Clarithromycin, Ketoconazole or Itraconazole, Gemfibrozil, Protease Inhibitors, Niacin(>1000 mg/day). [#] Includes two (2) protocol violators.
[††] Includes one (1) protocol violator.

Appendix IV.

Table 12. Follow-up Cholesterol Test for Ongoing Use Decision

Adherence to Label Criteria	AL	AB	NAB	NAS	Unknown	Total
Adhered to label criteria	275	37	0	29	5	346
Got a cholesterol test within 4-12 weeks	275	37	0	29	5	346
• LDL-C < 130 mg/dL and continued	225	32	0	23	2	282
• LDL-C ≥ 130 mg/dL and discontinued	17	1	0	3	3	24
• LDL-C ≥ 130 mg/dL and Physician interaction	9	0	0	2	0	11
• Don't know LDL-C, cont., with Phys. Interaction	24	4	0	1	0	29
Closely adhered to label criteria	33	98	0	20	2	153
Got a cholesterol test outside of 4-12 weeks	33	98	0	20	2	153
• LDL-C < 130 mg/dL and continued	7	76	0	10	0	93
• LDL-C ≥ 130 mg/dL and discontinued	2	5	0	1	2	10
• LDL-C ≥ 130 mg/dL and Physician interaction	1	13	0	5	0	19
• Don't know LDL-C, cont., with Phys. Interaction	23	4	0	4	0	31
Did not adhere to label criteria	0	0	391	46	0	437
Got a cholesterol test	0	0	145	15	0	160
• LDL-C ≥ 130 mg/dL and continued	0	0	122	13	0	135
• LDL-C < 130 mg/dL and discontinued - Cured	0	0	0	0	0	0
• Don't know LDL-C, cont., without Phys. interac.	0	0	21	1	0	22
• LDL-C missing, cont., without Phys. interac.	0	0	2	1	0	3
No cholesterol test, cont. without Phys. interaction	0	0	246	31	0	277
Discontinued – Missing Assessment	40	11	0	6	66	123
No cholesterol test‡	37	10	0	5	64	116
• Learned not right	19	3	0	0	29	51
• Physician advised not right	10	1	0	0	11	22
• Other reason for discontinuation	9	6	0	5	26	46
Got a cholesterol test – not a factor in discontinuation	3	1	0	1	2	7
Total	348	146	391	101	73	1059

AL: according to label; AB: adequate benefit; NAB: not adequate benefit; NAS: not adequate safety; ‡Participants may be counted in more than one subgroup.

Appendix V.

Table 14. Number of Participants by Adherence to Label Criteria Emergent Events for Ongoing Use Decision

Adherence to Label Criteria	AL	AB	NAB	NAS	Unknown	Total
Experienced Emergent Events	130	90	102	44	0	366
Adhered to label criteria	128	24	62	14	0	228
Diagnosed with new medical condition and did inform HCP* about MOTC	51	17	32	5	0	105
Began Rx medication and did inform HCP about MOTC	111	19	55	11	0	196
Developed unexplained muscle pain, did D/C MOTC and inform HCP about MOTC	11	2	5	2	0	20
Closely adhered to label criteria	1	66	39	11	0	117
Diagnosed with new medical condition and did not informed HCP about MOTC	1	30	18	4	0	53
Began non-interacting Rx med. and did not inform HCP	1	37	28	6	0	72
Developed unexplained muscle pain, informed HCP but did not D/C MOTC	0	8	1	0	0	9
Developed unexplained muscle pain, D/C MOTC but did not inform HCP	0	12	3	3	0	18
Did not adhere to label criteria	1	0	1	19	0	21
Allergy to MOTC, liver disease, or became pregnant, did not inform HCP	0	0	0	0	0	0
Began interacting Rx med but did not inform HCP	0	0	0	2	0	2
Developed unexplained muscle pain, did not D/C MOTC or inform HCP	1	0	0	15	0	16
Developed CHD, Diabetes or Stroke, did not inform HCP	0	0	1	2	0	3
No Emergent Medical Conditions or Situations	218	56	289	57	73	693
Total	348	146	391	101	73	1059

* HCP: Health Care Provider; AL: according to label; AB: adequate benefit; NAB: not adequate benefit; NAS: not adequate safety.

Appendix VI.

Table 24. Number (%) of Subjects with Drug-Related Clinical Adverse Experiences by Body System

	Users N=1061 (%)
Subjects with one or more adverse experience	180
Subjects with no adverse experience	881
Ear and Labyrinth Disorders	**1 (0.1)**
Tinnitus	1 (0.1)
Gastrointestinal Disorders	**57 (5.4)**
Abdominal distension	3 (0.3)
Abdominal pain NOS	4 (0.4)
Abdominal pain upper	10 (0.9)
Anal hemorrhage	1 (0.1)
Constipation	5 (0.5)
Diarrhea NOS	11 (1.0)
Dry mouth	1 (0.1)
Dyspepsia	7 (0.7)
Eructation	1 (0.1)
Flatulence	18 (1.7)
Gastrointestinal disorder NOS	1 (0.1)
Gastrointestinal irritation	1 (0.1)
Glossodynia	1 (0.1)
Loose stools	3 (0.3)
Nausea	2 (0.2)
Swollen tongue	1 (0.1)
Tongue disorder NOS	1 (0.1)
Vomiting NOS	2 (0.2)
General Disorders and Administration Site Conditions	**16 (1.5)**
Asthenia	4 (0.4)
Chest tightness	1 (0.1)
Fatigue	3 (0.3)
Feeling abnormal	1 (0.1)
Feeling hot	1 (0.1)
Feeling jittery	1 (0.1)
Nodule	1 (0.1)
Edema peripheral	2 (0.2)
Pain NOS	2 (0.2)
Sluggishness	1 (0.1)
Immune System Disorders	**1 (0.1)**
Hypersensitivity NOS	1 (0.1)
Infections And Infestations	**1 (0.1)**
Sinusitis NOS	1 (0.1)
Injury, Poisoning And Procedural Complications	**1 (0.1)**
Epicondylitis	1 (0.1)
Investigations	**1 (0.1)**
Blood pressure increased	1 (0.1)
Heart rate increased	1 (0.1)

Table 24. Number (%) of Subjects with Drug-Related Clinical Adverse Experiences by Body System (cont.)

Musculoskeletal And Connective Tissue Disorders	**93 (8.8)**
Arthralgia	16 (1.5)
Arthritis NOS	1 (0.1)
Back pain	3 (0.3)
Joint swelling	1 (0.1)
Muscle cramp	6 (0.6)
Muscle spasms	1 (0.1)
Muscle stiffness	1 (0.1)
Muscle twitching	2 (0.2)
Muscle weakness NOS	12 (1.1)
Musculoskeletal stiffness	1 (0.1)
Myalgia	57 (5.4)
Neck pain	2 (0.2)
Pain in extremity	9 (0.8)
Pain in jaw	1 (0.1)
Nervous System Disorders	**22 (2.1)**
Burning sensation NOS	1 (0.1)
Depressed level of consciousness	1 (0.1)
Dizziness	7 (0.7)
Headache	13 (1.2)
Paralysis NOS	1 (0.1)
Psychiatric Disorders	**8 (0.8)**
Anxiety	2 (0.2)
Depression	1 (0.1)
Insomnia	4 (0.4)
Nervousness	1 (0.1)
Restlessness	1 (0.1)
Reproductive System And Breast Disorders	**3 (0.3)**
Erectile dysfunction NOS	2 (0.2)
Sexual dysfunction NOS	1 (0.1)
Respiratory, Thoracic And Mediastinal Disorders	**5 (0.5)**
Cough Dyspnea	2 (0.2)
Nasal Congestion	1 (0.1)
Sinus Congestion	1 (0.1)
Skin And Subcutaneous Tissue Disorders	**10 (0.9)**
Acne NOS	1 (0.1)
Contusion	1 (0.1)
Erythema	1 (0.1)
Face edema	1 (0.1)
Rash NOS	6 (0.6)
Vascular Disorders	**1 (0.1)**
Peripheral coldness	1 (0.1)

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