MEDICAL OFFICER'S DRAFT REVIEW OF NEW DRUG APPLICATION

NDA #: 21-198
Sponsor: Bristol-Myers Squibb
Product: Pravastatin sodium 10 mg tablets
Indication: nonprescription availability of pravastatin 10 mg tablets for the treatment of mild-to-moderate hypercholesterolemia in adults without evidence of cardiovascular disease or diabetes
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TABLE OF CONTENTS	Page
Introduction	2
Cholesterol as a Risk Factor for Cardiovascular Disease	2
National Guidelines for the Treatment of Hypercholesterolemia	3
Sponsor's Rationale for Nonprescription Pravastatin	4
Definition of the OTC Population	5
OTC Clinical Development Program	6
Issues to Address in the Review of Nonprescription Pravastatin	6
Actual-Use Trials	8
PREDICT – Pravachol Experience Documented in a Consumer-Use Trial	8
OPTIONS – OTC Pravachol Trial in an Observed Naturalistic Setting	23
Comments on the OTC Clinical Development Program	32
What is the expected mean percent reduction in LDL-C for the targeted population?	32
Is there evidence that treatment with this drug to this degree of LDL-C lowering in this population will result in a clinical benefit?	33
Will the consumer adhere to taking the medication chronically to treat an asymptomatic condition whose deleterious effects may not be manifested until several years later?	33
Are consumers making appropriate decisions regarding the initiation of drug treatment?	34
Conclusions on the Review of NDA 21-198	35
References	36

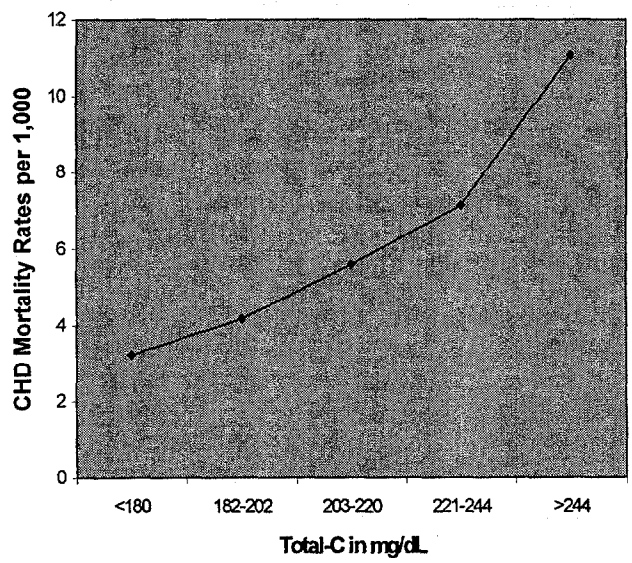
INTRODUCTION

CHOLESTEROL AS A RISK FACTOR FOR CARDIOVASCULAR DISEASE

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

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

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



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

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

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

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

NATIONAL GUIDELINES FOR THE TREATMENT OF HYPERCHOLESTEROLEMIA

Concurrent with the conduct of these large statin clinical trials, the National Cholesterol Education Program (NCEP) published the second report of the Expert Panel on Detection, Evaluation, and Treatment of hypercholesterolemia in adults in June 1993.[9] The guidelines for treating hypercholesterolemia from this report are summarized in the table shown below.

Table 2. Treatment Recommendations Based on LDL-C levels

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

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

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

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

AFCAPS/TexCAPS was a randomized, placebo-controlled primary prevention trial which demonstrated a reduction in the relative risk of experiencing an initial acute coronary event (defined as myocardial infarction, unstable angina, or cardiac death) in patients treated with lovastatin 20 to 40 mg per day during a median follow-up period of 5.1 years. Based on the CHD risk factors and baseline lipid profile of the 6,605 patients randomized in this trial, only 16.6% of the cohort would have qualified for drug treatment by NCEP guidelines.

SPONSOR'S RATIONALE FOR NONPRESCRIPTION PRAVASTATIN

Despite the compelling evidence that treatment of hypercholesterolemia with lipid-altering drugs results in clinical benefit, in the current application, BMS (sponsor) argues that the US population remains inadequately treated. The sponsor provided a referenced publication in which an analysis of the National Health and Nutrition Examination Survey (NHANES) III Phase 2 data revealed that a large proportion of the US population were not meeting NCEP LDL-C treatment goals based on CHD risk factors and that many of these individuals qualified for drug therapy (Table 3).[10]

Table 3. U.S. Population by CHD Risk Group Not Meeting NCEP Treatment Goals

	CHD Risk Group		
	Without CHD		With CHD
	< 2 risk factors	≥ 2 risk factors	
Not at LDL-C goal estimated no. (millions) percent of risk group	15.7 12.9%	26.6 54.6%	8.4 82.5%
Qualify for Drug Therapy estimated no. (millions) percent of risk group	4.7 3.8%	11.0 22.6%	5.5 54.2%
Qualify for Drug Therapy but not Receiving Any estimated no. (millions) percent of risk group	2.6 2.1%	7.1 14.6%	3.0 29.4%
Estimated no. in Risk Group (millions)	121.1	48.7	10.2

Source: revised table from *Am J Cardiol 1998;82:61-65*

From an analysis sample (n=7,423) of a population surveyed from September 1991 to October 1994 (n=15,427), nationally representative estimates of individuals within certain CHD risk groups for this time period were obtained. The study revealed that although the population with established CHD had the highest proportion of individuals not meeting recommended LDL-C levels or receiving appropriate drug treatment, the estimated number of people not at goal or receiving drug treatment was greater in the group without CHD but ≥ 2 risk factors due to the higher number of individuals comprising this category (48.7 million).

BMS asserts that increased public awareness of cholesterol as a CHD risk factor has resulted in improvements in lifestyle and dietary habits but despite these efforts many are not achieving an optimal cholesterol level. In particular, many individuals within the primary prevention population are inadequately treated. Based on the efficacy and safety data supporting the approval of pravastatin 10 mg in 1991, BMS proposes that the availability of this dose as a nonprescription drug will allow individuals without evident CHD who are motivated, a safe and effective alternative for achieving NCEP LDL-C goals.

DEFINITION OF THE OVER-THE-COUNTER POPULATION

Bristol-Myers Squibb (BMS) designed their OTC clinical program to support use of pravachol 10 mg in the following OTC population[†]:

- people who have been told by their physician to lower their cholesterol but have not been placed on prescription therapy (Total-C 200-240 mg/dL, LDL-C > 130 mg/dL)
- generally healthy people who do not have CHD or diabetes
- people with LDL-C levels not at NCEP goal despite lifestyle modifications
- people who will derive significant benefit from pravachol 10 mg defined as reaching their NCEP goals

[†] as defined in NDA 21-198 volume 2, item 3.H

The program specifically stated that nonprescription use of pravachol is not intended for use in:

- those who have been told to take prescription lipid-lowering drugs
- those who have CHD or diabetes
- children or pregnant women
- those who do not have elevated cholesterol (criteria not provided but presumably Total-C < 200 mg/dL or LDL-C ≤ 130 mg/dL)

THE OTC CLINICAL PROGRAM

The goals of the OTC clinical program were to evaluate whether pravachol 10 mg per day could be used safely and responsibly in an OTC-like setting and whether this additional approach to lifestyle modifications would improve cholesterol management in the general population. The decision to evaluate the 10 mg dose for nonprescription use was based on efficacy data obtained from studies previously submitted to NDA 19-898 and IND for pravastatin. These studies demonstrated a 17 to 22 percent LDL-C lowering with daily use of pravastatin 10 mg compared to placebo. Based upon these results it was estimated that a majority of the OTC-population with total-C levels between 200 and 240 mg/dL could achieve their NCEP lipid goals with pravastatin 10 mg per day. In order to determine if the appropriate patient population would initiate treatment with nonprescription pravachol and responsibly manage hypercholesterolemia in conjunction with a healthcare provider, the sponsor conducted a label comprehension study and 2 consumer-use trials. These 3 studies encompassed the clinical development program submitted to this new drug application.

The **label comprehension study** was conducted in 20 different geographical areas to determine if consumers would seek physician advice prior to initiating treatment with nonprescription pravachol and whether consumers understood the product purpose and its intended population. This study and its results will be reviewed jointly by the Division of Over-the-Counter Drug Products (DOTCDE) and the Division of Drug Marketing, Advertising, and Communications (DDMAC). Two actual-use trials were conducted: **the Pravachol Experience Documented In a Consumer Trial (PREDICT)** and **OTC Pravachol Trial In an Observed Naturalistic Setting (OPTIONS).** Both of these studies evaluated the consumer's behavior in the setting of OTC availability of pravastatin with respect to medical consultation. The lipid-altering effects of pravastatin 10 mg per day in the OTC population were assessed in PREDICT.

In addition to the above-mentioned studies, the sponsor provided pooled safety data from 3 placebo-controlled studies using pravastatin 10 mg and 3 large placebo-controlled clinical outcome trials using pravastatin 40 mg. These studies have been submitted and previously reviewed by the Agency.

ISSUES ADDRESSED IN THE REVIEW OF NONPRESCRIPTION PRAVASTATIN

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

Efficacy

Historically, efficacy in the lipid-altering drug class refers to the ability of the drug to lower LDL-C levels at a minimum of 15% from baseline relative to placebo in individuals adhering to a low-fat diet.[11] This measure of efficacy has been proven to be a reliable

surrogate marker for clinical benefit and remains the primary endpoint by which new drugs developed for lipid-altering are evaluated. In the absence of clinical cardiovascular benefit, the lipid-altering results from adequate and well-controlled studies are summarized in drug labeling accompanied by a disclaimer to that effect. In the nonprescription environment the evaluation of drug efficacy will focus on the following:

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

Safety

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

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

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

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

PRAVACHOL EXPERIENCE DOCUMENTED IN A CONSUMER USE TRIAL (PREDICT)

Study Design

PREDICT was a 6-month, open-label, randomized, parallel, actual-use clinical trial designed to evaluate behavior, compliance, efficacy, and safety of pravachol 10 mg in a group of patients provided the drug as an over-the-counter product (OTC group) versus another group of patients provided the drug as a prescription product (Rx group).

Objectives

Primary objective

The primary objective was to determine the proportion of OTC randomized subjects who, having purchased OTC pravastatin, **consulted a physician** within 2 months of using the study medication.

Secondary objectives

The secondary objectives were:

1. to compare the proportions of subjects in the OTC and Rx groups who consulted a physician for follow-up after the initial study visit and who complied with proper study medication dosage regimen
2. to compare the safety of OTC pravachol 10 mg to that of Rx pravachol
3. to compare the cholesterol lowering effects of pravachol in the OTC group versus the Rx group

Tertiary objective

The tertiary objective was to determine the proportion of subjects who maintained appropriate lifestyle behaviors after exposure to pravachol regardless of use of the medication.

The review of this NDA will specifically focus on the lipid-altering effect of pravachol in the actual-use setting compared to the prescription environment. The safety and tolerability of daily pravachol 10 mg use will also be compared between the two treatment groups. Other efficacy measures such as compliance, label comprehension, and consumer behavior, will be addressed in the reviews conducted in DOTCDE in conjunction with DDMAC.

Eligibility Criteria

Inclusion criteria

- individuals ≥ 18 years of age

Exclusion criteria

- participation in another clinical research trial within the past 30 days
- females of childbearing potential (not surgically sterile or naturally menopausal for ≥ 1 year with ≥ 24 months since last menstrual cycle)
- breastfeeding

Study Subject Recruitment

Subjects were recruited through radio, television, and print advertisements targeting generally healthy men and women with total-C levels between 200 and 240 mg/dL . The advertisement stated that some subjects will have an opportunity to take a prescription

proven cholesterol-lowering medication without a prescription and were referred to a toll-free number where operators directed interested individuals to a nearby screening site located in enclosed shopping malls, strip malls, or professional buildings.

Individuals visited the screening sites where trained non-medical personnel administered a screening questionnaire and assessed literacy level based on a standardized test which categorized literacy level based on the number of words correctly read from a provided list. Subjects were randomized to either the OTC or RX group after stratification by literacy level. This visit was considered Assessment 1 in the study protocol.

The screening questionnaire inquired about medical history, demographics, education and socioeconomic level, cholesterol awareness, lifestyle habits, and study eligibility criteria. Subjects randomized to the OTC group were given a prototypical OTC Pravachol 10 mg print advertisement for review and were informed of the price of the product while those randomized to the Rx group were shown a direct-to-consumer-like advertisement. If the individuals remained interested in study participation they could obtain pravachol 10 mg through the following routes:

OTC group only: purchase medication at screening site
Rx group only: obtain medication through a study physician after undergoing a medical evaluation

Study Medication Dispensing
All study subjects were provided a list of study physicians and no further contact was made with the subjects for 6 months. The rationale for minimal contact with study participants was to reduce any factors which may alter behavior towards purchasing or adherence to medication use. An individual randomized to the OTC group had the opportunity to purchase a 2-month supply of pravachol 10 mg at the screening site after the initial assessment, but further purchase of the medication was prohibited unless the subject had been evaluated by a study physician. Individuals randomized to the Rx group were informed that they would need to contact the study physician to obtain prescription pravachol but were not encouraged by the screening site personnel to make this visit.

OTC-treated subjects were reimbursed the cost of study medication at the end of the study but were not informed of this prior to study completion. The Rx-treated subjects could purchase pravachol through their own health insurance plan or could sign up for a study prescription coverage program.

Study Visits, Laboratory Assessments, and Treatment Guidelines
This 6-month study was designed to evaluate patient behavior while taking a nonprescription lipid-lowering agent and to assess consumer interest in the product. All study visits (or assessments) were initiated by the study participants with the exception of the last (6-month) visit.
Assessment 1 corresponded with the screening visit as described under the *Study Subject Recruitment* section of this review.
Assessment 2 was the initial MD contact. This visit was necessary for the subjects randomized to the Rx group to receive initial prescriptions for pravachol 10 mg and timing of this visit was dependent on the interested individual. In the OTC group, this visit was required only for further purchasing of nonprescription medication although an

individual could also schedule a visit irrespective of medication supply. Since the initial dispensing of medication only provided a 2-month supply of pravachol, the timing of some visits in the OTC group would likely fall within this time frame due to the prompting of individuals by the study site personnel after an unsuccessful attempt at re-purchase.

The study physician saw subjects from both the OTC and Rx group and would make his/her recommendation to initiate (Rx +/or OTC group) or continue treatment (OTC group) based on the following guidelines:

Table 4. Treatment Guidelines for Initiating or Titrating Pravastatin 10 mg

Risk Category	Baseline LDL-C Value	LDL-C Treatment Goal
No CHD or diabetes but with 2 other risk factors* for CHD including age	LDL-C ≥ 130 mg/dL but < 190 mg/dL	LDL-C goal < 130 mg/dL
No CHD or diabetes but with 1 or no risk factors for CHD	LDL-C ≥ 160 mg/dL but < 190 mg/dL	LDL-C goal < 160 mg/dL

*risk factors were defined as age (males ≥ 45, females ≥ 55 or postmenopausal w/o ERT); family history of CHD; current smoking; hypertension; HDL-C < 35 mg/dL; DM)

More aggressive therapy with prescription lipid-lowering drug was recommended by the study physician if the subject had one of the following:

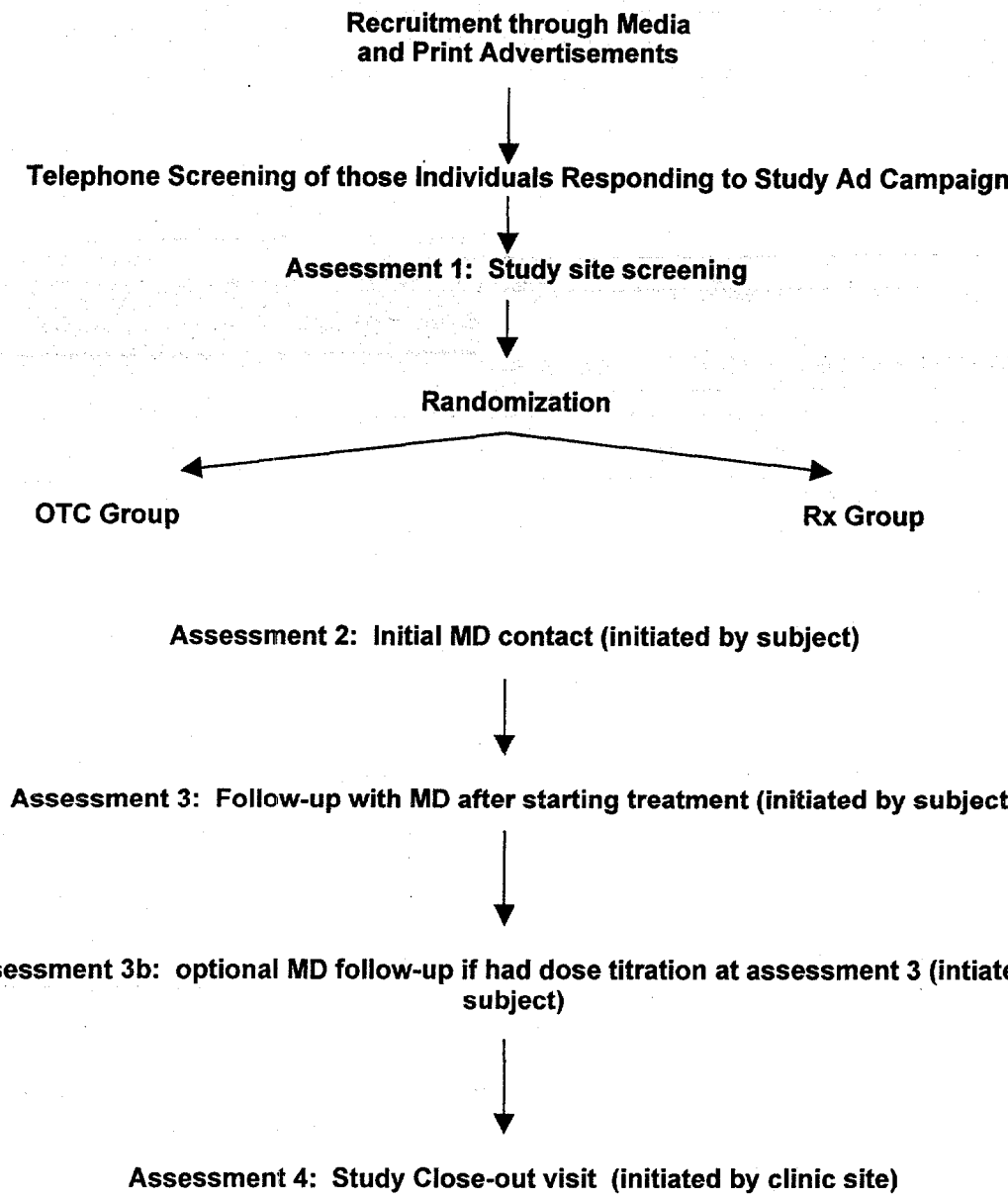
- CHD
- no CHD but 2 or more risk factors not including age and LDL-C > NCEP goal
- no CHD and LDL-C > 190 mg/dL.

Assessment 3 was the follow-up visit after the initial MD contact. This protocol allowed for dose titration in either treatment group if the individual had not reached his/her LDL-C treatment goal based on the treatment guidelines (Table xxx). Participants in both treatment groups could be titrated to a maximal daily dose of 40 mg. Individuals in the OTC group were provided with a prescription for the higher dose but this did not preclude them from purchasing additional pravachol 10 mg, continuing at the same dose, or doubling the 10 mg dose.
Assessment 3b was an optional visit for those subjects whose dose of pravachol was titrated.
Assessment 4 (6-month) was initiated by the study site for study completion.

The following laboratory tests and information were obtained at study assessments 2, 3, and 4: lipid profile; AST; ALT; medication compliance; safety assessment; and diet. TSH, blood glucose, and renal function were obtained only during assessment 2. Assessment 3b obtained the same information as assessment 3 with the exception of dietary information. All lipid determinations were obtained after 10 hours of fasting and included total-C, LDL-C, HDL-C, and TGs. LDL-C values were calculated using the Friedewald equation; no LDL-C values were available for subjects with TGs > 400 mg/dL.

The following diagram (Figure 2) illustrates the study schematic.

Figure 2. Study Schematic of PREDICT.

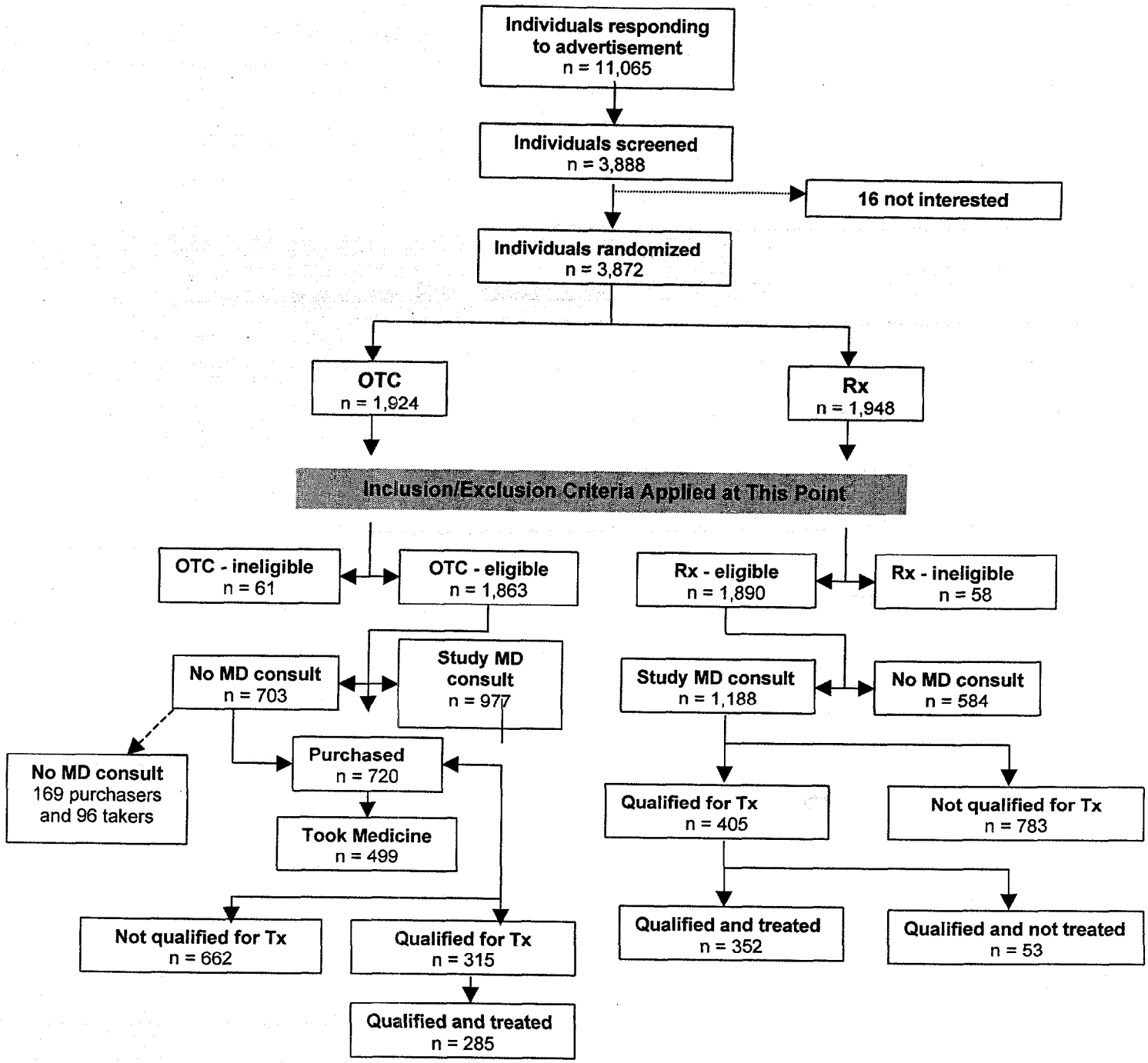


RESULTS OF PREDICT

Subject Disposition

The design of this study allowed individuals in the OTC group to make their own decisions regarding the purchase and initiation of pravastatin. Both treatment groups were not scheduled or encouraged to seek a physician's advice although the Rx group could not initiate treatment without the physician's involvement. Consequently, there were many different consumer behavioral responses in this trial post-randomization; this was particularly evident in the OTC group. The following schematic (Figure 3) provides an overview of the complexity of consumer behavior in this trial. The summary of subject disposition will refer to this diagram for ease of review.

Figure 3. Disposition of Study Participants



Population Responding to Advertisement and Screened

There were 11,065 subjects who responded to the media and print advertisements by calling a toll-free scheduling number. Telephone operators responding to these calls were trained to direct interested individuals to nearby screening study sites; they were

not responsible for any screening with the exception of excluding women of childbearing potential or who were breastfeeding. Of the 11,065 subjects, 7,177 (64.9%) did not undergo a screening site visit. The remaining 3,888 (35.1%) were eligible for the study site screen of which, 3,872 (35%) were randomized to the OTC-purchase (n=1,924) or Rx-population (n=1,948). Sixteen subjects did not express an interest in study participation and were therefore not randomized.

Randomized Population and Study Eligible Population
A total of 3,872 subjects were randomized to the OTC group (n=1,924) and Rx group (n=1,948) after completion of screening questionnaire and literacy test. The study inclusion/exclusion criteria were not applied to the study participants until after randomization.

A similar number of subjects from each treatment group were deemed ineligible for study participation based on the inclusion/exclusion criteria. Table 5 summarizes the reasons for ineligibility; a subject could be assigned more than 1 reason.

Table 5. Reasons for Excluding Individuals From Study Participation

	OTC	Rx
Randomized, no. of subjects	**1924**	**1948**
Ineligible		
• <18 yrs of age	1	0
• breastfeeding	0	1
• childbearing potential	23	38
• participated in another research study within 30 days	18	17
• not determined due to termination of screening	21	4
Ineligible for Study	**61**	**58**
Eligible for Study*, n (%)	**1863 (96.8%)**	**1890 (97%)**

*eligible for study based on inclusion/exclusion criteria and did not represent qualifying for drug treatment

Since women were informed by the telephone operator that the study was not open to those who were pregnant, of childbearing potential, or nursing, the number of women excluded for these reasons is likely higher than provided in table 5.

Consulted Physician
After a subject was considered eligible for study participation a list of study physicians was provided for medical consultation but no contact was made by the study personnel to encourage subjects to schedule physician appointments. Subjects also had the flexibility of seeing his/her own physician to discuss the treatment of hypercholesterolemia.

Of those who were randomized and considered eligible for the study, 977/1,863 (52.4%) of the OTC group and 1,188/1,890 (62.9%) of the Rx group consulted a study physician.

Consulted a Physician and Qualified for Treatment
The number of subjects who sought medical advice and qualified for treatment was determined at Assessment 2. For the Rx group this would correspond with the initiation of treatment. The OTC group could have subjects who purchased the study drug at the initial visit and used the drug, purchased the study drug at not taken any, and not

purchase the study drug prior to the first physician contact. Qualifying for pravastatin therapy was determined by treatment guidelines (Table 4) and these guidelines were similarly applied by the study physician to participants in either treatment group.

Among the OTC and Rx subjects who sought advice from a study physician approximately **two-thirds of the consult population** from each group were NOT considered qualified for treatment.

The reasons for treatment ineligibility related primarily to cholesterol values not within the range appropriate for pravastatin 10 mg daily therapy (either already at NCEP goals or required more aggressive lipid-altering treatment). Table 6 summarizes the reasons for treatment ineligibility as provided by the study physicians.

Table 6. Reasons for Treatment Ineligibility as Determined by Study Physicians

	OTC	Rx
Randomized	1,924	1,948
Eligible for Study	1,863	1,890
Consulted Study MD	977	1,188
Treatment Eligible	315	405
Treatment INeligible	662	783
already at NCEP goal	420	451
qualified for more aggressive treatment	189	249
elevated triglycerides	40	68
CHD	5	3
other	3	4
administrative reasons	2	3
withdrew consent	0	4
other disease	2	0
diabetes	0	1
on current prescription lipid-altering therapy	1	0

OTC Purchasers (only in OTC Group)
This population of subjects consisted only of those who bought nonprescription pravastatin regardless of medical consultation. Of those subjects who were eligible for study participation in the OTC group (n=1,863); 720 (38.6%) were interested enough in the product to purchase pravastatin in the nonprescription setting.

Treated Population
This population consisted of those OTC- or Rx-study eligible subjects who took any amount of study medication. This population contributed to the denominator for determining the incidence of adverse experiences in this trial. There were 499 subjects in the OTC group and 355 in the Rx group who took study medication.

Qualified and Treated Population
These subjects had an Assessment 2 study visit where they saw a study physician, were considered eligible for pravastatin treatment, and took any amount of study medication. Within the OTC group there were 285 subjects and in the Rx group there were 352 subjects who met this definition of being qualified and received treatment. This population of study participants was considered primary in the determination of lipid-altering efficacy.

Dose Titrated
Subjects who were qualified, treated, and returned for an Assessment 3 study visit had lipid values assessed and the study physician could titrate their pravastatin dose to a maximum of 40 mg daily in order to achieve their NCEP LDL-C goal (see Treatment Guidelines, Table 4). The number of subjects who required dose titration were 53 in the OTC group and 60 in the Rx group.

The provision for dose titration in this actual-use trial is unusual since the proposed nonprescription dose is 10 mg daily and any further increase in daily dose would reside in the prescription environment. Since Assessment 2 excluded subjects who required more aggressive lipid-lowering therapy from initiating or continuing pravastatin 10 mg therapy, any estimate of subjects requiring dose-titration in this study may actually be higher in the unrestricted nonprescription environment since consumers will not have exclusion criteria prohibiting them from purchasing and using the product.

Summary of Patient Accounting as Provided by Sponsor
The following table summarizes the number of subjects fulfilling the definition of specific subgroups generated after the screening process.

Table 7. Different Study Population Generated Post-Screening in PREDICT*

	OTC	Rx	Total
Randomized	1,924	1,948	3,872
Eligible to Continue in Study	1,863	1,890	3,753
Consult (any MD) Consult Study MD	1,160 (62.3%) 977 (52.4%)	1,306 (69.1%) 1,188 (62.9%)	2,466 2,165
Qualified (as determined by Study MD only)	315 (16.9%)	405 (21.4%)	720
OTC Purchasers	720 (38.6%)	0	720
Treated	499 (26.8%)	355 (18.8%)	854
Qualified and Treated	285 (15.3%)	352 (18.6%)	637
Dose Titrated	53	60	113

*percentages were calculated using the number of subjects eligible for study continuation NOT the randomized population because the inclusion/exclusion criteria were applied AFTER randomization

The number of patients eventually qualifying for treatment AND receiving treatment accounted for a very small proportion of the study-eligible population in both the OTC group (15.3%) and the Rx group (18.6%).

Study Discontinuations and Withdrawals
Study discontinuations are presented in this section within the following groups: those who discontinued study medication and those who self-selected to discontinue from the study after the initial visit and hence never consulted a physician. Summary of discontinuation by these categories are to provide insight on the safety and tolerability of the study medication and a subject's initial interest in the nonprescription or prescription availability of the product.

Study Drug Discontinuation
A significantly greater number of subjects in the OTC group discontinued study medication (291/499; 58.3%) as compared to the Rx group (68/355; 19.2%). The reasons for discontinuing study medication are described in table 8.

Table 8. Reasons for Discontinuing Study Medication in PREDICT*

	OTC	Rx
Number of Subjects Initiating Treatment	499	355
Reasons for Discontinuing Medication**		
MD Discontinued Treatment	**123**	**3**
• cholesterol level/risk factor too high	32	0
• treatment not appropriate for other reasons	16	0
• normal cholesterol levels	60	0
• on prescription lipid-lowering drug	8	0
• unknown	7	3
Other	65	0
Adverse Events	39	16
Withdrew Consent	23	19
Protocol Violation	14	20
Lost to follow-up	14	8
Unknown	13	2
Total	**291 (58.3%)**	**68 (19.2%)**

Source: NDA 21-198 Appendix B1
*Reasons for discontinuation reclassified based on Table 1.0.2
** A subject could have more than 1 reason for discontinuing study medication

Of all subjects discontinuing study medication, 'recommendation to discontinue by a physician' as a reported reason, was overwhelmingly greater in the OTC group (123/291; 42.3%) versus the Rx group (3/68; 4.4%). Since individuals in the OTC group were allowed to purchase and initiate therapy after visit 1 without physician oversight, it is not surprising that later MD consultation would result in recommendations for discontinuation. These findings; however, suggest that the consumer is at risk for making an inappropriate decision regarding drug treatment of hypercholesterolemia without involving the healthcare professional.

Other than 'protocol violation', the number of OTC subjects within each reported category for discontinuation exceeded that of the Rx group (including adverse events). It must be pointed out that within the OTC group, there were 96 subjects who never consulted a physician after initiating treatment hence data were incomplete in 19.2% of those who took study medication in the OTC group.

Subjects Not Initiating Physician Consultation Post-Screening

After study eligibility criteria were applied to the randomized groups, 703 OTC subjects and 584 Rx subjects never returned for physician consultation. Data were not available in these subjects with respect to lipid profile or reasons for disinterest in product. These subjects accounted for approximately one-third of the randomized cohort [36.5% (OTC) and 30.0% (Rx)].

Baseline Demographics and Study Participant Characteristics

The baseline characteristics of study participants are summarized by the randomized population for the 2 treatment groups and for the OTC purchase population to provide insight into the type of individual who might consider initiating treatment with pravastatin in the nonprescription environment.

Table 9. Baseline Demographics and Study Participant Characteristics

	Randomized Population		Purchase Population (n=720)
	OTC (n=1,924)	RX (n=1,948)	
Age in years			
mean (SD)	55.4 (12.1)	55.6 (11.7)	55.7 (11.4)
range	18-86	19-88	27-86
Gender, n (%)			
male	1225 (64%)	1171 (60%)	480 (67%)
female	697 (36%)	777 (40%)	240 (33%)
unknown	2 (<1%)	0	0
Age Category in Females, n (%)			
<35 yrs	9 (1.3%)	10 (1.3%)	4 (1.7%)
35-54	248 (35.6%)	264 (34%)	83 (34.6%)
55-74	394 (56.5%)	446 (57.4%)	137 (57.1%)
≥ 75	46 (6.6%)	56 (7.2%)	16 (6.7%)
unknown	0	1 (<1%)	0
Age Category in Males, n (%)			
<35 yrs	74 (6.0%)	66 (5.6%)	17 (3.5%)
35-54	564 (46%)	563 (48.1%)	224 (46.7%)
55-74	521 (42.5%)	492 (42%)	212 (44.2%)
≥ 75	65 (5.3%)	46 (3.9%)	27 (5.6%)
unknown	1 (<1%)	4 (<1%)	0
CHD Risk Factor (RF)			
CHD present	89 (4.6%)	104 (5.3%)	29 (4%)
No CHD, ≥ 2 RF	606 (31.5%)	598 (30.7%)	224 (31.1%)
No CHD, < 2 RF	1229 (63.9%)	1246 (64%)	467 (64.9%)
H/O DM	71 (3.7%)	67 (3.4%)	17 (2.4%)
CHD and DM	9 (<1%)	17 (<1%)	3 (<1%)
H/O HTN	410 (21.3%)	386 (19.8%)	147 (20.4%)
+ Family Hx	497 (25.8%)	508 (26.1%)	180 (25%)
Current smoker	186 (9.7%)	192 (9.9%)	53 (7.4%)
Age	1286 (66.8%)	1345 (69.0%)	494 (68.6%)
HDL < 35 mg/dL in Consult Population			
N	1,160	1,306	597
n (%)	129 (11.1%)	125 (9.6%)	71 (11.9%)

Source: NDA 21-198, vol 5, Tables 2.0.0, 9.0.0, 2.1.0, and 9.1.0

The baseline characteristics were similar across the 2 treatment groups (OTC and Rx) and the purchase population (subset of OTC group). The mean age was approximately 55 years old with approximately one-third of women enrolled and purchasing the medication being within the age category with a high likelihood of being premenopausal

Summarizing the demographics by CHD risk factor reveals that the majority of the study cohort and the population purchasing nonprescription pravastatin were within the primary prevention population with no CHD and fewer than 2 risk factors for heart disease. The most common risk factor present in all populations was age followed by family history of premature CHD. Individuals with established CHD or CHD with DM comprised a population for whom treatment of dyslipidemia should be administered by a healthcare professional; these patients accounted for a small percentage of the randomized and purchase population.

Lipid-Altering Results

Lipid-altering effects in the qualified and treated population were compared between the OTC and Rx-groups. There were 285 OTC subjects and 352 Rx subjects who were qualified and treated. Changes in LDL-C from baseline were evaluated in 253 OTC subjects and all qualified and treated 352 Rx subjects. Thirty-two OTC subjects were excluded from analysis because of missing cholesterol values in 2 subjects and initiation of drug treatment for at least 2 weeks prior to obtaining baseline labs in 28 subjects. Lipid values obtained at Assessment 2 were considered baseline in those OTC-randomized subjects who took less than 2 weeks supply of pravastatin or had not taken any lipid-lowering drugs.

The following table summarizes the changes in LDL-C values at weeks 8 and 24 in the qualified and treated population for both the OTC and Rx group. Subjects with missing data had a last observed value carried forward; complete data at 24 weeks were available in only 166 OTC and 250 Rx subjects. These numbers represented 33.3% of the OTC-treated population and 70.4% of the Rx-treated population.

Table 10. Percent Changes in LDL-C From Baseline at 8 and 24 weeks in OTC and Rx Treated and Qualified Population

Lipid Profile	OTC	Rx
Baseline, mg/dL	n=253	n=352
mean (SD)	161.3 (17.5)	162.6 (16.9)
median	162	163
range	97-215	109-203
% Change at 8wks		
mean (SD)	-18.2 (14.3)	-19 (13.1)
median	-19	-20
range	-57 to +21	-54 to +15
% Change at 24wks		
mean (SD)	-17 (16.4)	-18.4 (14.8)
median	-20	-20
range	-57 to +43	-53 to 42

Source: NDA 21-198, volume 7, Tables 22.1.0 and 22.3.0

The mean percent reduction for LDL-C values were similar at 8 and 24 weeks in both the OTC and Rx treatment group as analyzed for the qualified and treated population. At 8 weeks, those who were qualified and treated in the OTC group had a –18.2% reduction in LDL-C value compared to –19.0% in the Rx group. Similarly, at 24 weeks this change was –17.0% and –18.4%, respectively. These results are comparable to the mean percent reductions observed in the placebo-controlled efficacy trials for pravastatin 10 mg submitted to the original NDA (-17 to –22%).

Conclusions on Lipid-Altering Results of PREDICT

From the results of PREDICT, the sponsor concluded that treatment of subjects in the OTC environment with pravastatin 10 mg daily achieved similar LDL-C lowering to those subjects treated with prescription pravastatin at similar dosage and administration. This conclusion is not valid for the following reason:

The determination of lipid-response was only in a subgroup of treated individuals in both populations, with the OTC-treated population significantly underrepresented (50.7%) compared to the treated Rx population (99.2%).

Table 11. Difference in Lipid Response Data Ascertainment Between OTC and Rx Population

	OTC	Rx
No. of Subjects Treated	499	355
Qualified and Treated	285	352
No. of Subjects Considered in Lipid-Response Assessment	253 (50.7%)	352 (99.2%)

Estimates of drug effectiveness in the Rx-population was reasonably accurate since the number of subjects who took any amount of drug (i.e. treated population) was adequately accounted for in the efficacy analysis in this group. In contrast, estimates of the lipid-response to pravastatin treatment in the OTC-population are limited due to missing efficacy data in approximately half of the treated population.

Safety and Tolerability of Pravastatin 10 mg in PREDICT

Adverse Events Reported

Adverse events were summarized by treatment groups for those subjects who initiated treatment [499 (OTC); 355 (Rx)]. Reported clinical adverse events were collected in all subjects who took any amount of study medication. For those subjects who did not consult a physician, telephone calls were made at the end of study to ascertain clinical AEs. Laboratory AEs such as LFTs and CK levels, however, would only be available for those subjects who sought medical consultation after initiating therapy.

Overall Incidence of AEs Reported

A total of 133 (27%) and 144 (41%) AEs were reported in the OTC and Rx groups, respectively. Table 12 summarizes the incidence of AEs reported by body systems and lists the specific events with incidence rates > 2.0%.

Table 12. Incidence of AEs by Body System

Body System Category	OTC	Rx
Respiratory	34 (7%)	36 (10%)
URI	12 (2%)	6 (2%)
common cold	6 (1%)	9 (3%)
sinusitis	4 (<1%)	6 (2%)
Gastrointestinal	24 (5%)	10 (11%)
nausea	6 (1%)	8 (2%)
diarrhea	1 (<1%)	6 (2%)
abdominal pain	1 (<1%)	6 (2%)
constipation	0	6 (2%)
Musculoskeletal/Connective	28 (6%)	33 (9%)
back pain	2 (<1%)	6 (2%)
General	28 (6%)	22 (6%)
influenza	5 (1%)	6 (2%)
Nervous System	19 (4%)	26 (7%)
headache	8 (2%)	10 (3%)
insomnia	2 (<1%)	6 (2%)
Cardiovascular	12 (2%)	15 (4%)
Dermatologic	8 (2%)	15 (4%)
Renal/Genitourinary	12 (2%)	6 (2%)
Endocrine/Metabolic	6 (1%)	4 (1%)
Hepatic/Biliary	6 (1%)	3 (<1%)
Special Senses	6 (1%)	2 (<1%)
Immunology/Sensitivity	2 (<1%)	2 (<1%)

Disorder		
Drug Interaction	0	1 (<1%)
Hematopoietic	1 (<1%)	0

The most commonly reported AEs were GI-related in the Rx group and respiratory-related in the OTC group.

Incidence of Serious AEs Reported

Twelve SAEs were reported by OTC-treated subjects (2.4%) compared to 4 (1.1%) in the Rx-treated group. None of the reported AEs were considered related to study drug. Serious AEs involving the renal/genitourinary system accounted for the majority of reported cases in the OTC group [prostate cancer (2), bladder neoplasm (1), urolithiasis (1)] whereas there was no predominant body system reported in the Rx group.

Incidence of Drug-Related AEs

Of the AEs reported in the OTC (n=133) and Rx (n=144) groups, 45 (33.8%) and 42 (29.2%) were considered drug-related in each group, respectively. The body system in which the majority of drug-related AEs occurred was gastrointestinal followed by musculoskeletal/connective tissue. The most common drug-related symptom in the OTC group was myalgias (5; 3.8%) versus 2 (1.4%) in the Rx group.

Incidence of Discontinuations Due to AEs

Thirty-nine (7.8%) of OTC subjects exposed to pravastatin 10 mg discontinued treatment due to an AE compared to 16 (4.5%) subjects in the Rx group. The most common body system involved in the OTC group was musculoskeletal/connective tissue (9 cases) with myalgias, muscle cramps or weakness listed as the reason for discontinuation in 8 subjects. In the Rx group the most common body system involved was the nervous system (7 cases) with headache reported as the reason for discontinuation in the majority of cases. Myalgias or muscle aches were reported in 2 Rx-treated subjects.

Musculoskeletal and CK Abnormalities

Twenty-eight OTC-treated subjects (5.6%) reported musculoskeletal/connective tissue complaints compared to 33 (9.3%) in the Rx-treated group. Specific complaints of myalgias, muscle aches, or cramps were reported in < 1% of treated subjects for both groups. Creatinine kinase values were obtained in only 4 subjects reporting myalgias (3 OTC, 1 Rx) with the highest value reported in the Rx-treated subject [402 (normal 24-195)]. There were no reports of rhabdomyolysis or myoglobinuria.

Liver Abnormalities or Elevations of Hepatic Transaminases

The effects of pravastatin therapy on liver function tests (LFTs) were available in only a subset of those individuals who took study medication due to the lack of medical consultation in some of the OTC and Rx-randomized subjects. Of the 499 treated OTC subjects and 355 Rx subjects, LFTs were available in 209 and 324 individuals, respectively, at 8 weeks. The number of available patients significantly declined by weeks 16 and 24, making any conclusion regarding the LFT results in this trial tenuous.

Table 13. Number of Available Subjects with LFT Values During PREDICT

	OTC-treated n=499	Rx-treated n=355
ALT		
8 weeks	208	322
16 weeks	36	70
24 weeks	13	12
AST		
8 weeks	209	324
16 weeks	36	71
24 weeks	13	12

Abnormalities of LFTs were recorded as normal, high (1-1.5 x ULN), or very high (≥ 1.5 x ULN). Two OTC-treated subjects had very high ALT values observed versus 8 subjects in the Rx group and no AST elevations ≥ 1.5 x ULN compared to 4 in the Rx group. Since the number of treated OTC subjects with available LFT values was much lower than the Rx group no conclusion on the effects of pravastatin treatment on liver function tests in the OTC population can be made relative to the prescription population.

Conclusions on Safety and Tolerability Findings from PREDICT

Thorough evaluation of results from any clinical trial requires discussion of the study design, conduct, and acquisition of data. Given this premise, the safety assessment of the nonprescription use of pravastatin in PREDICT is limited for several reasons. The inability to capture all laboratory tests for safety in all subjects exposed to pravastatin treatment reduces the validity of the incidence rates provided by the sponsor. Although clinical adverse experiences occurring with pravastatin use were collected in all treated individuals, the reporting in the OTC group is subjected to recall bias in some individuals. For example, those participants who purchased study medication and never sought medical consultation were queried about clinical AEs at 24 weeks through telephone contact. It is plausible that an individual may have discontinued the study medication soon after initiation and forgotten the accurate reasons for discontinuation. In contrast, the collection of clinical AEs in the Rx group by a study physician was close to 100% (354 of the 355 treated subjects sought medical attention), increasing the reliability of these reports.

Despite the incompleteness of safety assessments from PREDICT it is reassuring that there were no reported cases of serious hepatic injury or rhabdomyolysis. From the available data, a more toxic profile for pravastatin in the nonprescription setting was not apparent. The absence of these adverse events, however, does not indicate that nonprescription pravastatin use does not share similar safety concerns as seen in the prescription environment. The rare, and potentially life-threatening side-effects attributed to pravastatin use are frequently detected in spontaneous, post-marketing reports and are not observed in controlled clinical trials of short duration.

Finally, the tolerability of nonprescription pravastatin use compared to prescription use appeared worse in the nonprescription population. The percentage of OTC-treated subjects discontinuing treatment secondary to AEs (7.8%) was higher than the Rx group (4.5%) and AE-related discontinuation rates obtained from the 10 mg placebo-controlled trials (4.0%). Since the treatment of hypercholesterolemia requires chronic lifestyle modification and intervention, the poor tolerability rates in the OTC group as demonstrated in this trial of relatively short duration calls into question the overall benefit

to the population in the management of hypercholesterolemia if adherence to chronic medication use is poor.

CONCLUSIONS ON PREDICT

In summary, PREDICT was a 24-week open-label study in which consumers were randomized to receive treatment with pravastatin 10 mg as a nonprescription drug or receive treatment as a prescription drug as provided only through a study physician. The primary objective was to determine the proportion of OTC randomized subjects who, having purchased OTC pravastatin, **consulted a physician** within 2 months of using the study medication. Other objectives included comparing lipid-altering efficacy in the qualified and treated population of both OTC and Rx-treatment groups, determine overall safety and tolerability, and evaluate consumer behavior in both treatment groups.

The endpoint measure of interest in DMEDP was cholesterol-lowering in the nonprescription versus prescription population. This trial, however, did not provide reliable data for drug efficacy of pravastatin 10 mg in the nonprescription environment. The poor efficacy data ascertainment in the OTC-treated group versus near complete data collection in the Rx group (50.7% vs. 99.1%) does not support the assertion that use of pravastatin 10 mg per day will result in similar LDL-C reduction in the OTC population as observed in the prescription setting. Since the efficacy data in 49.3% of those individuals in the OTC group who took any amount of drug were never obtained, an accurate estimate of the lipid response to drug treatment in the OTC population cannot be determined.

OTC PRAVACHOL TRIAL IN AN OBSERVED NATURALISTIC SETTING (OPTIONS)

Study Design

OPTIONS was a 3-month, multicenter, pharmacy-based, open-label, actual-use study evaluating pravastatin 10 mg daily use among subjects enrolled in Health Maintenance Organizations (HMOs).

Study Centers and Investigators

The study was conducted at 20 pharmacy sites located in 6 states. Fourteen of these sites were pharmacies affiliated with staff model HMOs and 6 were retail pharmacies participating with an Independent Practice Association (IPA) model HMO. A staff model HMO refers to a health plan that owns its own clinics and employs salaried physicians and other health care professionals providing care exclusively to the HMO enrollees. IPA model HMO refers to a health plan where physicians operated their own private practices but had managed care contracts with the selected HMO.

The investigators included non-medical interviewers, registered pharmacists, and HMO-employed or contracted physicians. The interviewers were responsible for the study enrollment, providing the interested subjects with the prototypical advertisements and price of nonprescription pravastatin, administration of the medical questionnaire and literacy test, obtaining the consent forms, and informing the primary care physician of a subject's study enrollment. For those subjects who purchased medication, the interviewer was responsible for selling, dispensing, and tracking the return of study medication.

The pharmacist was available for subject counseling if requested and were instructed to utilize the study medication package label during the counseling session. If the subject inquired about the appropriateness of drug treatment the pharmacist would recommend that the individual review the package label and make his/her decision as if the drug were any other OTC medication.

The study physician reviewed the medical history for cardiovascular risk factors and other medical histories, assessed adverse event reports, documented if the subject initiated contact with a healthcare professional after study enrollment, and made recommendations on the appropriateness of pravastatin 10 mg treatment. The study physician also oversaw the primary care physicians and served as the medical contact for study related issues.

Study Objectives

Primary

1. to determine the proportion of subjects who, having purchased Pravachol 10 mg, contact their health care provider within 2 months of using the medication to discuss the appropriateness of therapy with Pravachol 10 mg
2. to determine the proportion of subjects who, having purchased Pravachol 10 mg, do not take it subsequent to contacting their health care provider and being told that therapy is not recommended

Secondary

1. to determine the proportion of subjects who, having purchased Pravachol 10 mg, contact their health care provider within 2 months of product use and/or self-select appropriately in accordance with the label, as defined as: no coronary heart disease; no diabetes; no liver disease; not pregnant; or not currently using prescription lipid-lowering medication
2. to evaluate the safety of Pravachol 10 mg in an OTC-like environment

Tertiary

1. to describe the study population (all enrolled subjects) with respect to the decision to purchase or not to purchase pravachol 10 mg
2. to determine the appropriateness of the product purchase decision amoung subjects who do not purchase with respect to behavior to contact a health care provider and in the absence of a health care provider, the medical history of each subject

The endpoint of interest in this review will be the safety of pravachol 10 mg in this study cohort. There are no lipid-altering efficacy data for review. Although compliance, subject behavior, and product label comprehension are discussed briefly in this review, a detailed evaluation of these endpoints are reviewed separately in DOTCDE and DDMAC.

Eligibility Criteria

Inclusion Criteria

- male or female ≥ 18 years of age
- a member of the participating HMO for at least 6 months

Exclusion Criteria

- participation in a research study within the last 30 days
- women who were pregnant or breastfeeding

Study Subject Recruitment

Study subject recruitment employed newpaper and radio advertising and mailers were sent to a random sample of the HMO enrollees. Subjects visiting participating pharmacies for other reasons were also exposed to advertisement displays. The message on all of the advertising materials indicated that generally healthy individuals with total-C levels between 200 and 240 mg/dL had a opportunity to participate in a study where they may be able to take a proven prescription cholesterol-lowering drug without a prescription.

Study Subject Screening and Study Visits

Assessment 1

Individuals responding to mailers or advertisements by visiting the participating pharmacy were directed to the non-medical interviewers and HMO membership was verified. After an informed consent was obtained granting study personnel permission to interview the study candidate, a prototypical product advertisement and price of study medication were presented to the subject. A questionnaire designed to collect demographic data and a literacy test were administered. If the subject was interested in purchasing the study medication he/she was screened for inclusion/exclusion criteria, asked to sign a second written informed consent and asked to provide written permission for study personnel to review medical records. Subjects qualifying for study participation were allowed to return to the pharmacy for purchase of study medication up

to 3 months after the initial visit date. No further contact was initiated by study personnel until the 12 week follow-up assessment (Assessment 2).

All data obtained from screened subjects were sent to their primary care physicians with a standard notification letter, a risk factor assessment form, and a physician contact form. The notification letter indicated that the patient had elected to participate in this trial and had the option to purchase pravastatin 10 mg. The letter also requested that the physician not contact the patient unless treatment with pravastatin presented a substantial risk. The subject's medical history obtained from the screening questionnaire was confirmed by the primary care physician on the risk factor assessment form along with whether the physician recommended treatment. Any physician contact initiated by the subject was documented on the contact form. Completion and return of these forms to the pharmacy study site were required for additional purchase of study medication by the study subject.

Assessment 2
All screened subjects were assessed at 12 ± 4 weeks after the initial visit or product purchase date, whichever occurred later. Contact was initiated by telephone in order to collect information on behavior to contact the primary care physician, lifestyle modifications, medication compliance, and safety. All subjects who purchased medication were asked to return all unused drugs and empty blister cards to the pharmacy site.

Study Medication Dispensing
All subjects meeting inclusion/exclusion criteria and have a signed written informed consent were allowed to purchase an initial 1 month supply of pravastatin 10 mg. Subjects who initiated medical consultation and were considered appropriate candidates for treatment were allowed repurchase of up to 3 months supply.

All study subjects purchasing drug were reimbursed for the cost of study medication at the end of the study but were not informed of this at any point before the final visit.

Results of OPTIONS
Study Population
The following study populations were generated post-screening:
Enrolled population: This population referred to all subjects who completed the assessment 1 questionnaire.
Purchased population: This population referred to any subject who purchased the study medication regardless of use.
Consulted population: This population referred to any subject who consulted a health care provider at any time regarding the appropriateness of using pravastatin 10 mg.
Treated population: This population referred to any subject who took at least one dose of pravastatin 10 mg.

Subject Disposition and Demographics
Population Receiving and Responding to Advertisement and Population Eventually Enrolled in Study
A total of 161,322 HMO members were mailed the study announcements at least once. Newspaper and radio advertising were also used for recruitment in the IPA model HMOs but statistics on number of subjects receiving this method of advertising are not attainable.

Of the 161,322-plus individuals who were targeted in the study recruitment phase, only 2,207 responded and were screened (approximately 1.4% of recruited population). Of these individuals who responded by visiting the pharmacy site, only 782 enrolled in the trial. Table 14 summarizes the population response to study advertisement and although incomplete, reasons why individuals chose not to enroll in the study are also provided.

Table 14. Summary of Population Responding to Study Advertisements

	N
Population Targeted in Advertising Campaign	161,322-plus*
Population Responding to Advertising	2,207
Population Enrolled	**782**
Population Choosing Not to Enroll	1,425
Reasons Provided for Not Enrolling	
Just curious	594
Time	252
Other	246

* an underestimate since data not attainable for number of subjects receiving radio and print advertisements

Purchased Population

Of those who were interested in study participation and met inclusion/exclusion criteria (i.e. enrolled), 404 purchased pravastatin 10 mg. The demographics comparing the enrolled and purchase population are summarized in Table 15.

Table 15. Baseline Demographics of Enrolled and Purchase Population in OPTIONS

	Enrolled N=782	Purchase N=404
Age		
mean (SD)	51 (10)	51 (10)
range	18-80	18-80
Gender		
Male	356 (46%)	200 (50%)
Female	423 (54%)	204 (50%)
Missing	3 (<1%)	0 (0%)
Age Group		
<35	43 (5%)	14 (3%)
35-54	251 (58%)	233 (58%)
55-74	274 (35%)	153 (38%)
≥75	9 (1%)	4 (<1%)
unknown	5 (<1%)	0 (0%)
Age Category in Females, n (%)		
<35 yrs	27 (6%)	7 (3%)
35-54	239 (57%)	115 (56%)
55-74	152 (36%)	80 (39%)
≥ 75	4 (<1%)	2 (<1%)
unknown	1 (<1%)	0
Age Category in Males, n (%)		
<35 yrs	16 (4%)	7 (4%)
35-54	212 (60%)	118 (59%)
55-74	122 (34%)	73 (37%)
≥ 75	5 (1%)	2 (1%)

	Enrolled N=782	Purchase N=404
unknown	1 (<1%)	0
Race		
Asian	21 (3%)	11 (3%)
Black	166 (21%)	70 (17%)
Hispanic	36 (5%)	17 (4%)
Native American	10 (1%)	7 (2%)
Caucasian	533 (68%)	296 (73%)
Other	5 (<1%)	3 (<1%)
Unknown	11 (1%)	0 (0%)
CHD Risk Factor (RF)		
CHD present	44 (6%)	20 (5%)
No CHD, ≥ 2 RF	183 (41%)	96 (39%)
No CHD, < 2 RF	231 (52%)	137 (55%)
H/O DM	87 (13%)	39 (10%)
CHD and DM	15 (2%)	6 (2%)
H/O HTN	270 (39%)	135 (35%)
+ Family Hx	236 (31%)	119 (29%)
Current smoker	90 (12%)	50 (12%)
Age	391 (50%)	218 (54%)
HDL < 35 mg/dL	57 (12%)	27 (10%)

Source: NDA 21-198, volume 41, tables 2.0.0, 6.0.0, 2.1.0, and 6.1.0

The two populations were similar with respect to baseline demographics and characteristics. Similar to the characteristics of the PREDICT study population, the majority of individuals in OPTIONS were without established CHD and < 2 risk factors. The proportion of women enrolling and purchasing in this study, however, was higher than observed in PREDICT with 54% of the enrolled population and 50% of the purchased population in OPTIONS comprised of women. When evaluating the age distribution by gender, more than half the women purchasing pravastatin as an over-the-counter product were within the age category for which there would be a greater likelihood of being premenopausal (age categories <35 yrs or 35-54 yrs).

Lipid-altering effects of pravastatin 10 mg were not evaluated in this trial; however, the most recent lipid profiles were available in 80% (n=323) of the purchase population from medical records surveyed (Table 16).

Table 16. Lipid Profile in Subset of Purchased Population Prior to Study Enrollment

Lipid Parameter	Purchased Population n=323
Total-C mg/dL	
mean (SD)	239 (56)
range	115-1033
median	235
LDL-C mg/dL	
mean (SD)	150 (30)
range	48-231
HDL-C mg/dL	
mean (SD)	51 (17)
range	20-184
Triglycerides mg/dL	
mean (SD)	215 (463)
range	10-7836

The lipid profiles available in a subset of the purchase population reveals that approximately half of the purchase population with available baseline lipid data had total-C levels above the range for which the nonprescription pravastatin label is recommended.

Treated Population
Three hundred and twenty-one (321) subjects took any amount of study drug. This population was evaluated for safety and tolerability to pravastatin 10 mg. Approximately half (147; 45.8%) of these subjects never consulted a physician.

Study Drug Discontinuation
Of those subjects who initiated therapy with pravastatin 10 mg (n=321), approximately half discontinued treatment prematurely (51.4%); the mean duration of treatment was 51 days. The reasons for study drug discontinuation are listed in table 17.

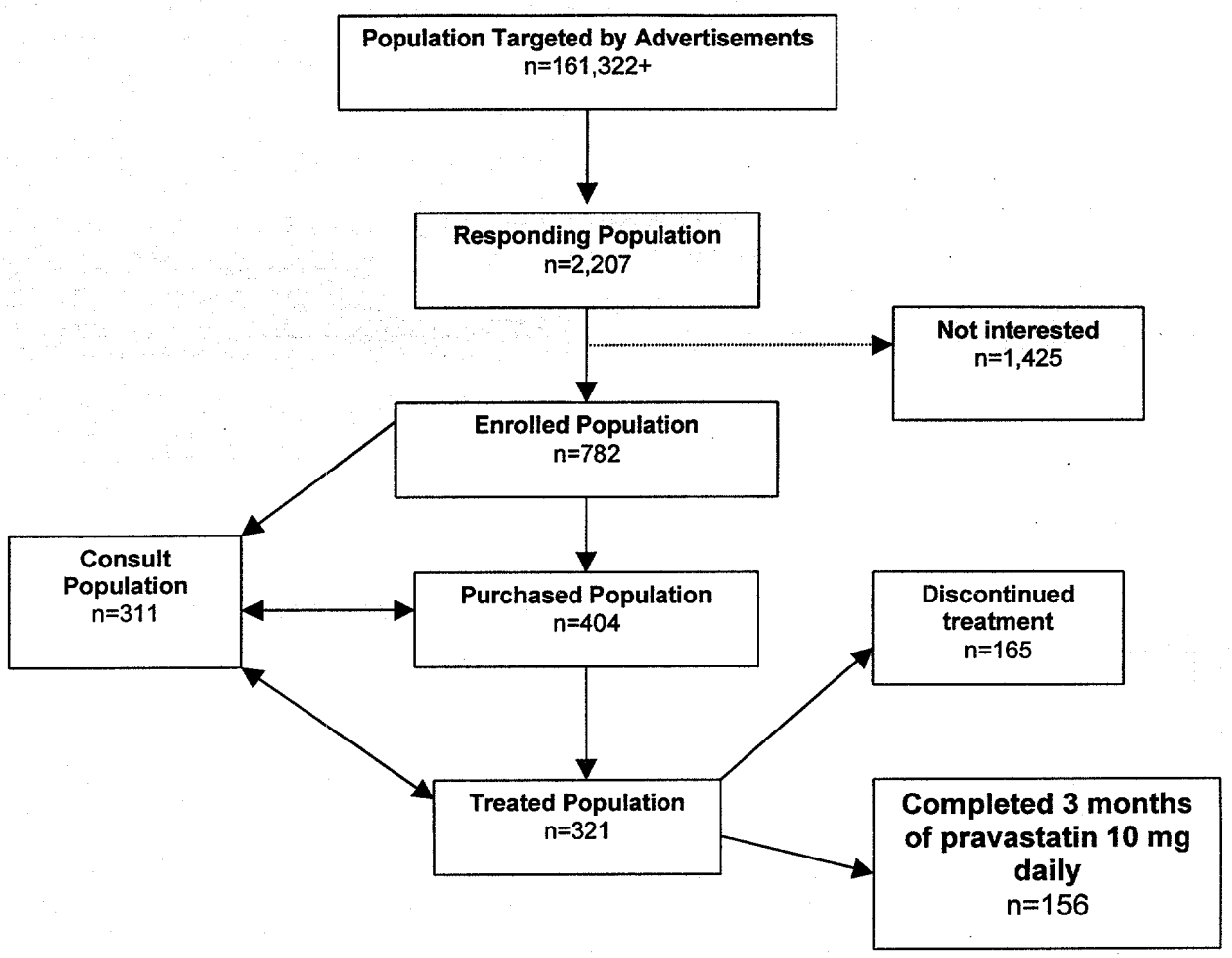
Table 17. Reasons for Discontinuing Study Medication

Reason for Study Drug Discontinuation	Treated Population N=321
Non-compliance	68
Wanted MD advice first	14
Denied repurchase because no MD consult initiated	4
Adverse events	22
MD did not recommend treatment	20
Intercurrent illness	7
Other	8
Unknown	19
Treatment failure	2
Lost to follow-up	1
Total	**165**

The most common reason for discontinuing drug treatment was non-compliance. This category encompassed reasons listed as too busy, forgot to take, inconvenient pharmacy hours etc. The second most common reason for study drug discontinuation was adverse events. This will be discussed under the safety review of this trial.

Overall, only 156 subjects purchased and took the study medication for the entire study duration of 3 months. This number represents 48.6% of the treated population (n=321), 38.6% of the purchased population (n=404), and 19.9% of the enrolled population (n=782). Figure 4 summarizes the study schematic of OPTIONS.

Figure 8. Study Schematic and Subject Disposition in OPTIONS



Safety of Pravastatin 10 mg in OPTIONS

Overall Incidence of Adverse Events

There were 80/321 (24.9%) participants who reported 138 adverse events while receiving treatment with pravastatin. The AEs were categorized by body systems with the most frequently reported events involving the gastrointestinal or dermatologic body systems (7%) followed by general or musculoskeletal/connective tissue body systems (4%). The following table summarizes AEs reported in the treated population categorized by body systems with the individual events occurring at ≥ 2% incidence rates listed.

Table 18. Overall Incidence of AEs Reported

	Treated population n=321
Total number of subjects reporting AEs	80 (24.9%)
Gastrointestinal nausea	23 (7%) 5 (2%)
Dermatologic	21 (7%)
General	14 (4%)
Musculoskeletal/connective tissue	14 (4%)

Respiratory sinusitis	13 (4%) 5 (2%)
Nervous system	10 (3%)
Cardiovascular	8 (2%)
Special senses	8 (2%)
Endocrine/Metabolic/Electrolyte Imbalance	4 (1%)
Renal/Genitourinary	4 (1%)
Hepatic/Biliary	1 (<1%)
Immunology/Sensitivity Disorder	1 (<1%)

Serious Adverse Events
Five individuals (1.6%) treated with pravastatin reported a serious AE; none of these were considered drug-related. These events were pancreatitis, squamous cell carcinoma of the skin, pericardial cyst, thyroid nodule, and heartburn. All SAEs resolved with interventions other than study drug discontinuation. No deaths occurred in this trial.

Adverse Events Resulting in Study Discontinuation
Twenty-two individuals (6.9%) experienced an AE that resulted in study discontinuation. Nine of these people described events involving the gastrointestinal body system with nausea (4), diarrhea (2), and abdominal cramps (2) comprising the common complaints.

Drug-related Adverse Events
Thirteen subjects (3.7%) reported 17 AEs that were considered drug-related. Almost half of these events were GI-related (8) followed by 5 events occurring in the nervous system [dizziness (3), anxiety (1), insomnia (1)].

Myalgias and Liver-Related Adverse Events
Only 2 people (<1%) reported myalgias during this trial; none were considered serious, drug-related, or required study discontinuation.

Twenty-three individuals (7.2%) reported a total of 26 AEs within the GI body system and 1 person reported an increase in alkaline phosphatase level. Abnormalities in CK levels and hepatic enzymes were not reported since labs were not routinely obtained as per the study protocol.

Conclusions on Safety and Tolerability of Pravastatin 10 mg in OPTIONS
The most commonly reported adverse event experienced in this 12-week actual-use trial was nausea, a labeled event occurring at incidence rates >2% in other controlled clinical trials. The gastrointestinal body system accounted for the majority of AEs that resulted in study discontinuation, were considered drug-related, or were serious. None of the GI-related events were reported as hepatic injury. The incidence of myalgias in this trial (0.6%) was lower than observed in the pooled evaluation of the 3 placebo-controlled trials involving pravastatin 10 mg per day which reported an incidence of 2.3%.

The study drug discontinuation rate was similar to that observed for the OTC-group in PREDICT (51.4% vs. 58.3%, respectively) with AEs accounting for a similar proportion of reasons for discontinuation in both trials (13.3% vs. 13.4%, respectively). The discontinuation rate in the nonprescription group is significantly higher than seen in controlled clinical trials involving the 10 mg doses of pravastatin. In the 3 placebo-controlled trials of 8 to 12 weeks duration, the discontinuation rate was <5% for the pravastatin-treatment groups. Although some of this disparity can be attributed to physicians recommending treatment discontinuation in the OTC group the overall

adherence to drug therapy is still lower in the OTC group compared to the prescription environment.

CONCLUSIONS ON OPTIONS

In summary, OPTIONS was a 12-week, open-label study evaluating the consumer behavior in response to the availability of pravastatin 10 mg as an over-the-counter medication and the safety profile of pravastatin 10 mg in those individuals who chose to purchase and take the medication among enrollees in an HMO.

OPTIONS is unique from PREDICT and other controlled-clinical trials in that unrestricted access to all enrolled subjects' medical records provided investigators the opportunity to describe the baseline characteristics and to observe responses to treatment in an environment mimicking the usual healthcare setting. The findings from this trial may be predictive of the consumer's response to the availability of nonprescription lipid-altering drugs.

The sponsor's primary objective was to determine what proportion of the purchase population would contact his/her healthcare provider within 2 months of purchase to discuss use of nonprescription pravastatin. Of the 404 individuals who purchased study medication, 178 (44%) consulted a physician within 2 months. Although the sponsor provided a 95% confidence interval for this value, it is unclear what the clinical significance of this finding represents.

This reviewer finds more revealing, the extremely small number of individuals who express an interest in nonprescription pravastatin to purchase the medication, initiate treatment, and remain on treatment for 3 months. The clinical benefit of a lipid-altering drug in the treatment of hypercholesterolemia can only be realized if an individual remains on treatment chronically. A study discontinuation rate of > 50% in this 12-week trial suggests that most individuals will not remain on nonprescription pravastatin therapy to derive a clinical benefit.

COMMENTS ON THE OTC CLINICAL DEVELOPMENT PROGRAM

Bristol-Myers Squibb proposes that lovastatin 10 mg per day is an effective and safe over-the-counter treatment approach to lowering cholesterol in a selected population with mild-to-moderate cholesterol elevations but no evidence of CHD or diabetes. This effectiveness will allow most individuals to achieve their NCEP cholesterol goals and lower their risk for CHD. The targeted population consists of people with total-C levels between 200 and 240 mg/dL and LDL-C > 130 mg/dL.

In support of an indication for nonprescription use of pravastatin 10 mg, the sponsor conducted 2 consumer-use trials, and a label comprehension study. The label comprehension study was reviewed in DOTCDE and DDMAC. The 2 consumer-use trials reviewed in DMEDP were:

1. The Pravachol Experience Documented In a Consumer Trial (PREDICT): a 24-week, randomized, open-label trial comparing pravastatin 10 mg provided as a nonprescription drug versus pravastatin 10 mg provided as a prescription drug
2. OTC Pravachol Trial In an Observed Naturalistic Setting (OPTIONS): a 3-month, open-label, uncontrolled study of the consumer behavior to the availability of nonprescription pravastatin

During the review of this application, the following questions were addressed by this reviewer:

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

This section will answer each of these questions based on the review of the nonprescription pravastatin clinical development program.

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

The lipid-altering efficacy of pravastatin 10 mg per day was evaluated in PREDICT. In this trial, study participants were randomized to receive pravastatin 10 mg as a nonprescription drug (OTC group) or pravastatin 10 mg as a prescription drug (Rx group). Subjects in the OTC group were reported to have an approximate 17-18% reduction in LDL-C levels after 8 and 24 weeks of treatment compared to 18 to 19% reductions observed in those subjects randomized to the Rx group. Based on these data, the sponsor concluded that treatment in the OTC environment with daily pravastatin 10 mg dosing achieves similar lipid-lowering results as demonstrated with the prescription drug.

The conclusion that daily use of pravastatin 10 mg by the nonprescription population would result in a similar lipid-lowering response as the prescription drug population with an expected LDL-C reduction of 17 to 18% is invalid for the following reason:

- The lipid response data were not adequately ascertained in the OTC-treated population compared to the Rx-treated population.

Table 19. Difference in Lipid Response Data Ascertainment Between OTC and Rx Population

	OTC	Rx
No. of Subjects Treated	499	355
Qualified and Treated	285 (57.1%)	352 (99.1%)
No. of Subjects Considered in Lipid-Response Assessment	253 (50.7%)	352 (99.2%)

In conclusion, given that the lipid-response in 49.3% of those individuals in the OTC group who took any amount of drug was never ascertained, an estimate of response to pravastatin treatment in the OTC population cannot be adequately determined.

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

The outcome of interest in patients treated with lipid-lowering agents is reduction in morbidity and mortality due to cardiovascular events. Pravastatin is approved for the reduction in risk of experiencing MIs, undergoing myocardial revascularization, and cardiovascular mortality in the hypercholesterolemic patient population without clinically evident coronary heart disease. This approved labeling was based on data obtained from the West of Scotland Primary Prevention Study (WOSCOPS). The patient population in this study was comprised of only men between 45 to 64 years of age with mean total-C and LDL-C levels of 272 mg/dL and 192 mg/dL, respectively. The clinical outcome data from this primary prevention population cannot be extrapolated to the nonprescription population for several reasons.

- The pravastatin dose studied in WOSCOPS was 4 times higher than the proposed nonprescription pravastatin dose.
- The mean LDL-C reduction in WOSCOPS (26.0%) was higher than that in current trials of the 10 mg dose (17 to 18%).
- A significant proportion of the population enrolled in WOSCOPS would not be qualified for treatment with nonprescription pravastatin based on significantly elevated baseline cholesterol levels.
- The treatment duration in WOSCOPS was an average of 4.9 years with a study discontinuation rate of 29.6% after 5 years. In contrast, the consumer-use studies were of 12 and 24 weeks duration with study discontinuation rates being greater than 50% in both trials.

In summary, there are no clinical outcome data for the 10 mg dose of pravastatin in the OTC population nor can the clinical outcome data derived from WOSCOPS be predictive of clinical benefit for nonprescription pravastatin use.

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

Of the individuals initiating therapy with pravastatin 10 mg per day in PREDICT (n=499), only 208 (41.7%) remained on treatment at the end of 6 months. Similarly, in OPTIONS the number of treated participants (n=321) remaining on therapy after 12 weeks was only 156 (48.6%). Hypercholesterolemia is an asymptomatic chronic condition with

complications arising often many years after diagnosis. So too, its treatment is long term. ***The study discontinuation rates of >50% after only 12 and 24 weeks of treatment observed in both consumer-use trials undermines the effectiveness of nonprescription pravastatin therapy for this chronic asymptomatic condition.***

The results of PREDICT also demonstrate that ***adherence to pravastatin therapy is better when the patient is receiving the treatment as a prescription drug requiring physician management versus when he/she takes the medication as an over-the-counter product.*** The percentage of the treated population discontinuing medication was 58.3% in the OTC group compared to 19.2% in the Rx group.

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

The 2 consumer-use trials suggest that consumers may not be able to make appropriate decisions regarding nonprescription treatment of hypercholesterolemia in the following situations:

- individuals for whom nonprescription pravastatin would be inappropriate treatment because they had ideal cholesterol levels or they required more aggressive treatment

Of the OTC patients in PREDICT who consulted a study physician (n=977) regarding the use of nonprescription pravastatin, 662 (67.8%) of these were told they were ineligible for treatment. Of those ineligible for treatment, the most common reason provided was 'already at NCEP goals' (n=420; 63.4%) followed by 'qualified for more aggressive treatment' (n=189; 28.5%).

The targeted total-C range for nonprescription pravastatin treatment as proposed by the package label is 200 to 240 mg/dL. Approximately half of those individuals purchasing nonprescription pravastatin in OPTIONS had a baseline total-C level higher than 240 mg/dL.

- individuals who have minimal risk of developing CHD and therefore do not require the need for drug therapy

An example of low-risk individuals not requiring drug treatment include premenopausal women. Although CHD is the leading cause of mortality for both men and women, the risk of CHD in women is not evident until after menopause. The proposed product label for nonprescription pravastatin include treatment of adults over age 18. This proposal would include the treatment of premenopausal women. These individuals represent a group of patients for whom the risk of CHD are minimal but early and long term exposure to drug therapy may increase the risk for drug-related toxicities, including unknown risk to the pregnant or nursing woman.

The consumer-use studies demonstrate that in those women who were interested in buying the nonprescription product, a significant proportion of these fell into a low CHD risk category by age. Evaluation of the gender characteristics for both consumer-use trials reveals that a significant number of women interested in using this product may be in the childbearing and/or premenopausal age group. ***In PREDICT, 36.3% of the female purchase population were younger than 55 years of age. In OPTIONS, 59% of the female purchase population fell into this age range.***

CONCLUSIONS ON THE REVIEW OF NDA 21-198

The determination of whether a drug should be made available for nonprescription use requires a thorough evaluation of the benefit-to-risk relationship of the drug within the targeted population. As previously argued, the benefit associated with pravastatin 10 mg use in the targeted OTC population has not been adequately studied with respect to lipid-altering efficacy and no reductions in cardiovascular morbidity or mortality have been established for either this dose or this patient population. The risk of nonprescription pravastatin use in this setting includes not only the drug-related toxicities (e.g. rhabdomyolysis) but also the risk associated with the inadequate or inappropriate treatment of dyslipidemia.

The results of the 2 consumer-use studies suggest that the unrestricted availability of pravastatin results in the following:

- poor adherence to drug treatment in the nonprescription environment compared to the prescription environment
- inappropriate initiation of treatment by certain individuals, particularly the individuals at low-risk for CHD

The lack of physician oversight in the management of this asymptomatic chronic condition may result in the undertreatment of high-risk CHD patients, overtreatment of low-risk CHD patients, and inappropriate treatment of individuals at risk for experiencing drug-related adverse events.

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