Joint Meeting of Nonprescription Drugs Advisory Committee and Endocrinologic & Metabolic Drugs Advisory Committee

July 14, 2000

Advisory Committee Meeting Briefing Book

For the Rx-to-OTC Switch of:

NDA 21-198 Pravachol® (Pravastatin Sodium)10 mg Tablets

Bristol-Myers Squibb
Worldwide Consumer Medicines
1350 Liberty Avenue
Hillside, New Jersey 07207-6050

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT READACTION

Executive Summary

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This briefing book presents the data to be discussed at the Joint Meeting of the Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committees on July 14, 2000. The Committees will be asked to consider the switch of Pravachol 10 mg daily from prescription (Rx) to over-the-counter (OTC) status for use in conjunction with diet and exercise to lower low density lipoprotein cholesterol (LDL-C). The OTC proposition is described as follows:

- Intended dose: Pravachol 10 mg once daily
- Use: Cholesterol lowering with diet and exercise
- Target population: Men > 35 years and women > 45 years who:
  - Have been told by physician to lower cholesterol
  - Are not at desirable cholesterol level despite diet modification and exercise
  - but not taking prescription therapy
- Total cholesterol: 200 – 240 mg/dl, LDL-C > 130 mg/dl
- No coronary heart disease (CHD) or diabetes

Rationale for OTC Pravachol 10

Despite extraordinary therapeutic advances over the last decades, cardiovascular disease (CVD) remains the number one killer of adults in the United States. CVD (of which most is CHD) can be largely prevented by control of many of the etiologic factors responsible for the development of the pathogenic atherosclerotic plaque. One of the major approaches to such control is lowering of blood LDL-C concentrations. For primary prevention, the National Cholesterol Education Program (NCEP) defines desirable Total-C as <200 mg/ml and desirable LDL-C levels as <130 mg/ml and ideally, all persons without established CHD should have cholesterol levels below these values. Indeed, most coronary events occur in individuals with cholesterol levels considered “normal” or only moderately elevated. Thus, there is an opportunity to reduce the burden of CHD by preventing its occurrence in those who are at risk but not yet afflicted.

For patients in whom long-term risk is high or lifestyle changes have been inadequate, use of lipid lowering drugs may be warranted. There is, however, a large population with mildly elevated cholesterol at risk for development of CHD who will not reach desirable levels with dietary intervention alone. Despite the overwhelming evidence from large clinical trials that certain HMG-CoA reductase inhibitors can save lives and prevent illness in both primary and secondary prevention across a wide spectrum of lipid levels and cardiovascular risk, most appropriate candidates are not receiving optimal therapy. In fact, it is estimated that less than 15% of eligible people who have had a prior cardiac event are receiving lipid lowering therapy; this proportion falls to less than 5% of those in the primary prevention category. Indeed, despite large expenditures on DTC advertising, the growth of the HMG-CoA reductase market has slowed.

This is counter balanced by consumer interest in self-care, especially for disease prevention. Consumers are increasingly turning to, and physicians are recommending, non-prescription LDL-C lowering adjuncts such as fiber, plant stanols/sterols and soy protein. Consumers are also frequently utilizing other less well-characterized over-the-counter therapies. As we consider the spectrum of choices individuals are making, it is reasonable to include the OTC option of Pravachol 10 mg which has an excellent and well established safety profile and provides predictable and meaningful LDL-C reduction to this lower risk population.

OTC Pravachol Program

The OTC Pravachol program was designed to evaluate whether Pravachol 10 mg could be used safely and responsibly in an OTC setting as an adjunct to diet and exercise to improve cholesterol management. The overall program and individual study designs were developed to address questions and issues surrounding the OTC availability of lipid lowering medications that have been extensively discussed with both the FDA over time, and with the Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committees concerning the OTC Switch application of another lipid lowering agent [NDA, #20-879 (QUESTRAN) and #20-880 (QUESTRAN LIGHT)] held on September 27, 1995 and May 13, 1997.

The OTC Pravachol Program was designed specifically to address the issues previously raised by the FDA and Advisory Committees during review of the Questran submission. The key questions addressed in the clinical program for OTC Pravachol pertain to 1) the properties of the molecule itself and 2) availability and use in an OTC environment, and are outlined below:

<u>The Molecule</u>

- The first priority of the OTC Pravachol 10 mg program was to establish that Pravachol has an excellent and well established safety profile that is predictable, well characterized and fits within the spectrum of currently available OTC therapies where there could potentially be less involvement of a learned intermediary. Specifically, the following questions were addressed:
  - What is the potential for drug interactions in a broader population taking multiple medications?
  - What is the consequence of consumers overdosing or taking more than the label recommends?
  - What is the consequence to women who inadvertently become pregnant while taking the product?
  - What is the risk for myopathy?
  - What is the potential for liver injury and is biochemical monitoring of hepatic enzymes necessary?

- The next objective of the program was to establish that the biologic activity of Pravachol 10 mg is adequate and appropriate for the OTC population. The OTC dose was selected from the results of randomized placebo-controlled studies. The

goal of consumer use studies was to assess whether similar LDL-C reduction could be achieved in a less supervised environment.

The efficacy and safety of pravastatin have been extensively documented. These issues were addressed using the following data:

1) Randomized, placebo-controlled dose response studies in the original NDA that utilized Pravachol 10 mg: Protocols 27201-2, 27201-42 and 27201-89.

2) The Pravastatin Pooling Project (Prava 3) that was pre-specified, integrated safety analysis of the three long-term placebo controlled studies which evaluated the effect of Pravachol 40 mg on cardiovascular morbidity and mortality:

- WOSCOPS (West of Scotland Coronary Prevention Study), Protocol CV27201-66)
- CARE (Cholesterol and Recurrent Events), Protocol CV2721-67
- LIPID (The Long Term Intervention with Pravastatin in Ischaemic Disease), Protocol CV27201-95)

It was anticipated that this safety database of 19,768 subjects studied for a mean duration of 4.6 years, comprising > 100,000 patient years experience (64,000 patient years of pravastatin 40 mg therapy) would permit detection and assessment of clinically meaningful uncommon adverse events and laboratory abnormalities. Specifically, it was intended that this analysis could provide an accurate assessment of musculoskeletal adverse events (AEs) and CPK elevations. In addition, analysis could provide an assessment of the effect of Pravachol 40 mg on transaminase levels and whether biochemical monitoring was necessary.

3) In addition to pharmacokinetic studies conducted to support the prescription NDA, many additional studies, mostly at doses higher than the intended OTC dose, assessed the likelihood of clinically significant drug interactions, particularly with drugs metabolized by the cytochrome P450 3A4 system.

4) In order to assess the safety of Pravachol 10mg in the event that it was taken inadvertently by a pregnant woman, both preclinical and clinical data were extensively reviewed.

5) To assess safety in the broader population represented by general prescription use, Post Marketing Surveillance information collected by Bristol-Myers Squibb (BMS) from February 29, 1990 to May 31, 1999 which represents >22 million patient years was analyzed. Since no new safety issues emerged, special emphasis was placed on adverse events in the hepatobiliary and musculoskeletal body systems.

OTC Use

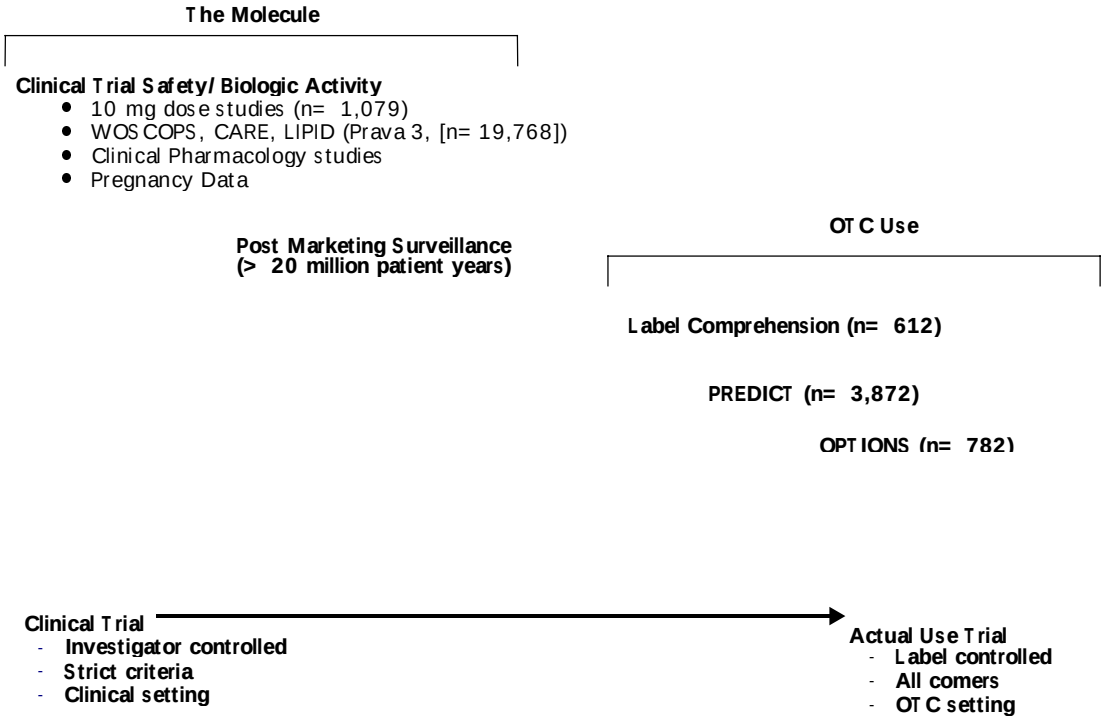
While traditional clinical trials evaluate the safety and efficacy of the molecule, the purpose of consumer use studies is to evaluate the efficacy of the OTC label in directing consumers to behave appropriately.

The key issues that were addressed in consideration of OTC status for Pravachol 10 mg are summarized below:

- Will the product be used appropriately in an OTC setting?
- Will the defined OTC population utilize the product?
- Will physician involvement be established initially and as appropriate, maintained over time? If not, what risk is incurred by a consumer who takes an OTC lipid-lowering product and does not consult a physician?
- Will compliance with the OTC product result in a similar profile of biologic activity to that with prescription use?
- Will use of OTC Pravachol 10 mg in a less supervised environment result in a safety profile similar to that with prescription use?
- What is the likelihood that a consumer will shift from current prescription lipid lowering medication to an OTC product?

To answer questions regarding OTC use, a Label Comprehension study and two consumer use clinical trials (Pravachol Experience Documented In a Consumer Trial [PREDICT], protocol 800-01-97 and OTC Pravachol Trials In an Observed Naturalistic Setting [OPTIONS], protocol 800-03-97) were conducted.

Outline of OTC Pravachol Program



Safety of Pravachol

The review of the safety experience with pravastatin encompasses over 22 million patients years of use (90% at doses above the proposed OTC dose) and more than 100,000 patient years of placebo controlled clinical trial experience (mostly with the 40 mg dose). The data from this extensive safety database allows one to conclude:

- The adverse event profile of pravastatin in doses of 10-40 mg per day in short and long term clinical trials, in real world prescription use, and in simulated OTC environments is benign and appropriate for OTC availability.

- Because pravastatin is not metabolized by the cytochrome P450 system to a clinically significant extent, there is an extremely low risk of drug interactions, which has been confirmed by an extensive array of pharmacokinetic studies and clinical experience.

- Doses of 160 mg/day (16 x the proposed OTC dose) have been shown to be safe and well tolerated in clinical trials of 6 weeks in duration. Overdoses of greater than 1000 mg of pravastatin (equivalent to > 3 OTC cartons containing a 1 month supply) were observed in Post Marketing Surveillance; and there were no clinically significant transaminase of CPK elevations. The OTC package will consist of 28 doses packaged in calendar pack blister cards. This is designed to not only to maximize compliance, but make overdose very unlikely.

- Preclinical and clinical data support that Pravachol 10 is safe if taken inadvertently by a pregnant woman. Oral reproductive toxicology animal studies have found no untoward reproductive or teratogenic effects, embryo-fetal toxicity or anatomic abnormalities associated with high doses of pravastatin. There have been 43 reports of pregnancies in Post Marketing Surveillance, and the outcome is known in 29. There were 5 abortions (3 spontaneous and 2 elective). Of the 24 cases with known outcomes carried to term, there were no congenital malformations; in many of these cases the mothers took pravastatin well into the first trimester, and, in some cases, took for the majority of the pregnancy. The average birthweight of all newborns did not significantly differ from the average weight of newborns in the US.

- There is no difference between pravastatin 40 mg and placebo in the development of liver function abnormalities. This is seen in subjects with normal baseline liver function tests as were as those with pre-existing mild liver function abnormalities who would be representative of the public at large with mild asymptomatic liver disease. Based on these data, biochemical monitoring of liver function tests is unnecessary.

- Symptoms referable to the musculoskeletal system are mild and similar to placebo in clinical trials. In the 10 mg dose response studies there were no musculoskeletal deaths, serious adverse events or reports of myopathy. Musculoskeletal adverse events were less frequent in the pravastatin-treated subjects vs. placebo-treated subjects (16% vs. 24%, $p = 0.049$). In the Prava 3 analysis of Pravachol 40 mg vs. placebo, the incidence of musculoskeletal system adverse events was not significantly different between the treatment groups. There were no cases of myopathy or documented rhabdomyolysis. In the long term experience where each subject had a mean of 11.9 determinations of CPK levels, there was no difference in post baseline abnormalities of CPK, either overall, or by severity, between Pravachol 40 mg and placebo. In post marketing surveillance, serious adverse events of the musculoskeletal system have been rare. There have been 122 cases of rhabdomyolysis reported worldwide for all doses; 27 of these were reported in the US none of which occurred with the 10 mg dose. Twenty percent (20%) of the reported cases occurred in patients taking concomitant fibrate medications and many others were associated with rhabdomyolysis. The profile of musculoskeletal adverse events in the consumer use trials was benign.

  The OTC package label warns consumers to report symptoms of myalgias and this was overwhelmingly understood by 93% of respondents in the in Label Comprehension Study. Moreover, the OTC label tells consumers to speak to a physician or pharmacist if they are taking other prescription lipid lowering medications.

- The hepatic profile of Pravachol supports OTC status and elimination of biochemical monitoring of hepatic function. In the Prava 3 analysis there were no deaths due to hepatic failure; the incidence of adverse events that were serious, that led to discontinuation, and overall, were rare and occurred in the same percentage of Pravachol 40 mg vs. placebo treated patients. In order to access more fully the degree of laboratory abnormalities occurrences for ALAT and ASAT, an assessment of post-treatment abnormalities overall and by ranges of severity was performed in 18,637 patients for ALAT and 11,704 patients for ASAT who had a mean of 13.1 and 13.2 evaluations performed, respectively. Overall, there were no differences in post-baseline abnormalities of ALAT (8.8% pravastatin vs. 8.2% placebo, CI 95%; -0.21, 1.42) or ASAT (4.4% pravastatin vs. 4.0% placebo, 95% CI: -0.39, 1.11) overall, or in any range of severity. In the 579 subjects (3%) in the Prava 3 cohort who had mild abnormalities of ALAT and/or ASAT at baseline, there was no difference between pravastatin-treated vs. placebo-treated subjects in the incidence of post baseline abnormalities, either overall or by ranges of severity. There were no treatment differences noted for subjects ≥ 65 (n = 4,338) or ≥ 70 (n=1,628) or when assessed by gender. These data support the safety of Pravachol in the broad spectrum of the population, including those with mild asymptomatic liver disease. In the post marketing surveillance database there have been 6 deaths reported attributable to the hepatobiliary system: 3 were due to metastatic Cancer, 2 were due to alternative drug toxicity (diclofenac, trazodone) and 1 report contained incomplete data. Serious AEs were rare.

  In consumer use studies, transaminase elevations were rare and in the range of 1.2-2.2 x ULN; in most cases they normalized while treatment was continued.

  The OTC package label warns people with liver disease, or those who consume 3 or more alcoholic drinks per day to “Do not use”. This was understood by 80% of respondents in the Label Comprehension Study.

Efficacy of Pravachol 10 mg

A review of the data supports the biological efficacy and safety of Pravachol for use in an OTC environment, and consumer use studies demonstrate that Pravachol 10 mg will be used appropriately in an OTC environment. In the 10 mg dose response studies, a statistically significant and clinically meaningful reduction in LDL-C, of 18% to 22% was seen. In PREDICT, a similar reduction of LDL-C was achieved at 8 weeks and maintained over 1 year; this reduction in LDL-C brought 83% of the OTC population to their NCEP defined LDL-C goals.

Consumer Use

The consumer use program, consisting of the Label Comprehension Study, PREDICT and OPTIONS was designed to assess whether consumers would understand and act in accordance with the key label messages so that:

- The population that utilizes the product is, indeed, the intended population.
- The consumer maintains involvement in the health care system.
- The OTC consumer returns for appropriate follow up
- The safety and efficacy profile of Pravachol 10 mg in an OTC setting is similar to a prescription setting.

To evaluate these questions, 3 studies were conducted among varied populations. The Label Comprehension Study was a mall intercept study conducted among people who *a priori* were not required to have interest in or knowledge of cholesterol or other CHD risk factors. This study was conducted in 20 geographically diverse communities and augmented for low literacy (27% of the respondents read below 9th grade level).

PREDICT was also carried out in 20 diverse communities and advertised broadly in both print and broadcast media, telling people that if they were generally healthy and their "cholesterol was 200-240 mg/dl they may be able to purchase a prescription medication without a prescription. In order to simulate an environment where consumers could freely purchase Pravachol 10 mg, the subjects were randomized to either an OTC environment (where Pravachol 10 mg was available for purchase) or a prescription environment, prior to any knowledge about their medical conditions or lipid status. After randomization, there was no further contact with subjects for 6 months. Eight percent (8%) of the randomized population read below 9th grade level.

OPTIONS assessed the behavior of participants who were able to purchase Pravachol 10mg in their own pharmacies. The study was conducted utilizing the participants' own "non-research" primary care physicians. In order to access medical records and collect reliable data in the absence of study physicians, health maintenance organization (HMO) populations were chosen; these consisted of both Individual Physician Association (IPA) and staff model HMO's. Thus, while there was no contact with subjects for three months after enrollment, patient charts could be reviewed for medical history, laboratory parameters, and CHD risk factor profile, confirmation of physician contact and adverse events. Twelve percent (12%) of subjects enrolled read below 9th grade level.

<u>Baseline Findings</u>

- There is a strong interest in the problem of hypercholesterolemia. Sixty-one percent (61%) of the general population, as reflected in the Label Comprehension Study were concerned about cholesterol. In PREDICT , more than 10,000 subjects responded to the advertisement within 6 months. In OPTIONS, 782 HMO subjects were recruited in less than 15 weeks, and 52% were willing to pay out of pocket for OTC medication.

- Subjects interested in the OTC proposition, as reflected by the Randomized population in PREDICT and the Enrolled population in OPTIONS, were motivated and physician oriented: 83% and 96% respectively saw their physician yearly, and 25% and 31% respectively had seen the physician specifically about cholesterol. Seventy-two percent (72%) of PREDICT subjects had prescription coverage.

- The majority of subjects were aware of having elevated cholesterol. Twenty-five percent (25%) and 23% of the PREDICT and OPTIONS participants were aware of their elevated cholesterol for > 5 years. Most had implemented lifestyle changes to manage cholesterol levels. Fifty-six percent (56%) of PREDICT subjects and 58% of OPTIONS subjects reported modifying their diet (in PREDICT, where an objective tool [MEDFICTS] was used to categorize AHA diet status, 81% of subjects were following an AHA diet, consistent with dietary trends reported in National Surveys. In both PREDICT and OPTIONS, approximately 50% of women were taking hormone replacement therapy. Nonetheless, subjects were using prescription lipid lowering medications infrequently: in PREDICT, only 9% were currently using prescription medications and in OPTIONS, 16% were utilizing Rx therapies. In contrast, 18% of participants in PREDICT and 26% of participants in OPTIONS indicated they were currently taking non-prescription therapies to manage cholesterol.

- Despite interest and access to health care, subjects were infrequently at their ideal cholesterol level: in PREDICT only 10% and in OPTIONS only 27% of of participants with a prior cardiac event had an LDL-C < 100 mg/dl. In the primary prevention group < 30% of PREDICT subjects and < 25% of OPTIONS subjects had an LDL-C < 130 mg/dl.

- Participants were able to self-select appropriately based on their CHD risk factor and lipid profiles. In PREDICT and OPTIONS, 95% and 94% of respondents to the advertisement, respectively, were free of CHD; 86% of the PREDICT population and 85% of the OPTIONS population who had lipid levels measured had a baseline total-C > 200 mg/dl.

Results

- Subjects overwhelmingly understood label messages (Label Comprehension Study) and the vast majority behaved appropriately (PREDICT and OPTIONS). In the Label Comprehension Study open-end and closed-end (multiple choice) comprehension, 95% and 94% of subjects, respectively, indicated they would "see their doctor" before using Pravachol 10 mg. In PREDICT, 90% of OTC subjects demonstrated appropriate behavior: 77% of the subjects who purchased Pravachol 10 mg consulted a physician within 2 months of product use (the primary endpoint); an additional 5% of subjects consulted the physician, but outside the prespecified 2 month window; and 8%

never consulted but never took medication. Of the 10% of subjects who took medication and never consulted, no serious adverse events occurred. In OPTIONS, 93% of subjects who purchased OTC Pravachol 10 mg exhibited appropriate behavior: 44% had a documented consultation with the physician within 2 months of product use (the primary endpoint); an additional 5% consulted the physician, but outside the 2 month window. In addition, there were 32% of subjects who took Pravachol 10 mg, did not consult but appropriately self-selected according to pre-specified criteria and 12% did not consult but did not take medication. Because this was a "naturalistic" study utilizing the subject's own (non-research) primary care physician, patient charts may have been incomplete; by the subjects' self-report, 58% contacted the physician, 53% within 2 months of product use and 5% outside this window. Of the subjects in the Purchase population who took medication and did not specifically consult their physician about Pravachol 10 mg, 75% had discussed their cholesterol problem with their doctor within 6 months of starting the OPTIONS study.

- In the Label Comprehension Study, understanding of the primary objective of "see the doctor" was the same for the $< 9^{th}$ grade and $\geq 9^{th}$ grade literacy subgroups and across the other predefined subgroups of age, race and gender.

  In PREDICT, behavior to consult a physician was the same for men and women and subjects in the $< 9^{th}$ grade vs. $\geq 9^{th}$ grade literacy groups. Overall appropriate behavior was slightly lower in the minority groups. Black and Hispanic subjects were somewhat less likely to consult a physician, although the sample size in these demographic groups was small due to lower purchase interest.

  In OPTIONS, behavior of pre-defined subgroups (gender, race, and literacy) was similar to the Purchase population overall, with 90% ± 5% demonstrating appropriate behavior.

- In PREDICT, where a randomized OTC cohort could be compared to an Rx cohort the following was seen:

  - Behavior of OTC subjects was as good as Rx subject in follow up with physician after the start of therapy: 85% of OTC subjects vs. 83% of Rx subjects (p=NS). Behavior was similar across the subgroups. In addition, longer term follow up was similar in both groups. The behavior is consisted with results of the Label Comprehension Study, were 82% of respondents indicated that cholesterol levels should be rechecked at 8 weeks and 1 year, respectively.

  - For qualified participants who took at least one dose of Pravachol 10 mg, a statistically significant and clinically meaningful reduction in LDL-C was seen at 8 weeks in both the OTC and Rx groups, (-18% vs.

–19%, p=NS, C.I. –1.5%, 3.0%), and was sustained at 6 months. Importantly, 83% OTC and 77% Rx subjects (p= 0.544) achieved their NCEP defined LDL-C goal. In the PREDICT Extension Protocol, 52% of OTC participants and 53% of Rx participants remained on therapy for 1 year. LDL-C reduction was 22% at weeks 8, 24, and 48 in this cohort.

- Consistent with results of long and short term clinical trials comprising over 64,000 patient years of exposure to pravastatin and 22 million patient years of post marketing exposure, the safety profile of Pravachol in an OTC setting was benign. In PREDICT, the overall incidence in adverse events was similar between the OTC and Rx groups, 27% vs. 41% and 90% of the AEs were mild to moderate in nature. There were no deaths and none of the serious adverse events were related to Pravachol 10 mg therapy. Importantly, there were no cases of myopathy, drug-drug interactions or significant transaminase abnormalities. In OPTIONS, the overall incidence of AEs was 25%, > 99% of which were mild to moderate in nature. There were no deaths or serious AEs experienced related to OTC Pravachol 10 mg therapy.

  These results are consistent with the Label Comprehension Study, where 93% of respondents understood the need to report adverse experiences (muscle pain) to a doctor.

- Utilization of OTC Pravachol 10 mg by the appropriate OTC population was assessed in both PREDICT and OPTIONS.

  <u>Shift from prescription to OTC Pravachol 10 mg Therapy</u>

  - With regard to consumers understanding that Pravachol 10 mg should not be used as a replacement for their current prescription lowering therapy, PREDICT demonstrated that 2% of the 183 subjects already taking prescription lipid lowering medication at baseline shifted to OTC Pravachol 10 mg. In OPTIONS, 11% of the 99 subjects taking prescription lipid lowering therapy at baseline shifted to OTC Pravachol 10 mg.

  <u>Subjects Requiring More Aggressive Therapy</u>

  - Of those 321 subjects in PREDICT who qualified for more aggressive prescription therapy at baseline, 46% reported having seen their personal physician and 29% had begun taking prescription lipid lowering medications when contacted for 6 month follow up status. There was no difference between the OTC and Rx groups.

Conclusion

There is a need for additional approaches to improve treatment of hypercholesterolemia. Despite a significant increase in cholesterol awareness, adoption of diet modification and knowledge about prescription lipid lowering

therapies, it is estimated that nearly 38 million adults with mildly elevated cholesterol levels have not reached their LDL-C goal with dietary intervention alone and therefore remain at long-term risk for developing CHD. Consumers are increasingly pursuing non-prescription remedies to manage their cardiovascular disease risks: consumer research indicates that in 1999 nearly twice as many Americans used non-prescription lipid lowering remedies compared to those who used cholesterol lowering prescription medication, and this has been confirmed in consumer research studies. Expanding pravastatin use to the OTC setting so that a broader lower-risk population could participate in the benefits of an effective and safe product serves an important long-term prevention strategy.

Accordingly, we conclude that the OTC availability of Pravachol 10 mg, with regulated, informative labeling will provide lower-risk, prevention-oriented consumers with a safe and effective treatment to help them attain their NCEP defined goals. This approach provides an option for the growing population interested in self-care and has the potential to complement and broaden current efforts in lowering cholesterol levels in the US population.

Briefing Book

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LIST OF ABBREVIATIONS AND TERMS

Term	Definition
ADE	Adverse Drug Event Related to Treatment
AE(s)	Adverse Event(s)
AHA	American Heart Association
ALAT	Alanine transaminase
ASAT	Aspartate transaminase
BMS	Bristol-Myers Squibb
BRC	Business reply card
CARE	Cholesterol and Recurrent Events
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CIOMS	Council for International Organization of Medical Sciences
Cmax	Maximum Mean Concentration
CME	Continuing Medical Education
CK	Creatine Kinase
CPK	Creatine phosphokinase
CV	Cardiovascular
CVD	Cardiovascular Disease
FDA	Food and Drug Administration
HDL-C	High-density lipoprotein cholesterol
HMG CoA	3-hydroxy-3 methlglutaryl coenzyme A
HMO	Health Maintenance Organization
IND	Investigational New Drug
IPA	Independent Practice Association
IU/L	International Units Per Liter
ICGR	Intrauterine Growth Retardation
KAPS	Kuopio Atherosclerosis Prevention Study
kg	Kilogram
LDL-C	Low-density lipoprotein cholesterol

LFT	Liver function test
LIPID	Long-term intervention with Pravastatin in Ischemic Disease
MEDFICTS	Meats, Eggs, Dairy, Fried Foods, In Baked Goods, Convenience Foods, Table Fats, Snacks
mg	milligram
mg/dl	milligram per deciliter
MI	Myocardial infarction
mm/Hg	Millimeters of mercury
N, n	Number
NCEP	National Cholesterol Education Program
NDA	New Drug Application
NEC	Not Elsewhere Classified
ng	nanogram
NOS	Not Otherwise Specified
NS	Not significant
OTC	over-the-counter
PRAVA 3	Prospective Pravastatin Pooling
PREDICT	Pravachol Experience Documented in a Consumer Use Trial
OPTIONS	OTC Pravachol Trials In an Observed Naturalistic Setting
REALM	Rapid Estimate of Adult Literacy in Medicine
Rx	Prescription
SAE(s)	Serious Adverse Event(s)
SD	Standard Deviation
TOTAL-C	Total Cholesterol
TIA	Transient Ischemic Attack
TG	Triglycerides
ug	Microgram
ULN	Upper Limit of Normal
US	United States
Tx	Treatment
WOSCOPS	West of Scotland Coronary Prevention Study

I. INTRODUCTION

This briefing book presents the data to be discussed at the Joint Meeting of the Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committees on July 14, 2000. The Committees will be asked to consider the switch of Pravachol 10 mg daily from prescription (Rx) to over-the-counter (OTC) status for use in conjunction with diet and exercise to lower low density lipoprotein cholesterol (LDL-C). The OTC proposition is described as follows:

- Intended dose: Pravachol 10 mg once daily
- Use: Cholesterol lowering with diet and exercise
- Target population: Men > 35 years and women > 45 years who:
  - Have been told by physician to lower cholesterol
  - Are not at desirable cholesterol level despite diet modification and exercise but not taking prescription therapy
- Total cholesterol: 200 – 240 mg/dl, LDL-C > 130 mg/dl
- No coronary heart disease (CHD) or diabetes

With regard to age recommendations in the OTC labeling, while OTC Pravachol 10 Mg is not intended for a younger population, the original NDA did not include an age recommendation other than not to use in persons < 18 years of age. However, following discussions with the FDA and other lipid experts, Bristol- Myers Squibb had determined it would be appropriate to include older age recommendations in the OTC labeling to be consistent with the population who would most benefit from OTC availability of Pravachol 10 mg. Thus the proposed labeling provided in this briefing book reflects use in men > 35 years and women> 45 years. As this labeling was very recently proposed, the FDA's briefing book may not reflect this change.

Pharmacologic Class

PRAVACHOL® (pravastatin sodium) is an inhibitor of 3-hydroxy-3-methglutaryl-coenzyme (HMG-CoA) reductase. These agents lower blood Total cholesterol and LDL-C values by competitively inhibiting of 3-hydroxy-3-methglutaryl-coenzyme A HMG-CoA reductase, the enzyme which catalyzes the rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate.

Pravastatin produces its lipid-lowering effect in two ways. First, as a consequence of its reversible inhibition of HMG-CoA reductase activity, it causes modest reductions in intracellular pools of cholesterol. This action results in an increase in the number of LDL-C receptors on cell surfaces and enhanced receptor-medicated catabolism and clearance of circulating LDL-C. Second, pravastatin inhibits LDL-C production by inhibiting hepatic synthesis.

However, while the lipid lowering effects of pravastatin are similar to other drugs in this class, as seen in Table 1, pravastatin differs from other HMG-CoA reductase inhibitors in several ways, which may be important when considering the safety profile of Pravachol. Unlike most other HMG-CoA reductase inhibitors, Pravachol is not metabolized by the cytochrome P450 system to a clinically significant extent, thus reducing the potential for cytochrome P450 mediated drug interactions, which occur when two drugs are metabolized by the same isozyme. Further, Pravachol is not lipophilic and is eliminated mainly without biotransformation through the kidneys making it potentially less likely to effect sites of action such as muscle cells. In addition, Pravachol is less protein bound than other statins which also contributes to reducing potential for cytochrome P450 mediated drug interaction which occur when two drugs compete for the same binding site. (Ref. 1)

Table 1: Pharmacokinetics of HMG-CoA Reductase Inhibitors

HMG-CoA	CYP 450 Isoenzyme Metabolism	Lipophilic	Protein Binding	Increased Concentration With CP450 Inhibitors
Atorvastatin	3A4	Yes	> 95%	Yes
Cerivastatin	3A4	Yes	> 95%	Yes
Fluvastatin	2C9	Yes	> 95%	Yes
Lovastatin	3A4	Yes	> 95%	Yes
Pravastatin	None	No	~ 50%	No
Simvastatin	3A4	Yes	> 95%	Yes

Development and Regulatory History

Pravastatin has been extensively studied in protocols since October 1985 and has been approved for marketing in the United States (US) since October 1991. Pravastatin in doses of 10, 20 and 40 mg per day is currently approved in the US as an adjunct to diet to reduce elevated Total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels in patients with primary hypercholesterolemia and mixed dyslipidemia (Frederickson Types IIa and IIb) who do not respond adequately to dietary modifications. Additional indications based on the results of large long term clinical trials that have been approved by the Food and Drug Administration (FDA) are described below.

Primary Prevention of Coronary Events

The Pravastatin Primary Prevention Study (Protocol CV27201-66: West of Scotland Coronary Prevention Study – [WOSCOPS]) involved 6,595 male patients treated with pravastatin sodium (N=3,302) or placebo (N=3,293) for a median duration of 4.8 years. This study formed the basis for the July 2, 1996 approval of the following indications for pravastatin:

- In hypercholesterolemic patients without clinically evident coronary heart disease, Pravachol is indicated to:

  - Reduce the risk of myocardial infarction (MI)

- Reduce the risk of undergoing myocardial revascularization procedures
- Reduce the risk of cardiovascular mortality with no increase in death from noncardiovascular causes.

Secondary Prevention of Cardiovascular Events

Four placebo-controlled trials which included 1,891 hypercholesterolemic subjects who had been treated for an average of 2.5 years (955 received pravastatin and 936 received placebo) formed the basis for approval of secondary prevention indications for pravastatin in 1996.

- In hypercholesterolemic patients with clinically evident coronary heart disease, including prior myocardial infarction, pravastatin is indicated to:
    - Slow progression of coronary atherosclerosis
    - Reduce the risk of acute coronary events

On the basis of the results of Protocol CV27201-67: The Cholesterol and Recurrent Events Study (CARE), where 4,159 patients (2,081 randomized to pravastatin and 2078 to placebo) were treated for an average of 4.9 years, pravastatin was approved for the following indications in people with normal cholesterol levels in 1998:

In patients with previous myocardial infarction and normal (below the 75th percentile of the general population) cholesterol levels, Pravachol is indicated to:

- Reduce the risk of recurrent myocardial infarction
- Reduce the risk of undergoing myocardial revascularization procedures
- Reduce the risk of stroke or transient ischemic attack (TIA).

Based on the results of Protocol CV27201-95: Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) where 9,014 patients were treated (4,512 with pravastatin and 4,502 with placebo) for a mean duration of 5.1 years, pravastatin was approved for the following indications on February 10, 2000:

- Reduce risk of total mortality by reducing coronary death in subjects with a history of myocardial infarction or unstable angina.
- All secondary indications previously mentioned were broadened by removing the requirement for patients to be hypercholesterolemic.

As more information about the safety of pravastatin has been accumulated during the clinical trials as well as the prescription use, there have also been modifications to the warnings sections of the package insert as discussed below.

History of relaxing the requirements for hepatic enzyme monitoring are listed below:

- New Drug Application (NDA) Approval 1991: baseline; every 6 weeks for 3 months after drug initiation; every 8 weeks for 9 months thereafter
- 1994 (based on Post Marketing Experience): baseline; at 6 and 12 weeks following drug initiation or following dose elevation; periodically/semiannually thereafter
- 1996 (based on analysis of hepatobiliary AEs and transaminase levels in WOSCOPS): baseline; at 12 weeks following drug initiation or dose elevation

In addition, on January 18, 2000, the FDA approved the following changes:

- The starting dose was expanded to include 40 mg/day
- Dosing at bedtime was removed and changed to dosing at anytime of day with or without food.
- Indicated as adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Frederickson Type IV)
- Indication for the treatment of patients with primary dysbetalipoproteinemia (Frederickson Type III) who do not respond adequately to diet.

A copy of the currently approved prescription package insert for PRAVACHOL® tablets reflecting all the recently approved changes is provided in Appendix A.

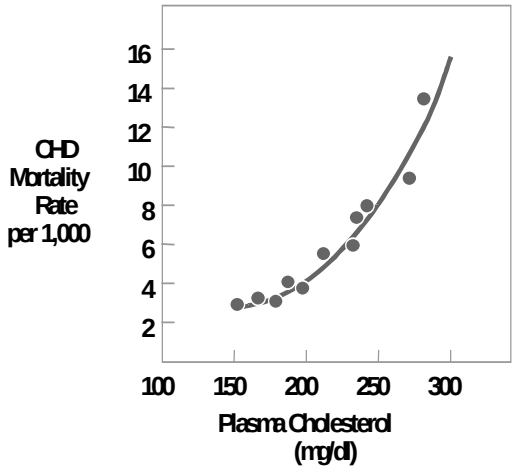
Following the extensive battery of pharmacokinetic testing, drug interaction warnings were modified to indicate that pravastatin in not metabolized by cytochrome P450 3A4 inhibitors to a clinically significant extent, and therefore the risk of drug interactions with many commonly taken medication or foods are minimal. Pravastatin has no clinically significant drug interactions with drugs with a very narrow therapeutic/toxicity indices, such as warfarin and digoxin and common OTC drugs such as aspirin, antacids, cimetadine.

Rationale For OTC Pravachol

Despite extraordinary therapeutic advances over the last decades, cardiovascular disease (CVD) remains the number one killer of adults in the United States and accounts for nearly 1 million deaths per year, more than the next seven leading causes of death combined (Ref. 2). CVD (of which most is CHD) can be prevented by control of many of the etiologic factors responsible for the development of the pathogenic atherosclerotic plaque (Ref. 3). One of the major approaches to such control is lowering of blood LDL-C concentrations.

Epidemiologic observations have shown a positive, continuous, independent and graded relationship between plasma Total cholesterol across a wide range of concentrations, including those considered normal or mildly elevated, and of incidence of CHD (Refs. 4, 5, 6) (Figure 1). Moreover, many randomized placebo controlled trials with certain cholesterol-reducing HMG-CoA reductase inhibitors like Pravachol have demonstrated the ability to reduce the risk of cardiovascular events in both primary (free of overt cardiovascular disease) and secondary (have previously sustained a cardiovascular event) prevention populations across a wide spectrum of cholesterol levels (Refs. 7, 8, 9, 10, 11).

Figure 1: **MRFIT: CHD Mortality Rate vs Total Cholesterol Levels (n = 361,662)**



For primary prevention, the National Cholesterol Education Program (NCEP) defines desirable Total-C as <200 mg/ml and desirable LDL-C levels as <130 mg/ml (Ref. 3, 12) and ideally, all persons without established CHD should have cholesterol levels below these values. Indeed, most coronary events occur in individuals with cholesterol levels considered "normal" or only moderately elevated. Sixty-nine percent (69%) of the CHD deaths in the first 6 years of follow-up in the Multiple Risk Factor Intervention Trial occurred in subjects with Total-C levels of 182-264 mg/dl (Ref. 13), and in the first 16 years of the Framingham Heart Study, 40% of those developing a MI had Total-C levels of 200-250 mg/dl (Ref. 14). Thus, there is an opportunity to reduce the burden of CHD by preventing its occurrence in those who are at risk but not yet afflicted.

It is likely that any single coronary risk factor can lead to premature CHD if left untreated over a period of many years (Ref. 3). To reduce long-term risk of atherosclerotic complications most effectively, each of the major risk factors should be addressed, even when the short-term absolute risk may not be as high as in secondary prevention. The focus of long-term risk reduction for CHD is modification of lifestyle (e.g. diet modification, weight control, and physical activity). The current NCEP guidelines were

published in 1993, prior to the results of the large statin trials which demonstrated a treatment related reduction in cardiovascular morbidity and mortality and prior to the safety experience of statins resulting from long term exposure in large numbers of individuals. For this reason, current NCEP guidelines are relatively cautious regarding drug treatment recommendations overall, and particularly with respect to primary prevention. (Ref. 15). For patients in whom long-term risk is high or lifestyle changes have been inadequate, use of lipid lowering drugs may be warranted (Ref. 3, 11). There is, however, a large population with mildly elevated cholesterol at risk for development of CHD who will not reach desirable levels with dietary intervention alone (Ref. 16).

Efforts by government, academia and industry have led to increased awareness in the general population about the importance of elevated cholesterol as one of the major cardiovascular risk factors which has lead to a dietary shift in the US population toward lower consumption of saturated fats, and this in turn, has lead to a decrease in Total cholesterol levels. However, despite the overwhelming evidence from large clinical trials that certain HMG-CoA reductase inhibitors can save lives and prevent illness in both primary and secondary prevention across a wide spectrum of lipid levels and cardiovascular risk (Refs. 7, 8, 9, 10, 11), most appropriate candidates are not receiving optimal therapy (Ref. 17). In fact, it is estimated that less than 15% of eligible people who have had a prior cardiac event are receiving lipid lowering therapy; this proportion falls to less than 5% of those in the primary prevention category (Ref. 17). Indeed, despite large expenditures on DTC advertising, the growth of the HMG-CoA reductase market has slowed (Ref. 7).

This is counter balanced by consumer interest in self-care, especially for disease prevention. Consumers are increasingly turning to, and physicians are recommending, non-prescription LDL-C lowering adjuncts such as fiber, plant stanol/sterols and soy protein. Consumers are also frequently utilizing other less well-characterized over-the-counter therapies. As we consider the spectrum of choices individuals are making, it is reasonable to include the OTC option of Pravachol 10 mg which has an excellent and

well established safety profile and provides predictable and meaningful LDL-C reduction to this lower risk population.

Expanding pravastatin use to the OTC setting so that a broader lower-risk population could participate in the benefits of an effective and safe product serves an important long-term prevention strategy. As will be demonstrated in this Briefing Book, Pravachol has an excellent and well established safety profile, fitting well within the spectrum of current OTC products, the LDL-C reduction seen with Pravachol 10 mg in the OTC environment is meaningful and maintained over time and brings the vast majority of OTC participants to their NCEP goal. Additionally, OTC pravastatin appeals to the defined target OTC population. The data from rigorously designed consumer use trials also demonstrates that the additional OTC approach is a complement to and not a distraction from current efforts: there is minimal shifting from prescription therapy or lifestyle modification to the OTC option and this is more than off-set by the consumer-physician dialogue that is promoted which results in a larger population being treated appropriately with lifestyle modification, OTC Pravachol 10 mg or prescription therapy, depending on the level of risk. The availability of Pravachol 10 mg in an OTC setting has the potential to expand treatment in disease prevention minded individuals without established vascular disease, who are already motivated to take greater responsibility for self maintenance of their long term cardiovascular health.

Overview of OTC Program

The OTC Pravachol program was designed to evaluate whether Pravachol 10 mg could be used safely and responsibly in an OTC setting as an adjunct to diet and exercise to improve cholesterol management. The overall program and individual study designs were developed to address questions and issues surrounding the OTC availability of lipid lowering medications that have been extensively discussed with both the FDA over time, and with the Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committees concerning the OTC Switch application of another lipid lowering agent

[NDA, #20-879 (QUESTRAN) and #20-880 (QUESTRAN LIGHT)] held on September 27,1995 and May 13, 1997.

At the most recent Advisory Committee Meeting held in May 1997, most Committee members indicated that the results of the consumer use study had answered the questions the protocol was designed to address, and concluded that the safety and efficacy profile of Questran supported OTC Status. However, the following concerns remained:

- Was the demographic profile and health care status characteristics demonstrated in the consumer use studies a true finding or a result of selection bias?
- Was the finding that the overwhelming majority of subjects saw a physician for initial diagnosis generalizable to the true "OTC" population
- As the proposition represented an evolution for OTC medication, the Committee recommended extensive educational programs for both health care professionals and consumers.

The OTC Pravachol Program was designed specifically to address the issues previously raised by the FDA and Advisory Committees during review of the Questran submission. The key questions addressed in the clinical program for OTC Pravachol pertain to 1) the properties of the molecule itself and 2) availability and use in an OTC environment, and are outlined below:

<u>The Molecule</u>

- The first priority of the OTC Pravachol 10 mg program was to establish that Pravachol has an excellent and well established safety profile and fits within the spectrum of currently available OTC therapies. Specifically, the following questions were addressed:
  - What is the potential for drug interactions in a broader population taking multiple medications?

  - What is the consequence of consumers overdosing or taking more than the label recommends?
  - What is the consequence to women who inadvertently become pregnant while taking the product?
  - What is the risk for myopathy?
  - What is the potential for liver injury and is biochemical monitoring of hepatic enzymes necessary?
- The next objective of the program was to establish that the biologic activity of Pravachol 10 mg is adequate and appropriate for the OTC population. The OTC dose was selected from the results of randomized placebo-controlled studies. The goal of consumer use studies was to assess whether similar LDL-C reduction could be achieved and maintained in a less supervised environment.

The efficacy and safety of pravastatin have been extensively documented. These issues were addressed using the following data:

1) Randomized, placebo-controlled dose response studies in the original NDA that utilized Pravachol 10 mg: Protocols 27201-2, 27201-42 and 27201-89.

2) The Pravastatin Pooling Project (Prava 3) was pre-specified, integrated safety analysis of the three long-term placebo controlled studies which evaluated the effect of Pravachol 40 mg on cardiovascular morbidity and mortality:

- WOSCOPS (West of Scotland Coronary PreventionStudy), Protocol CV27201-66)
- CARE (Cholesterol and Recurrent Events), Protocol CV2721-67
- LIPID (The Long Term Intervention with Pravastatin in Ischaemic Disease), Protocol CV27201-95)

It was anticipated that this safety database of 19,768 subjects studied for a mean duration of 4.6 years, comprising > 100,000 patient years experience (64,000 patient years of pravastatin 40 mg therapy) would permit detection and assessment of clinically

meaningful uncommon adverse events and laboratory abnormalities. Specifically, it was intended that this analysis could provide an accurate assessment of musculoskeletal adverse events (AEs) and CPK elevations. In addition, analyses could provide an assessment of the effect of Pravachol 40 mg on transaminase levels and whether biochemical monitoring was necessary. These studies were selected because their similar study designs, duration and dose allowed for pooling of data. Also, the entry criteria were less rigid than for previous studies, allowing subjects with mildly abnormal liver function to be treated with pravastatin 40 mg or placebo for extended periods of time. Because no new safety considerations emerged from the Prava 3 analysis, the data presented in this report will focus on adverse events and laboratory results in the hepatobiliary and musculoskeletal body systems.

3) In addition to pharmacokinetic studies conducted to support the prescription NDA, many additional studies, mostly at doses higher than the intended OTC dose, assessed the likelihood of clinically significant drug interactions, particularly with drugs metabolized by the cytochrome P450 3A4 system.

4) In order to assess the safety of Pravachol 10mg in the event that it were taken inadvertently by a pregnant woman, both preclinical and clinical data were extensively reviewed.

5) To assess safety in the broader population represented by general prescription use, Post Marketing Surveillance information collected by Bristol-Myers Squibb (BMS) from February 29, 1990 to May 31, 1999 which represents >22 million patient years was analyzed. Since no new safety issues emerged, special emphasis was placed on adverse events in the hepatobiliary and musculoskeletal body systems.

These data are discussed in detail in Sections II and III.

OTC Use

While traditional clinical trials evaluate the safety and efficacy of the molecule, the purpose of consumer use studies is to evaluate the efficacy of the OTC label in directing consumers to behave appropriately.

The key issues that were addressed in consideration of OTC status for Pravachol 10 mg are summarized below:

- Will the product be used appropriately in an OTC setting?
- Will the defined OTC population utilize the product?
- Will physician involvement be established initially and as appropriate, maintained over time? If not, what risk is incurred by a consumer who takes an OTC lipid lowering product and does not consult a physician?
- Will compliance with the OTC product result in a similar profile of biologic activity to that with prescription use?
- Will use of OTC Pravachol 10 mg in a less supervised environment result in a safety profile similar to that with prescription use?
- What is the likelihood that a consumer will shift from current prescription lipid lowering medication to an OTC product?

To answer questions regarding OTC use, a Label Comprehension study and two consumer use clinical trials (Pravachol Experience Documented In a Consumer Trial [PREDICT], protocol 800-01-97 and OTC Pravachol Trials In an Observed Naturalistic Setting [OPTIONS], protocol 800-03-97) were conducted.

The Label Comprehension Study was designed to assess whether consumers, especially low literacy consumers, would understand key messages of the OTC Pravachol label. These key messages included: need to speak to a physician prior to using Pravachol 10 mg; product indication to lower cholesterol; intended consumer profile, i.e., Total-C 200-240 mg/dl, and no coronary heart disease (CHD), diabetes or liver disease; need for

periodic follow-up; and need to stop medication and see a physician for muscle ache. Six hundred twelve (612) subjects, 27% of whom read below 9th grade reading level, participated in this study.

The two consumer use studies were designed to assess:

- the profile of consumers interested in the OTC proposition
- the behavior of consumers with respect to their understanding of the OTC label
- the consequences of this behavior, i.e., LDL-C reduction and safety

While every effort was made to make these studies as naturalistic as possible, it is recognized that a true OTC environment cannot be easily simulated in an investigational study. Thus, two very different study designs were employed to attract as broad a spectrum of the general population as possible in order to determine whether the convergence of data allowed a conclusion that results were generalizable to the true OTC population.

The first consumer use study, PREDICT, randomized subjects in 20 communities to an OTC or Rx environment prior to any knowledge about their medical history or cholesterol levels. OTC subjects could purchase Pravachol 10 mg at any time while Rx subjects would need to obtain a prescription from a physician. At the end of 6 months, all subjects were contacted to evaluate behavior. The primary objective of this study was to see whether OTC subjects would see a physician within two months of using Pravachol 10 mg. Secondary objectives of the study compared OTC and Rx subjects with respect to physician follow-up, LDL-C reduction, maintenance of appropriate lifestyle behaviors (diet and exercise) and safety. The study also evaluated behaviors of OTC subjects who were not appropriate for OTC treatment, specifically, those who were already taking prescription lipid lowering medications, and those who required more aggressive higher dose prescription therapy. This study randomized 3,872 subjects, of whom 8% were low literacy. PREDICT was subsequently extended for an additional 6

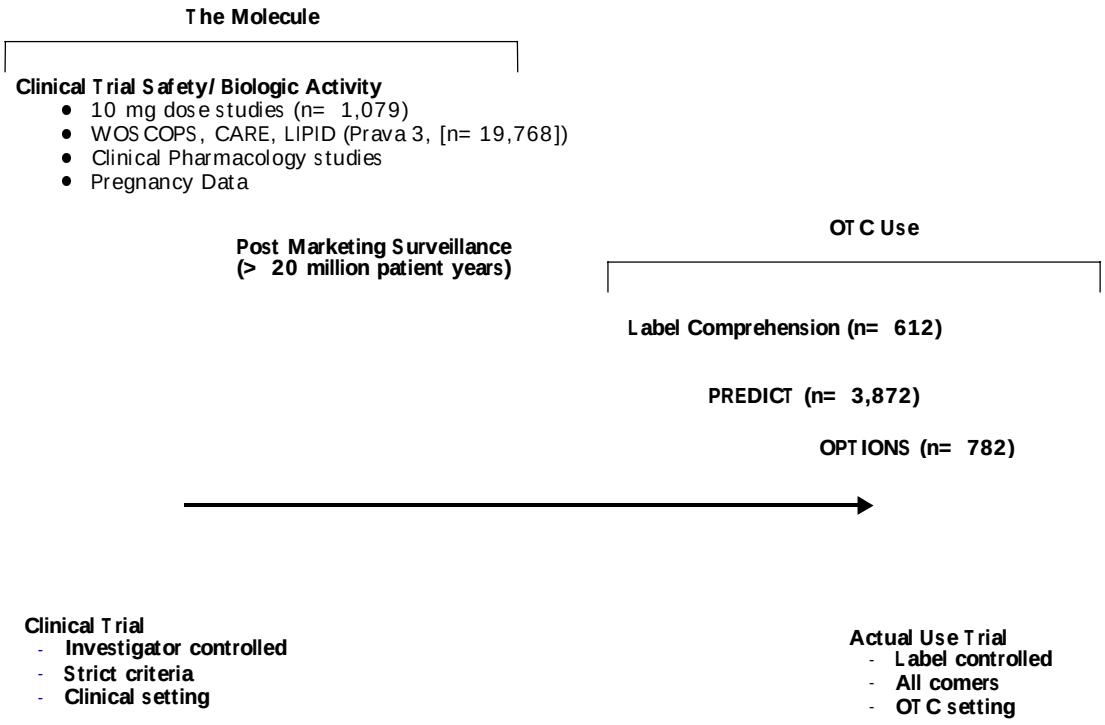
months in order to evaluate behavior of an LDL-C reduction in OTC and Rx subjects for a longer period of time.

The second consumer use study, OPTIONS, observed the behavior of subjects able to purchase Pravachol 10 mg in their own pharmacies. In order to verify data, Health Maintenance Organization (HMO) populations in 20 communities were utilized. Like PREDICT, the primary objective of this study was to see whether subjects consulted a physician within two months of using Pravachol 10 mg. Secondary evaluations in this study included incidence of appropriate self-selection, and safety. This study also evaluated behavior of those subjects already taking prescription lipid lowering medication. This study enrolled 782 subjects, of whom 12% were low literacy.

These studies are discussed in further detail in Section IV, V and VI of this document.

A schematic summary of the OTC Pravachol clinical program is shown in Figure 2.

Figure 2: Outline of OTC Pravachol Program



II. SAFETY OF PRAVACHOL

This section presents data from: 1) the three dose-response studies that utilized Pravachol 10 mg, 2) a prospectively defined pooled analysis of the safety of three long-term, randomized, double-blind studies of pravastatin 40 mg (4 times the OTC dose) versus placebo (WOSCOPS, CARE, and LIPID), 3) pharmacokinetic studies that assessed potential of drug interactions, 4) preclinical and clinical studies assessed pregnancy data, and 5) Post Marketing Surveillance data (90 % at doses greater than the OTC dose). Since pravastatin is a marketed compound that has already been established as safe for use in hypercholesterolemic subjects as shown from the data in the original application and several subsequent safety updates, the studies described below will focus on issues of particular importance in consideration of expanded access in a potentially less supervised environment.

10 mg Dose Response Studies

Methods

Safety assessments consisted of adverse events (AEs) and laboratory measurements. AEs were defined as any illness, sign or symptom noted by the investigator during the course of treatment regardless of the investigator's opinion as to its relationship to the test drug. Serious adverse events (SAEs) were defined as those events which are fatal or life-threatening, permanently disabling, resulting in hospitalization, congenital anomaly, cancer or overdose.

Clinical laboratory abnormalities were pooled and analyzed for the pivotal studies (27201-2 and 27201-42) which were conducted under a similar experimental design. Protocol 27201-89 was not included in the pooled analysis because the raw data was not available. Criteria for laboratory abnormalities were defined as:

- Aspartate transaminase (ASAT) > 3 times upper limit of normal, or, if baseline value is abnormal, > 4 times upper limit

- Alanine transaminase (ALAT) > 3 times upper limit of normal, or, if baseline value is abnormal, > 4 times upper limit
- Creatine phosphokinase (CPK) > 4 times pre-treatment value

Results

There were seven clinical studies which included pravastatin 10 mg comprising 1,079 randomized subjects: 550 to pravastatin 10 mg, 212 to placebo, 317 to a comparitor, an additional 275 subjects were randomized to either 20 mg or 40 mg of pravastatin and are not included in the total of 1, 079. Two of the studies conducted in the US were part of the original clinical program and 1 was subsequently filed. These 3 studies were pooled for safety which included a total of 173 patients exposed to pravastatin 10 mg vs 188 patients exposed to placebo for a mean duration of 71 vs 75 days, respectively. The other four studies were conducted outside the US and are not addressed within this report however, the safety in these 4 non-US studies individually as well as the 3 US studies was similar to the pooled analysis.

In the pooled analysis, one (0.6%) pravastatin-treated subject died. A 60 year old white male with a history of atherosclerotic heart disease, myocardial infarction and coronary artery bypass graft died of a cardiac arrest 5 weeks after initiation of pravastatin therapy. This event was not found to be related to treatment. This event also accounts for the one SAE reported in pravastatin-treated subjects. No deaths were reported in placebo-treated subjects. There was no difference in the occurrence of AEs between pravastatin 10 mg and placebo (65% vs. 70%, p=0.369). The most common AEs reported were attributed to the "gastrointestinal system" pravastatin 21% vs. placebo 27%, p=0.177; and "respiratory system" pravastatin 20% vs. placebo 21%, p=0.897. Musculoskeletal AEs occurred at a significantly greater rate in the placebo group compared to the pravastatin group (24% vs. 16%, p=0.049). The most common AEs were musculoskeletal pain (pravastatin 7% vs. placebo 11%), diarrhea (pravastatin 7% vs. placebo 9%), upper respiratory infection (pravastatin 5% vs. placebo 8%), rhinitis (pravastatin 6% vs. placebo 6%), and headache (pravastatin 6% vs. placebo 4%). There were no significant differences among the pravastatin and placebo groups for marked abnormalities specific

to ASAT, ALAT and CPK. Discussion of events related to the musculoskeletal and hepatic systems can be found in the Special Safety Considerations for OTC Availability Section.

Prava 3 Analysis

Methods

Of the 19,768 subjects studied, 176 (enrolled in WOSCOPS) were not included in the safety analysis: 150 subjects discontinued study participation prior to receiving study medication, 13 were non-participants for whom no compliance information was available, and 13 other subjects discontinued on the day of randomization. The remaining 19,592 (9,809 pravastatin 40 mg, 9,783 placebo) were included in the safety analysis.

Adverse Events: In LIPID, WOSCOPS and CARE, all deaths, SAEs, AEs leading to discontinuation and AEs considered related to treatment (ADEs) were reported; non-serious, unrelated AEs were reported in WOSCOPS and CARE but not in LIPID. Therefore the analysis of deaths, SAEs, AEs leading to discontinuation and ADEs include the full safety cohort of 19,592, while the AE analysis is based on the combined WOSCOPS and Care population. the AE analysis (n=10,578: pravastatin 40 mg 5,297, placebo 5,281.

Clinical Laboratory Evaluations: The incidence of laboratory abnormalities were calculated based on the total number of subjects with at least one post baseline value for that parameter. In LIPID, the upper limit of normal range (ULN) for CPK was not defined, therefore, CPK is only summarized for WOSCOPS and CARE. In addition, ASAT was collected only rarely in LIPID so the total numbers of subjects evaluated for changes in ALAT vs. ASAT are not the same. ALAT, ASAT and CPK were obtained at baseline and according to the schedule shown in Table 2 below:

Table 2: Prava 3: Schedule of Clinical Laboratory Tests

	WOSCOPS	CARE	LIPID
CPK	3, 6, 9 and 12 mos, then biannually	3, 6, 9 and 12 mos, then annually	Annually
ALAT	" "	" "	3, 6, 9 and 12 mos, then biannually
ASAT	" "	" "	Rarely

Results

In the Prava 3 analysis, a total of 1,204 (6.1%) deaths were reported among the 19,592 subjects randomized. Of these, fewer pravastatin-treated subjects died, compared with placebo-treated subjects (5.5% vs. 6.8%, $p < 0.001$). For all three studies, the most common cause of death was cardiovascular in nature occurring in 4.0% of pravastatin and 5.1% of placebo-treated subjects. The incidence of death in all other body systems were similarly distributed between pravastatin and placebo treatment groups. Non-cardiovascular deaths occurred in 1.5% of pravastatin-treated subjects and 1.6% of placebo-treated subjects. Of the non-cardiovascular deaths, malignancy was the most common cause, with comparable incidence (1.0%) in both treatment groups. Fourteen (0.1%) pravastatin-treated and 13 (0.1%) placebo treated subjects died from suicide/violence/trauma.

The incidence of SAEs in pravastatin-treated subjects was less than placebo-treated subjects (55.0% vs. 57.2%, p=0.003). SAEs of the cardiovascular system, occurring in 31.5% of pravastatin-treated subjects and 35.1% of placebo-treated subjects, were the most common. The three most common SAEs occurred in the cardiovascular system, more frequently in the placebo-treated subjects: angina pectoris (pravastatin 16.0% vs. placebo 17.4%; p=0.006), invasive cardiac procedure (pravastatin 13.9% vs. placebo 16.1%; p<0.001), and myocardial infarction (pravastatin 6.9% vs. placebo 9.3%; p<0.001). Surgical and nonsurgical procedures (urologic, invasive gastrointestinal, and orthopedic) were the most frequently occurring noncardiovascular SAEs. By body systems, noncardiovascular SAEs were comparable between the treatment groups for all except for the renal/genitourinary system, in which more pravastatin-treated subjects

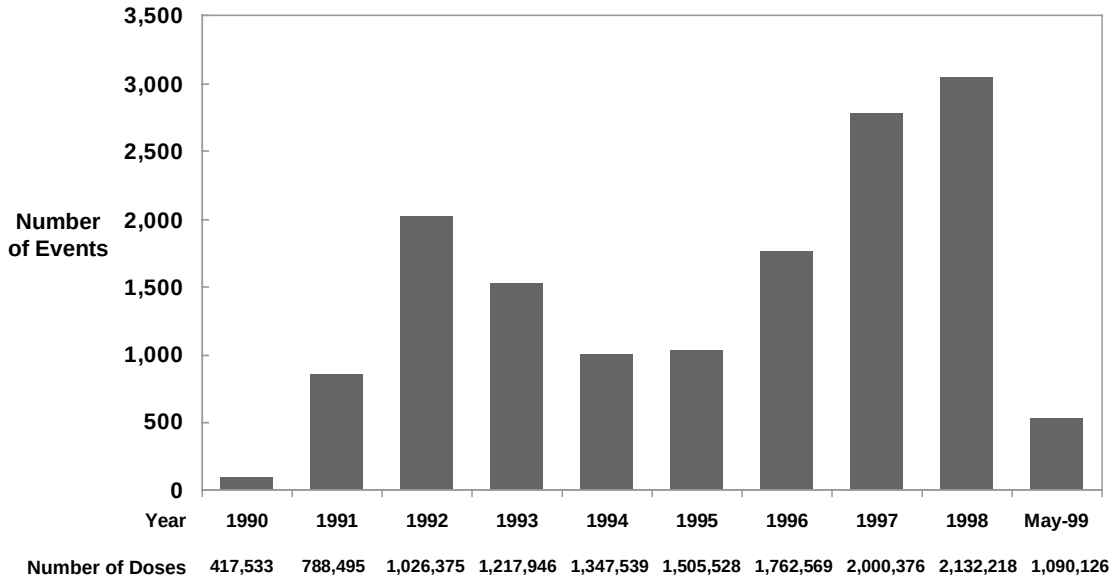
experienced SAEs than did the placebo cohort (11.9% vs 11.0%, p=0.048). The latter observation is accounted for by a large number of surgical/nonsurgical procedures that occurred more frequently in the pravastatin-treated subjects; in this body system, true clinical events were experienced by 315 (3.2%) pravastatin-treated subjects compared to 357 (3.6%) placebo-treated subjects.

Due to the five-year length of the studies, a high percentage of subjects in both treatment groups (94.1% pravastatin, 93.1% placebo; p=0.027) experienced at least one adverse event. AEs occurred most commonly in the following body systems: musculoskeletal/connective tissue (pravastatin 65.8%, placebo 64.7%; p=0.261), respiratory (pravastatin 62.3%, placebo 60.2%; p=0.028), general (pravastatin 53.4%, placebo 52.0%; p=0.155) and GI (pravastatin 47.6%, placebo 47.1%; p=0.586. Overall, the 3 most common AEs were: musculoskeletal pain (pravastatin 45.6% vs. placebo 45.1%; p=0.612), upper respiratory infection 41.2% vs. placebo 39.3%; p=0.043), and angina pectoris (pravastatin 22.7% vs. placebo 23.8%; p=0.174). AEs occurring in the musculoskeletal/connective tissue body system were generally considered mild and there were no confirmed cases of rhabdomyolysis.

Post Marketing Surveillance

The Post Marketing Surveillance database for Pravachol in a broader population receiving prescription therapy is consistent with the benign safety profile of Pravachol defined in the clinical trials. This database includes over 22 million patient years of marketed exposure to pravastatin (13.3 billion doses distributed: approximately 10% at 10 mg, 60% at 20 mg and 30% at 40 mg). All reports, regardless of causability, are centered into this database. Between February 23, 1990 and May 31, 1999, 8,782 reports (14,641 events) have been received worldwide of which 1,308 reports (2,634 events) describe what were considered serious adverse events. Figure 3 shows the annual distribution of reports and doses distributed worldwide during this period.

Figure 3: Post Marketing Surveillance: Worldwide Spontaneous Adverse Events Reports for Pravastatin



Since February 1990, 68 deaths have been reported: 50 through spontaneous or literature sources and 18 through Phase IV studies. The mean age of those who died was 64.5 years. Twenty-five (25) deaths occurred in the US, one of which was reported for the 10 mg dose. As seen in Table 3 , in 21 of the 68 deaths, the cause of death was not attributed to a specific body system; 21 died of cardiovascular causes and 6 died of hepatobiliary disorders. Of the 6 hepatobiliary deaths, 3 two were due to metastatic cancer, 2 to alternative drug toxicity (diclofenac and trazodone), and 1 had inconclusive data. The death attributed to the musculoskeletal/connective tissue/bone body system is summarized in the Section that discusses Special Safety Considerations for OTC Availability. Summaries of the deaths can be found in Appendix B.

Table 3: Post Marketing Surveillance: Number of Deaths by System Organ Class (13.3 billion doses/20 million patient years)

System Organ Class	Number of Deaths
Total Deaths	68
Blood and Lymphatic System	1
Cardiac	14
Gastrointestinal	3
General Disorders/Administration Site Conditions	2
Hepatobiliary	6
Injury/Poisoning	1
Metabolism and Nutritional Disorders	2
Multi-Organ Failure	2
Musculoskeletal/Connective Tissue/Bone	1
Neoplasms,Benign/Malignant	3
Renal/Urinary	2
Respiratory/Thoracic/Mediastinal	3
Vascular	7
System Organ Class Not Identified	21

One thousand three hundred and eight (1,308) reports of SAEs (2,634 events) accounted for 14.9% of the total AEs received worldwide. A summary of SAEs by system organ class can be found in Table 4. The most frequently reported SAEs involved musculoskeletal/connective tissue/bone disorders system (361 events: 13.7% of all SAEs reported).

Table 4: Post Marketing Surveillance: Frequency of Serious Adverse Events as a % of Reported SAEs by System Organ Class (13.3 billion doses/20 million patient years)

System Organ Class	Number of Events	(%) Of Total SAEs
Total Serious Events	2,634	(100)
Blood and Lymphatic System	74	(2.8)
Cardiac	187	(7.1)
Congenital/Genetic	4	(0.2)
Ear/Labyrinth	14	(0.5)
Endocrine	7	(0.3)
Eye	118	(4.5)
Gastrointestinal	204	(7.7)
General Disorders/Administration Site Conditions	333	(12.6)
Hepatobiliary	168	(6.4)
Immune System	22	(0.8)
Infections/Infestations	70	(2.7)
Injury/Poisoning	36	(1.4)
Investigations	232	(8.8)
Metabolism/Nutrition	55	(2.1)
Musculoskeletal/Connective Tissue/Bone	361	(13.7)
Neoplasms,Benign/Malignant	76	(2.9)
Nervous System	215	(8.2)
Pregnancy/Puerperium/Perinatal	3	(0.1)
Psychiatric	51	(1.9)
Renal/Urinary	102	(3.9)
Reproductive/Breast	26	(1.0)
Respiratory/Thoracic/Mediastinal	69	(2.6)
Skin & Subcutaneous Tissue	128	(4.9)
Social Circumstances	1	(<0.1)
Vascular	78	(3.0)

Among the SAEs, only 15 preferred terms were encountered at a frequency of $\geq$1%, and are listed in Table 5. The most commonly reported SAE was rhabdomyolysis which is discussed in detail in the Special Safety Considerations for OTC Availability Section.

Table 5: Post Marketing Surveillance: Serious Adverse Events Occurring at A Frequency of ≥ 1% of All Reported SAEs (13.3 billion Doses/20 million patient years)

Preferred Term	Number of Events
Total Serious Events	2,634
Rhabdomyolysis	116
Condition aggravated	86
Myalgia	82
CPK increased	54
Cataract NEC	47
Myocardial infarction	45
Hepatitis NOS	42
Hepatic function abnormal NOS	40
Drug interaction NOS	35
Pancreatitis NOS	34
Chest pain	30
Coronary artery disease NOS	30
Muscle weakness NOS	28
Alanine aminotransferase increased	27
Aspartate aminotransferase increased	27

NOS = Not Otherwise Specified
NEC= Not Elsewhere Classified

AEs were reported infrequently (8,782 reports comprising 14,641 events/22 million patient years), as shown in Table 6. The greatest numbers of events were reported in the following system organ classes; musculoskeletal/connective tissue/bone disorders (n=2447; 16.7%); general disorders and administration site conditions (n=1733; 11.8%); and gastrointestinal disorders (n=1710; 11.7%).

Table 6: Post Marketing Surveillance: Frequency of All Adverse Events as a percentage of reported AEs by System Organ Class (13.3 billion doses/20 million patient years)

System Organ Class	Number of Events	(%) of Total Events
Total Adverse Events	14,641	(100)
Blood and Lymphatic System	195	(1.3)
Cardiac	427	(2.9)
Congenital/Genetic	6	(<0.1)
Ear/Labyrinth	94	(0.6)
Endocrine	38	(0.3)
Eye	341	(2.3)
Gastrointestinal	1710	(11.7)
General Disorders/Administration Site Conditions	1733	(11.8)
Hepatobiliary	484	(3.3)
Immune System	64	(0.4)
Infections/Infestations	161	(1.1)
Injury/Poisoning	70	(0.5)
Investigations	1704	(11.6)
Metabolism/Nutrition	416	(2.8)
Musculoskeletal/Connective Tissue/Bone	2447	(16.7)
Neoplasms,Benign/Malignant	93	(0.6)
Nervous System	1473	(10.1)
Pregnancy/Puerperium/Perinatal	61	(0.4)
Psychiatric	415	(2.8)
Renal/Urinary	257	(1.8)
Reproductive/Breast	314	(2.1)
Respiratory/Thoracic/Mediastinal	256	(1.7)
Skin & Subcutaneous Tissue	1667	(11.4)
Social Circumstances	1	(<0.1)
Vascular	214	(1.5)

As shown in Table 7, only 20 different types of AEs occurred at a frequency ≥1% of all reported AEs; the most frequent was myalgia, occurring in 7.5% of all AEs reported worldwide.

Table 7: Post Marketing Surveillance: Adverse Events Occurring at a Frequency of ≥ 1% of All Reported AEs (13.3 billion doses/20 million patient years)

Preferred Term	Number of Events	(%)
Total Events	14,641	(100)
Myalgia	1,095	(7.5)
CPK Increased	444	(3.0)
Condition Aggravated	399	(2.7)
Alopecia	344	(2.3)
Dermatitis NOS	325	(2.2)
Nausea	314	(2.1)
Headache NOS	309	(2.1)
Arthralgia	280	(1.9)
Hepatic Function Abnormal NOS	225	(1.5)
Dizziness Exc. Vertigo	211	(1.4)
Abdominal Pain NOS	205	(1.4)
Pruritus NOS	202	(1.4)
Diarrhoea NOS	187	(1.3)
Drug Ineffective	179	(1.2)
Gamma-Glutamyltransferase Incr.	168	(1.1)
Fatigue	166	(1.1)
Muscle Cramps	153	(1.0)
Muscle Weakness NOS	153	(1.0)
Chest Pain	145	(1.0)
Insomnia NEC	143	(1.0)

NOS = Not Otherwise Specified
NEC= Not Elsewhere Classified

Special Safety Considerations for OTC Availability

In consideration of OTC status for an HMG CoA reductase inhibitor, several safety issues were examined in detail because of potential clinical concern or of regulatory authority interest. The following sections present data on drug interactions, overdose, inadvertent use during pregnancy, musculoskeletal adverse events, and hepatobiliary adverse events as well as laboratory evaluations of transaminase and CPK levels.

Drug Interactions

A standard battery of interaction studies has been conducted with pravastatin and the results of the battery are summarized in Table 8. Pravastatin has no clinically significant drug interactions including drugs with a very narrow therapeutic/toxicity indices, such as warfarin and digoxin and common OTC drugs such as aspirin, antacids, cimetadine.

While some HMG-CoA are metabolized by the cytochrome P450 system, an extensive battery of *in vitro* and *in vivo* studies indicate that pravastatin is not metabolized by the cytochrome P450 system to any clinically significant extent. Pharmacokinetic studies with pravastatin have shown no significant P450-mediated interactions with medications or foods either in the gastrointestinal transporter system or in the liver (Ref. 19).

Table 8 Summary of Drug Interactions Reported in the Prescription Pravastatin Package Insert

Drug	Protocol (Dose)	Results
Antacids	Protocol # 27201-43 (20 mg)	No statistically significant differences in pravastatin bioavailability when antacids were given one hour before pravastatin
Antipyrine	Protocol # 27201-16 (5, 10, 20 m	Pravastatin has no effect on clearance of antipyrine
Aspirin	Protocol # 27201-6 (10 mg)	No statistically significant differences in pravastatin bioavailability
Cimetidine	Protocol # 27201-43 (20mg)	AUC for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin given alone
Digoxin (DG)	Protocol # 27201-72 (20 mg)	No effect on bioavailability of DG or pravastatin plus its metabolites
Warfarin	Protocol # 27201-59 (20mg)	No clinically significant effect on prothrombin time
Cyclosporine (CY)	Protocol # 123-141 (20 mg)	No clinically meaningful elevations in CY levels; AUC for pravastatin increased 4-fold.
Diltiazem	Azie, 1998 (20 mg)	No effect on the pharmacokinetics of pravastatin
Erythromycin	Protocol # 123-177 (40 mg)	Risk of myopathy is increased with concurrent use of other HMG reductase inhibitors
Itraconazole (IT)	Protocol # 123-168 (40 mg)	AUC and Cmax for pravastatin were increased by 1.7 – 2.5 fold in a single dose study, however, in a larger multiple dose study, no effect was obtained.
Cholestyramine (CH) Colestipol (CO)	Protocol # 27201-6 (10 mg) Protocol # 27201-18 (20 mg)	Concomitant administration results in 40-50% decrease in the mean AUC of pravastatin; there was no clinically significant decrease in bioavailability or therapeutic effect when pravastatin was given 1 hour before or 4 hours after CH or 1 hour before CO w/standard meal
Gemfibrozil	Protocol # 27201-18 (20 mg)	Decrease in urinary excretion and protein binding of pravastatin; increase in pharmacokinetic parameters of metabolite SQ 31,906
Probucol	Protocol # 27201-18 (20 mg)	No statistically significant differences in pravastatin bioavailability
Niacin	Protocol # 27201-6 (10 mg)	No statistically significant differences in pravastatin bioavailability

Pravachol pharmacokinetics have been shown to be unaffected by cytochrome P450 isozyme inhibitors such as azole antifungals (e.g., itraconazole, fluconazole), calcium-channel blockers (e.g., diltiazem, mibefradil, verapamil), nefazodone, and grapefruit juice. Erythromycin can produce small increases in pravastatin serum concentrations, but the magnitude of these increases is not sufficient to result in adverse consequences. Cyclosporine may produce 4 to 5-fold increases in serum concentrations of pravastatin, however, neither myopathy nor significant increases in CPK levels have been observed in three reports of 100 post-transplant patients treated for up to two years with cyclosporine and pravastatin (Ref. 20). Because pravastatin is hydrophilic, the risk of muscle injury is

low despite modest increase in serum levels of pravastatin and is less likely to be absorbed from the gastrointestinal tract and gain access to sites of action within the cells (Ref. 1)

Although gemfibrozil, and to a lesser extent, niacin, have been associated with myositis when combined with some statins, in addition to the studies reported in the prescription package insert, several clinical studies have demonstrated the safety of combination of pravastatin with these lipid-lowering agents. These studies are summarized in Table 9.

Table 9: Pravastatin-Fibrate and Pravastatin-Nicotinic Acid Studies

Trial	Doses	# of Pt's	Duration (Weeks)	Myopathy
Gemfibrozil				
Wiklund (Ref.21)	40 Mg	65	12	0
Athyros (Ref. 22)	20 mg	135	116	0
Lliadis (Ref. 23)	22 mg (mean)	83	176	0
Total		293	-	0
Fenofibrate		63	104	0
Ellen (Ref. 24)	20 mg			
Niacin				
Davignon (Ref. 25)	40 mg	48	88	0
HARP (Ref. 26)	40 mg	40	52	0
Total		88	-	0
Gemfib/Niacin				
HARP (Ref. 26)	Prava 40 mg	12	43	0

The incidence of adverse events due to drug interaction with pravastatin in clinical trials and from Post Marketing Surveillance has been low [114/14,641(0.8%)]; these events have not been clearly attributable to pravastatin.

Overdose

Preclinical Data

Results of extensive preclinical safety evaluation studies [NDA 19-898] of pravastatin, in which threshold doses and/or systemic exposure values for specific target-organ toxicity were defined, established a substantial margin of safety for the maximum prescription dose of 40 mg. The safety of pravastatin has been evaluated in a battery of in-vitro and in-vivo tests, including multiple-dose toxicity testing and carcinogenicity studies of up to 2 years duration. The minimum toxic dose from multidose studies in animals was more than 100 times (i.e., greater than 3x the total amount of pravastatin in a one month supply OTC package) the expected human daily OTC dose of 10mg (Ref. 27). Based on acute oral animal toxicity data, clinical signs and/or pathologic findings were reported to occur only at doses more than 4000 times the single OTC dose (over 140 times the total amount of pravastatin in a one-month supply OTC package) (Ref. 28). Pravastatin has very limited potential for toxicity in human acute overdose situations.

Clinical Experience

Studies of pravastatin have been conducted with doses of 10-160 mg. The long-term trials WOSCOPS, CARE, LIPID utilized a 40 mg daily dose. Pravastatin has been administered at doses up to 80 mg/day in 322 patients followed during extensions of early clinical studies; there were no safety issues at the 80 mg dose. An ascending single dose pharmacokinetics study of pravastatin (Protocol CV 123-162) has shown that single doses of 40, 80, and 160 mg pravastatin are safe and well tolerated.

Protocol CV 123-161 was a placebo-controlled dose response study was conducted in which pravastatin was administered once daily for 6 weeks in doses of 40, 80, and 160 mg which are equivalent to 4, 8, and 16 times the expected daily OTC dose. No deaths or SAEs occurred during the active treatment period. The most common AEs in order of decreasing in frequency were headache, upper respiratory tract infection, musculoskeletal pain, fatigue and abdominal pain. There was a dose-related increase in frequency of AEs

with the 160 mg dose being associated with a higher frequency of AEs in the gastrointestinal, respiratory, and investigator-identified renal/genitourinary body systems. These AE frequencies at the 80 mg dose were comparable to placebo. No clinically meaningful changes in liver function tests or serum chemistries were noted in the study.

Post Marketing Surveillance

A total of fourteen reports (9-spontaneous/literature; 5-Phase IV trials) of pravastatin overdose have been collected in the BMS Post Marketing Surveillance System. A listing of these cases can be found in Table 10 and details are included in the Council for International Organization of Medical Sciences (CIOMS) reports in Appendix C.

Table 10 Post Marketing Surveillance: Listing of Overdose Reports

Case # Country	Category	Type	Sex/Age	Tablet	Total Dose	Outcome
MO28192 (US)	Spon/Lit	AC	M/20m	20 mg	40 mg	Recovered No sequelae
MO52870 (US)	Spon/Lit	AC	F/77y	20 mg	160 mg	Recovered
MO86918 (US)	Spon/Lit	AC	F/0	10 mg	1,200 mg	Recovered
BO21414 (UK)	Spon/Lit	AC	F/0	10 mg	20 mg	Recovered
BO28411 (NE)	Spon/Lit	OD	M/56y	20 mg	1,040 mg	Recovered
B035760 (FR)	Spon/Lit	OD	M/37y	Unk	280 mg	Recovered
B006907 (FR)	Spon/Lit	OD	F/57y	Unk	14 tabs	Recovered
B016782 (FR)	Spon/Lit	OD	M/14y	Unk	Unk	Recovered
B042920 (FR)	Spon/Lit	OD	M/59y	Unk	30 tabs	Death
BO15763 (FR)	PhIV	AC	M/59y	20 mg	80 mg	Recovered
10100592 (AU)	PhIV	AC	M/55y	20 mg	N/A	Recovered
B018873 (FR)	PhIV	OD	M/67y	Unk	Unk	Recovered
B019261 (FR)	PhIV	OD	M/53y	20 mg	Unk	Recovered
BO46237 (AU)	PhIV	OD	M/45y	20 mg	Unk	Recovered

AC = accidental, OD = overdose, non-accidental
NL=Netherlands; GB=United Kingdom; FR=France; AU=Australia; US=United States
0=Not given; m=months; y=years

In two of these reports, the 10 mg tablet was identified. In the first case (MO86918) a female patient, whose daily dose was 10 mg, accidentally took ten 10 mg tablets twice a day for 6 days. Therapy was discontinued and the patient was hospitalized. Monitoring of liver function tests, creatine kinase (CK) other laboratory parameters showed no abnormalities. A second female patient (BO21414) took her 10 mg evening dose of pravastatin and the next morning, inadvertently took another 10 mg dose. No adverse consequences were reported.

Eight of nine spontaneous/literature overdose patients had either no significant AEs, no significant sequelae, or completely recovered. One of the nine patients (B042920),

ingested concomitant overdoses of amlodipine, pravastatin, captopril, and verapamil along with alcohol, developed cardiogenic shock and subsequently died of cardiopulmonary arrest.

Of the 8 patients who recovered, one (MO28192) included a 20 month old child who ingested 40 mg. Another (MO86918) involved the 10 mg tablet has been discussed above. A third case (BO28411) was a patient who ingested 6 to 10 units of alcohol followed by 52 pravastatin 20 mg tablets (1,040 mg) along with 90 metoprolol 10 mg tablets, and 46 acetylsalicylic acid 80 mg tablets in a suicide attempt. He experienced an elevation in ALAT of 41 IU/L (normal range = 5 – 40 IU/L) on one of five determinations, no elevations in ASAT (5 determinations), and an increased alkaline phosphatase of 136 IU/L (normal range = 30-125 IU/L) on one of three determinations. This patient recovered without sequelae.

Among the five overdose reports received from Phase IV pravastatin clinical studies, two were considered overdoses with drugs other than pravastatin (10100592 and B046237). Of the three other Phase IV overdose reports, two were in subjects who ingested more tablets than specified by the double-blind study protocol (B018873 and B019261), and may have been receiving pravastatin or placebo. One (B018873) experienced asymptomatic CK elevations of 271 IU/L with eventual resolution; the other was asymptomatic. A third overdose case, took pravastatin 20 mg 4 times a day instead of twice a day with no adverse effects noted.

The OTC package will consist of 28 doses packaged in calendar pack blister cards. This is designed not only to maximize compliance, but also to make overdose very unlikely.

Pregnancy

While OTC Pravachol 10 mg is not intended for routine use in pregnant women, we nonetheless recognize that it is possible that a woman might inadvertently take OTC Pravachol, or a physician might decide that the benefits outweigh the risks for an individual patient during pregnancy. Accordingly, like all OTC medications, the

proposed OTC Pravachol 10 mg label states “If pregnant or breast feeding ask a health professional before use”.

As a background, currently all prescription statins contain Category X labeling, thus precluding their use in pregnancy. This is largely due to the fact that the data available at the time of approval of the first member of statin class (lovastatin) demonstrated reproductive toxicity in animal models, albeit at doses substantially higher than those approved for clinical use. Pravastatin, in contrast, was found to have no untoward affects on reproduction in rats and did not cause any fetal toxicity or anatomic abnormalities in rats or rabbits. However, based largely on the lovastatin data, lack of sufficient countervailing clinical toxicity data, and difficulty in attributing a true benefit to the treatment of hyperlipidemia in pregnant women, all statins have been given class labeling and approved for marketing with pregnancy Category X labeling for use during pregnancy.

In order to support the currently proposed OTC label statement for Pravachol 10 mg, and in order to assess the safety of Pravachol if taken inadvertently by a pregnant woman, the complete historical preclinical and clinical data were extensively re-reviewed. Completion of such a review, including all available clinical data in cases of women who inadvertently took pravastatin during pregnancy, allowed the conclusion that the Pregnancy Category X labeling is not appropriate for pravastatin, but rather support the proposed OTC labeling. These data have been submitted to the FDA for their consideration of this application.

Preclinical Data

Oral reproductive toxicology animal studies have found no untoward reproductive or teratogenic effects, embryo-fetal toxicity or anatomic abnormalities associated with high doses of pravastatin. Studies in rats and rabbits at 240 and 20 times the human therapeutic dose, respectively, show no adverse effects on any reproductive or teratogenic parameter, including: congenital malformations, number of corpora lutea, number of

implantations, early resorptions (implantation loss), fetal growth at term, or post-partum growth. Since mutagenicity tests with pravastatin have all been negative, and there is no evidence of pravastatin-related embryo-fetal toxicity, or growth retardation at high doses in reproductive toxicity studies in animals, it is clear that at doses approved for clinical use, pravastatin is not genotoxic, teratogenic or embryotoxic.

Clinical Experience

BMS has collected post marketing surveillance reports of exposure to Pravachol during pregnancy. The majority of these exposures occurred well into the first trimester and universally exposed the embryo during the most sensitive stages of early organogenesis and early fetal development. In some cases, exposure continued throughout a substantial portion of or all of the full term pregnancies. As of December 7, 1999, there were 43 reports describing pravastatin exposure during pregnancy in 41 female patients (two females became pregnant twice while on Pravachol). A summary of these reports is presented in Table 11.

Table 11: Post Marketing Surveillance: Reports of Pravastatin Exposure in Pregnant Women

Pregnancy Outcome	Number	Average Maternal Age (years)	Average dose in mg/day	Average Birthweight (grams)
Total Pregnancies	43			3282
Normal Infants (One set of twins)	23	31.4	26	3342
Results not reported	14	31.0	18	
Spontaneous Abortion*	3	31.7	20	
Elective Abortion	2	23.5	10	
Newborn cholelithiasis**	1	27	20	3250
Intrauterine growth retardation***	1	31	10	2353

*These reports are also listed as SAEs in Table 4 of this briefing document
** The newborn of this mother was born with cholelithiasis (based on abdominal ultrasound evaluation) which reportedly resolved after six days.
*** A singleton pregnancy. Intrauterine growth retardation (IUGR) diagnosed ultrasonographically. The mother had glomerulonephritis, renal hypertension, and proteinuria (all known risk factors for IUGR), but delivered a newborn without congenital malformations and a birthweight of 2353g.

The outcome of the pregnancy was reported in 29 of the 43 cases. Duration of treatment during pregnancy in these 29 cases were: 4 weeks in 8 cases; 5 – 8 weeks in 12 cases; 10 –14 weeks in 6 cases; and ≥ 34 weeks in 3 cases. In 22 cases, a normal newborn was delivered. There were no congenital malformations in the pregnancies with known outcomes that went to term. The average weight of all newborns for whom birthweight was reported (18) was 3282 grams (7.22 lbs), which is not significantly different from the average weight of newborns in the US of 3296 grams (7.25 lbs). In one case, intrauterine growth retardation attributed by the reporter to the mother's medical condition of renal hypertension and glomerulonephritis was encountered. In this case, the infant was born without congenital malformations and a weight of 2353 grams.

One newborn developed vomiting on the second post partum day and was found to have "gallstones" based on an abdominal ultrasound. The vomiting had resolved within 6 days and gallstones were not present on repeat ultrasound. The mother had received multiple concomitant drugs (amitriptyline HCL, lorazepam, cyamemazine, and dihydroergotamine) during the pregnancy.

In all but one of the cases for which the information was available, pravastatin therapy was discontinued when the pregnancy was recognized. In one case, pravastatin 20 mg therapy was not discontinued. The 28-year-old woman delivered healthy twin boys by Cesarean section at 34 weeks of gestation: one infant weighed 2080 grams and the other, 2170 grams. The mother had received hormone therapy for induction of pregnancy and, according to the reporter, she delivered prematurely because of a bronchial infection.

Breast Feeding

Exposure to pravastatin through breast milk is unlikely to affect cholesterol metabolism in a developing infant. A study (Protocol CSA-113) was conducted to assess the risk to infants of breast feeding mothers . This study included 11 healthy lactating women. The results indicated that:

- If a 50 kg mother taking 20 mg of pravastatin twice daily ingests 400 μg/kg per day this would result in a maximum mean concentration (C_{max}) of pravastatin in breast milk of 3.9 ng/ml
- If a 5 kg infant consumes 5 oz (150 ml) of breast milk at each feeding, he/she ingests 3.5 μg
- Assuming the bioavailability is the same in infants and adults, namely 20%, this results in an infant serum concentration of 0.7 μg/kg; thus the infant dose is 0.18% the maternal dose.

Although preclinical data and post-marketing surveillance data do not indicate that pravastatin represents a risk for fetal development, OTC use of Pravachol 10 mg in pregnant and lactating women is not recommended. The proposed OTC label states, "If pregnant or breast feeding ask a health professional before use" which was understood by 87% of respondent who participated in the Label Comprehension study (see Section IV).

Musculoskeletal System

Uncomplicated myalgia, elevations of CPK, and rare cases of rhabdomyolysis have been reported with pravastatin and other drugs in this class. This section summarizes pravastatin clinical and laboratory data related to the musculoskeletal system.

10 mg Dose Response Studies

In the 10 mg dose response studies, there were no deaths, SAEs, or discontinuations due to AEs of the musculoskeletal system. There were no reports of myopathy, defined as muscle aching or muscle weakness with CPK > 10 x ULN and no cases of rhabdomyolysis. Musculoskeletal AEs were less frequent in pravastatin-treated subjects vs. placebo-treated subjects (16% vs. 24%, p=0.049). In most cases the musculoskeletal pain was associated with an underlying condition such as viral infection, arthritis, fatigue, tendonitis or trauma. Of the 13 subjects (6 pravastatin vs. 7 placebo) who had an AE of increased CPK, five (3 pravastatin vs. 2 placebo) were reported as marked abnormalities

defined as 4x pretreatment value. None of the marked abnormalities were serious or caused discontinuation of study medication.

Prava 3 Analysis

Results of the Prava 3 analysis of Pravachol 40 mg vs. placebo studied in 19,768 patients for a mean of 4.6 years showed that the incidence of musculoskeletal system adverse events was not significantly different between the treatment groups. Two-hundred eight (208/9,809 [2.1%]) pravastatin-treated subjects and 220/9,783 (2.2%) placebo-treated subjects experienced myalgia and/or myositis. There were no cases of myopathy defined as muscle aching or muscle weakness in conjunction with increases in CPK > 10xULN.. There was 1 report of rhabdomyolysis in a pravastatin-treated subject; however the CPK was less than 2 x ULN and no urinalysis was performed to confirm the presence of myoglobinuria and thus this case did not meet the definition of rhabdomyolysis. The event resolved and the subject continued on study medication.

Adverse events relevant to skeletal muscle function, (muscle ache, muscle weakness, myalgia, myositis), shown in Table 12, occurred in 5.7% and 5.6% of pravastatin-treated and placebo-treated subjects, respectively. They were infrequently regarded as serious (occurring in 0.2% of both study groups), were comparably considered related/possibly related/unknown (occurring in 1.4% of both study groups), and uncommonly led to study discontinuation (0.2% pravastatin, 0.3% placebo).

Table 12: Prava 3: Skeletal Muscle SAEs and AEs

	SAE's		AEs	
	Pravastatin 40 mg n= 9,809	Placebo n= 9,783	Pravastatin 40 mg n= 5,297	Placebo n = 5,281
	N (%)	n (%)	n (%)	n (n)
Muscle Ache	0	0	110 (2.1)	103 (2.0)
Muscle Weakness	5 (<0.1)	5 (<0.1)	21 (0.4)	12 (0.2)
Myalgia	11 (0.1)	8 (<0.1)	168 (3.2)	178 (3.4)
Myositis	0	3 (<0.1)	2 (<0.1)	4 (<0.1)
Total	**16 (0.2)**	**16 (0.2)**	**301 (5.7)**	**297 (5.6)**

*(LIPID not included in AE reports, only SAEs and ADEs reported in that study)

In addition to the clinical AE profile of pravastatin, this very large database allowed for assessment of CPK elevations overall and by severity. Subjects had CPK measurements taken at baseline and at 3, 6, 9 and 12 months after initiation and then biannually in WOSCOPS and annually in CARE. In these studies, 10,576 subjects had a mean of 12 measurements taken. The incidence of any post-baseline abnormality in CPK was comparable between the pravastatin-treated and the placebo-treated subjects overall and by severity. Table 13 displays the incidence of post-baseline CPK (> 1.5 x ULN regardless of baseline value) by severity in the pravastatin-treated subjects compared to the placebo-treated cohort. Nine pravastatin-treated and two placebo-treated subjects developed on-therapy CPK elevations of > 9 x ULN. For eight of these cases, the CPK level normalized on treatment. In one subject, CPK level was elevated on day 538 of treatment at 3,240 U/L. A day prior to this elevation an adverse event of influenza was reported. Thirty days later, the CPK level decreased to 701 U/L, but remained elevated throughout the remainder of the study. The subject complained of musculoskeletal pain throughout the study and underwent hip surgery on day 217 and had arthritis reported on day 1007. All nine subjects either completed the study or at least 4 years of treatment.

The frequency of clinically significant abnormalities in CPK values was low which is consistent with the fact that myopathy was not reported. There was no difference in the incidence of CPK abnormalities by gender. For subjects ≥ 65, a significant difference (p=0.048) was noted in pravastatin treated subjects compared to placebo treated subjects which was due to a greater incidence of elevated CPK >1.5, ≤ 3 x ULN for the pravastatin treated group.

Table 13: Prava 3: Post Baseline Abnormalities in CPK by Severity

Characteristic		Number (Percent of Subjects)* Pravastatin 40 mg	Placebo	95% C.I.
CPK		**587/5,245 (11.2%)**	**563/5,233 (10.8%)**	**-0.78, 1.65**
> 1.5 x ULN,	≤ 3 x ULN	480/5,245 (9.2%)	460/5,233 (8.8%)	-0.40, 0.59
> 3 x ULN,	≤ 5 x ULN	84/5,295 (1.6%)	79/5,233 (1.5%)	-0.40, 0.59
> 5 x ULN,	≤ 7 x ULN	8/5,245 (0.2%)	16/5,2330 (.3%)	-0.36, 0.05
> 7 x ULN,	≤ 9 x ULN	6/5,245 (0.1%)	6/5,233 (0.1%)	-0.15, 0.15
> 9 x ULN,		9/5,245 (0.2%)	2/5,233 (<0.1%)	-0.02, 0.28

*Percentages are based on the total number of subjects with at least one post-baseline value for the parameter. If subjects had an abnormal value in more than one category, they are only counted in the highest category. The upper limit of the normal range for CPK was not defined in the LIPID study, therefore CPK is only summarized for WOSCOPS and CARE. *p-value CPK is 0.492

Post Marketing Surveillance

In the Post Marketing Surveillance database which comprises over 20 million patient years of marketed use, there were a total of 2,447 events, reported worldwide for all doses for Musculoskeletal, Connective Tissue, and Bone Disorders. Of these, there was 1 death and 361 were serious events (Table 14). An 85 year female with a history of degenerative joint disease with compression fracture developed myositis/myopathy after 3 months of therapy. CPK level increased to 5500 U/L. The subject was hospitalized and treated with prednisone, and CPK levels returned to within normal limits. The subject was subsequently re-hospitalized for a bleeding gastric ulcer from which she died. The reporting physician felt that the patients underlying muscle weakness may attributed to the course of events.

Table 14: Post Marketing Surveillance: Musculoskeletal, Connective Tissue and Bone Disorders

Preferred Term	Number of Events	
	Total	Serious
Musculoskeletal events	2,447	361
Muscle Weakness NOS	153	28
Myalgia	1095	82
Myopathy	79	20
Myositis	63	16
Rhabdomyolysis	122	116
Other	935	99

There were 1,095 events of myalgia reported worldwide for all doses of pravastatin; 82 of these cases were reported as serious adverse events.

There were 122 reports of rhabdomyolysis. Twenty seven (27) of these cases were reported in the US and none occurred with the 10 mg dose. Several of the reported cases occurred in patients taking concomitant medications associated with rhabdomyolysis. There were 25 cases (21% of reported cases) reported in which fibrates, which have a known association with rhabdomyolysis, were used concomitantly. Most cases reported a medical history of coronary or vascular events, and several cases reported underlying other medical conditions also known to predispose to rhabodomyolysis including trauma and vigorous exercise, collagen vascular disease, thyroid disease, alcohol use, and Parkinson's were reported in 24% of reports.

The proposed OTC label states, "Stop use and ask a doctor if you have any unusual muscle pain or weakness not caused by a cold, flu, recent injury or sprain. This is very important if you also feel weak or have a fever." As discussed in Section IV, 93% of consumers understood this label warning message in the Label Comprehension Study.

Hepatobiliary System

Like other lipid lowering therapies, some HMG-CoA reductase inhibitors have been associated with mild abnormalities of transaminase levels. When pravstatin was approved in 1991, it was recommended that liver function tests be performed prior to initiation, every 6 weeks for 3 months and then every 8 weeks for 9 months. Since its approval, pravastatin has received reductions of label requirements for liver function testing. In 1994, based on the Post Marketing Surveillance experience, the label was changed to recommend that testing be performed prior to initiation, at 6 and 12 weeks following initiation of therapy or dose elevation, and periodically thereafter. In 1998 another reduction of label requirements was approved by FDA based on the analysis of the WOSCOPS data. The current prescription package insert recommends testing prior to the time of initiation of use of pravastatin and another measurement after 3 months of

pravastatin. This section reviews clinical and biochemical data referable to hepatic function, with particular attention to the recently completed Prava 3 analysis.

10 mg Dose Response Studies

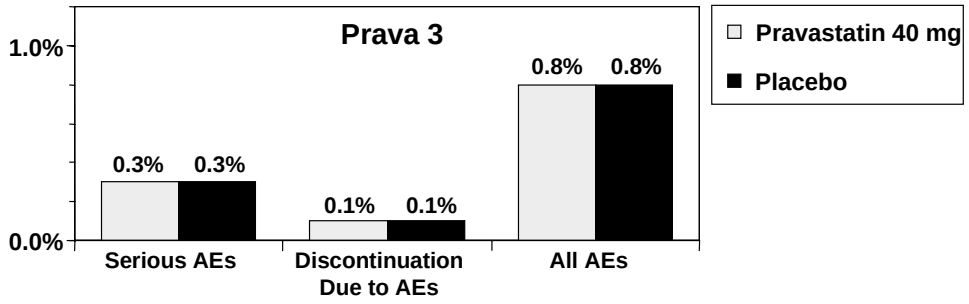
In the 10 mg studies there were no deaths or SAEs and no pravastatin-treated subjects discontinued from study medication for AEs related to the hepatobiliary system. In the pooled analysis of the 10mg studies (Protocols 27201-2 and 27201-42) there was no difference between the pravastatin-treated and placebo-treated subjects for marked abnormalities of ALAT/ASAT (2/100 vs. 2/150 and 0 vs. 2/150, respectively). There were no marked abnormalities for ALAT/ASAT in Protocol 27201-89.

Prava 3 Analysis

The Prava 3 analysis provided an opportunity to assess specific clinical safety indices of hepatic function in a randomized placebo controlled database of 19,768 subjects comprising > 100,000 patient years at four times the OTC dose. In these studies, measurements of transaminase levels were done frequently. Each subject had a determination of transaminase on a mean of 13 occasions for both ALAT and ASAT. Moreover, in these trials, subjects were allowed to enter the study even if they had with mild transaminase abnormalities at baseline. Of the subjects who had hepatic enzymes measured, 579 (3.2%) had mild abnormalities of hepatic enzymes at baseline, thus providing a population that may represent those with chronic asymptomatic liver disease. As discussed in detail subsequently, this analysis demonstrates that there is no statistically significant difference between patients taking pravastatin 40 mg compared with those taking placebo in percentage of subjects experiencing treatment emergent clinical adverse events in the hepatobiliary system or post baseline elevations in transaminase levels.

In the Prava 3 analysis there were no deaths due to hepatic failure. As shown in Figure 4, hepatic adverse experiences that were serious, that lead to discontinuation, and overall occurred in the same percentage of pravastatin and placebo treated subjects.

Figure 4: Prava 3: Hepatic Adverse Events



While the overall incidence of AEs of the hepatic body system was 0.8% for pravastatin and placebo-treated subjects, the AE of liver disease occurred in a greater number of pravastatin-treated (10/5,297) vs. placebo-treated (2/5,281) subjects (p=0.038). However, of the ten pravastatin-treated subjects, nine continued on medication and completed the study while one subject died of unrelated causes.

In order to determine more fully the degree of laboratory abnormalities occurring for ALAT and ASAT in subjects treated with pravastatin 40 mg vs placebo, an assessment of post-treatment abnormalities overall as well as in ranges of severity (i.e., 1.5-3, 3-5, 5-7, 7-9, and >9 x ULN), is presented in Table 15. This analysis includes any post baseline value that were > 1.5 x ULN, regardless of baseline value.

Table 15: Prava 3: Incidence of Post-baseline Abnormalities of ALAT and ASAT

		Pravastatin 40 mg n/N (%)	Placebo n/N (%)	95% C.I.
ALAT		**804/9, 185 (8.8)**	**746/9,152 (8.2)**	**-0.21, 1.42**
> 1.5 x ULN,	≤ 3 x ULN	676/9,185 (7.4)	615/9,152 (6.7)	-0.11, 1.39
> 3 x ULN,	≤ 5 x ULN	84/9, 185 (0.9)	90/9, 152 (1.0)	-0.36, 0.22
> 5 x ULN,	≤ 7 x ULN	24/9, 185 (0.3)	19/9, 152 (0.2)	-0.10, 0.21
> 7 x ULN,	≤ 9 x ULN	6/9, 185 (<0.1)	9/9, 152 (<0.1)	-0.13. 0.06
> 9 x ULN,		14/9, 185 (0.2)	13/9, 152 (0.1)	-0.11, 0.13
ASAT		**253/5,775(4.4)**	**232/5,775(4.0)**	**-0.39, 1.11**
> 1.5 x ULN,	≤ 3 x ULN	196/5, 775 (3.4)	177/5775 (3.1)	-0.33, 0.99
> 3 x ULN,	≤ 5 x ULN	34/5, 775 (0.6)	35/5, 775 (0.6)	-0.32, 0.28
> 5 x ULN,	≤ 7 x ULN	11/5, 775 (0.2)	11/5, 775 (0.2)	-0.18, 0.18
> 7 x ULN,	≤ 9 x ULN	3/5, 775 (<1.0)	5/5, 775 (<1.0)	-1.15, 0.08
> 9 x ULN,		9/5, 775 (0.2)	4/5, 775 (<1.0)	-0.06, 0.23

There were no statistically significant differences in patients seen between the pravastatin-treated and placebo-treated populations.

Kaplan-Meier plots of time from randomization to first occurrence of abnormal laboratory value > 1.5 x ULN are presented for ALAT (Figure 5) and ASAT (Figures 6). The distributions of the cumulative incidence of abnormal laboratory values for pravastatin and placebo treatment groups reveals no significant differences between the two treatment groups (ALAT, p=0.786, ASAT, p=0.876).

Figure 5: **Prava 3: Analysis of Time to First Occurrence of ALAT Abnormality > 1.5 x ULN**

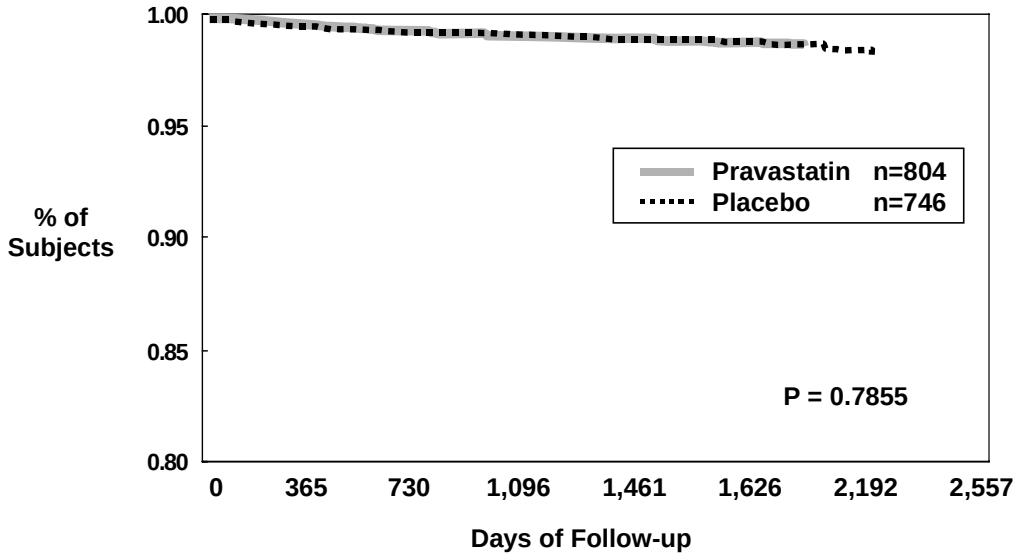
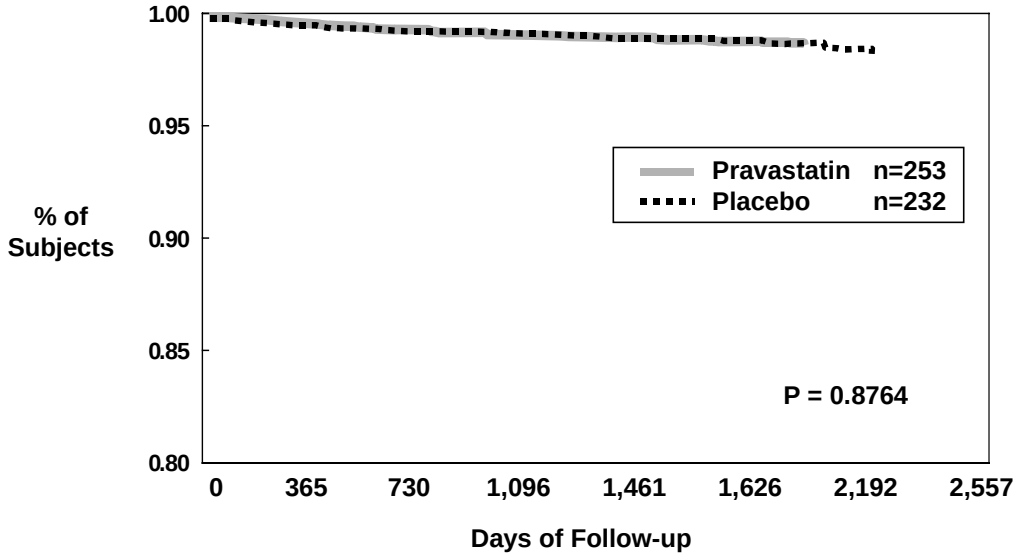


Figure 6. **Prava 3: Analysis of Time to First Occurrence of ASAT Abnormality > 1.5 x ULN**



This analysis was also performed for time to first occurrence of abnormal laboratory value > 5 x ULN for ALAT and ASAT and, again, there were no differences observed between the pravastatin and placebo populations.

In the Prava 3 database there were 579 patients with an ALAT measurement between 1-1.5 x ULN at baseline and 112 patients with measurements of ASAT between 1-1.5xULN at baseline. The subsequent changes in hepatic enzymes in this cohort was of special interest, as they could represent the population of people with asymptomatic liver disease who could be exposed to OTC Pravachol 10 mg, despite a labeled warning about use in liver disease.

As seen in Table 16, the incidence of post-baseline ALAT and ASAT elevations > 1.5 x ULN was comparable between pravastatin-treated and placebo-treated subjects when assessed overall or by degrees of severity, and reveal similar tolerability of pravastatin and placebo in subjects with mild impairment of hepatic function.

Table 16: Prava 3: Post-baseline Abnormalities > 1.5 x ULN of ALAT and ASAT by Severity in Subjects with an Elevated Baseline Value

		Pravastatin 40 mg n/N (%)	**Placebo** n/N (%)	**95% C.I.**
ALAT		**143/317 (45.1)**	**120/262 (45.8)**	**-9.20, 7.82**
> 1.5 x ULN,	≤ 3 x ULN	127/317 (40.1)	101/262 (38.5)	-6.84, 9.87
> 3 x ULN,	≤ 5 x ULN	11/317 (3.5)	16/262 (6.1)	-6.58, 1.30
> 5 x ULN,	≤ 7 x ULN	4/317 (1.3)	2/262 (0.8)	-1.61, 2.60
> 7 x ULN,	≤ 9 x ULN	0/317 (-)	0/262 (-)	-1.03, 1.03
> 9 x ULN,		1/317 (0.3)	1/262 (0.4)	-1.60, 1.47
ASAT		**22/54 (40.7)**	**21/58 (36.2)**	**-15.46, 24.52**
> 1.5 x ULN,	≤ 3 x ULN	19/54 (35.2)	15/58 (25.9)	-9.68, 28.33
> 3 x ULN,	≤ 5 x ULN	2/54 (3.7)	3/58 (5.2)	-11.57, 8.63
> 5 x ULN,	≤ 7 x ULN	0/54 (-)	2/58 (3.4)	-11.06, 4.16
> 7 x ULN,	≤ 9 x ULN	1/54 (1.9)	1/58 (1.7)	-7.65, 7.91
> 9 x ULN,		0/54 (-)	0/58 (-)	-5.28, 5.28

The Prava 3 analysis also allowed for an assessment of the effect of pravastatin 40 mg in a large cohort of elderly subjects. In Table 17, the incidence of post-baseline abnormalities of ALAT and ASAT is presented for the 4,338 subjects ≥ 65 years and the 1,628 subjects ≥ 70 years. As can be seen, the occurrence of post-baseline abnormalities was infrequent, and no statistically significant treatment differences either for patient

baseline abnormal overall or by degrees of severity, were noted for subjects ≥ 65 or ≥ 70 years of age. In addition, no treatment differences were noted by gender for these laboratory test results as well.

Table 17: Prava 3: Incidence of Post-baseline Abnormalities of ALAT or ASAT in the Elderly

		Subject ≥ 65 Years		Subject ≥ 70 Years	
		Pravastatin n (%)	Placebo n(%)	Pravastatin (%)	Placebo (%)
ALAT		**144/2, 151 (6.7%)**	**152/2, 187 (7.0%)**	**44/777 (5.7%)**	**49/851 (5.8%)**
> 1.5 x ULN,	≤ 3 x ULN	114 (5.3)	122 (5.6)	35 (4.5)	39 (4.6)
> 3 x ULN,	≤ 5 x ULN	21 (1.0)	18 (0.8)	6 (0.8)	6 (0.7)
> 5 x ULN,	≤ 7 x ULN	4 (0.2)	4 (0.2)	0	2 (0.2)
> 7 x ULN,	≤ 9 x ULN	2 (< 0.1)	4 (0.2)	1 (0.1)	1 (0.1)
> 9 x ULN,		3 (0.1)	4 (0.2)	2 (0.3)	1 (0.1)
ASAT		**49/890 (5.5%)**	**47/877 (5.4%)**	**21/335 (6.3%)**	**23/343 (6.7%)**
> 1.5 x ULN,	≤ 3 x ULN	36 (4.0)	32 (3.6)	17 (5.1)	15 (4.4)
> 3 x ULN,	≤ 5 x ULN	6 (0.7)	10 (1.1)	2 (0.6)	6 (1.7)
> 5 x ULN,	≤ 7 x ULN	2 (0.2)	1 (0.1)	1 (0.3)	0
> 7 x ULN,	≤ 9 x ULN	1 (0.1)	2 (0.2)	0	1 (0.3)
> 9 x ULN,		4 (0.4)	2 (0.2)	1 (0.3)	1 (0.3)

Post Marketing Surveillance

In the Post Marketing Surveillance database, there have been 6 deaths attributable to hepatobiliary causes; 3 were due to metastatic cancer, 2 were due to alternative drug toxicity (diclofenac, trazodone) and 1 report contained incomplete data. These are summarized in Appendix B. There were a total of 484 events of hepatobiliary disorders reported which represents 3.3% of the total events for all doses. Of these events, 168 were serious adverse events. Table 18 highlights the key preferred terms in the hepatobiliary system. The most frequently reported event was “hepatic function abnormal NOS” with 225 events reported (220 were spontaneous and literature reports with 5 from phase IV studies). Of these 225 events, 18 were reported for the 10 mg dose.

Table 18: Post Marketing Surveillance: Hepatobiliary Disorders

Preferred Term	Number of Events	
	Total	Serious
Hepato-biliary events	484	168
Hepatic Cirrhosis NOS	4	3
Hepatic Failure	10	10
Hepatic Function Abnormal NOS	225	40
Hepatitis NOS	69	42
Hepatomegaly	8	2
Hyperbilirubinaemia	16	5
Jaundice NOS	37	16
Liver Fatty	6	1
Other	109	49

Appendix D summarizes the serious adverse events for the preferred terms hepatic failure, jaundice and hepatitis. These reports indicate that other underlying disease or other concomitant medications were reported as causative in most cases.

While analysis of the data from both long term clinical trials and Post Marketing Surveillance, most of which is at doses 4x the OTC dose, does not indicate that Pravachol causes any degree of hepatic injury, as a safety precaution the OTC Pravachol 10 label warns people with liver disease or those who consume 3 or more alcoholic drinks a day (as a surrogate market of liver disease) not to use the product. This was understood by 87% in the Label Comprehension Study.

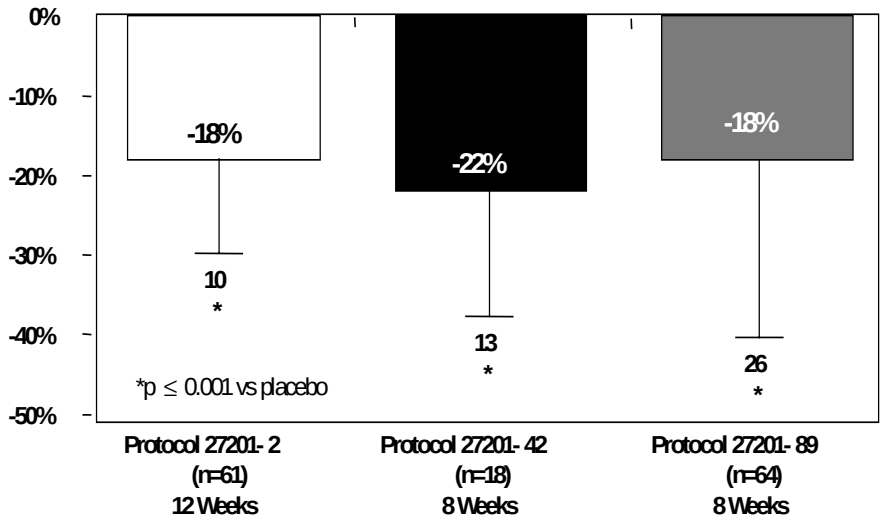
III. EFFICACY OF PRAVACHOL 10 mg

The approval of Pravachol to lower cholesterol was supported by results of adequately designed and well-controlled clinical studies (NDA 19-898).

The data supporting the biological activity of Pravachol 10 mg comes from three randomized placebo controlled dose response studies (27201-2, 27201-42, 27101-89). As shown in Figure 7 a consistent significant ($p<0.001$ vs placebo) and clinically meaningful reduction of 18% to 22% in LDL-C in addition to the effect of diet was seen

across the three pivotal studies over an 8 to 12 week period. Consistent and statistically significant percent reductions in Total-C were also observed in all studies, ranging from 13% to 19%. Statistically significant changes from baseline vs. placebo were also observed for HDL-C and triglycerides in studies 27201-2 and 27201-42. A summary of the efficacy results can be found in Appendix E.

Figure 7: Dose Response Studies: Summary of Results of LDL-C % Reduction (mg/dl) ± SE



Importantly, as will be demonstrated in the Consumer OTC Studies discussed in Sections V and VI, a similar reduction of LDL-C was achieved and maintained in an OTC environment, and the vast majority of the OTC population achieved their NCEP goal.

Consumer OTC Studies

Extensive clinical investigations of pravastatin have demonstrated that it is a safe and effective drug for the treatment of hypercholesterolemia. To evaluate use in an OTC environment, three consumer studies, The Label Comprehension Study, PREDICT, and OPTIONS, were conducted. The objectives of these studies were:

- Label Comprehension
  - To develop a label that consumers can understand
  - Test recall and comprehension in a broad-based, representative population, with special attention to low literacy

- Consumer Use Studies
  - To assess behavior by creating naturalistic environments and allowing subjects a myriad of behavior options
    - PREDICT: Simulate OTC and Rx environments to assess comparability
    - OPTIONS: Capture a real-world OTC setting
  - Generate generalizable data using broad based advertising and ensuring study accessibility to all
  - Collect reliable data by verifying self-reported behavior

IV. OTC LABEL DEVELOPMENT

OTC Label Messages: Rationale

To evaluate whether Pravachol 10 mg could be used appropriately in an OTC environment, BMS undertook an extensive label development program. The objective of this program was to develop a label that would clearly direct consumers in the safe and effective use of Pravachol 10 mg. According to FDA regulations, labeling "shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use" (21CFR 330.10(a)(4)(v).

The key program messages designed to allow the average consumer to read the label and safely undertake treatment decisions are: Pravachol 10 mg should be used to lower cholesterol after a program of diet and exercise; the intended population has TOTAL-C levels between 200-240 mg/dl; and people who have CHD or diabetes are not candidates for OTC therapy. The label directs subjects to consult their doctors before use, 8 weeks after starting Pravachol 10 mg, and yearly. The "see your doctor" message was meant to direct subjects who do not know their current medical condition (i.e., do not know cholesterol levels or risk of heart disease) to have a proper evaluation, and that subjects would have the effects of treatment assessed at 8 weeks following the initiation of treatment, (although the vast majority of the defined OTC population will achieve their LDL-C goal on Pravachol 10 mg) as well as maintain their regularly scheduled annual physician visits, so as not to delay appropriate diagnosis of changes in CHD risk factors over time. The label was developed to communicate key safety messages conveyed in the prescription package insert indicating who should not use Pravachol 10 mg (e.g., people with liver disease, abuse alcohol) and what to do if experiencing an adverse event (i.e., muscle pain) that may require professional attention.

Label Development

In the first phase of the program, a draft label was created based upon the key program messages, the efficacy and safety profile of pravastatin 10 mg, the current approved prescription labeling for pravastatin and the NCEP Expert Panel Treatment Guidelines. The wording and layout of the draft label were refined and revised using qualitative testing with three iterative rounds of focus groups in which the communication and comprehension profiles of the various elements of the label were assessed among target consumers and primary care physicians.

In the second phase, a label comprehension study was conducted in 735 male and female consumers in 20 geographically diverse areas. Of the 735, approximately 12% had low-literacy levels (i.e., below ninth grade) as assessed by Rapid Estimate of Adult Literacy in Medicine (REALM) test results (Ref. 29). This study showed that, overall, consumers understood the key communication messages on the label; however, lower comprehension was observed among those with below-ninth-grade reading levels.

Based on these results, revisions were made to the layout and to the wording of the label in an effort to increase comprehension even further in the general population and specifically in low-literacy individuals. Many of the layout changes involved incorporation of the FDA final rule regarding Drug Facts format (Ref. 30). The label was then analyzed by the Flesch Reading Ease and Flesch-Kincaid Grade level software programs. Based on this program, the label was revised to allow consumer comprehension at the ninth grade reading level.

A second consumer research study was undertaken in 612 male and female consumers in 20 geographically by diverse areas. Twenty-seven percent (27%) had below 9^{th} grade reading levels. The primary objective of the study was to determine whether consumers understand that they should see a doctor before using Pravachol 10 mg. Secondary objectives of the study were to determine whether consumers understand the purpose of

Pravachol 10 mg, who should and should not use Pravachol 10 mg, the need for follow-up evaluations, and that muscle pain should be reported to their doctor. The study is discussed in detail below.

Label Comprehension Study

This study utilized the mall intercept methodology and was conducted in 20 diverse communities across the US. The study was meant to be as inclusive as possible and the sample was drawn to ensure that the demographics of the study population would reflect a broad cross section of consumers, including those for whom Pravachol 10 was not appropriate. The demographic variables of literacy, age and gender were identified a priori as being of special interest and race was identified retrospectively. Quotas were established as follows: 25-34 year old (20%); 35-49 year old (25%) and 50+ (55%); males (50%), females (50%). In addition, to enhance the power of the study to test comprehension among low literacy individuals (i.e., below ninth grade reading level as assessed by the REALM) a total of 150 (25%) low-literacy consumers were recruited. Interview markets were selected so there would be an even distribution in each of four geographic quadrants in the US: North/Northeast, South/Southeast, Midwest, and West. The approximate distribution of the type of residential area reached by these markets were: urban 30%, suburban 60%, and rural 10%.

Subjects were not required to have hypercholesterolemia or interest in or knowledge about cholesterol to participate in the study, and were only asked about cholesterol awareness after completion of the test questionnaire so as not to influence their study responses. Each qualifying subject was given a package and asked to read and examine it as if preparing to decide whether or not to purchase the product. The subject was allowed as much time as he/she desired. After the subject had examined and read the package, the interviewer took the package back prior to asking the first two open-end questions designed to assess recall of key messages. The subject was then given back the package for reference, while answering the remaining three open-end questions, which tested

comprehension. All responses were recorded verbatim, and interviewers were not allowed to probe or respond to inquiries about the questions' intent.

After completing Part 1 of the questionnaire, subjects self-administered Part 2 which consisted of 16 closed-end (multiple choice) questions (Q.7-22) designed to evaluate comprehension of the label, and 15 questions (Q23-37) that collected information on demographics, medical history, knowledge of cholesterol action, and cholesterol awareness.

Six hundred twelve (612) interviews were included in the analysis (546 basic random sample, 66 supplemental low-literacy sample). The mean age was 51.8; 76% were Caucasian, 9% were Black and 2% were Hispanic; 51% of subjects were female; and 27% read below the ninth grade level.

Results of the study demonstrated that subjects overwhelmingly understood the key communication messages on the label. As shown in Table 19, for the key pre-purchase instruction, "See Your Doctor", both recall and comprehension were excellent.

Table 19: Label Comprehension: What Should You Do Before Using Pravachol 10 mg? Objective: See Your Doctor

		Open-End		Closed-End
		Recall (%)	Comprehension (%)	Comprehension (%)
Total	(n=612)	82	95	94
Literacy				
< 9th Grade	(n=163)	82	95	91
≥ 9th Grade	(n=449)	82	95	96

The secondary label communication objectives were also very successfully conveyed. Respondents understood the product purpose in response to open-end questions, 90% recalled and 95% comprehended that Pravachol 10 mg was used to lower cholesterol.

With respect to conditions where Pravachol 10 mg may not be the optimal therapy due to the need for more aggressive prescription therapy or other underlying medical conditions, for the open-end questions, 93%, 82%, and 80% of responders understood that people with heart disease, diabetes, and liver disease, respectively, should not use the product. In the closed-end questions, 90% selected heart disease, 89% selected diabetes, 88% selected liver disease, 87% selected pregnant women, and 87% selected people who drink more than 3 alcoholic beverages a day. Comprehension was similar for $< 9^{th}$ grade and $\geq 9^{th}$ grade literacy groups as well as for the age, race, and gender subgroups.

With regard to the communication of who should use Pravachol 10 mg, respondents understood that Pravachol 10 mg was intended for "consumers with Total cholesterol levels between 200 and 240" (76%).

The need for follow-up evaluations was also well communicated (Table 20). High comprehension of this message suggests people will remain in the healthcare system, resulting in appropriate diagnosis of development over time of other cardiovascular risk factors or further elevations of cholesterol level which may require a prescription. The need for reporting adverse experiences was also well understood irrespective of literacy. Ninety-three percent (93%) of respondents understood the need to report the adverse experience of muscle pain to a doctor.

Table 20: Label Comprehension: Follow-up Requirements for Pravachol 10 mg Use (Closed-End Comprehension)

		After 8 Weeks (%)	After 1 Year (%)	For Side Effects of Muscle Pain (%)
Total	(n=612)	82	86	93
Literacy				
< 9th Grade	(n=163)	79	87	93
≥ 9th Grade	(n=449)	83	85	93

Label communications about who should not use Pravachol 10 mg, conveyed less strongly as those described above (i.e. <75%), include: "consumers with Total cholesterol level more than 240" (73%), "consumers taking prescription cholesterol medication"(73%), and "consumers taking erythromycin" (65%). Comprehension was similar to the total population across the subgroups.

Label Modifications

Based on the results of this study, label changes were made to increase awareness of messages regarding who should not use Pravachol 10 mg that were not conveyed as strongly as other messages. In addition, results of additional clinical studies and consumer use trials, as well as the FDA final rule on Labeling Requirements for Over-the-Counter Human Drugs (Drug Facts), were considered in developing layout changes. These changes are described below.

1. Use Section:

- Changed the icon from 

to 

and simplified wording and layout to increase awareness and recall of the Total cholesterol treatment range of "200 – 240".

- With regard to age recommendations in the OTC labeling, following discussions with the FDA and other lipid experts, Bristol-Myers Squibb had determined it would be appropriate to include older age recommendations in the OTC labeling to be consistent with the population who would most benefit from OTC availability of

Pravachol 10 mg. Thus, the proposed labeling provided in this briefing book reflects use in men > 35 years and women > 45 years. As this labeling was very recently proposed, the agency's briefing book may not address this change.

- To help consumers more accurately determine whether OTC Pravachol 10 mg is the appropriate treatment to lower their cholesterol levels, the treatment level for LDL-C (>130mg/dl) was added to the Total cholesterol.

2. Warnings:

- "Drug Facts" headings mandated by recently issued final rule were incorporated.

- Results of the pharmacokinetic study (Protocol CV123-177 submitted to IND 27,201 on June 17, 1998) did not show a clinically meaningful interaction between erythromycin and multiple doses of pravastatin 40 mg; therefore this warning was deleted.

3. Directions:

- Simplified wording for 8-week follow-up.

- Allowed for physician discretion/input into frequency of follow-up cholesterol testing by adding "(or as directed by your doctor)" to the bullet regarding the 1 year follow-up.

A copy of the back panel of the proposed OTC labeling can be found in Figure 8.

Figure 8: Proposed OTC Labeling (Back Panel)

Drug Facts

Active ingredient (in each tablet) — **Purpose**
Pravastatin sodium, 10 mg ..... Cholesterol reducer

Use
- lowers mildly elevated cholesterol which is a total between 200-240mg/dl and an LDL ("bad" cholesterol) over 130mg/dl.
- for men over 35 years of age and women over 45 years of age.
- helps manage a risk factor for heart disease. For women, the risk of heart disease increases after menopause.
- to be used with a program of diet and exercise.

Warnings
Do not use
- if you have liver disease or regularly drink 3 or more alcoholic beverages daily.
- if you are allergic to pravastatin or any of the inactive ingredients.

Before use, ask a doctor about
- your cholesterol levels (total, LDL, HDL, triglycerides).
- your risk factors for heart disease.

Ask a doctor before use if you have any of the following conditions because you may need the prescription strength of this product:
- heart disease
- diabetes
- total cholesterol that is above 240mg/dl.

Ask a doctor or pharmacist before use if you are already taking prescription medication to lower your cholesterol.

Stop use and ask a doctor if
- you have any unusual muscle pain or weakness not caused by a cold, flu, recent injury or sprain. This is very important if you also feel weak or have a fever.

If pregnant or breast feeding, ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
- **take** 1 tablet every day.
- **8 weeks after starting,** check your cholesterol again.
  - If you have reached a healthy cholesterol level, keep taking one tablet daily to stay at a healthy level.
  - If you haven't reached a healthy cholesterol level, you may need the prescription strength of this product.
- **once a year** check your cholesterol level.
- **continue** to exercise and stay on a low-fat diet.

Other information
- This product is very low in sodium.
- Read all product information before using.
- Keep this box and educational leaflet for important information.
- Tamper resistant inner unit. Do not use if foil seal is torn or broken.
- Do not store above 86°F (30°C). Protect from moisture and light.

Inactive ingredients croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, povidone and red ferric oxide.

Questions or comments? Call 1-877-PRAVA10 (1-877-772-8210) Free enrollment in Pravachol Partners Program.

V. PRAVACHOL EXPERIENCE DOCUMENTED IN A CONSUMER USE TRIAL (PREDICT)

The PREDICT study was conducted from April 14, 1998 to May 28, 1999. The purpose of the study was to advertise the opportunity to take an OTC cholesterol lowering medicine and then to randomize people who responded to simulated OTC and Rx environments prior to any knowledge about their medical conditions to observe their behavior over 6 months. This study was intended to address the following issues:

- Characterize who is interested in OTC lipid lowering therapy (i.e., whether the defined OTC population would, in fact, be the one to utilize this product)
- Evaluate whether Pravachol 10 mg could be used responsibly in an OTC environment
- Determine whether the safety and efficacy profile that has been demonstrated in the prescription environment would be maintained in an OTC environment

Objectives

The primary objective was to determine the proportion of OTC randomized participants who, having purchased OTC Pravachol, consult a physician within 2 months of using medication. The secondary objectives were to compare OTC versus Rx participants who qualified for Pravachol 10 for:

- Physician follow-up
- LDL-C reduction
- Safety

Further analyses were also conducted to address how the following special populations might behave if Pravachol 10 mg were available OTC:

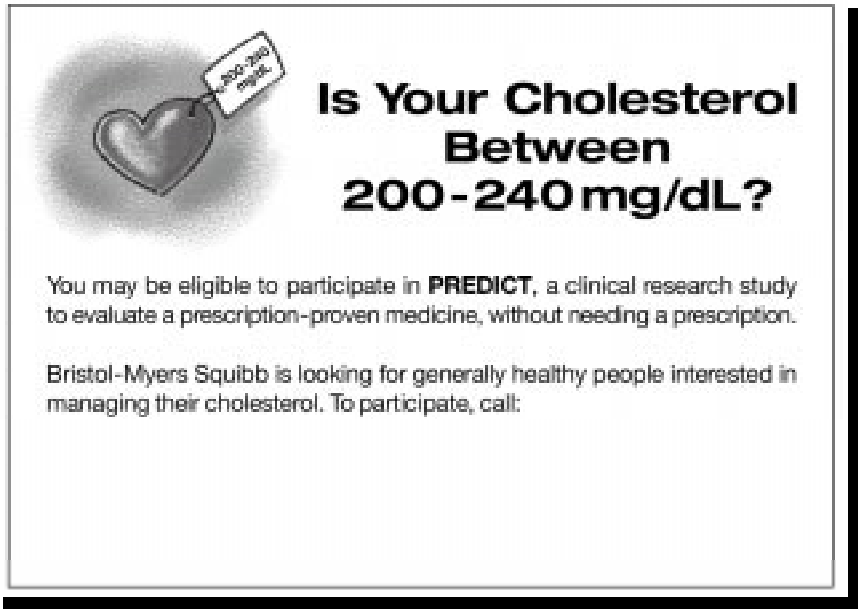
- Profile of people who take OTC Pravachol 10 mg and never consult the doctor
- Behavior of people who are already taking prescription medication and have the opportunity to purchase OTC Pravachol 10 mg
- Behavior of people who are interested in the OTC proposition, but upon evaluation by a physician, need prescription therapy.

PREDICT was subsequently extended for 6 months (PREDICT Extension protocol 800-08-98) to follow participants (OTC and Rx) who qualified for lipid lowering therapy at the start of the parent study and evaluate their behavior to consult a physician either for an annual visit or prior to discontinuation of study drug.

Methodology

To attract as broad a spectrum of the general population as possible, PREDICT was carried out in 20 geographically diverse regions throughout the United States utilizing 1-2 retail sites and 2-3 clinic sites per region. To ensure that no specific demographic subgroups were excluded, retail sites were selected in locations in the southern and western corridors of the country containing predominantly Black and Hispanic populations and neighborhoods with easy access to public transportation. Participants were recruited via broad-based advertising through radio, television, and print. As shown in Figure 9, advertising indicated that if an individual was generally healthy with a cholesterol level of 200 - 240 mg/dl, he/she may be able to take a prescription-proven cholesterol-lowering medication without prescription. No other defining characteristics (such as age or absence of CHD or diabetes) were included in the advertisements. To ensure that study advertising was not directed at populations with selected demographic attributes, all media vehicles used during the study were systematically evaluated and found to have demographics (age, gender, race, education, and income) that were representative of the local population. To further increase the probability that no specific demographic subgroup was excluded from participation in the study, advertisements were strategically placed on Hispanic and Gospel radio stations as well as in magazines and newspapers. The advertisement provided a toll free number to a call center where operators directed participants to a local retail site.

Figure 9: PREDICT Advertising



The call center was staffed with operators who were trained to receive calls and utilized a standard script that was designed to provide only directions to the retail site and the hours of operation. The operators were trained not to provide information about the study and participants were not screened in any way, or excluded from participation, with the exception of women of childbearing potential.

Every effort was made to make this study as naturalistic as possible. The retail sites were set up like "store fronts" and were placed in shopping malls (38%) and office buildings (62%). A typical site is shown in Figure 10.

Figure 10: PREDICT: OTC Retail Site

The sites were staffed with non-medical personnel trained in administering questionnaires. There was no connection with the study physicians or coordinators and the retail sites were geographically remote from clinic sites.

All participants who presented to the retail site signed an Institutional Review Board (IRB) approved abbreviated written consent form (Appendix F), typical of what is used in noninvasive household survey, that permitted the interviewer to initiate the screening questionnaire. The screening questionnaire collected data on demographics, cholesterol awareness, and health care status. Literacy was measured using the REALM Literacy Test (Ref. 29). A detailed dietary assessment was completed by use of the Meats, Eggs, Dairy, Fried Foods, In Baked goods, Convenience Foods, Table Fats, Snacks (MEDFICTS) Questionnaire which is a valided tool recommended by the NCEP ATP II guidelines for assessment by AHA diet status. (Refs. 31, 32). Lifestyle behaviors specific to exercise and smoking were also evaluated. Those wishing to continue were then randomized to either the OTC or Rx group, within strata defined by literacy. To permit evaluation of behavioral endpoints that would be exhibited if a person could purchase the product freely in a store, randomization occurred prior to evaluation of medical conditions or lipid level assessment which would determine the appropriateness of Pravachol 10 mg.

Participants randomized to the OTC group were shown a prototypical OTC Pravachol 10 mg print advertisement, package and price and those in the Rx group were shown a direct-to-consumer-like advertisement. The price for the initial supply of OTC medication was: $14.95 for a maintenance kit or $15.95 for a starter kit. All participants (OTC and Rx) were then asked about interest in continuing in the study; those participants interested in continuing were screened for further participation in the study according to protocol dictated minimal inclusion and exclusion criteria.

Inclusion Criteria

- ≥ 18 years

Exclusion Criteria

- Participated in a research study within the last 30 days

- Women of child-bearing potential or breastfeeding

Participants who did not meet these criteria were excluded from further participation in the trial.

OTC participants were allowed an initial purchase of 2 cartons of Pravachol 10 mg, providing a 2-month supply of medication. The package size, type and contents were prototypes of the actual OTC product that would ultimately be marketed. OTC Pravachol 10 mg was available for purchase by OTC participants only at the retail screening site and not at the clinic site. OTC participants had the choice of purchasing either a Pravachol 10 mg starter kit or maintenance package. Along with 4 blister cards each containing 7 tablets of Pravachol 10 mg, the starter kit contained: a PRAVACARE educational booklet, an enrollment card for the PRAVACARE Newsletter Program, a rebate coupon for subsequent purchases, and a package insert (Appendix H). The Pravachol 10 mg maintenance kit contained medication and a package insert only.

A subsequent IRB approved consent was obtained prior to purchasing medication and/or clinic visit procedures.

Participants randomized to the Rx group who wanted to take medication (Pravachol 10 mg) were told that they would have to be evaluated by a study physician to determine whether or not they qualified for therapy and to receive a prescription.

Upon leaving the retail screening site, all randomized participants were given a list of names, addresses, and telephone numbers of the 2-3 study physicians in the area who were participating in the trial. Of the 57 physicians who participated in the study, 42% were primary care physicians and 58% specialized in internal medicine, the majority of whom were not lipid specialist; there were 5 cardiologist and 3 endocrinologist. The interviewers underwent extensive training prior to study initiation emphasizing that they were not to direct participants to contact the physician. The intent was to simulate the

situation when people enroll in a health plan and are given the names of participating physicians.

After OTC and Rx participants left the retail site, no further contact was made with them for 6 months, at which time a study closure assessment was conducted on all randomized participants whether or not they purchased product or consulted a physician.

Figure 11 presents the schedule of clinic evaluations if a participant decided to call and make an appointment to consult a physician.

Figure 11: PREDICT: Clinic Evaluation if Physician Consulted

Initial physician consultation (**PARTICIPANT DECISION)** • Lipid evaluation • Therapy recommendation	Assessment 2 (Week 0)
↓	
Follow-up (**PARTICIPANT DECISION)**	Assessment 3 (Week 8)
↓	
Follow-up if needed (**PARTICIPANT DECISION)**	Assessment 3B (Week 16)
↓	
Completion of Study (**ALL RANDOMIZED)** • Cholesterol questionnaire • Lipid profile • Diet assessment (MEDFICTS)	Assessment 4 (Week 24)
↓	
6 months extension **(OPTIONAL)**	Assessment 5 (Week 48)

All participants who decided to consult the study physician were evaluated according to the study treatment guidelines outlined in Table 21. Any given study physician saw both OTC and Rx participants, and utilized the same study treatment guidelines for all participants so that follow-up behavior and changes in lipid parameters could be compared between OTC and Rx participants.

Table 21: PREDICT: Treatment Guidelines

	Initiate Treatment/ LDL-cholesterol	**Goal**
No CHD or diabetes and 2 risk factors (age plus 1 risk factor)	≥ 130 mg/dl, < 190 mg/dl	< 130 mg/dl
No CHD or diabetes ≤ 1 risk factor	≥ 160 mg/dl, < 190 mg/dl	< 160 mg/dl

Risk factors were defined according to the NCEP ATP II Guidelines as:

- Age (males ≥ 45 years, females ≥ 55 years or premature menopause without estrogen replacement)
- Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other male first–degree relative, or before 65 years of age in mother or other female first-degree relative)
- Current smoking
- Hypertension (blood pressure ≥ 140/90 mm/Hg, or on antihypertensive medications)
- HDL-cholesterol < 35 mg/dl
- Diabetes mellitus

Those Rx participants who consulted a physician and qualified for treatment were given a prescription for Pravachol 10 mg to be filled at a local pharmacy of the participant's choice. A study prescription coverage program was implemented for all participants with pre-existing prescription coverage so that the cost of obtaining a prescription would not be an impediment and potential bias in the study.

Participants with CHD, diabetes, or multiple CHD risk factors who were not at NCEP goal, as well as participants with LDL-C levels > 190 mg/dl, were advised to follow-up with their personal physician for further treatment.

For participants for whom Pravachol 10 mg was appropriate, a week 8 visit was recommended for follow-up safety and efficacy evaluations. In addition, if titration was necessary, an optional follow up visit at week 16 (Assessment 3B) were conducted for all randomized participants. A 6 month study closure visit was conducted in all participants.

In order to ensure uniformity and minimize bias of study site personnel, all interviewers were required to receive uniform training on screening site interview procedures. In addition, all investigators and research study coordinators were given guidelines regarding the proper manner to conduct the study office visit. This included instructions regarding the length of the study clinic visit (designed to mimic a typical primary care office visit) and the discussion with the participants regarding the medical history, physical examination, laboratory assessment and follow-up. It was emphasized that OTC and Rx participants should be treated in the same manner.

While a structure was in place to ensure validity of the data, all attempts were made to allow for unlimited behavioral options as to when consumers could purchase Pravachol, take Pravachol, and consult a physician, as would be seen in a true OTC environment. Table 22 lists possible behaviors that OTC and Rx participants could have demonstrated.

Table 22: PREDICT: Post Screening Behavior Options

OTC Group	Rx Group
No Pravachol Purchase→ No MD Consult	No MD Consult→ No Prescription
Purchase Pravachol→ Take Pravachol→ No MD Consult	MD Consult→ Receive Prescription→ Fill or Don't Fill Prescription
Purchase Pravachol→ Don't Take Pravachol→ No MD Consult	MD Consult→ Receive Prescription→ Fill Prescription→ Take or Don't Take Pravachol
Purchase Pravachol→ Don't Take Pravachol→ MD Consult→ MD Recommendation→ Take or Don't Take Pravachol	MD Consult→ No Prescription
Purchase Pravachol→ Don't Take Pravachol→ MD Consult→ No MD Recommendation→ Take or Don't Take Pravachol	
Purchase Pravachol→ Take Pravachol→ MD Consult→ MD Recommendation→ Continue or Discontinue Pravachol	
Purchase Pravachol→ Take Pravachol→ MD Consult→ No MD Recommendation→ Continue or Discontinue Pravachol	
MD Consult→ MD Recommendation→ Purchase Pravachol→ Take or Don't Take Pravachol	
MD Consult→ No MD Recommendation→ Purchase Pravachol→ Take Pravachol	

PREDICT could not employ the same level of advertising, media messages or consumer and professional promotions that would occur in the real OTC environment. PREDICT was able to offer on educational program element that would be available OTC: participants could choose to enroll into a PRAVACARE newsletter program (OTC Participants) or Pravachol Partners (Rx Participants) newsletter program during this study. The education program consisted of a booklet (identical to the starter kit booklet, Appendix H) newsletters and reminder post-cards that reinforced key label communication messages and were designed to promote compliance and proper medication use. Additional elements of the PRAVACARE program can be found in Appendix I.

OTC participants could enroll either by mailing in a business reply card, contained in the Pravachol 10 mg starter kit (OTC only) or via a toll-free number that was provided on the package label. One third of the Rx subjects were randomly selected to receive the

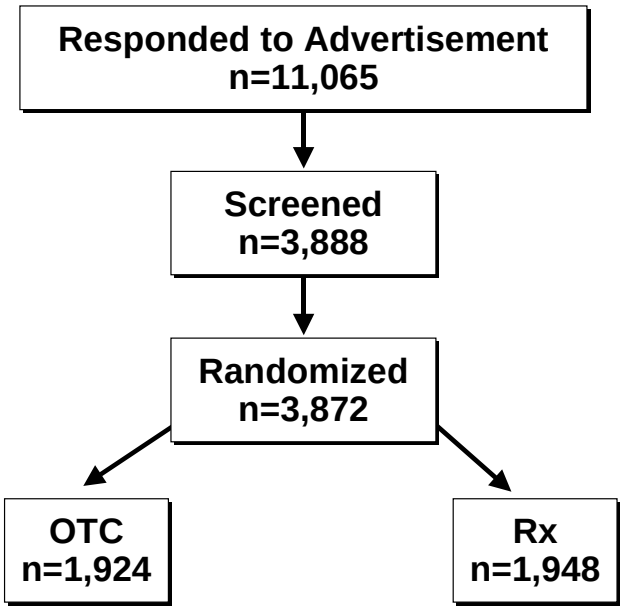
existing educational booklet that provided a toll free number to enroll into the educational program. This random sample represents the proportion of current Pravachol prescription users who receive the booklet from their personal physician.

Study Results

Disposition

The enrollment period began April 14, 1998 and completed October 28, 1998. Eleven thousand and sixty five (11,065) participants responded to the advertisements via the call center. The call center did not screen participants for study eligibility, with the exception of excluding women of childbearing potential. Subsequently, 3,888 participants presented to the retail site. Approximately 80% of participants learned of the study through advertisements and 20% were walk through. Of the 3,888 who presented to the retail site, 16 did not complete the screening interview and 3,872 were randomized (1,924 OTC and 1,948 Rx). Of the 3,872 participants randomized, 119 (3%) participants (61 OTC vs. 58 Rx) were deemed ineligible to participate for the following reasons: 1 (<1%) less than 18 years, 1 (< 1%) breast-feeding, 57 (2%) woman of childbearing potential, 35 (1%) participated in a research study within the last 30 days, and 25 (<1%) did not have eligibility determined because the interview was discontinued. Study participant disposition is shown in Figure 12.

Figure 12: PREDICT: Disposition of All Participants



Baseline Characteristics of Population Interested in OTC Proposition

Table 23 summarizes the demographic characteristics of the population interested in the OTC proposition based solely on seeing or hearing the study advertisement prior to receiving any additional information. These people were middle aged (56 ± 12); only 4% were less than 35 years old. Sixty-two percent were male, 94% had at least a high school education, and 8% read below a 9th grade reading level. Racial representation included 84% Caucasian, 8% Black, 5% Hispanic, 2% Asian and 1% Native American.

Table 23 PREDICT: Demographic Characteristics (Randomized Population n=3,872)

		OTC (n=1,924)	Rx (n=1,948)	p-value
Mean Age (yrs ± SD)		55 ± 12	56 ± 12	0.691
		%	%	
Age Group (yrs)	< 35	4	4	0.952
	35 –54	42	42	
	55 – 74	48	48	
	≥ 75	6	5	
Gender	Male	64	60	0.020*
	Female	36	40	
Race	Asian	2	1	0.692
	African American	8	8	
	Caucasian	84	84	
	Hispanic	5	6	
	Native American	1	1	
	Other	< 1	< 1	
Income	< $25,000	20	22	0.462
	$25,000 - $49,999	35	34	
	$50,000 - $99,000	31	30	
	≥ $100,000	10	11	
Education	No High School	1	1	0.376
	Some High School	5	5	
	High School Graduate	49	48	
	College Graduate	45	46	
Literacy (REALM)	≤ 6^{th} Grade	< 1	1	0.253
	7^{th} – 8^{th} Grade	7	7	
	≥ 9^{th} Grade	91	91	

*Significant at the 0.050 level

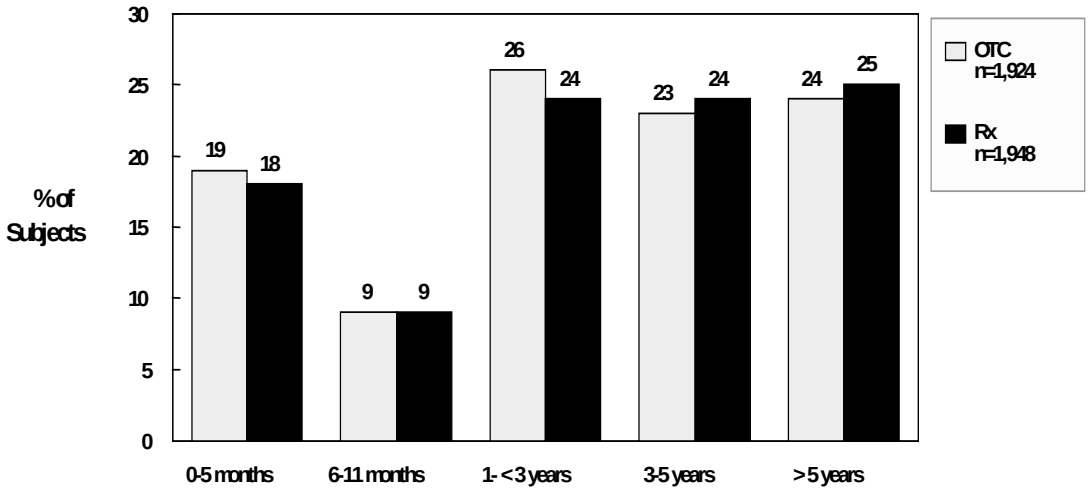
Participants interested in an OTC option had access to health care and prescription medication coverage (Table 24). Eighty five percent (85%) had a personal physician, 83% saw their physician regularly, 25% had seen a physician specifically about cholesterol, and 72% had prescription medication coverage. Most participants were somewhat to extremely concerned about their cholesterol (96%) and stated that they learned most about cholesterol from their physician (74%).

Table 24: PREDICT: Health Care Status (Randomized Population n = 3,872)

	OTC (n = 1,924) (%)	Rx (n =1,948) (%)
Have a Doctor	85	86
Visit MD at Least Yearly	83	83
Told of High Cholesterol	86	86
See MD Specifically for Cholesterol	24	25
Have Prescription Coverage	72	72
On Hormone Replacement Therapy (Post-menopausal women only)	53	52

Seventy-two percent OTC and 73% Rx participants were first told of high cholesterol at least one year prior to study entry; 25% had known of high cholesterol for more than 5 years (Figure 13).

Figure 13: PREDICT: When First Told of High Cholesterol* Randomized Population)

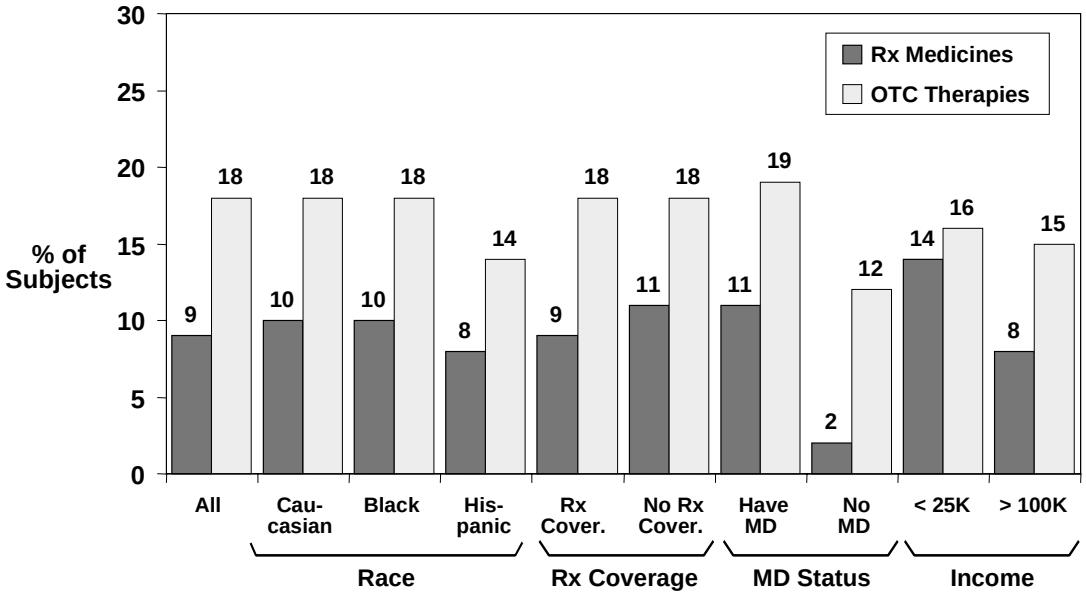


*Based on the number of subjects who were told they have high cholesterol. (n= 3,316)

Despite having access to healthcare and being a motivated, disease prevention population, only 9% of all randomized participants were currently taking a prescription lowering medication while 18% were currently using dietary supplements or OTC

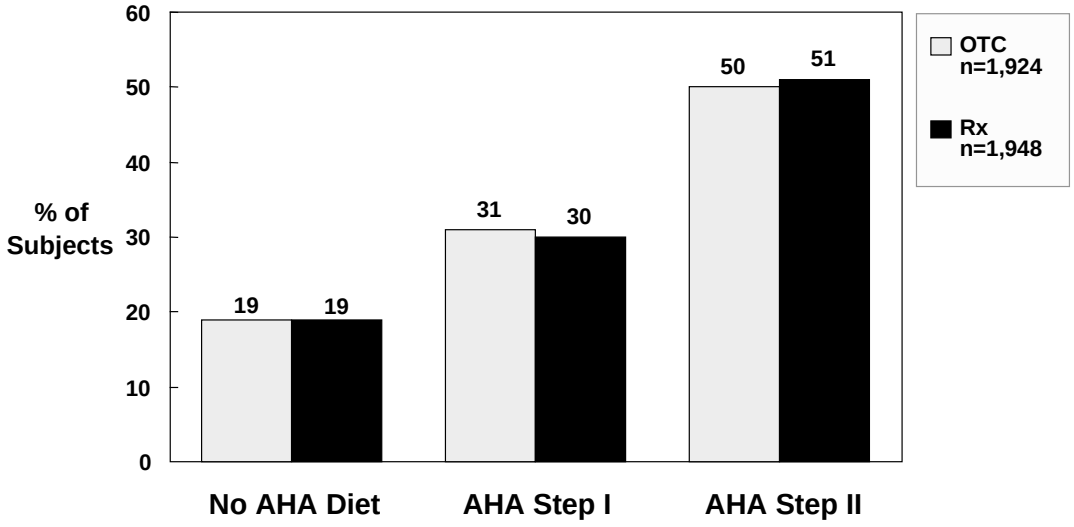
medications for this purpose. As can been seen in Figure 14, this was very consistent irrespective of demographics or access to health care.

Figure 14: PREDICT: Cholesterol Action by Subgroups (Randomized Population n= 3,872)



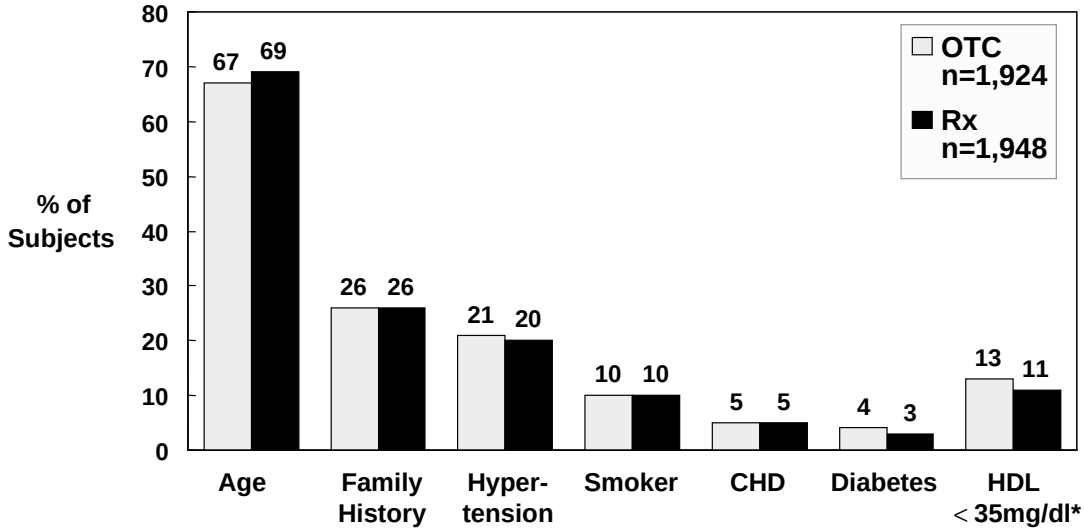
As assessed by MEDFICTS, 81% of randomized participants were following an AHA diet at baseline, again suggesting that participants were a disease prevention oriented population and had already initiated dietary modifications. (Figure 15).

Figure 15: PREDICT: Baseline AHA Diet Level (MEDFICTS) (Randomized Population n=3,872)



While the advertisement did not mention that Pravachol 10 mg was not indicated for people with CHD or diabetes mellitus, the majority of participants responding to the advertisement were a lower risk population. As presented in Figure 16, the most frequently reported risk factors were age, followed by family history of CHD and hypertension. Only 10% of respondents were smokers, as compared with a prevalence of smoking of more than 20% in the general population, again suggesting that participants tended to be aware and active in CHD prevention.

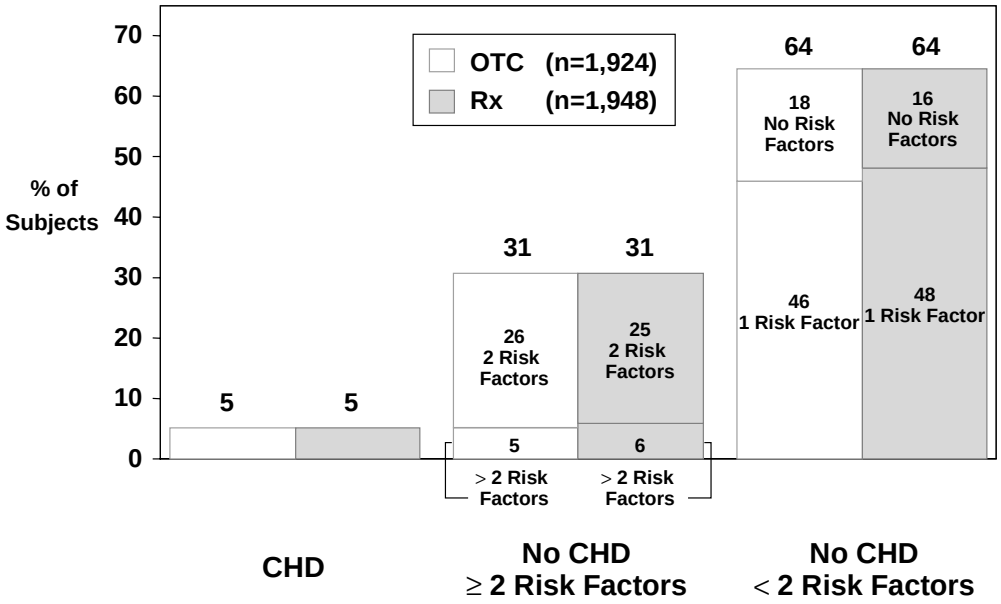
Figure 16: PREDICT: CHD Risk Factors (Randomized Population n=3,872)



*Based on number of subjects in Consult population with HDL performed at Assessment 2.

The baseline data characterizing the NCEP-defined high (CHD), moderate (no CHD ≥ 2 risk factors), and low (no CHD < 2 risk factors) risk factor profiles are shown in Figure 17 for the Randomized population, and demonstrates that, for the most part, the defined OTC population responded to the advertisement.

Figure 17: PREDICT: CHD Risk Factor Profile at Baseline (Randomized Population n=3,872)



Data Source: Appendices B.6 (Table 9.0.0) D.8 (Table 9.2.0)

As shown in Figure 18, of the 3,872 participants, 2,466 (64% of the randomized population) consulted a physician: 1,160 (60%) OTC and 1,306 (67%) Rx ($p < 0.001$). The differences in consultation rates may be explained by OTC self-selection based on label information and warnings; 18% of OTC participants decided not to purchase because of recognition of labeled warnings. This information was not available for the Rx group.

Figure 18: PREDICT: Participant Disposition – Calculation of Consult Population

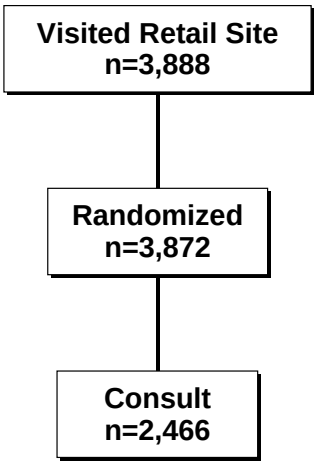


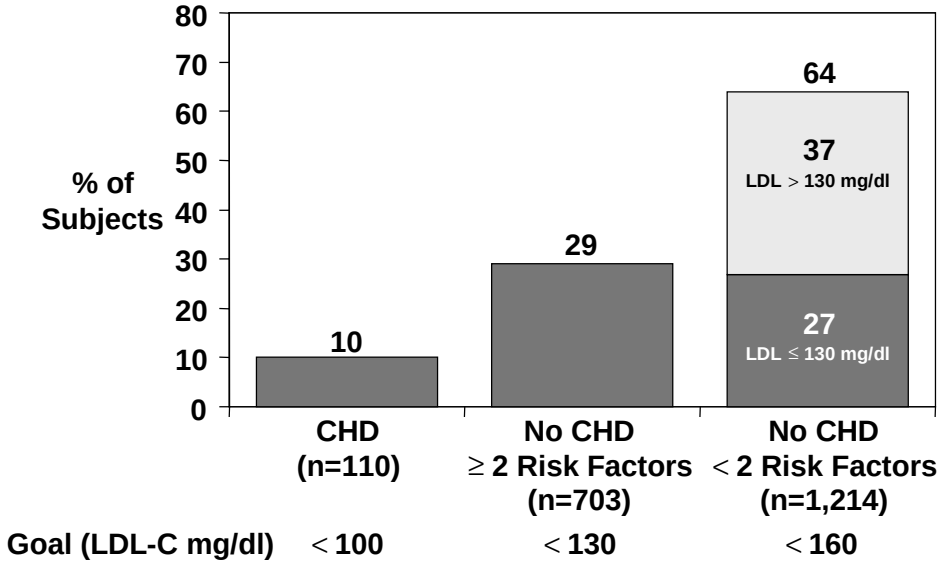
Table 25 presents the baseline lipid profile for those participants who were interested in the OTC proposition and had laboratory data available. Eighty-six (86%) had a Total-Cholesterol > 200 mg/dl.

Table 25: PREDICT: Mean Baseline Lipid Profile (Consult Population n= 2,466)

	OTC (n = 1,160)	Rx (n = 1,306)
Baseline (mg/dl) mean ± SD	(%)	(%)
Total-Cholesterol	234 ± 36	237 ± 38
LDL-C	147 ± 33	149 ± 33
HDL-C	50 ± 15	51 ± 15
- Female	58 ± 16	60 ± 15
- Male	45 ± 12	45 ± 12
Triglycerides	190 ± 112	189 ± 119

Based on current NCEP guidelines, the percentage of participants who were at goal by CHD risk factor profile is presented in Figure 19. Of the Randomized population with a prior cardiac event, only 10% had a LDL-C < 100 mg/dl; < 30% of those in the primary prevention category had an LDL-C < 130 mg/dl.

Figure 19: PREDICT: Participants at NCEP Goal at Baseline by CHD Risk Factor (Consult Population n = 2,027)



The disposition of the population interested in the OTC proposition is presented in Figure 20. Of the 1,924 OTC participants randomized, 720 participants purchased OTC Pravachol 10 mg. Although recruitment efforts were successful in randomizing participants in minority groups (300 Blacks, 212 Hispanics, 113 Other), purchase rates were lower among some minorities. Of the participants randomized to the OTC group 33% Caucasian, 26% Blacks and 32% Hispanics purchased. The reasons for lack of purchase interest by the OTC population is shown in Table 26.

Figure 20: PREDICT: Disposition of Randomized Population

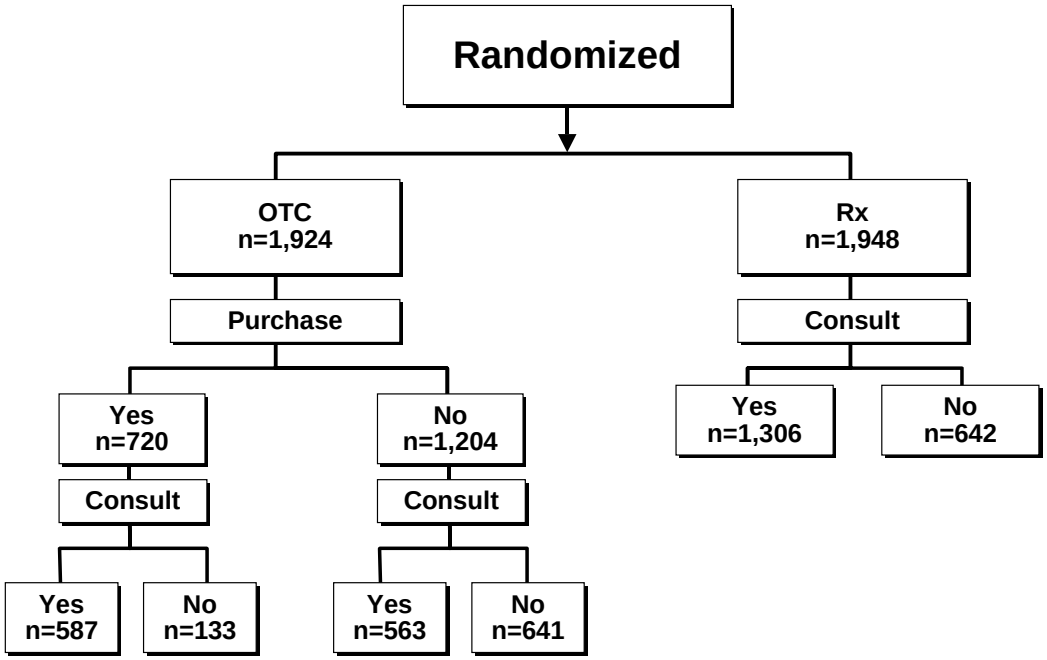


Table 26: PREDICT: Reason for Lack of Purchase Interest (OTC Randomized Population*

	(%)
Wanted to consult MD	47
Cost	15
Recognized label warning	18
Did not know cholesterol level	9
Label warning or risk factors too high	3
Cholesterol not between 200-240 mg/dl	3
Already being treated	3
Need more information	9
Not interested/other	3
Concerned about side effects	2
Try other methods first	2
Unknown	2

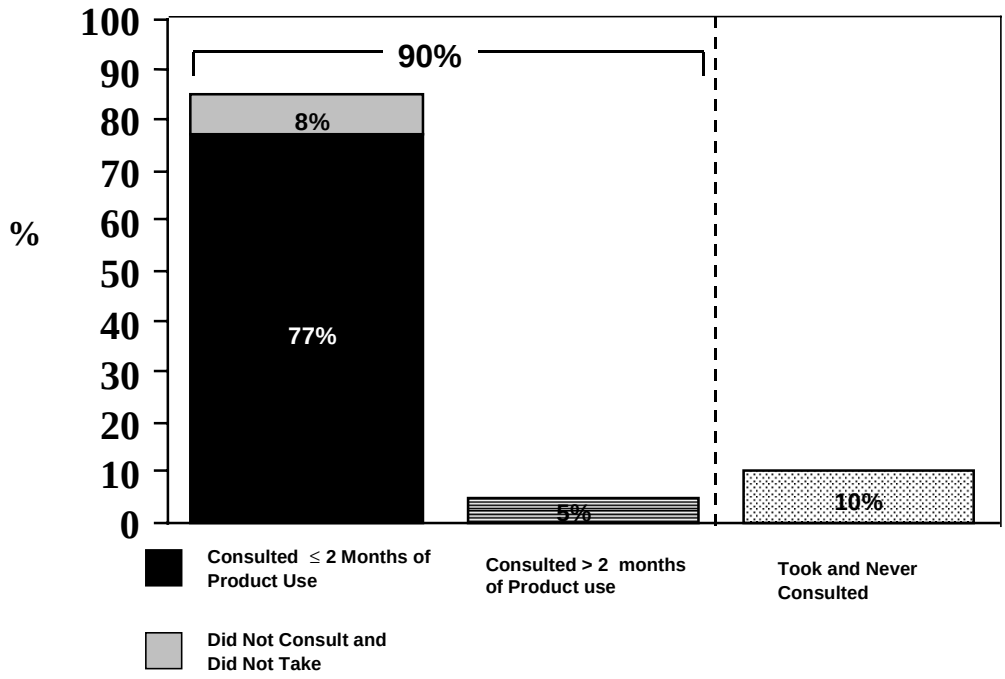
*Based on the number of participants who did not purchase (n=1,204)

Behavior of Study Population

Consumer Behavior: OTC Environment

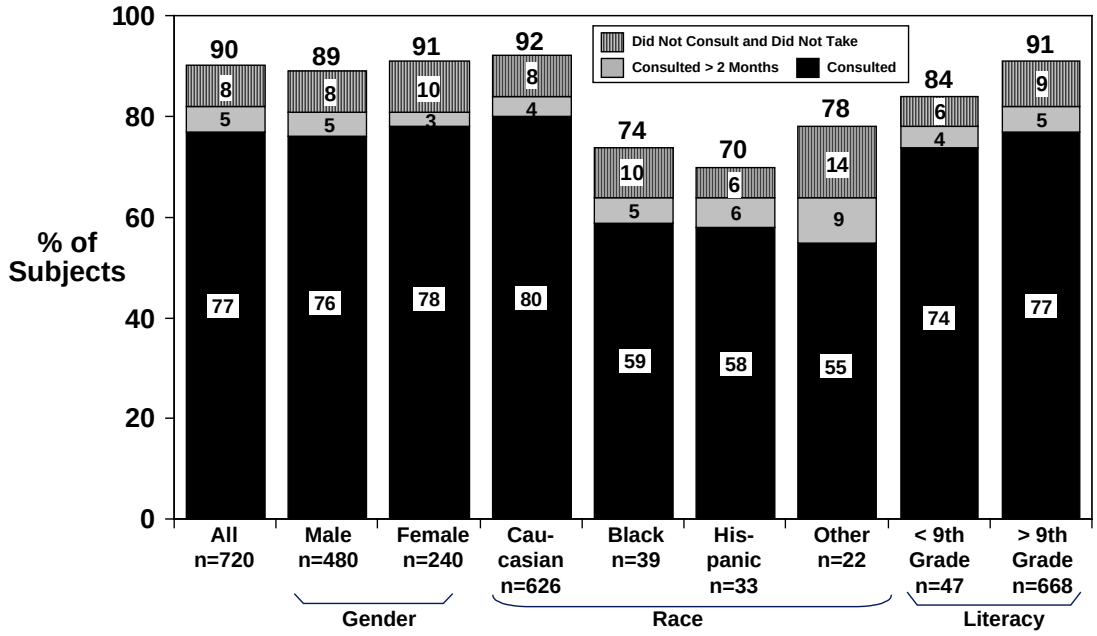
The results of the behaviors of the OTC purchase population to consult a physician are shown in Figure 21. Of the 720 OTC participants who purchased Pravachol 10 mg, 553 (77%) fulfilled the primary objective by consulting a physician within 2 months of product use. Additionally, 34 participants (5%) consulted, but did so after the predefined 2 month window of product use and were thus not included as meeting the primary objective; none of these participants were prompted to consult following an attempt to repurchase additional medication. Sixty-one participants (8%) never consulted a physician but never took their medication. Seventy-two participants (10%) took Pravachol 10 mg and never consulted; of these, only 10 participants attempted to repurchase medication.

Figure 21: **PREDICT: OTC Behavior to Consult a Physician (Purchase Population n =720)**



The number and percentage of OTC participants who consulted a physician within 2 months of product use by gender, race and literacy is presented in Figure 22. Gender and literacy did not appear to have an impact on whether a subject would consult a physician. Although the sample size is small, Black and Hispanic subjects were somewhat less likely to consult than Caucasians.

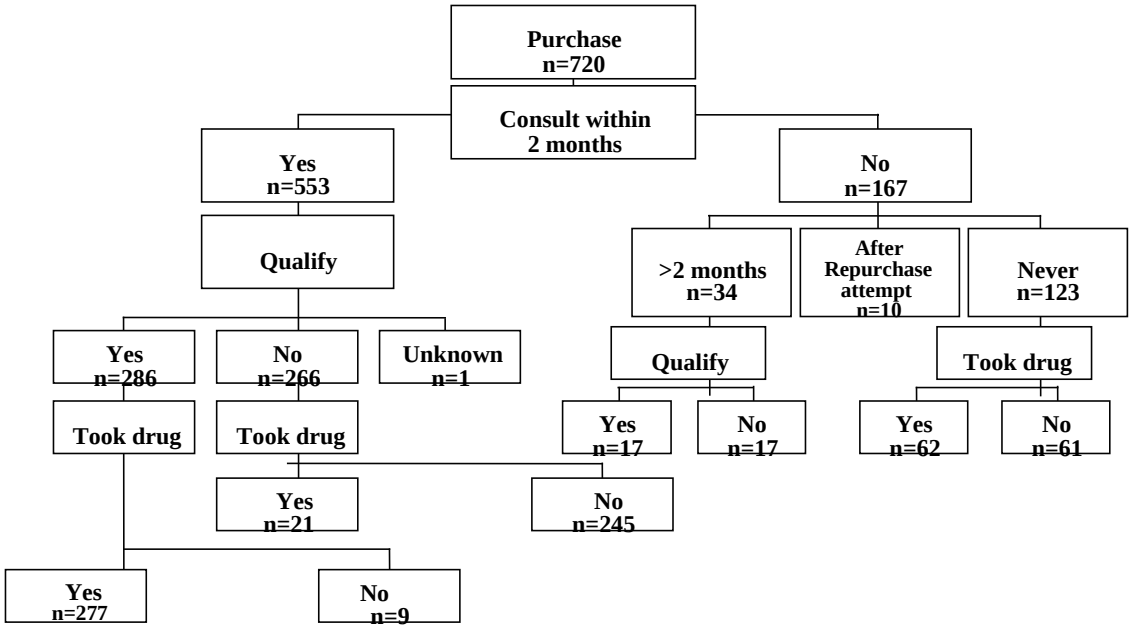
Figure 22: PREDICT: OTC Behavior to Consult a Physician by Demographic Characteristics (Purchase Population N=720)



Of the 1,924 participants randomized to the OTC group, 1,852 (96%) demonstrated behavior that presented no potential harm: 1,204 (63%) never purchased Pravachol 10 mg, 587 (31%) purchased Pravachol 10 mg and consulted a physician, 61 (3%) purchased Pravachol 10 mg and never consulted a physician but did not take Pravachol 10 mg. Only 72 participants purchased Pravachol 10 mg, never consulted a physician and took at least one dose of medication. Of these, 90% never attempted to repurchase additional medication.

Of the OTC participants who purchased Pravachol 10 mg, consulted a physician within 2 months and did not qualify for treatment (n=266), 92% either never took Pravachol 10 mg or stopped taking medication after being told they did not qualify. A summary of the behaviors of the OTC purchase population is summarized in Figure 23.

Figure 23: PREDICT: Behavior of OTC Purchase Population



Consumer Behavior: OTC vs. Rx Environment

Maintenance of Physician Relationship

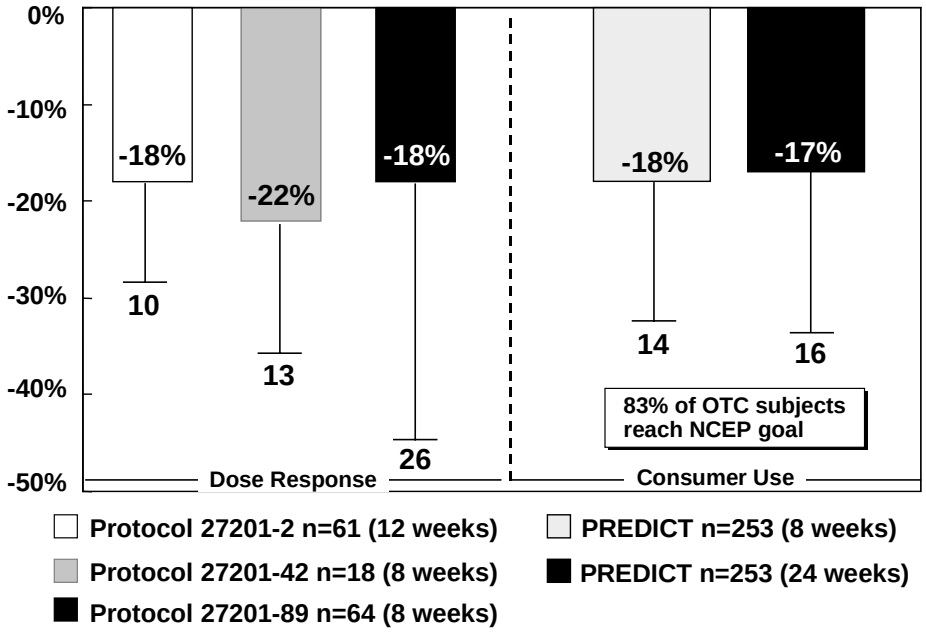
Despite an environment where, other than the PRAVACARE newsletters, there were none of the advertising supportive messages or educational materials that would be found in a true OTC environment, follow-up physician consultation was excellent. Of the 720 OTC and Rx participants who were told by the physician that they qualified for Pravachol 10 mg, 85% of OTC vs 83% of Rx qualified participants (CI: -3.4%, 7.5%), followed-up at 8 weeks after the initial visit.

Effects on Cholesterol

Baseline lipid parameters were comparable for the OTC and Rx participants who qualified for Pravachol 10 mg therapy and took at least 1 dose of medication. In this population, statistically significant and clinically meaningful reductions were observed for LDL-C at Week 8 and Week 24: -18% and –17% for the OTC group and –19% and -18 % for the Rx group, respectively. There was no significant difference in the reduction

seen between the OTC and Rx groups. As shown in Figure 24, the magnitude of the LDL-C reduction was similar to that observed in placebo-controlled dose response clinical trials.

Figure 24: PREDICT: LDL-C Reduction: Dose Response vs PREDICT



Importantly, 83% OTC and 77% Rx participants achieved their NCEP defined LDL-C goal during the study. A summary of the lipid results is presented in Table 27. There were no significant differences among the gender or racial subgroups.

Table 27: PREDICT: Percent Change in Lipids from Baseline

	OTC n=285	Rx n=352	95% CI
Total-C mg/dl			
Baseline	243	245	
% change Week 8	-13%	-14%	(-0.8%, 2.6 %)
% change Week 24	-13%	-14%	(-0.4%, 3.1%)
LDL-C mg/dl			
Baseline	161	163	
% change Week 8	-18%	-19%	(-1.5%, 3.0 %)
% change Week 24	-17%	-18%	(-1.7%, 3.4%)
HDL-C mg/dl			
Baseline	50	51	
% change Week 8	0.3%	-0.9	(-1.5%, 3.2 %)
% change Week 24	3%	0.3%	(-0.5%, 5.1%)
Triglycerides mg/dl			
Baseline	165	159	
% change Week 8	0%	-1.4%	(-4.1%, 6.9%)
% change Week 24	-6%	-8%	(-2.0%, 8.5%)

Note: Missing values at Week 8 and 24 were replaced by the last observation (including baseline) carried forward to calculate percent change.

Safety Profile: OTC vs. Rx Environment

The safety profile of Pravachol in the OTC setting was consistent with results of long and short term clinical trials and 22 million patient years of post marketing exposure. Overall, Pravachol was well tolerated: fewer participants in the OTC group experienced AEs compared to the Rx group (133 OTC [27%]) vs. (144 Rx [41%]). The most frequent adverse events were attributed to the "respiratory system" (34 OTC [7%] vs. 36 Rx [10%]) and "gastrointestinal" (24 OTC [5%] vs. 40 Rx [11%]).

Musculoskeletal adverse events occurred in 28 (6%) OTC vs. 33 (9%) of Rx participants. None of these adverse events were serious. Myalgia was reported in 7 (1%) of the OTC participants and 4 (1%) of the Rx participants; 5 participants (4 OTC and 1 Rx) discontinued treatment. CPK levels were measured on 3 OTC and 1 Rx participant because of symptoms. One participant with an AE of myalgia had a CPK elevation of 402 IU/L; this person completed the study on therapy and the myalgia resolved prior to

study completion. All other CPK values were within the normal range and none required follow up measurements. CPK levels were measured on 26 additional participants at the discretion of the investigator; none of these values were greater than 1.7 x ULN.

Adverse events related to the hepatobiliary system occurred in 6 (1%) OTC participants and 3 (< 1%) Rx participants. These events included seven (four OTC vs three Rx) transaminase abnormalities, 2 cholecystectomies, and 1 cholelithiasis. All seven of the transaminase elevations were mild, ranging from 1.1 to 2.2 x ULN. Three of the participants discontinued treatment, two for protocol violations and one for myalgia. Of the four who continued on treatment, three participants had transaminase levels which returned within the normal range.

There were no adverse events of drug interactions reported.

Considering only those AEs judged by the investigator as related to (certain, probable, possible) study medication (ADE), there were no differences noted between the OTC and Rx participants. ADEs were reported by 45 participants (9%) in the OTC group and 42 participants (12%) in the Rx group. ADEs reported in the "gastrointestinal system" (10 [2%] OTC vs. 15 [4%] Rx) and "musculoskeletal system" (15 [3%] OTC vs. 8 [2%] Rx) were the most common. There were no preferred terms reported with an incidence of > 1% (Table 28). Nausea and dyspepsia were the most frequently reported gastrointestinal system ADRs in the OTC group; abdominal pain, nausea and constipation were the most frequently reported gastrointestinal system ADEs in the Rx group. Myalgia and muscle ache were the most frequently reported musculoskeletal system ADEs in both groups. ADEs related to the hepatobiliary system occurred in 4 (<1%) OTC participants and 3 (< 1%) Rx participants.

Table 28: PREDICT: ADE's by Body System > 1% (Treated Population n = 854)

Body System	OTC N = 499		Rx N = 355	
	n	**%**	**n**	**%**
Total	45	9	42	12
Gastrointestinal	10	2	15	4
Nausea	3	<1	3	<1
Dyspepsia	3	<1	2	<1
Abdominal Pain	0	---	4	1
Constipation	0	---	3	<1
Musculoskeletal	15	3	8	2
Muscle Ache	4	<1	3	<1
Myalgia	5	1	2	<1
Pain, Joint	1	<1	1	<1

Data Source: Appendix F.12 (Table 31.0.0)

No deaths were reported during the study. A total of 19 participants (11 OTC and 8 Rx) experienced one serious adverse event either during the study or within 1 month after cessation of treatment. None of these events were related to Pravachol therapy. An additional participant (25-3345) reported a tumor of the right lung hilum 105 days after cessation of treatment. A participant listing of all SAEs can be found in Table 29 and a short narrative description of each case is provided in Appendix G.

Table 29: PREDICT: Listing of SAE's (Treated Population n = 854)

Tx Group Region# - Participant #	Age	Sex	Tx Duration (days)	Relation to Medication	Event
OTC (N= 499)					
10-3604	49	M	28	Unrelated	Myocardial Infarction
17-3343	60	M	141	Unrelated	Coronary heart disease
18-3006	56	M	7	Unrelated	Perforated stomach ulcer
19-3006	62	M	161	Unrelated	Gastroesophageal reflux disease
21-3636	57	M	134	Unrelated	Myocardial infarction
21-3642	83	F	125	Unrelated	Bladder cancer/bladder removal
25-3345	56	M	62	Unrelated	Tumor, right hilum lung
25-3627	56	M	178	Unrelated	Ureterolithiasis
26-3008	52	M	97	Unrelated	Incision and drainage rectal abscess
26-3038	65	M	28	Unrelated	Prostate cancer
26-3042	53	M	42	Unrelated	Cholecystectomy
26-3345	65	M	87	Unrelated	Prostate cancer
Rx (N= 355)					
10-4627	61	F	151	Unrelated	Breast cancer
12-4304	57	M	129	Unrelated	Myocardial infarction
15-4619	71	F	38	Unrelated	Wrist infection
15-4627	62	M	42	Unrelated	Urethral blockage
19-4032	53	M	169	Unrelated	Coronary heart disease
19-4623	63	M	60	Unrelated	Transurethral resection of prostate
20-4620	70	M	13	Unrelated	Prostate cancer
28-4325	62	M	41	Unrelated	Coronary vessel stenosis

Populations of Special Interest

In order to assess the potential risks and benefits of OTC availability of lipid lowering medication, we evaluated the consumers who took Pravachol 10 mg without consulting a physician; the frequency of OTC consumers shifting from current prescription lipid lowering mediation to an OTC product; and the behavior of participants who, after consulting the physician, were told they required higher strength prescription medication.

<u>OTC Participants Who Took Medication and Never Consulted a Physician</u>

Sixty-two (62) OTC subjects took study medication and never consulted a physician. An additional 10 subjects were instructed to consult a physician after they attempted to repurchase study medication without consulting; therefore a total of 72 subjects are included in this population.

The demographics of the population that did not consult were not very dissimilar to those who did. The mean age of the non-consulting population was 53 ± 13. Seventy-two percent were male; 65% were Caucasian, 14% Black, 14% Hispanic, 6% Native American and 1% Asian; 95% had at least a high school education and 10% read below a 9th grade reading level. The health care status for this population and the Consult population is summarized in Table 30. Similar to the Consult population, participants who chose not to consult also had access to health care, and appeared involved in the health care dialogue with their physician.

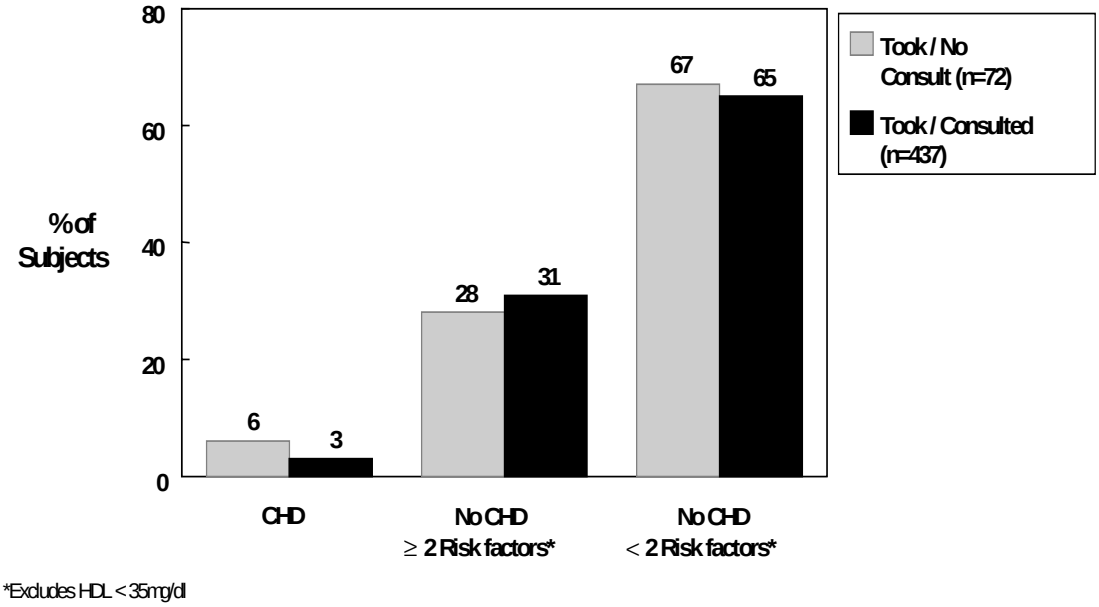
Table 30: PREDICT: Health Care Status for Participants Took/No Consult vs Took/Consulted (OTC Randomized Population)

	Took/No Consult (n = 72) (%)	Took/Consulted (n = 437) (%)
Have a Doctor	88	85
Visit MD at Least Yearly	86	83
Told of High Cholesterol	94	91
See MD Specifically for Cholesterol	28	23
Have Rx Coverage	69	70
On Hormone Replacement*	60	54

*Post-menopausal women only.

NCEP-defined risk factor profiles at baseline are shown in Figure 25; The people who did not consult did not have increased incidence of CHD or diabetes. The most common risk factors were age (56%), family history (28%), hypertension (17%) and smoking (10%).

Figure 25: PREDICT: CHD Risk Factor Profile: Consult vs Non-Consult



*Excludes HDL < 35mg/dl

The overall incidence of adverse events for those participants who took and never consulted was very low: 2 of the 72 participants (3%) experienced adverse events: 1 participant experienced musculoskeletal pain and 1 participant underwent prostate surgery.

Participants Taking Prescription Lipid Lowering Medication at Randomization

There were 183 OTC participants who were taking prescription lipid lowering medication when they entered PREDICT, thus putting them at risk for potentially shifting to less efficacious medication, since they had the opportunity to purchase OTC Pravachol 10 mg. Only 4 participants, 2% of the total number of OTC participants taking lipid lowering therapy at baseline, took Pravachol 10 mg and never consulted; none of them attempted to repurchase additional Pravachol 10 mg and 1 had resumed taking prescription therapy by Week 24; the status of the other 3 was unknown at study closure. Thus, 2% of the 183 OTC participants at risk for shifting from a prescription lipid lowering medication to Pravachol 10 mg actually did so.

Participants Requiring More Aggressive Therapy

There were a total of 321 (132 OTC and 189 Rx) participants who were told when they consulted the study physician that they required more aggressive prescription therapy. These people were defined by a risk factor/lipid profile of any of the following: CHD, diabetes, > two risk factors, and/or LDL-C > 190 mg/dl. The study physicians had been instructed to advise these participants that they required prescription therapy and should see their personal physician. When these participants were contacted at Week 24, 46% reported they had consulted with their personal physician and 29% stated that they were now taking prescription medication. There was no difference between those initially randomized to OTC vs. Rx. (Table 31)

Table 31: PREDICT: Cholesterol Action at Week 24 in Participants Who Required More Aggressive Therapy (n=321)

	All (n = 318)	OTC (n = 130)	Rx (n = 188)
Saw Physician Within 6 Months	46%	48%	44%
Using Rx Medication	29%	32%	27%
Using Dietary Supplements/"OTC Medication"	20%	17%	22%
Made Dietary Changes	40%	43%	38%
Lost Weight	21%	20%	22%
Increased Exercise	21%	20%	22%

Data Source: Appendix N.6 (Table 43.1.0.16)

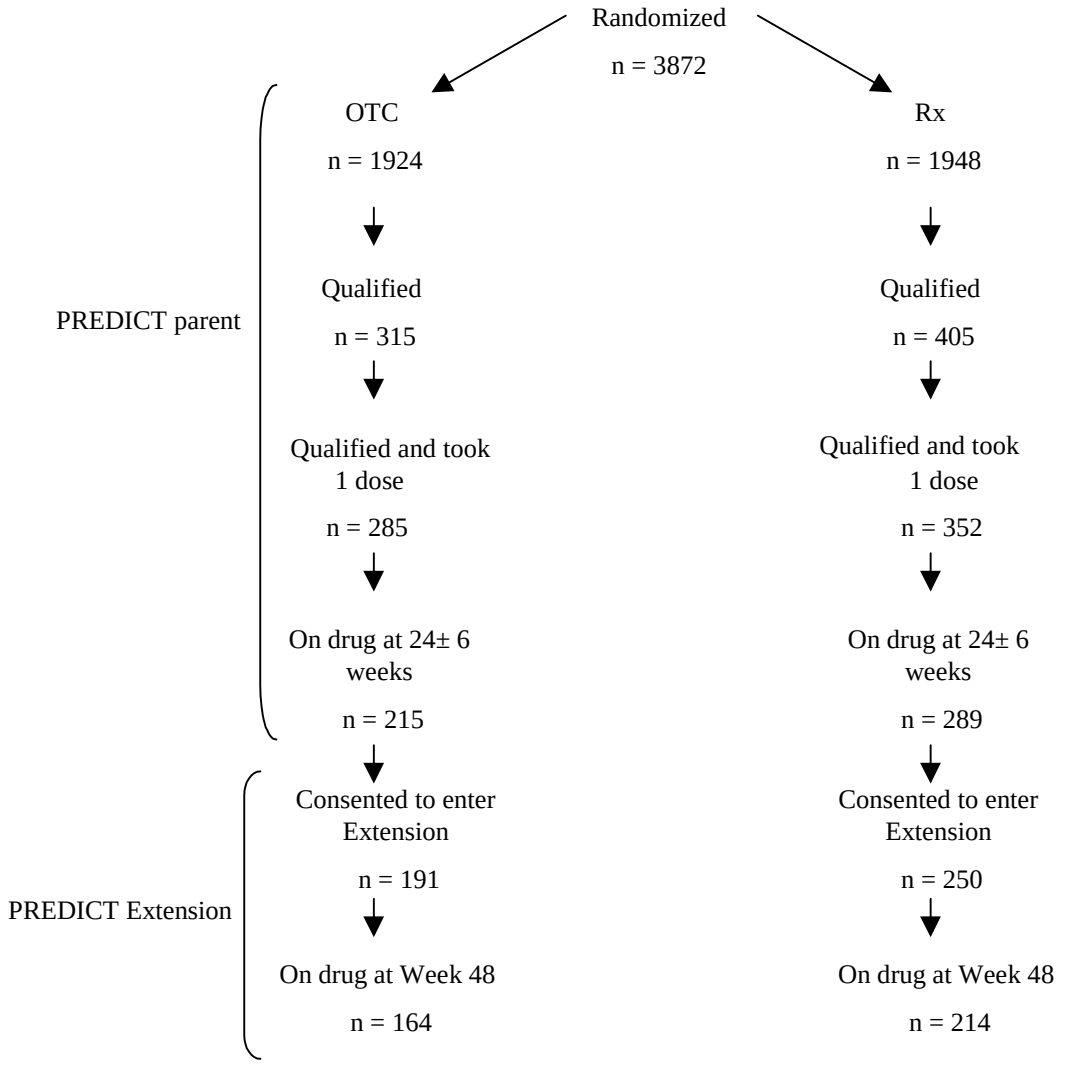
PREDICT Extension

PREDICT Extension, Protocol 800-01-98, enrolled participants who qualified for lipid lowering therapy at the start of the PREDICT 800-01-97 and followed them for an additional 6 months to evaluate consumer behavior at one year. The primary objective was to determine the number of OTC and Rx participants who, having qualified for Pravachol 10 mg therapy at the start of Protocol 800-01-97 and were on drug (within 6 weeks) at Assessment 4 (6 month visit), consult a physician for an annual follow-up visit and/or consult a physician prior to discontinuation of study drug.

Participant Disposition

A total of 441 participants (OTC n=191, Rx n=250) consented to participate in the PREDICT Extension Protocol. Figure 26 describes the flow of participants from the time they were randomized in the parent protocol to their Week 48 treatment status. At the end of 1 year, 52% OTC participants and 53% Rx participants who qualified for treatment in the parent protocol, remained on study medication.

Figure 26: PREDICT Extension: Participant Disposition



Maintenance of Physician Relationship

Of the 441 participants who agreed to participate in the extension study, 430 participants were included in the PREDICT Extension Behavior Population. Eleven subjects did not take study medication and were not included in the PREDICT Extension Behavior Population.

361 (154 OTC vs. 207 Rx) (84%) participants completed 48 ± 6 weeks of treatment and consulted a physician for an annual follow-up (154 [83%] OTC vs. 207 [85%] Rx), 95% CI (-9.1%, 5.0%). An additional 31 (7%) participants discontinued therapy prior to 48 ± 6 weeks without consulting a physician at the time of discontinuation, but consulted a physician for an annual follow-up (13 [7%] OTC vs. 19 [7%] Rx). Seven (2%) participants did not complete 48 ± 6 weeks of treatment but consulted a physician prior to the discontinuation of study medication (4 [2%] OTC vs. 3 [1%] Rx), 95% CI (-1.6%, 3.4%).

Lipid Profile at Week 48

Table 32 presents the percent change from baseline to Week 48 lipid measurements. These results were similar to the reduction seen at Weeks 8 and 24 of the parent protocol for this cohort and demonstrate that participants who continue on medication are very compliant.

Table 32: PREDICT Extension: Percent Change from Baseline Lipid Profile

	Statistic	OTC (n = 186)	Rx (n = 244)	95% CI*
LDL-C (mg/dl)	Mean BL ± SD	165 ± 16.1	165 ± 15.6	
	Mean %change ± SD			
	Week 8	-22 ± 12.5	-21 ± 12.2	(-3.4%, 1.9%)
	Week 24	- 23 ± 12.0	- 22 ± 12.2	(-4.1%, 1.0%)
	Week 48	-22 ± 13.6	- 22 ± 13.1	(-3.7%, 2.0%)
Total-C (mg/dl)	Mean BL ± SD	248 ± 20.4	247 ± 19.5	
	Mean % change ± SD			
	Week 8	-16 ± 9.0	-16 ± 8.7	(-2.2%, 1.6%)
	Week 24	-17 ± 8.5	-17 ± 8.3	(-2.5%, 1.1%)
	Week 48	-17 ± 9.9	- 16 ± 9.7	(-2.8%, 1.4%)
HDL-C (mg/dl)	Mean BL ± SD	50 ± 12.6	51 ± 13.3	
	Mean % change ± SD			
	Week 8	0.2 ± 15.3	-0.7 ± 13.3	(-2.0%, 3.6%)
	Week 24	4 ± 19.2	1± 14.9	(-1.2%, 5.5%)
	Week 48	0.5 ± 17.4	-0.7 ± 14.3	(-2.7%, 3.5%)
Triglycerides (mg/dl)	Mean BL ± SD	165 ± 71.9	156 ± 65.8	
	Mean % change ± SD			
	Week 8	-1 ± 32.4	-2 ± 34.1	(-5.0%, 9.1%)
	Week 24	-9 ± 28.4	-10 ± 31.6	(-4.2%, 8.3%)
	Week 48	-6 ± 32.2	-5 ± 37.2	(-8.5%, 6.2%)

BL= Baseline

VI. RESULTS OF OTC PRAVACHOL TRIAL IN AN OBSERVED NATURALISTIC SETTING (OPTIONS)

The OPTIONS study was conducted from February 1, 1999 to August 4, 1999. In this study, OTC Pravachol 10 was for sale in pharmacies, and the purpose of the study was to observe how Pravachol 10 mg would be used by people who could purchase it.

Objectives

OPTIONS was a pharmacy-based observational study. The primary objective was to determine the proportion of participants who, having purchased Pravachol 10 mg, consulted their health care provider within 2 months of using the medication. The secondary objectives were to determine the proportion of participants who appropriately self-selected to use the product according to the pre-specified criteria in the protocol as follows:

- do not have CHD, diabetes or liver disease
- not currently taking a prescription lipid lowering therapy
- not pregnant

The safety of Pravachol 10 mg in an OTC environment was also evaluated.

Special populations were also analyzed:

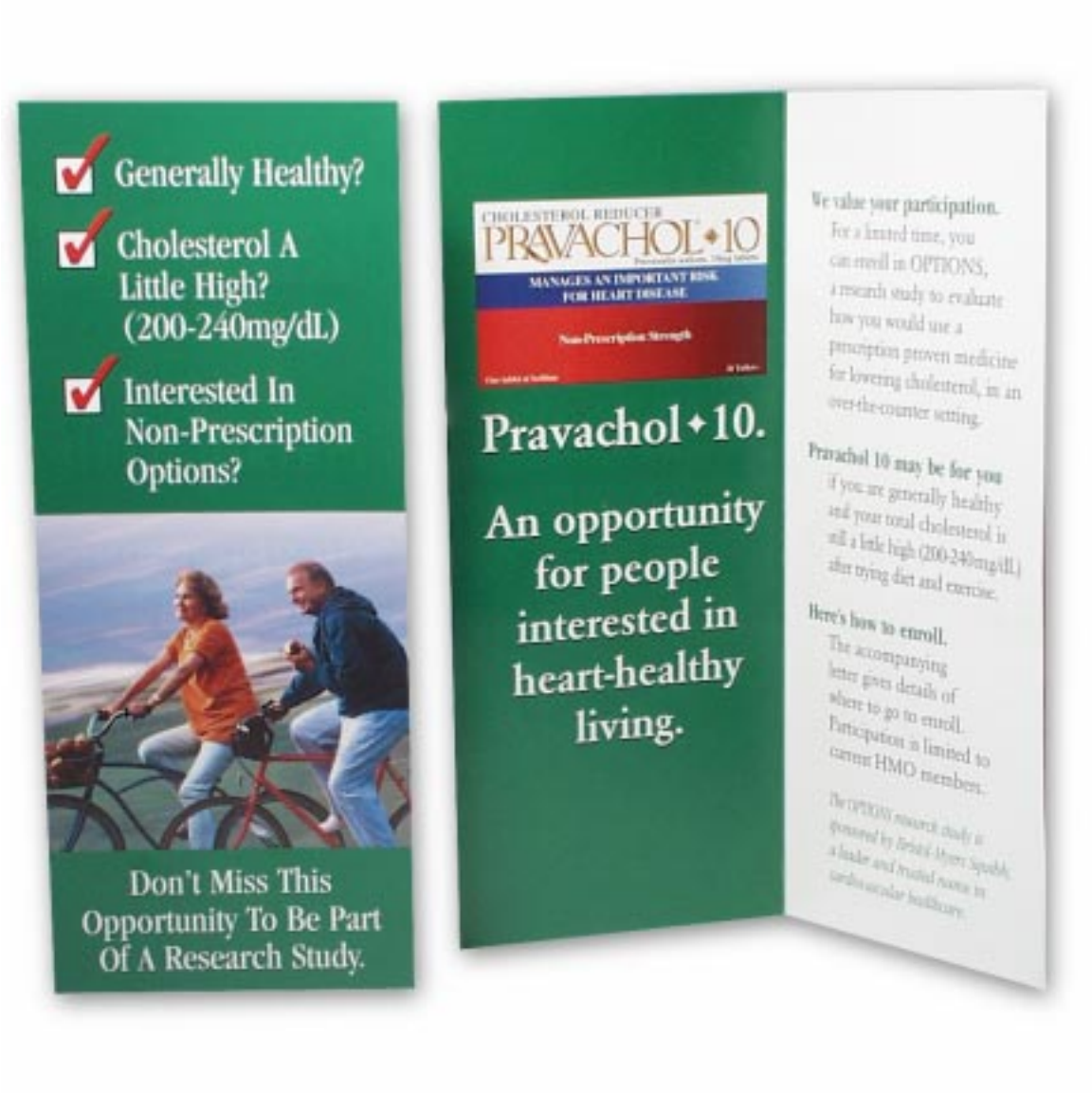
- participants who took OTC medication and never consulted the doctor
- participants who were taking prescription medication when they entered the OPTIONS study

Methodology

Twenty US pharmacies served as the study sites. Fourteen of the study sites were HMO staff model pharmacies and 6 were retail pharmacies that served Independent Practice Association (IPA) model HMOs. The principal investigator at each site was a Registered Pharmacist employed by the pharmacy. Each study site also had a physician who belonged to the participating HMO as the sub-investigator who was responsible for

addressing medical related issues, such as adverse events. Enrollment was limited to members of the participating HMOs. This was necessary in order to observe people in their natural environments (without utilizing study physicians) while collecting reliable data by maximizing access to participants' primary care physician and medical records. Both staff model and IPA settings provided a naturalistic environment in which to observe participant behaviors, since participants utilized their own health care provider and pharmacy. Sites were selected to increase the likelihood of enrolling low literacy and minority participants.

Figure 27: OPTIONS: Advertising



Participants were recruited via mailers (Figure 27) sent to a random sample of HMO members without knowledge of medical history, cholesterol levels, or demographic profile. In some cities, radio and newspaper advertising were also used. The study advertising was developed to be as "commercial" looking or sounding as possible and indicated that individuals with cholesterol levels between 200 –240 mg/dl who were generally healthy could have the opportunity to purchase a prescription proven

cholesterol lowering medication without a prescription. In order to attract the attention of walk-thru traffic, prototypical print advertisements, such as posters, floor displays (Figure 28) and counter-stands, were also displayed in the study site pharmacies. People interested in participating in the study were directed to an enrollment desk in the pharmacy where they met with non-medical personnel (not the pharmacist) trained in administering questionnaires.

Figure 28: OPTIONS: Floor Display

Once membership had been verified, participants were first asked to read and sign a short IRB approved consent form by which they agreed to be interviewed. They were then shown a prototypical advertisement/concept, the OTC product package and apprised of the purchase price.

All participants, then completed the screening questionnaire which collected information about demographics, literacy level as assessed by administering the REALM test (Ref. 29), cardiovascular risk factors, health care status, cholesterol awareness, and cholesterol lowering behaviors. After completing the questionnaire, participants interested in purchasing Pravachol 10 mg were screened for minimal inclusion/exclusion criteria:

Inclusion Criteria

- ≥ 18 years

Exclusion Criteria

- participated in a research study within the last 30 days
- pregnant or lactating

Participants were then asked to sign a second IRB approved consent form and provide permission for access to their medical records. Participants were not told that their medical records would be monitored to verify physician consults. Participants who did not purchase Pravachol 10 mg were only asked to provide written release for access to their medical records.

Once a participant was enrolled in the study, no further contact was initiated during the 12 week study period. The pharmacist could counsel the participant on Pravachol 10 mg, but only at the request of the participant.

The interviewers attended a special training session during the Investigator's Meeting that provided background information about the study, study procedures, scripts, and instruction on completion of the participant questionnaire. Study personnel did not instruct participants to contact their primary health care provider and the importance of not influencing the participant's decision to consult a physician was emphasized at the training sessions. The decision to contact a physician was to be made solely by the participant.

While the primary health care providers were notified regarding their patients' participation, they could not proactively contact their patient to tell them whether or not to enroll unless treatment with Pravachol 10 presented substantial risk. The participants' medical records were reviewed independently by the primary care physician to provide an independent documentation of cardiovascular risk factors and relevant medical history, document any contact with the participant since enrollment and provide a recommendation as to the appropriateness of Pravachol 10 mg.

Twelve weeks after the Assessment 1 visit or product purchase (whichever occurred later), participants were interviewed by telephone in order to collect information as to whether they contacted their primary care provider, interim changes in cholesterol awareness and action, and adverse experiences. Participants who had purchased medication were asked to return all unused medication as well as empty blister cards to the pharmacy site. This was the first contact initiated by the study staff after the participant enrolled in the study.

As in PREDICT, participants had the option of purchasing a Pravachol 10 mg starter kit or maintenance package, as described in Section V. Also similar to PREDICT, the PRAVACARE product promotion/education program was designed to simulate one of many programs that will be offered in the OTC environment. Enrollment in the education programs was entirely voluntary and designed to mimic how enrollment will

occur in an OTC environment. People could enroll by calling the toll free number listed on the label of both the starter kit and maintenance boxes.

People who enrolled in PRAVACARE were provided with the PRAVACARE booklet discussed in Section V. two newsletters sent 2 weeks and 1 month after enrollment; and two reminder postcards sent according to the same schedule as the newsletters, that reinforced key label communication messages (Appendix I).

Study Results

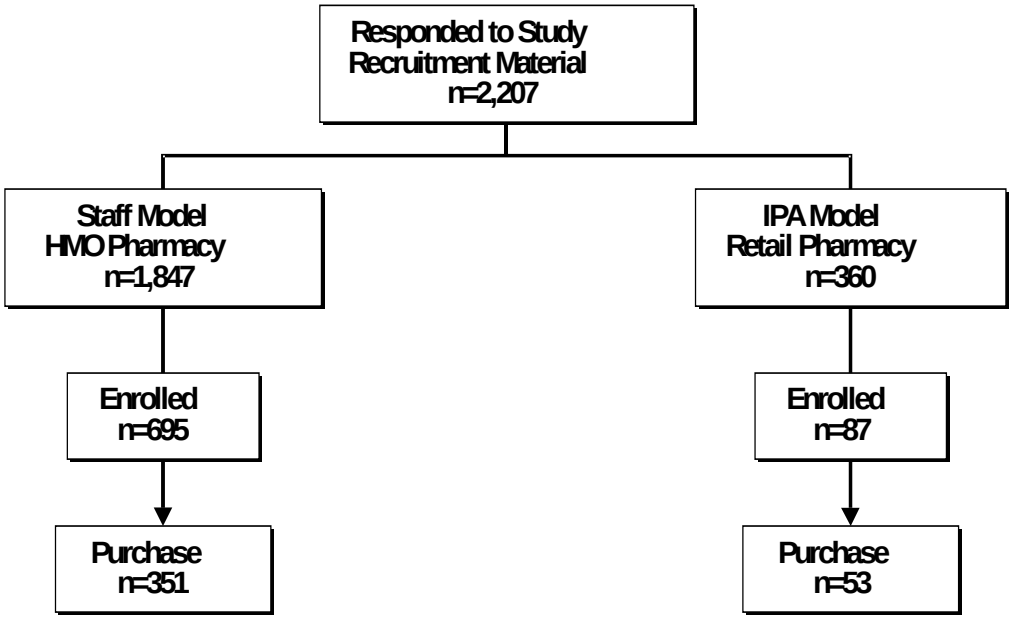
Disposition

The participant enrollment period began February 1, 1999 and was completed on May 11, 1999. Flyers were mailed to over 160,000 participants, as it was expected that a small percentage would respond, given the fact that these were sent to households without knowledge of demographics, cholesterol status or medical conditions. In addition, poster and floor stands were placed in pharmacies to attract walk-thru traffic. A total of 2,207 participants responded to the study recruitment materials. One thousand four hundred and twenty-five participants (65%) chose not to enroll for the following reasons: “Just curious” 630 (44%), “Time” 257 (18%), “Not an HMO member” 171 (12%), “Wanted to consult a physician” 134 (9%), “Label contraindication” 70 (5%), “Refused consent” 47 (3%), “Price” 16 (1%) and “No specific reason” 100 (7%). Of the 782 participants who enrolled, 355 (45%) responded to the mailer, 414 (53%) were walk-thru, 12 (2%) responded to the newspaper or radio advertising or by word of mouth, and for 1 (<1%) participant the reason was unknown. Of the 782 participants who enrolled in the study, 404 (52%) purchased at least one box of Pravachol 10 mg.

Study participant disposition is presented overall, and by staff vs IPA HMO model in Figure 29. One thousand eight hundred and forty-seven (84%) individuals were screened at the 14 HMO staff model pharmacies and 360 (16%) at the 6 retail pharmacies. A greater proportion of participants who enrolled at the retail pharmacies

compared to the HMO staff model pharmacies went on to purchase (61% vs. 51%, respectively).

Figure 29: OPTIONS: Participant Disposition



Characteristics of Population Interested in OTC Proposition

Table 33 summarizes demographic characteristics of the population who was interested in the OTC proposition based solely on seeing the study advertisement and not the package. As in PREDICT, the participants were middle aged with a mean age of 51 ± 10 years; only 5% were less than 35 years of age. Fifty-four percent (54%) of those enrolled were women; 93% had at least a high school education and 12% read below a 9th grade level., Sixty eight percent (68%) of participants were Caucasian; with African-American, Hispanics, Asian and Native Americans accounting for 21%, 5%, 3% and 1% respectively; the demographic profile may be a result of a concentration of sites in the southern areas of the US.

Table 33: OPTIONS: Demographic Characteristics

		Enrolled Population n=782	Purchase Population n=404
Mean Age (yrs ± SD)		51 ± 10	51 ± 10
		%	%
Age Group (yrs)	<35	5	3
	35 – 54	58	58
	55 – 74	35	38
	≥ 75	1	<1
Gender	Female	54	50
	Male	46	50
Race	Asian	3	3
	African American	21	17
	Hispanic	5	4
	Native American	1	2
	Caucasian	68	73
	Other	<1	<1
Education	No High School	1	1
	Some High School	4	3
	High School Grad.	55	54
	College Graduate	38	41
Literacy (REALM)	≤ 6th grade	2	2
	7th – 8th grade	10	10
	≥ 9th grade	85	87
Income	< $25,000	12	11
	$25,000 - $49,999	34	34
	$50,000 - $99,000	38	39
	≥ $100,000	12	15

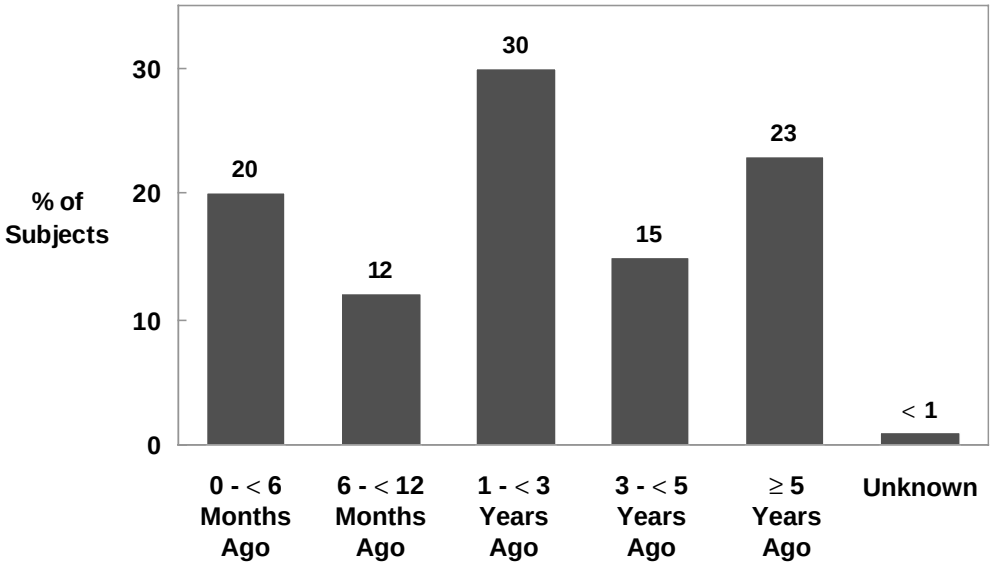
As shown in Table 34, nearly all participants saw a physician at least yearly and about one-third had seen their physician specifically for elevated cholesterol. As in PREDICT, despite having access to healthcare, many more participants reported they were currently taking a dietary supplement or OTC medication to lower cholesterol compared to a prescription lipid lowering medication. The most common supplements used by participants in each population were antioxidants, garlic, and fiber products.

Table 34: OPTIONS: Participants Responding to Advertisement Health Care Status/Cholesterol Action (Enrolled Population n= 782)

	(%)
Visit MD at Least yearly	96
See MD Specifically for Cholesterol	31
Discussed cholesterol with MD within the last 6 months	70
Cholesterol Lowering Therapies Currently Using	
Rx Medication	16
Use Non-Prescription Therapies	26

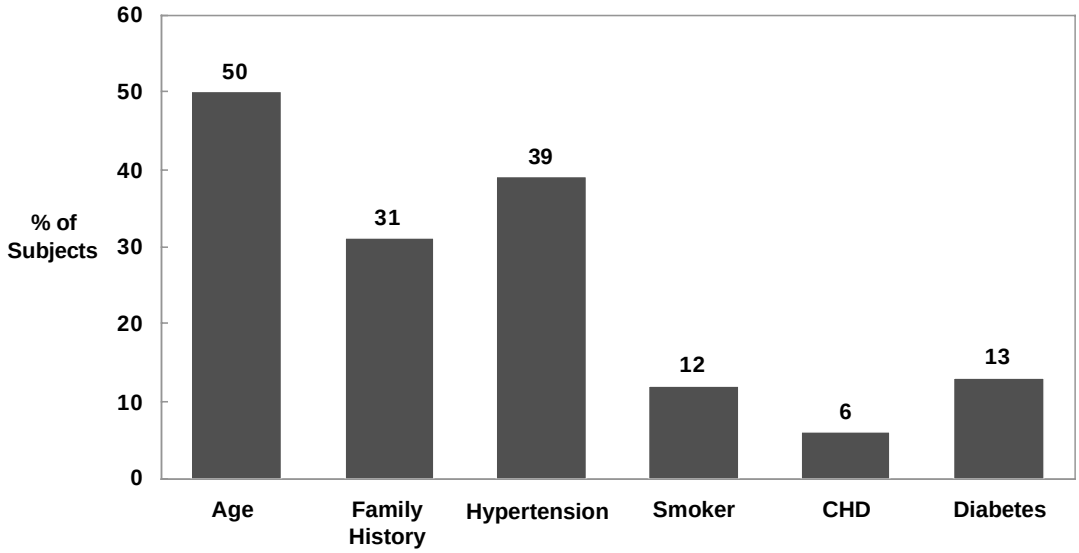
As presented in Figure 30, nearly one quarter of participants had known of their elevated cholesterol levels for at least 5 years. This finding was also similar to PREDICT.

Figure 30: OPTIONS: When First Told of High Cholesterol (Enrolled Population)



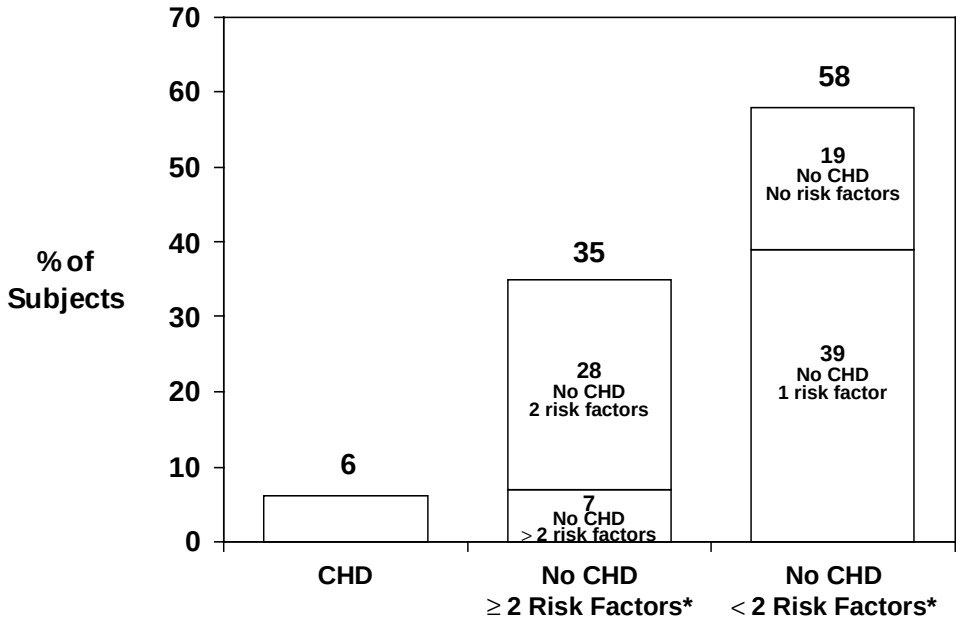
As presented in Figure 31, the most frequently reported CHD risk factors in the Enrolled population were age (50%), hypertension (39%), and family history (31%); CHD or diabetes were reported in 6% and 13% of participants, respectively.

Figure 31: OPTIONS: Distribution of CHD Risk Factors (Enrolled Population n=782)



The baseline data characterizing the NCEP defined risk factor profiles as assessed by the physician are shown in Figure 32. Similar to PREDICT, the majority of people interested in the OTC proposition were a lower-risk population.

Figure 32: OPTIONS: CHD Risk Factor Profile at Baseline (Enrolled Population n=782)



The percentage of participants who were at their NCEP defined goal by CHD risk factor profile is presented in Figure 33 for participants with complete lipid data. Twenty-seven percent of those participants with a prior cardiac event had an LDL-C < 100 mg/dl and less than 30% of those participants in the primary prevention category had an LDL-C < 130 mg/dl.

Figure 33: OPTIONS: Participants at NCEP Goal at Baseline by CHD Risk Factor (Enrolled Population)

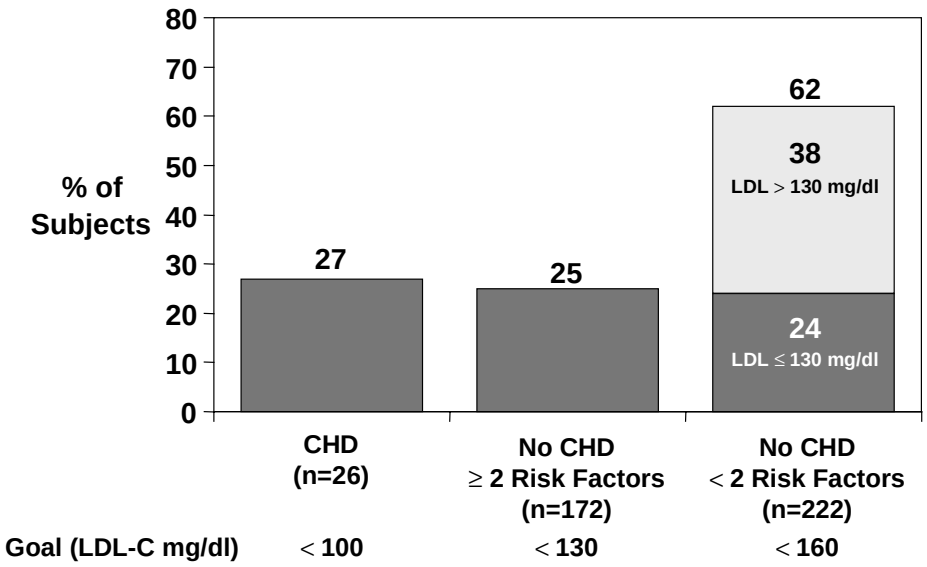


Table 35 presents the most recent laboratory lipid results for those with data available in the medical charts. Eighty five percent (85%) had a baseline Total cholesterol level greater than 200 mg/dl.

Table 35: OPTIONS: Mean Baseline Lipid Profile (Enrolled and Purchase Populations)

	Enrolled	Purchased
Mean ± SD		
Total Cholesterol (mg/dl)	234 ± 50	239 ± 56
	(n =579)	(n = 323)
LDL-Cholesterol (mg/dl)	148 ± 33	150 ± 30
	(n = 445)	(n=246)
HDL-Cholesterol (mg/dl)	51 ± 17	51 ± 17
	(n=466)	(n=260)
Triglycerides (mg/dl)	195 ± 353	215 ± 463
	(n=520)	(n=291)

Consumer Behavior in an OTC Environment

Behavior of Purchase Population

Four hundred and four (404) participants (52%) purchased Pravachol 10 mg. Although recruitment efforts were successful in enrolling minority participants, purchase rates were lower among minorities. Of the participants who enrolled into the study, 56% of Caucasians, 42% of Blacks, and 47% of Hispanics purchased at least one box of Pravachol 10 mg. Younger participants and those with lower household incomes were also less likely to purchase.

Three hundred and seventy-eight (378) participants did not purchase Pravachol 10 mg; as can be seen in Table 36, the primary reason for non-purchase was the interest in consulting a physician first (47%). Contraindications or other label warnings were the reasons given for non-purchase by 20% of participants. In addition, 61 participants (16%) cited "Other" reasons for not purchasing, of which the most frequent included: "Did not have money with them" (n=13); "Concerned about side effects" (n=5) ; felt their

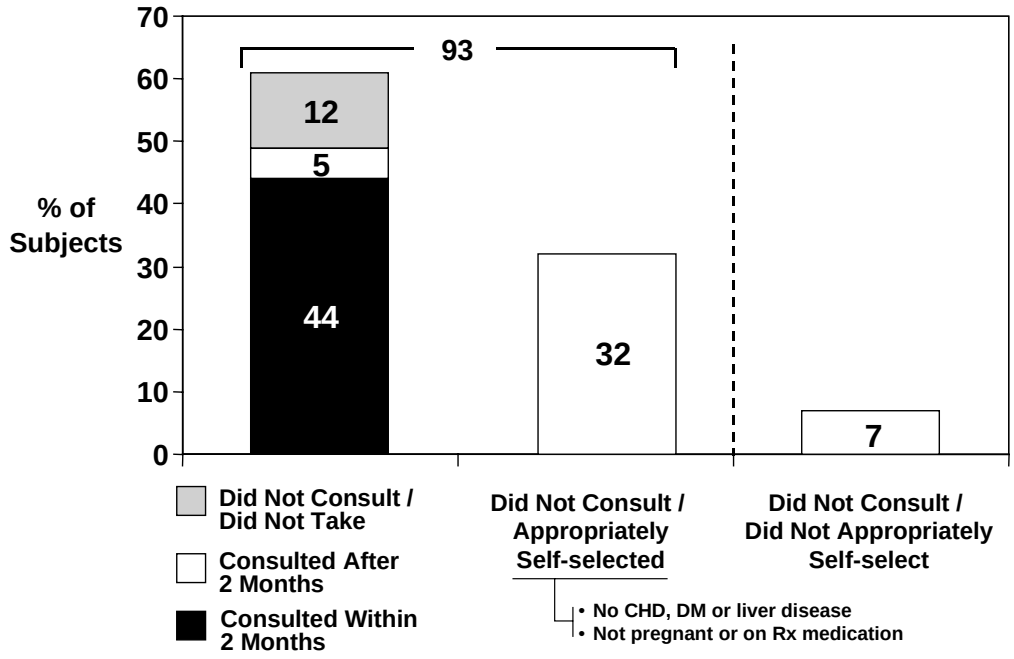
"Cholesterol was too low" (n=5); were "Concerned about label warnings" (n=4); and "Wanted more information" (n=4).

Table 36: OPTIONS:Reasons Participants Did Not Purchase Pravachol 10 (Enrolled Population n=782)

	(%)
Wanted to consult MD	47
No reason given	28
Recognized label warnings	20
Male < 35 years, female ≥ 55 years	6
Already being treated	5
Did not know cholesterol level	4
Noted label warning/risk factors too high	4
Cholesterol not between 200-240 mg/dl	1
Other	16
Cost	3
Wanted to consult a pharmacist	<1

Results of behaviors of the Purchase population are shown in Figure 34. Ninety-three percent of the participants in the Purchase population exhibited behavior that presented no potential harm. Of the 404 participants who purchased Pravachol 10 mg, 178 (44%, CI 39.2%, 48.9%) fulfilled the primary objective by consulting their health care provider within 2 months of product use. Additionally, 20 participants (5%) consulted, but outside the pre-defined 2 month window of product use and were thus not included as meeting the primary objective. Of the 206 participants who did not consult a health care provider, 49 participants (12% of the purchase population) had not taken any medication when contacted at 3 months, 129 (32% of the purchase population) participants took Pravachol 10 mg did not consult, but appropriately self-selected according to pre-specified criteria defined in the protocol: no CHD or diabetes; not pregnant; not currently taking prescription lipid lowering therapy. Only 28 people (7%) who took medication, did not consult and did not appropriately self-select.

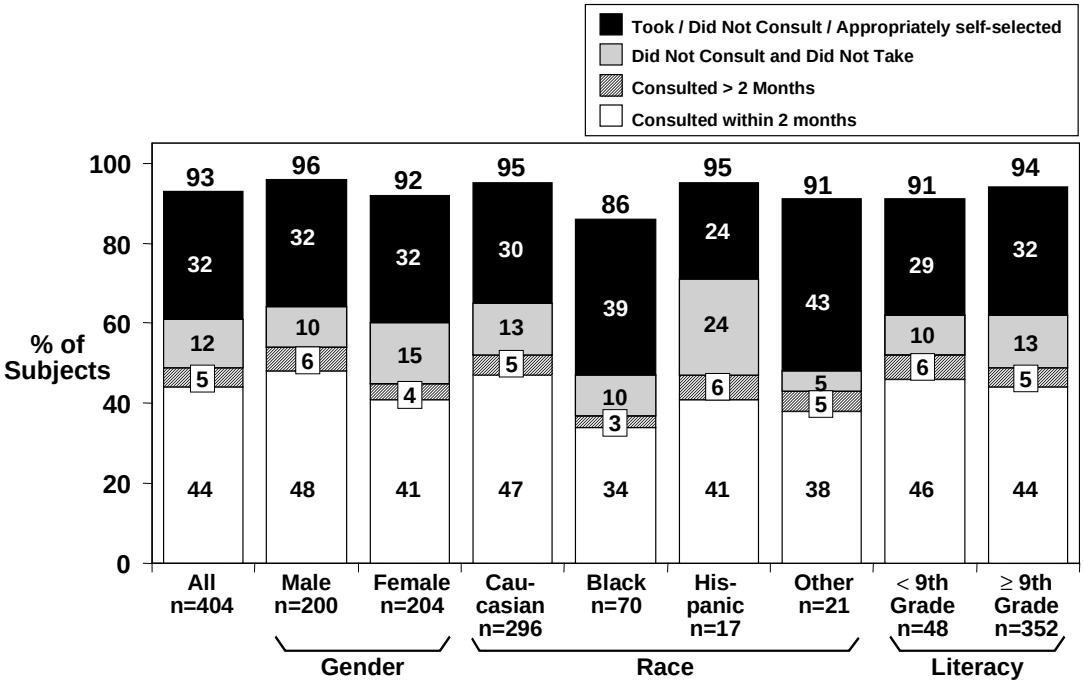
Figure 34: OPTIONS: Behaviors of Purchase Population (Physician Verified n=404)



The data used for the primary analyses represents the more conservative physician verified consultation with the participant. However, since the study was conducted in a "naturalistic" setting, using the participant's own non-research primary care physician, the patients charts were not always current. The results of an analysis based on the participants' self-reported physician contact were: 53% who took Pravachol 10 contacted their physician within 2 months of product use; 5% contacted, but beyond the 2 month window; 10% did not contact the physician but did not take the medication, 26% did not contact the physician but appropriately self-selected. Only 5% of the purchase population took medication and did not appropriately self select.

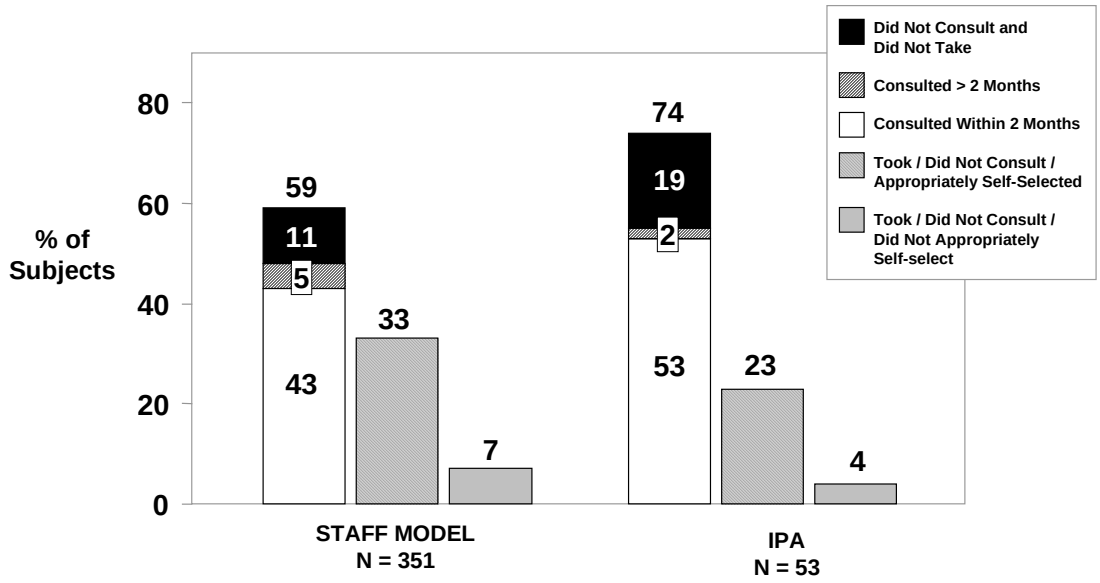
The behavior of product purchasers is presented by gender, race and literacy in Figure 35. The pre-defined subpopulations tended to behave in a similar fashion to the Purchase population as a whole, with 90% ± 5% demonstrating safe behavior.

Figure 35 **OPTIONS: Behavior To Consult a Health Care Provider by Demographic Subpopulation (Purchase Population)**



As shown in Figure 36, 92% and 97% of participants at the staff model and IPA model sites exhibited behavior that presented no potential harm.

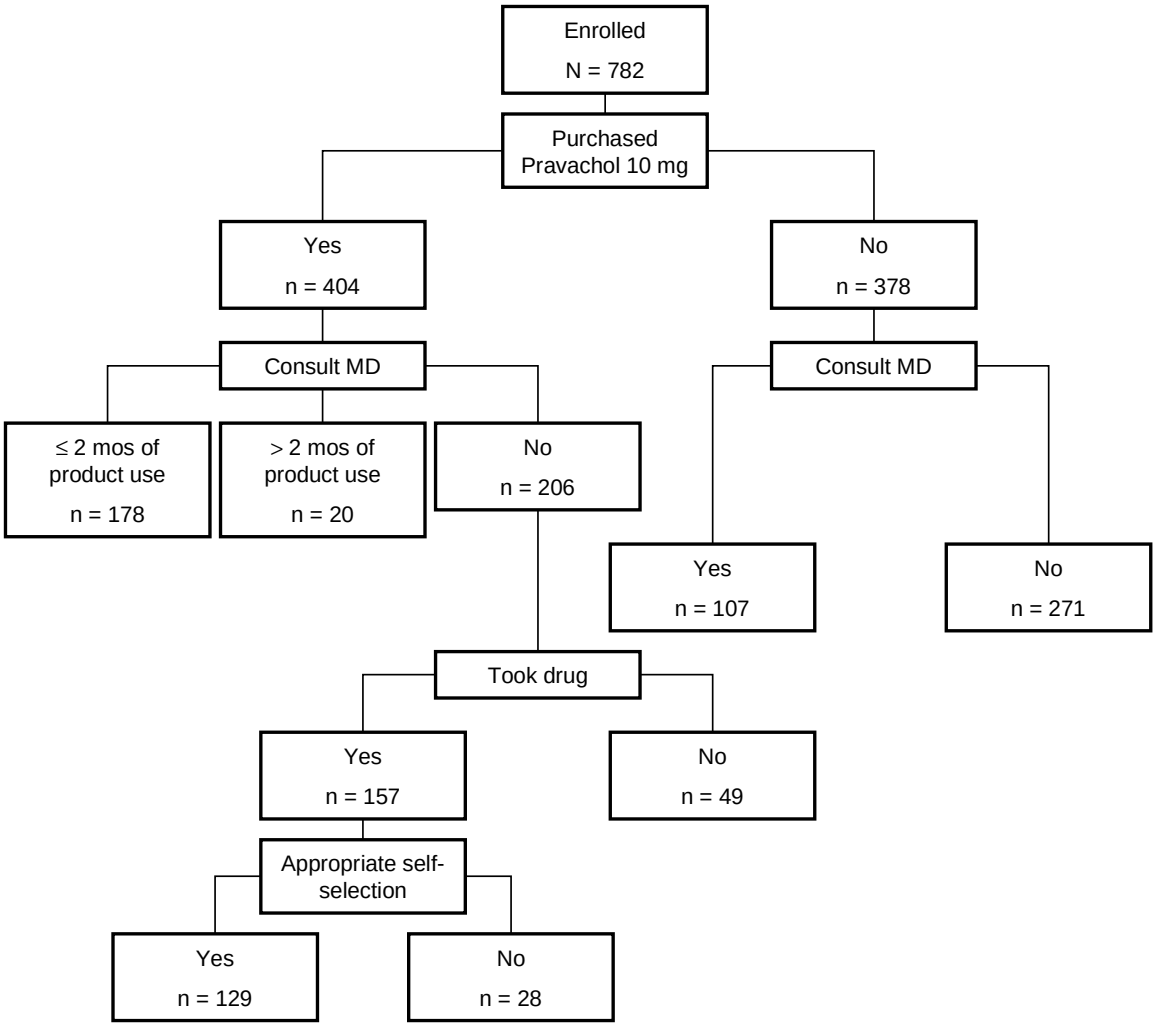
Figure 36: OPTIONS: Behavior to Consult a Physician : Staff Model vs IPA HMO (OTC Purchase Population n = 404)



Behavior of OTC Population

The summary of behaviors of the population who was interested in the OTC proposition is presented in Figure 37. Of the 782 participants who were interested in the OTC proposition and who had the opportunity to purchase Pravachol 10 mg, 754 (96%) demonstrated behavior that presented no potential harm: 378 (48%) never purchased Pravachol 10 mg; 198 (25%) purchased Pravachol 10 mg and consulted their health care provider; 129 (16%) took the product, did not consult a health care provider but self-selected appropriately based on pre-specified criteria in the protocol; 49 (6%) did not consult, but did not take the medication; only 28 (4%) took the product, did not consult a health care provider and did not appropriately self-select.

Figure 37 OPTIONS: Summary of Behaviors



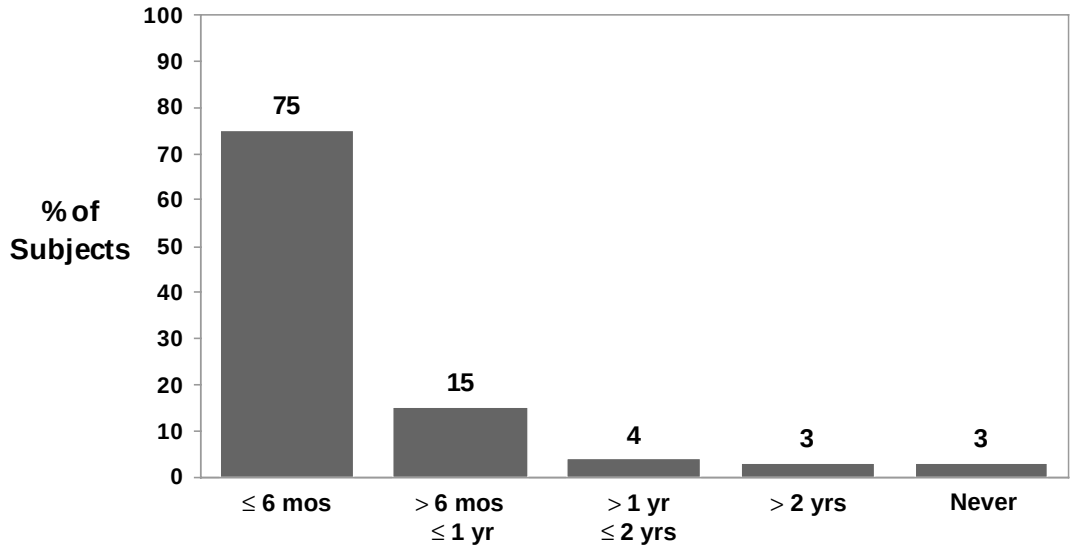
Participants Who Took and Never Consulted

A total of 157 participants took study medication and never consulted a physician. Of these 129 appropriately self-selected OTC Pravachol 10 mg treatment based on the pre-specified criteria in the protocol and 28 did not. Demographics were similar to the overall enrolled population: the mean age of the non-consulting population was 50 ± 9, 48% were male and 11% read below a 9th grade reading level. Sixty-six percent (66%) of

participants were Caucasian with African-American, and Hispanic accounting for 24% and 3% of participants, respectively.

Figure 38 shows 73% of the 157 participants who took but never consulted had spoken to their physician about their cholesterol within 6 months prior to entering the study.

Figure 38: OPTIONS: Cholesterol Discussed with MD Prior to Study Entry (Took/No Consult Population n = 157)



Of the 28 subjects who did not consult and did not appropriately self-select, 4 had CHD 14 had diabetes mellitus, 3 had liver disease and 10 were taking prescription cholesterol lowering medications. None of the 4 participants with CHD were taking prescription lowering cholesterol medications, despite the fact that 3 had LDL-C levels > 100 mg/dl. Of the 14 participants with diabetes mellitus, only 4 had LDL-C levels < 130 mg/dl. Three participants with diabetes mellitus were taking prescription cholesterol lowering medication at baseline; 1 shifted from prescription to OTC therapy.

Participants on Lipid Lowering Medication at Baseline

Ninety-nine participants were taking prescription lipid-lowering medications at baseline, thus putting them at risk for potentially shifting to less efficacious therapy; these, 27 took Pravachol 10 mg at some point in the study. Seventeen (17) participants consulted the physician who recommended OTC therapy to 14. Three participants took Pravachol 10 mg although the physician indicated it was not appropriate; however, 1 of these participants began prescription Pravachol 40 mg after taking the OTC product for 1 month; leaving 2 participants who ultimately shifted to OTC therapy. Ten participants took Pravachol 10 mg and never consulted; however, and 1 took OTC Pravachol 10 mg for 2 months instead of cholestyramine, but subsequently began prescription Pravachol leaving 9 participants who ultimately shifted to OTC. (Included in these 9 participants are two participants who substituted OTC Pravachol at an equal dose to the prior prescription dose.) Thus, 11 participants (11% of the total number of participants on prescription lipid lowering therapy at baseline) shifted from prescription therapy to OTC. Of these, 3 participants attempted to repurchase OTC Pravachol 10 mg without consulting a health care provider.

Safety Profile in OTC Environment

Eighty (25%) participants of the 321 participants who took at least one dose of medication reported AEs. Table 37 summarizes AEs by body system. The most frequently reported AEs involved the gastrointestinal system (7%) or were dermatologic in nature (7%). Myalgia was reported in 2 (<1%) participants and determined to be unrelated to study medication in both cases. Three participants with a history of liver disease took Pravachol 10 mg and did not consult a health care provider. One participant experienced the following adverse events: leg cramps, respiratory congestion, and a laceration to the left arm. Each of the events was considered mild in severity and unrelated to medication.

Table 37 OPTIONS: Overall Incidence of Adverse Events by Body System (Treated Population)

Body System	Treated Population N = 321	
	n	(%)
Total	80	(25%)
Gastrointestinal	23	(7%)
Dermatologic	21	(7%)
General	14	(4%)
Musculoskeletal/Connective Tissue	14	(4%)
Respiratory	13	(4%)
Nervous System	10	(3%)
Cardiovascular	8	(2%)
Special Senses	8	(2%)
Endocrine/Metabolic/Electrolyte Imbalance	4	(1%)
Renal/Genitourinary	4	(1%)
Immunology/Sensitivity Disorder	1	(<1%)
Hepatic Biliary	1	(<1%)

No deaths were reported during the study. A total of four participants experienced the following SAEs: pancreatitis, squamous cell cancer, pericardial cyst, and gastroesophageal reflux. None were considered to be related to Pravachol 10 mg. A summary of all SAEs can be found in Appendix J.

Laboratory tests were not a required procedure for this study. No increases in CPK or transaminases were reported.

VII. EDUCATIONAL PROGRAMS

In support of OTC Pravachol, BMS will implement comprehensive marketing and educational programs designed to ensure the responsible use of Pravachol in an OTC setting. These programs will target 3 key constituencies: consumers, physicians and other healthcare professionals. The objective of this program is to reinforce key messages communicated on the package label and educational leaflet to promote responsible use and maximize compliance of Pravachol 10 mg.

Consumer Program

Objectives

The key objectives of the consumer programs are:

- To encourage dialogue between consumers, physicians and allied health professionals
- To generate appropriate self selection
- To encourage responsible ongoing use

The principal vehicles for communicating key messages and promoting responsible use among consumers will be advertising, packaging, media outreach and the Pravachol Partners Program. Consumer communication will include message elements that encourage ongoing physician involvement, continued efforts at appropriate diet and exercise, and the importance of continued use.

Advertising

BMS plans an extensive introductory advertising and public relations effort aimed at building awareness of the health risks of high cholesterol and encouraging responsible use of Pravachol 10 mg among a target audience of generally healthy adults with mildly to moderately elevated cholesterol levels. The importance of ongoing physician involvement in management of cardiovascular risk factors will also be communicated.

Retailers will be encouraged to display key messages and provide tools to promote proper self-selection and physician involvement at store shelves where product is available. This will include "Questions to Ask Your Doctor" and "Cholesterol Progress Chart" tear-off pads that will be dispensed to consumers free of charge.

Packaging

The Pravachol 10 mg label and educational leaflet were developed with the goal of encouraging appropriate self selection and responsible use. The Pravachol 10 mg label was extensively tested; the results of the label comprehension study which tested key communication messages can be found in Section IV of this document. The behavioral impact of the label was tested in the PREDICT and OPTIONS studies. As demonstrated in these studies, consumers overwhelmingly understood the key communication messages and acted appropriately, with a resulting excellent OTC Pravachol profile of safety and meaningful LDL-C reduction.

The key label messages are: Pravachol 10 mg should be used to lower cholesterol along with a program of diet and exercise; the intended population has total cholesterol levels between 200-240 mg/dl and LDL-C > 130 mg/dl; and people who have CHD or diabetes are not candidates for OTC therapy. The label directs consumers to consult their doctors before use and subsequently 8 weeks, annually. These messages encourage physician dialogue, reinforce the need to have the effects of treatment monitored and raise awareness that CHD risk factors can change over time and should be discussed periodically with a physician. The label also effectively communicates key safety messages currently in the prescription package insert by defining who should not use Pravachol 10 mg (e.g., people with liver disease, or who abuse alcohol, which is considered a surrogate for liver disease) and how to recognize and handle adverse events (i.e., muscle pain) that may require professional attention.

The primary goal of the educational leaflet is to encourage responsible use and ongoing compliance by providing expanded information regarding cholesterol and heart disease

by reinforcing the information found in the Drug Facts section of the label. The product label (see Section IV) and educational leaflet will also provide the toll-free number and interactive web site address that consumers can access for questions and enrollment in the Pravachol Partners Program. The educational leaflet will be available in Spanish for those who request it via the toll free number and web site.

As was the case in the consumer use studies, PREDICT and OPTIONS, the consumer will have the option of purchasing 1) a Pravachol 10 mg Starter Kit containing: blister cards with a calendar pack configuration, an educational leaflet, a "Pravachol, Cholesterol and You" booklet (similar to the one used in PREDICT), a free enrollment card for the Pravachol Partners Program, and a rebate coupon for subsequent purchases, or 2) a Pravachol 10 mg maintenance kit containing medication and educational leaflet only. The booklet that was used in PREDICT is also provided as Appendix H of this document for the reader's convenience.

As demonstrated in the label comprehension and consumer use studies (Sections IV, V and IV) of this document), key messages required for self selection and responsible use are clearly communicated via the carton label and educational leaflet. However, consumers will be encouraged to purchase the retail starter kit since it contains the "Pravachol, Cholesterol and You" booklet which provided additional information about managing risk factors for heart disease, answers consumers' most frequently asked questions and encourages ongoing compliance. A similar starter kit will also be provided to physicians for distribution to their patients.

The blister cards will contain the messages, "See Your Doctor" and "Keep Your Doctor in the Loop." These messages will serve as a daily reminder encouraging responsible ongoing use of Pravachol 10 mg. We will also explore the opportunity of adding and/or rotating blister card messages over time to reinforce key messages about the importance of other risk factors, and help encourage compliance (e.g. maintaining hygienic measures, seeing your doctor for follow-up, importance of continued use).

A toll-free phone number will be provided on every Pravachol carton label. Reasons for calling this number will include: 1) product information/complaints, 2) adverse event reporting and 3) enrollment in the Pravachol Partners Program. Consumers may also order the label and educational leaflet in Spanish or on audiocassette (for low-literacy and vision impaired consumers). Initial phone contact will be via an automated voice system that will automatically remind the caller to consult a doctor before using Pravachol 10 mg. There will be a Spanish language option on the toll-free number. Schematic flow charts for the toll-free number can be found in Appendix K.

An interactive web site will be developed to provide an additional vehicle for consumers to access relevant information and get answers to healthcare and product related questions. Key elements of the web site will include: 1) up to date news on heart health related topics, 2) enrollment in Pravachol Partners program, 3) answers to frequently asked questions, 4) reporting of product complaints or promotion inquiries, 5) exercise and diet tips/recipes, 6) chat room success stories and 7) linkages to other web sites. Customer options will also be available to respond to consumer inquiries requiring specific feedback. A portion of the web site will be dedicated to health care professionals.

Pravachol Partners Program

The goal of the Pravachol Partners Program is to provide an additional tool to encourage responsible ongoing use of Pravachol 10 mg by increasing consumer understanding of heart health risks, promoting long term compliance and encouraging consumer dialogue with health care providers. Program elements include a series of newsletters and postcards, and the interactive web site. Enrollment will be facilitated through broad promotion and advertising of the toll free number, the interactive web site, and enrollment forms available from physicians and pharmacists. All details of individual enrollment data will be kept strictly confidential within BMS.

Consumers enrolling in Pravachol Partners will receive a fixed set of four initial newsletters in the first six months (Month 1, 2, 4 and 6). The newsletter will follow a similar format and content to that used in PREDICT and OPTIONS. Newsletter topics will reinforce key messages of doctor involvement and follow-up, management of risk factors for heart disease and the benefits of treatment. After the initial series of newsletters, consumers in the Pravachol Partners Program will receive 2 newsletters per year providing up to date information on relevant heart health issues and continuing to encourage compliance and doctor involvement.

In addition to the newsletters, consumers enrolled in Pravachol Partners will receive a series of reminder post cards with specific key messages. The postcards will be similar to those used in the PREDICT and OPTIONS consumer use studies. The first card (week 1) reinforces the key message to consult a doctor to discuss cholesterol levels and risk factors before using Pravachol 10 mg. The second card (week 5) reminds the consumer to schedule a follow-up physician visit. The third card (month 5) reminds the consumer about the importance of controlling their risk factors for heart disease and the need for additional physician interaction should the number of risk factors increase. The fourth card (month 11) reminds the consumer to schedule his or her annual physical and cholesterol evaluation. Copies of the newsletters and postcards used in the PREDICT and OPTIONS studies can be found in Appendix I. Consumers can discontinue their participation in the Pravachol Partners Program upon their request. The Pravachol Partners Program will be monitored and refined over time to ensure that it continues to meet consumers' needs.

BMS plans to collaborate with key health care constituency groups to conduct worksite and community outreach programs, particularly among under-served populations. These programs are intended to increase awareness of health risks associated with elevated cholesterol and to encourage action in screening and intervention.

Physician and Other Health Professionals Program

Physicians will continue to play an important role in the OTC treatment of hypercholesterolemia. Consequently, BMS is committed to a substantial program of physician education and to creating tools that facilitate a physician/patient dialogue regarding high cholesterol. These programs will go to a wide audience of physicians with practice specialties in Family Practice, Internal Medicine, Cardiology and Obstetrician-Gynecology. In addition, detection, evaluation and treatment of high blood cholesterol by non-physician professionals have been accomplished by nurses (Ref. 33), clinical pharmacists with physician-written prescriptions (Ref. 34), multidisciplinary teams (Ref. 35) and by retail pharmacists (Ref. 36). Accordingly, a variety of programs will be made available to other health care professionals with an interest in creating greater awareness, understanding and action about cholesterol and it's health effects. These efforts will be designed to complement, not supplant the critical role of the physician in the management of hypercholesterolemia and heart disease.

Physician Program Elements

Product Monographs will be disseminated and will discuss the role of Pravachol 10 mg in the management of elevated cholesterol. The monograph will also include general background information on the pathology and management of hypercholesterolemia.

Physicians will receive patient starter kits to distribute. These kits will contain a 1 week supply of Pravachol 10 tablets, and, similar to the retail starter kits, will include education materials and incentives to promote appropriate use. "Tips from your doctor" will be included on the back panel of the starter kit and will remind consumers to schedule a follow-up visit as directed in the labeling to ensure that their cholesterol levels are at desirable levels.

A portion of the interactive web site will be dedicated to providing additional information and links of interest to health care professionals.

Physicians will have the opportunity to earn Continuing Medical Education (CME) credits on such topics as the treatment of a primary prevention population, compliance and evolution of NCEP guidelines.

Other Healthcare Professionals' Program Elements

A New Product Bulletin will be provided to give background information including pathology of hypercholesterolemia, management of hypercholesterolemia and use of Pravachol 10 mg (mechanism of action, dosage and administration, efficacy, adverse effects). It will also provide answers to commonly asked questions from patients concerning Pravachol 10 mg.

Information will be provided to the Handbook for Nonprescription Drugs, a pharmacists' handbook for nonprescription drugs, to create a chapter on cholesterol lowering drugs. These chapters typically include: assessment criteria; pharmacoepidemiology of the condition; etiology of the condition; pathophysiology of the affected system; signs and symptoms of the condition; drugs indicated to treat the condition; contraindications to drug use; adverse effect profile; drug interactions and potential clinical consequences; product selection guidelines; administration and dosage guidelines; and guidelines for patient education and counseling.

Healthcare professionals will be given the opportunity to earn CME credits in accordance with their individual profession.

VIII. POST MARKETING SURVEILLANCE PROGRAM

Post launch, BMS is committed to proactively monitor the OTC environment in order to modify and optimize its consumer and health care provider educational programs. Collection of adverse events will be performed via traditional channels (e.g., toll-free number). As required, periodic reports will be submitted to the NDA. Separately, a post-marketing market research study will be conducted. The purpose of this study is to gather and analyze data on the impact of non-prescription statins on the level of

cholesterol awareness, concern and treatment among the general population and among a sub-set of prescription and non-prescription statin users. Key elements to be monitored in this study include cholesterol-related beliefs and behaviors, including prevalence of cholesterol testing and physician-patient interaction. An outline of the proposed study is provided below.

Impact of Expanded Statin Therapy Study

The primary objective of this study is to monitor and draw conclusions from the potential range of behaviors in a real world setting. It will be particularly important for BMS to identify inappropriate behaviors and their consequences. In order to accomplish these goals, the post marketing study will closely monitor cholesterol related beliefs and behaviors (including physician-patient interactions) among OTC statin users. The study will also measure changes in cholesterol related awareness, utilization and physician involvement pre and post OTC availability among the general population, Rx users, and adopters of new OTC statins.

Three telephone surveys will be conducted among a nationally representative sample of adults 18 years of age or older. The first survey will establish baseline data on non-users and Rx users of statins and will occur prior to wide distribution of OTC statin therapy. Two follow-up surveys (at 6 and 12 months from the beginning of broadcast advertising) will assess changes in beliefs and behaviors and will include non-users, Rx users and OTC users of statins.

Subjects for each of the three surveys will be selected randomly from all available residential telephone in the contiguous United States. All data will be weighted on an individual multifactorial basis to give appropriate population representation to key demographic and geographic variables (age, gender, income, region, race, etc). The current population survey from the US Census Bureau is used to determine the weighting targets for each of the key variables.

The target population for the first survey will be 1000 adults from the general population. Among the general sample of 1000 adults, it is estimated that approximately 60 will be Rx users and 940 will be non-users. The Rx statin user group will be augmented to yield a total of 400 users. The second and third studies will also be conducted among 1000 adults from the general population and augmented to yield a total 400 Rx users and 400 OTC statin users.

The nationally representative sample of 1000 adults will conservatively yield a confidence interval of ± 3.1% at the 95% confidence level (assuming estimated responses at the 50% level). For the Rx statin and OTC statin user samples, the confidence interval at the 95% confidence level would conservatively be ± 4.9%.

The following information will be collected:

- Demographics; CHD risk factors, health care status, education, income, and ethnicity.

- Cholesterol related health knowledge/beliefs; general cholesterol knowledge, connection between cholesterol and CHD, level of cholesterol concern, awareness of and attitudes toward cholesterol lowering products.

- Cholesterol related health behaviors; methods used to lower cholesterol, cholesterol testing, and physician consultations.

BMS is committed to fostering the safe and appropriate use of OTC Pravachol. The proposed post-marketing surveillance program will carefully monitor the marketing and educational programs outlined in Section VII and VIII. Data from the post-marketing surveillance program will identify any unanticipated issues and will be used to modify consumer communication and education programs accordingly.

IX. SUMMARY

Safety

The review of the safety experience with pravastatin encompasses over 22 million patients years of use (90% at doses above the proposed OTC dose) and more than 100,000 patient years of clinical trial experience (mostly with the 40 mg dose). The data from this extensive safety database allows one to conclude:

- The adverse event profile of pravastatin in doses of 10-40 mg per day in short and long term clinical trials, in real world prescription use, and in simulated OTC environments is benign and appropriate for OTC availability.

- Because pravastatin is not metabolized by the cytochrome P450 system to a clinically significant extent, there is an extremely low risk of drug interactions, which has been confirmed by an extensive array of pharmacokinetic studies and clinical experience.

- Doses of 160 mg/day (16 x the proposed OTC dose) have been shown to be safe and well tolerated in clinical trials of 6 weeks in duration. Overdoses of greater than 1000 mg of pravastatin (> 3 OTC cartons containing a 1 month supply) were observed in Post Marketing Surveillance; and there were no clinically significant transaminase of CPK elevations. The OTC package will consist of 28 doses packaged in calendar pack blister cards. This is designed to not only to maximize compliance, but make overdose very unlikely.

- Preclinical and clinical data support that Pravachol 10 is safe if taken inadvertently by a pregnant woman. Oral reproductive toxicology animal studies have found no untoward reproductive or teratogenic effects, embryo-fetal toxicity or anatomic abnormalities associated with high doses of pravastatin. There have been 43 reports of pregnancies in Post Marketing Surveillance, and the outcome is known in 29. There were 5 abortions (3 spontaneous and 2 elective). Of the 24 cases with known

outcomes carried to term, there were no congenital malformations; in many of these cases the mothers took pravastatin well into the first trimester, and, in some cases, took for the majority of the pregnancy. The average birthweight of all newborns did not significantly differ from the average weight of newborns in the US.

- There is no difference between pravastatin 40 mg and placebo in the development of liver function abnormalities. This is seen in subjects with normal baseline liver function tests as were as those with pre-existing mild liver function abnormalities who would be representative of the public at large with mild asymptomatic liver disease. Based on these data, biochemical monitoring of liver function tests is unnecessary.

- Symptoms referable to the musculoskeletal system are mild and similar to placebo in clinical trials. In the 10 mg dose response studies there were no musculoskeletal deaths, serious adverse events or reports of myopathy. Musculoskeletal adverse events were less frequent in the pravastatin-treated subjects vs. placebo-treated subjects (16% vs. 24%, $p = 0.049$). In the Prava 3 analysis of Pravachol 40 mg vs. placebo, the incidence of musculoskeletal system adverse events was not significantly different between the treatment groups. There were no cases of myopathy or documented rhabdomyolysis. In the long term experience, where each subject had a mean of 12 determinations of CPK levels, there was no difference in post baseline abnormalities of CPK, either overall, or by severity, between Pravachol 40 mg and placebo. In post marketing surveillance, serious adverse events of the musculoskeletal system have been rare. There have been 122 cases of rhabdomyolysis reported worldwide for all doses; 27 of these were reported in the US, none of which occurred with the 10 mg dose. Twenty percent (20%) of the reported cases occurred in patients taking concomitant fibrate medications and many others were associated with rhabdomyolysis. The profile of musculoskeletal adverse events in the consumer use trials was benign.

The OTC package label warns consumers to report symptoms of myalgias and this was overwhelmingly understood by 93% of respondents in the in Label Comprehension Study. Moreover, the OTC label tells consumers not to speak to a physician or pharmacist if they are taking other prescription lipid lowering medications.

- The hepatic profile of Pravachol supports OTC status and elimination of biochemical monitoring of hepatic function. In the Prava 3 analysis there were no deaths due to hepatic failure; the incidence of adverse events that were serious, that led to discontinuation, and overall, were rare and occurred in the same percentage of Pravachol 40 mg vs placebo treated patients. In order to access more fully the degree of laboratory abnormalities occurrences for ALAT and ASAT, an assessment of post-treatment abnormalities overall and by ranges of severity was performed in 18,637 patients for ALAT and 11,704 patients for ASAT who both had a mean of 13 evaluations performed. Overall, there were no differences in post-baseline abnormalities of ALAT (8.8% pravastatin vs 8.2% placebo, CI 95%; -0.21, 1.42) or ASAT (4.4% pravastatin vs 4.0% placebo, 95% CI: -0.39, 1.11) overall, or in any range of severity. In the 579 subjects (3%) in the Prava 3 cohort who had mild abnormalities of ALAT and/or ASAT at baseline, there was no difference between pravastatin-treated vs placebo-treated subjects in the incidence of post baseline abnormalities, either overall or by ranges of severity. There were no treatment differences noted for subjects ≥ 65 (n = 4,338) or ≥ 70 (n=1,628) or when assessed by gender. These data support the safety of Pravachol in the broad spectrum of the population, including those with mild asymptomatic liver disease. In the post marketing surveillance database there have been 6 deaths reported attributable to the hepatobiliary system: 3 were due to metastatic Cancer, 2 were due to alternative drug toxicity (diclofenac, trazodone) and 1 report contained incomplete data. Serious AEs were rare.

In consumer use studies, transaminase elevations were rare and in the range of 1.2-2.2 x ULN; in most cases they normalized while treatment was continued.

The OTC package label warns people with liver disease, or those who consume 3 or more alcoholic drinks per day to "Do not use". This was understood by 80% of respondents in the Label Comprehension Study.

Efficacy of Pravachol 10 mg

A review of the data supports the biological efficacy and safety of the Pravachol for use in an OTC environment, and consumer use studies demonstrate that Pravachol 10 mg will be used appropriately in an OTC environment. In the 10 mg dose response studies, a statistically significant and clinically meaningful reduction in LDL-C, of 18% to 22% was seen. In PREDICT, a similar reduction of LDL-C was achieved at 8 weeks and maintained over 1 year; this reduction in LDL-C brought 83% of the OTC population to their NCEP defined LDL-C goals.

Consumer Use

The consumer use program, consisting of the Label Comprehension Study, PREDICT and OPTIONS was designed to assess whether consumers would understand and act in accordance with the key label messages so that:

- The population that utilizes the product is, indeed, the intended population.
- The consumer maintains involvement in the health care system
- The OTC consumer returns for appropriate follow up
- The safety and efficacy profile of Pravachol 10 mg in an OTC setting is similar to a prescription setting.

To evaluate these questions, 3 studies were conducted among varied populations. The Label Comprehension Study was a mall intercept study conducted among people who *a priori* were not required to have interest in or knowledge of cholesterol or other CHD risk

factors. This study was conducted in 20 geographically diverse communities and augmented for low literacy (27% of the respondents read below 9th grade level).

PREDICT was also carried out in 20 diverse communities and advertised broadly in both print and broadcast media, telling people that if they were generally healthy and their "cholesterol was 200-240 mg/dl they may be able to purchase a prescription medication without a prescription. In order to simulate an environment where consumers could freely purchase Pravachol 10 mg, the subjects were randomized to either an OTC environment (where Pravachol 10 mg was available for purchase) or a prescription environment prior to any knowledge about their medical conditions or lipid status. After randomization, there was no further contact with subjects for 6 months. Eight percent (8%) of the randomized population read below 9th grade level.

OPTIONS assessed the behavior of participants who were able to purchase Pravachol 10mg in their own pharmacies. The study was conducted utilizing the participants' own "non-research" primary care physicians. In order to access medical records and collect reliable data in the absence of study physicians, health maintenance organization (HMO) populations were chosen; these consisted of both Individual Physician Association (IPA) and staff model HMO's. Thus, while there was no contact with subjects for three months after enrollment, patient charts could be reviewed for medical history, laboratory parameters, and CHD risk factor profile, confirmation of physician contact and adverse events. Twelve percent (12%) of subjects enrolled read below 9th grade level.

<u>Baseline Findings</u>

- There is a strong interest in the problem of hypercholesterolemia. Sixty-one percent (61%) of the general population, as reflected in the Label Comprehension Study were concerned about cholesterol. In PREDICT , more than 10,000 subjects responded to the advertisement within 6 months. In OPTIONS, 782 HMO subjects were recruited

in less than 15 weeks, and 52% were willing to pay out of pocket for OTC medication.

- Subjects interested in the OTC proposition, as reflected by the Randomized population in PREDICT and the Enrolled population in OPTIONS were motivated and physician oriented: 83% and 96% respectively saw their physician yearly and 25% and 31% respectively had seen the physician specifically about cholesterol. Seventy-two percent (72%) of PREDICT Subjects had prescription coverage.

- The majority of subjects were aware of having elevated cholesterol. Twenty-five percent (25%) of PREDICT and 23% of OPTIONS participants aware for > 5 years of elevated cholesterol. Most had implemented lifestyle changes to manage cholesterol levels. Fifty-six (56%) of PREDICT subjects and 58% of OPTIONS subjects reported modifying their diet (in PREDICT, where an objective tool [MEDFICTS] was used to categorize AHA diet status, 81% of subjects were following an AHA diet, consistent with dietary trends reported in National Surveys [Ref. 38]). In both PREDICT and OPTIONS, approximately 50% of women were taking hormone replacement therapy. Nonetheless, subjects were using prescription lipid lowering medications infrequently: in PREDICT, only 9% were currently using prescription medications and in OPTIONS, 16% were utilizing Rx therapies. In contrast, in 18% of participants in PREDICT and 26% of participants in OPTIONS indicated they were currently taking non-prescription therapies to manage cholesterol.

- Despite interest and access to health care, subjects were infrequently at their ideal cholesterol level: in PREDICT only 10% and in OPTIONS only 27% of participants with a prior cardiac event had an LDL-C < 100 mg/dl. In the primary prevention group < 30% of PREDICT subjects and < 25% of OPTIONS subjects had an LDL-C < 130 mg/dl.

- Participants were able to self-select appropriately based on their CHD risk factor and lipid profiles. In PREDICT and OPTIONS, 95% and 94% of respondents to the advertisement, respectively, were free of CHD; 86% of the PREDICT population and 85% of the OPTIONS population who had lipid levels measured had a baseline total-C > 200 mg/dl.

Results

- Subjects overwhelmingly understood label messages (Label Comprehension Study) and the vast majority behaved appropriately (PREDICT and OPTIONS). In the Label Comprehension Study open-end and closed-end (multiple choice) comprehension, 95% and 94% of subjects, respectively, indicated they would "see their doctor" before using Pravachol 10 mg. In PREDICT, 90% of OTC subjects demonstrated appropriate behavior: 77% of the subjects who purchased Pravachol 10 mg consulted a physician within 2 months of product use (the primary endpoint); an additional 5% of subjects consulted the physician, but outside the 2 prespecified month window; and 8% never consulted but never took medication. Of the 10% of subjects who took medication and never consulted, no serious adverse events occurred. In OPTIONS, 93% of subjects who purchased OTC Pravachol 10 mg exhibited appropriate behavior: 44% had a documented consultation with the physician within 2 months of product use (the primary endpoint); an additional 5% consulted the physician, but outside the 2 month window. In addition, there were 32% of subjects who took Pravachol 10 mg, did not consult but appropriately self-selected according to pre-specified criteria and 12% did not consult but did not take medication. Because this was a "naturalistic" study utilizing the subjects own (non-research) primary care physician, patient charts may have been incomplete; by the subjects' self-report, 58% contacted the physician, 53% within 2 months of product use and 5% outside this window. Of the subjects in the Purchase population who took medication and did not specifically consult their physician about Pravachol 10 mg, 75% had discussed their

cholesterol problem with their doctor within 6 months of starting the OPTIONS study.

- In the Label Comprehension Study, understanding of the primary objective of "see the doctor" was the same for the < 9^{th} grade and ≥ 9^{th} grade literacy subgroups and across the other predefined subgroups of age, race and gender.

In PREDICT, behavior to consult a physician was the same for men and women and subjects in the < 9^{th} grade vs. ≥ 9^{th} grade literacy groups. Overall appropriate behavior was slightly lower in the minority groups. Black and Hispanic subjects were somewhat less likely to consult a physician, although the sample size in these demographic groups was small due to lower purchase interest.

In OPTIONS, behavior of pre-defined subgroups (gender, race, and literacy) was similar to the Purchase population overall, with 90% ± 5% demonstrating appropriate behavior.

- In PREDICT, where a randomized OTC cohort could be compared to an Rx cohort the following was seen:

  - Behavior of OTC subjects was as good as Rx subject in follow up with physician after the start of therapy: 85% of OTC subjects vs. 83% of Rx subjects (p=NS). Behavior was similar across the subgroups. In addition, longer term follow up was similar in both groups. The behavior is consisted with results of the Label Comprehension Study, were 82% of respondents indicated that cholesterol levels should be rechecked at 8 weeks and 1 year, respectively.

  - For qualified participants who took at least one dose of Pravachol 10 mg a statistically significant and clinically meaningful reduction in LDL-C was seen at 8 weeks in both the OTC and Rx groups, (-18% vs. –19%, p=NS, C.I. –1.5%, 3.0%) and was sustained at 6 months. Importantly, 83% OTC and 77% Rx

subjects (p= 0.544) achieved their NCEP defined LDL-C goal. In the PREDICT Extension Protocol, 52% of OTC and 53% of Rx participants remained on therapy for 1 year. LDL-C reduction was 22% at weeks 8, 24, and 48 in this cohort.

- Consistent with results of long and short term clinical trials comprising over 64,000 patient years of exposure to pravastatin and 22 million patient years of post marketing exposure, the safety profile of Pravachol in an OTC setting was excellent. In PREDICT, the overall incidence in adverse events was similar between the OTC and Rx groups, 27% vs. 41% and 90% of the AEs were mild to moderate in nature. There were no deaths and none of the serious adverse events were related to Pravachol 10 mg therapy. Importantly, there were no cases of myopathy, drug-drug interactions or significant transaminase abnormalities. In OPTIONS, the overall incidence of AEs was 25%, > 99% of which were mild to moderate in nature. There were no deaths or serious AEs experienced related to OTC Pravachol 10 mg therapy.

These results are consistent with the Label Comprehension Study, where 93% of respondents understood the need to report adverse experiences (muscle pain) to a doctor.

- Utilization of OTC Pravachol 10 mg by the appropriate OTC population was assessed in both PREDICT and OPTIONS.

<u>Shift from prescription to OTC Pravachol 10 mg Therapy</u>

- With regard to consumers understanding that Pravachol 10 mg should not be used as a replacement for their current prescription lowering therapy, PREDICT demonstrated that 2% of the 183 subjects already taking prescription lipid lowering medication at baseline shifted to OTC Pravachol 10 mg. In OPTIONS, 11% of the 99 subjects taking prescription lipid lowering therapy at baseline shifted to OTC Pravachol 10 mg.

Subjects Requiring More Aggressive Therapy

Of those 321 subjects in PREDICT who qualified for more aggressive prescription therapy at baseline, 46% reported having seen their personal physician and 29% had begun taking prescription lipid lowering medications when contacted for 6 month follow up status. There was no difference between the OTC and Rx groups.

X. CONCLUSIONS

There is a need for additional approaches to improve treatment of hypercholesterolemia. Despite a significant increase in cholesterol awareness, adoption of diet modification and knowledge about prescription lipid lowering therapies, it is estimated that nearly 38 million adults with mildly elevated cholesterol levels have not reached their LDL-C goal with dietary intervention alone and therefore remain at long-term risk for developing CHD. Consumers are increasingly pursuing non-prescription remedies to manage their cardiovascular disease risks: consumer research indicates that in 1999 nearly twice as many Americans used non-prescription lipid lowering remedies compared to those who used cholesterol lowering prescription medication, and this has been confirmed in consumer research studies.

Accordingly, we conclude that the OTC availability of Pravachol 10 mg, with regulated, informative labeling will provide lower-risk, preventive oriented consumers with a safe and effective treatment to help them attain their NCEP defined goals. This approach provides an option for the growing population interested in self-care and has the potential to complement and broaden current efforts in lowering cholesterol levels in the US population.

XI. REFERENCES

1. Hansten PD. Understanding drug-drug interactions. *Science & Medicine* January/February: 16-25.

2. 1999 Heart and Stroke Statistical Update. American Heart Association, Dallas, Texas 1998.

3. Grundy SM. Primary Prevention of Coronary Heart Disease; Integrating Risk Assessment with Intervention. *Circulation* 1999; 100: 988-998.

4. Kannel WB. Range of Serum Cholesterol Values in the Population Developing Coronary Artery Disease. *Am J Cardiol* 1995; 76: 69C-77C.

5. Levine GN, Keaney JF, Vita JA. Cholesterol Reduction In Cardiovascular Disease. Clinical Benefits and Possible Mechanisms. *N Engl J Med* 1995; 332: 512-521.

6. Chen ZM, Peto R, Collins R, MacMahon S, Lu J, Li W. Serum cholesterol and coronary heart disease in population with low cholesterol concentrations. *BMJ* 1991; 303: 276-282.

7. Sacks FM, Pfeffer MA, Moye LA, Rouleau, JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wum CC, Davis BR, Braunwald E. for the Cholesterol and Recurrent Events Trial Investigators. The Effect of Pravastatin on Coronary Events After Myocardial Infarction in Patients with Average Cholesterol Levels. *N Eng J Med* 1996; 335: 1001-1009.

8. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of Cardiovascular Events and Death with Pravastatin in Patients

with Coronary Heart Disease and a Broad Range of Initial Cholesterol Levels. *N Eng J Med* 1998; 339: 1349-1357.

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

10. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKittop JH, Packard CJ for the West of Scotland Coronary Prevention Study Group. Prevention of Coronary Heart Disease with Pravastatin in Men with Hypercholesterolemia. *N Eng J Med* 1995; 333: 1301-1307.

11. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langenforfer,A, Stein EA, Kruyer W, Gotto AM, for the AFCAPS/TexCAPS Research Group. Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women with Average Cholesterol Levels. *JAMA* 1998; 279(20): 1615-1622.

12. National Cholesterol Education Program (NCEP). Second Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). NIH Publication No.93-3095; September 1993.

13. Stamler J, Wentworth D, Neaton JD, for the MRFIT Research Group. Is Relationship Between Serum Cholesterol and Risk of Premature Death From Coronary Heart Disease Continuous and Graded? Findings in 356,222 Primary Screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986; 256: 2823-2828.

14. Castelli WP. Cardiovascular disease in women. *Am J Obstet Gynecol* 1988; 158: 1553-1560.

15. Ansell B, Watson K, Fogelman A. An Evidence-Based Assessment of the NCEP Adult Treatment Panel II Guidelines. *JAMA* 1999; 282 (21): 2051- 2057.

16. Sempos CT, Cleeman JI, Carroll MD, Johnson CL, Bachorik PS, Gordon DJ, et al. Prevalence of High Blood Cholesterol Among US Adults: An Update Based on Guidelines From the Second Report of the National Cholesterol Education Program Adult Treatment Panel. *JAMA* 1993; 269 (23): 3009-3014

17. Hoerger TJ, Bala MV, Bray JW, Wilcosky TC, LaRosa J. Treatment Patterns and Distribution of Low-Density Lipoprotein Cholesterol Levels in Treatment-Eligible United States Adults. *Am J Cardiol* 1998; 82: 61-65.

18. IMS data; National Prescription Audit, Competitive Media Reporting: January 2000.

19. Pravastatin Package Insert Revised May 1998; 5154dm-09.

20. Acute Toxicological Study in Dogs Treated Orally with CS-514 (Sankyo Report April 11, 1984) NDA 19-898, Final Study Report Submitted September 7, 1988.

21. Wiklund O, Angelin B, Bergman M, Berglund L, Bondjers G, Carlsson A, Lindén T, Miettinen T, Ödman B, Olofsson S, Saarinen I, Sipilä R, Sjöström P, Kron B, Vanhanen H, Wright I. Pravastatin and Gemfibrozil Alone and in Combination for the Treatment of Hyperchlosterolemia. *Am J Med* 1993; 94: 13-20.

22. Athyros VG et al. Safety and efficacy of long-term statin-fibrate combinations in patients with refractory familial hyperlipidemia. *Am J Cardiol* 1997; 80: 608-613.

23. Iliadis E, Rosenson R. Long-Term Safety of Pravastatin-Gemfribrozil Therapy in Mixed Hyperlipidemia. *Clin Cardiol* 1999; 22: 25-28.

24. Ellen RLB, McPherson R. Long-Term Efficacy and Safety of Fenofibrate and a Statin in the Treatment of Combined Hyperlipidemia. *Am J Cardiol* 1998; 81: 60B-65B.

25. Davignon J, Roederer G, Montigny M, Hayden M, Tan MH, Connelly P, Hegele R, McPherson R, Lupien P, Gagné C, Little JA, Colin P. Comparative Efficacy and Safety of Pravastatin, Nicotinic Acid and the Two Combined in Patients with Hypercholesterolemia. *Am J Cardiol* 1994; 73: 339-345.

26. Pasternak R.C. et al. Ann Internal Med 1996; 125:529-540.

27. Department of Health and Human Services, Food and Drug Administration. Over-the-Counter Human Drugs; Labeling Requirements. Final Rule: *Federal Register* March 17, 1994; 64: 13253-13303.

28. NDA 19-898, Supplement S-019 Submitted on August 19, 1997 and Approved on May 20, 1998.

29. Murphy PW, Davis TC, Long SW, Jackson RH, and Decker BC. Rapid Estimate of Adult Literacy in Medicine (REALM): A quick reading test for patients. *J of Reading* 1993; 37 (2): 124-130.

30. Pravachol (pravastatin sodium) Tablets. NDA 19-898 Submitted September 7, 1988.

31. Srinath U, Shacklock F, Shannon BM, Mitchell DC, Kris-Etherton PM, Scott L, Jaax S, Pearson TA. MEDFICTS- A Dietary Assessment Instrument for Evaluating Fat and Cholesterol Intake. Presented at the 66th Scientific Session of the American Heart Association, Atlanta, GA. *Circulation* 1993; 88: I-634.

32. Srinath U, Shacklock F, Scott LW, Jaax S, Kris-Etherton PM. Development of MEDFICTS- A Dietary Assessment Instrument for Evaluating Fat, Saturated Fat, and Cholesterol Intake. *J Am Diet Assoc* 1993; 93S: A105.

33. Blair TP, Bryant FJ, Bocuzzi S. Treatment Of Hypercholesterolemia By A Clinical Nurse Using A Stepped-Care Protocol In A Nonvolunteer Population. *Arch Intern Med* 1988; 148: 1046-8.

34. Furmaga EM. Pharmacist Management Of A Hyperlipidemia Clinic. *Am J Hosp Pharm* 1993; 50: 91-5.

35. Schectman G, Hiatt J, Hartz A. Evaluation Of The Effectiveness Of Lipid-Lowering Therapy (Bile Acid Sequestrants, Niacin, Psyllium And Lovastatin) For Treating Hypercholesterolemia In Veterans. *Am J Cardiol* 1993; 71: 759-765.

36. Bluml B, McKenney J, Cziraky M, Elswick R. Interim Report From Project ImPACT: Hyperlipidemia. *J Am Pharm Assoc* 1998; 38(5): 1-6.

37. IMS data; Nielsen Retail and Household data; 1999 Gallup Focus Report on Consumer Use and Reaction to Total Cholesterol-Lowering Prescription Medication; 1999 Omnibus Study on Total Cholesterol Attitudes and Behavior: data on file.

38. National Center for Health Statistics. Healthy People 2000 Review, 1998-99. Hyattsville, Maryland: Public Health Service 1999.