OTC MEDICAL OFFICER'S REVIEW

NDA #: 21-198
Drug name: Pravachol® (pravastatin sodium) 10 mg Tablets

Sponsor: Bristol-Myers Squibb
Worldwide Consumer Medicines
1350 Liberty Avenue
Hillside, New Jersey 07205
Tel: (908) 851-6119

Pharmacologic Category: HmG-CoA reductase inhibitor
Proposed Indications: To lower mildly elevated cholesterol
Dosage Form and Route of Administration: Take one 10 mg tablet orally every day, at bed time

Submission Date: December 23, 1999
Review Date: June 1, 2000
Reviewer: Daiva Shetty, MD

Table of Contents:

Material Reviewed:

1. Actual Use Study PREDICT, Protocol # 800-01-97
2. Actual Use Study OPTIONS, Protocol # 800-03-97
3. Safety and efficacy data from the above mentioned studies

This is a clinical review of NDA 21-198 Pravachol 10 mg tablets for prescription (Rx) to over-the-counter (OTC) switch. Global efficacy and safety evaluation for Pravachol 10 mg will be covered by the reviewers in the Division of Endocrine-Metabolic drugs HFD-510. The Label Comprehension study will be reviewed by Dr. K. Lechter in the Division of Drug Marketing, Advertising and Communication (DDMAC) HFD-42.

Background:

Pravastatin sodium, a cholesterol lowering agents, is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor with the site of its action in the liver.

Bristol-Myer Squibb Company is requesting Agency approval to market 10 mg strength tablets of pravastatin sodium called Pravachol as an OTC drug product for the following indication: to lower mildly elevated cholesterol (total cholesterol between 200 and 240 mg/dl and LDL cholesterol over 130 mg/dl) in generally healthy adults. In support of this Rx to OTC switch NDA application, the sponsor has submitted for the consideration of the Agency, the results of two actual use trials, one label comprehension study, and a risk benefit analysis.

Current recommendations for treatment of hypercholesterolemia are based on National Cholesterol Education Program (NCEP) guidelines* as described in Table 1.

Table 1. LDL Cholesterol Treatment Guidelines

	Levels of LDL for Beginning Therapy, mmol/L (mg/dl)		
	Diet	Drugs	Goal
No CHD and less than two risk factors	≥4.1 (≥160)	≥4.9 (≥190)	<4.1 (<160)
No CHD but two or more risk factors	≥3.4 (≥130)	≥4.1 (≥160)	<3.4 (<130)
Presence of CHD	>2.6 (>100)	>3.4 (>130)	<2.6 (<100)

Risk factors include family history of premature coronary heart disease (CHD) (below age of 55 years in a male parent or sibling or below 65 in female relative), hypertension, cigarette smoking, diabetes mellitus, and low HDL (<35 mg/dl). In addition, age (men >45 years, women >55 years, or younger women with premature menopause without estrogen replacement) are also at risk. HDL cholesterol > 60 mg/dl is a negative risk factor, i.e., one other factor can be negated by a high HDL cholesterol level. According to the guidelines, assignment of patients to the possible treatment categories should be done on the basis of the average of two LDL-cholesterol determinations to account for biologic variations.

Regulatory History:

The original IND for pravastatin was submitted to FDA on October 3, 1985. The initial NDA #19-898 for pravastatin was submitted to FDA on September 7, 1988, which summarized data supporting use of Pravastatin in hyperlipidemia at doses of 10-40 mg/day. Approval in the United States was granted on October 31, 1991, and the product was launched under the trade name Pravachol®. Pravastatin is currently approved in the U.S. as an adjunct to diet to reduce

* Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). National Cholesterol Education Program. U.S. Department of Health and Human Services. NIH. September 1993.

elevated total cholesterol, low-density lipoproteins cholesterol, and triglyceride levels in patients with primary hypercholesterolemia and mixed dyslipidemia (Frederickson Type IIa and IIb) who do not respond adequately to dietary modifications. In addition, indications for primary and secondary prevention of coronary events were added in 1996-1998.

IND #55,100 was submitted to the Agency on January 27, 1998 to support the switch of Pravachol 10 mg tablets from Rx to OTC status. At that time Agency expressed significant concerns about appropriateness of Pravachol as an OTC switch candidate and did not support further development[†].

Foreign marketing experience:

Pravachol is marketed as a prescription drug in over 90 countries. It has not been withdrawn from any markets for reasons of safety or efficacy. As of June 1999, over 12 billion tablets have been dispensed worldwide representing an estimated global patient exposure of 22 million patient years. Currently, in the US approximately 10 % of Pravachol prescriptions are written for 10 mg tablets. Pravachol is not sold as an over-the-counter drug in any other country.

Clinical Studies:

Overview of Efficacy:

Only efficacy data from actual use trials will be discussed in this review. Global efficacy is reviewed by the Division of endocrine-metabolic drugs (HFD-510) and will be covered by their reviewers.

Review of Actual Use Trials

Result of two actual use trials for Pravachol 10 mg tablets are submitted in support of this application: PREDICT 800-01-97 and OPTIONS 800-03-97.

1. PREDICT 800-01-97

Objectives

Primary objective:
To determine the proportion of OTC randomized subjects who, having purchased OTC Pravachol 10 mg, consult a physician within two months of using medication.

Secondary objectives:
1. To compare the proportions of subjects in the OTC and Rx groups who:
   - consult a physician for follow-up after an initial visit
   - comply with proper study medication dosage regimen

[†] Guidance for Industry. OTC Treatment of Hypercholesterolemia. FDA.CDER. September 1997

2. To compare the safety of OTC Pravachol 10 mg to that of Rx Pravachol
3. To compare the cholesterol lowering effects of Pravachol in OTC and Rx subjects

Tertiary objective:
To determine the proportion of subjects who maintain appropriate lifestyle behaviors after exposure to Pravachol whether or not they take the product.

Design

This was a multicenter, randomized, parallel, open-label, actual use trial designed to simulate the OTC and Rx environments.

The study was performed by 20 professionally trained (non-medical) interviewers and 57 study physicians.

Subjects were recruited via radio and print advertising in 20 geographically diverse communities. Advertising indicated 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 a prescription. In addition to advertising in local newspapers and radio stations, advertisements were strategically placed on Hispanic and Gospel radio stations as well as in culturally oriented magazines to ensure that no specific subgroup was excluded from participation in the study. The advertisement provided a toll free number where operators directed subjects to a local screening site.

The call center was staffed with operators who were trained to receive calls and to utilize a standard script which was designed to provide directions to the screening site and the hours of operation. The operators were trained to inform subjects that the interviewer at the screening site would answer their questions, and they allowed the subject to make a screening site appointment by phone. The operators were also provided with information that included: the definition of women of childbearing potential, the medication name, and a brief description of the study including the amount of time the subject would spend at the screening site. This information was provided only if specific questions relating to those subjects were asked. During the phone screening, subjects were excluded from further information and participation if they were women of childbearing potential.

Comments
No detailed information was provided on the background of the study investigators. Even though the phone screening center was set up to direct possible participants into the study/screening site, it also served as a screening for potential exclusion criteria. These calls were not recorded and it is not clear what was the disposition of all people who called, or how many were interested but not qualified, and how many women of childbearing potential called and were excluded from the study before the enrollment.

Assessment 1

There were 24 screening sites and 57 clinic sites in 20 diverse communities throughout the USA. Screening sites were set up like "store fronts" in shopping malls (38%) and office buildings (62%). In all but one city (Portland, OR, Site # 21-001), the screening site was geographically separate from the physician's office and no medical personnel were present at the screening site.

All subjects who presented to the screening site signed an abbreviated written informed consent that permitted the interviewer to initiate the screening questionnaire. Subjects were then administered a questionnaire which collected data on demographics, cholesterol awareness, and health care status. Literacy was measured using the Rapid Estimate of Adult Literacy in Medicine (REALM) Test. Lifestyle behaviors specific to diet, exercise and smoking were also evaluated. A detailed dietary assessment was completed by use of the Meats, Eggs, Dairy, Fried Foods, In baked Goods, Convenience Foods, Table Fats, and Snacks (MEDFICTS) Questionnaire. Subjects who completed the screening questionnaire were randomized to either the OTC or Rx group. The randomization was carried out within strata defined by literacy as assessed by REALM test (low [REALM score of 60 or less] vs. normal [REALM greater than 60]). The randomization schedule was set up in blocks of eight, and within each block, randomization numbers were assigned in a 1:1 ratio. A subsequent informed consent detailing the risks and benefits associated with study participation was obtained prior to purchasing medication and/or clinic visit procedures.

Comments

Abbreviated written informed consent that permitted the interviewer to initiate the screening questionnaire has been reviewed and it was found to be adequate. REALM Literacy test used to assess medical knowledge level is widely used in label comprehension and actual use studies, and it is an acceptable tool for the study. Prior to the purchase of the drug, the screened randomized participants were provided with the main informed consent form. It emphasized the appropriateness of Pravachol and the importance of a physician's decision to use the drug. The screening, subsequent detailed questionnaires, and the main informed consent were given prior to subjects' purchasing of the drug. Information about the cholesterol awareness was given to the consumer by the sponsor, which could possibly bias subject's decision to purchase the drug. Thus, the label on the package wasn't the only factor in the decision to buy the product, as would be in a true OTC setting.

A goal of 6,000 subjects was established for enrollment, in order to yield approximately 1,950 subjects purchasing study drug in an OTC setting. In addition, it was estimated that 3,300 subjects of the 6,000 subjects enrolled would consult a study physician, 2,000 would qualify for treatment with Pravachol 10 mg, and 500 subjects would complete 24 weeks of follow-up on study medication.

Subgroups were prospectively defined by low literacy level and minority status since there is concern that subjects in these subgroups may be at increased risk for incorrect use of product. Target subgroup sample sizes of 500 randomized to OTC use and 500 purchasing study drug was planned to evaluate the primary endpoint – to consult a physician within two months after the purchase of the drug. With respect to reduction in LDL-C at 24 weeks, a subgroup sample

size of 150 subjects was targeted. It became clear early in the study that although targeted subgroups were being enrolled, their generally low interest in continued participation in the study was such that enrollment required for statistically meaningful results for the key secondary endpoints, follow-up compliance and LDL reduction, were not being achieved. Consequently, the decision was made to curtail enrollment at approximately two-thirds of that originally anticipated because without the ability to analyze targeted subgroups little was to be gained from continued enrollment of the majority population.

Following criteria were used for study population:

1. Inclusion criteria
- ≥ 18 years

2. Exclusion criteria:
- Participation in a research study within the last 30 days
- Females of childbearing potential (defined as women who have not undergone bilateral tubal ligation, bilateral oophorectomy or hysterectomy, or who are not post menopausal for ≥ 1 year [≥24 months since last menstrual cycle])
- Breast feeding females
- Less than 18 years old

OTC Group

Subjects randomized to the OTC group were shown a prototypical OTC advertisement, OTC Pravachol 10 mg package and price and were asked questions regarding their purchase interest. Those subjects who were interested in purchasing medication were then screened for inclusion/exclusion criteria. Subjects who were not interested in purchasing medication could decide to purchase at a later date or after consulting a physician. Subjects not fulfilling the inclusion criteria were withdrawn from further participation in the study.

Those subjects who continued had the option of purchasing a 1) Pravachol 10 mg starter kit which contained: a PRAVACARE educational booklet, an enrollment card for the PRAVACARE Newsletter Program, a rebate coupon for subsequent purchases, medication, and a package insert or 2) Pravachol 10 mg maintenance kit containing medication and package insert only. Medication was sold in units of two cartons, each carton contained four blister cards with seven tablets per card. Subjects were allowed an initial purchase but no subsequent purchases were allowed unless they had consulted with the physician. This procedure was implemented at the request of the IRB. Only after initial physician consultation were subjects allowed to purchase study medication at their own discretion, with or without subsequent approval from the study physician. Those subjects who wished to consult their personal physician, the study physician, or who wanted more time to decide before purchasing medication were allowed to return to the screening site to purchase medication at a later date. A card was given to subjects with a list of names, addresses and telephone numbers of participating study physicians in the area, or they could consult a study physician. All screening site personnel were instructed not to influence the subject's decision to follow-up with a physician in any way. To ensure that the screening site personnel were consistent in

implementing this practice, the following script was provided for the interviewer to recite when presenting the card to the OTC subject:
"If you choose to consult a physician while you are participating in this study, this is a list of physicians participating in this study. He/she is familiar with the study, and will be able to answer your questions and monitor your therapy appropriately".

Comments
OTC Pravachol package label used in this study was not identical to the currently designed and proposed labeling for possible OTC drug. Even though the primary objective of the study was to determine the proportion of OTC subjects who consult a physician within 2 months of using medication, the label clearly states to see the doctor before starting the treatment. The sponsor states that the initial planned enrollment was 6,000 subjects. However, the main consent form given to the participants says that planned enrollment is 9,000 subjects. Total and subgroup enrollments came up only to one half of planned.

Rx Group
Subjects randomized to the Rx group were shown a direct-to-consumer-like advertisement and were asked questions regarding their interest in taking Pravachol. Subjects who were interested in taking Pravachol were screened for inclusion/exclusion criteria. Those not fulfilling the inclusion criteria were withdrawn from further participation in the study. Those subjects who continued in the study were instructed that they must receive a prescription and were given a card with the names, addresses, and phone numbers of participating study physicians in the area they could contact if they decided to see a study physician.

Administration and Dosage
In order to simulate real OTC and Rx-like environments, subjects purchased Pravachol while participating in the study. OTC subjects could initially purchase a maximum 2 month supply of Pravachol 10 mg prior to consultation with a study physician. Rx subjects could only purchase Pravachol 10 mg with a prescription from the study physician. For both OTC and Rx participants, the study physician recommended or prescribed medication be taken in accordance with the medication labeling and the treatment guidelines outlined in Table 2.

Table 2. Treatment Guidelines

	Initiate Treatment/LDL-cholesterol mg/dl	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 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 an antihypertensive medications)
– HDL-cholesterol < 35 mg/dl
– Diabetes mellitus

More aggressive prescription therapy was recommended by the study physician if the subject met the following criteria: CHD, or no CHD and ≥ 2 risk factors not including age with a LDL-C above NCEP goal, or anyone with no CHD and a LDL-C > 190 mg/dl. The study physician provided all OTC and Rx subjects who required more aggressive prescription therapy a lipid profile results sheet containing their cholesterol levels and informed them that they should follow-up with their personal physician for further treatment.

Comments

Subjects enrolled in the study were screened for the risk factors above. Information about risk factors such as age, smoking, and family history can be easily obtained from the questionnaire. However hypertension, diabetes, serum cholesterol level or even coronary heart disease may not be obvious to the person and on many occasions, has to be diagnosed by the medical practitioner.

Assessment 2

For OTC subjects who purchased medication, this visit documented the primary objective: behavior to consult a physician. All subjects who decided to consult the study physician were evaluated for the appropriateness of Pravachol treatment. The study physician reviewed and verified the subject's profile collected at the screening site which included the medical history, risk factor profile, and concomitant medications. In addition, the study physician conducted a brief physical examination and obtained screening laboratory tests to obtain the subject's lipid profile, rule out a secondary cause of hyperlipidemia and to screen for medical conditions listed in the warnings or contraindications sections of the Pravachol label. The MEDFICTS dietary questionnaire, exercise, and smoking behaviors were also assessed. Laboratory tests included: creatinine, blood urea nitrogen (BUN), glucose, TOTAL-C, LDL-C, HDL-C, triglycerides (TG), T4 and thyroid stimulating hormone (TSH), alanine transaminase (ALT) and aspartate transaminase (AST), and serum pregnancy (females only). For subjects who initiated drug therapy prior to consulting the study physician, adverse event, dose duration and medication use information was obtained. OTC subjects who qualified for Pravachol 10 mg treatment, were instructed to begin therapy 10 mg daily in accordance with the label instructions.

Rx subjects who qualified for Pravachol treatment were given a prescription for Pravachol 10 mg once daily in accordance with the label instructions. OTC and Rx subjects who qualified were asked to schedule an 8-week follow-up visit. Subjects who did not qualify for treatment were advised not to initiate therapy or discontinue if they had already started; however, they were not required to return their medication. Subjects were given their cholesterol results and encouraged to continue healthy lifestyle habits if they were at their NCEP goal, or instructed to follow-up with their personal physician if more aggressive treatment with prescription therapy was indicated or if other medical conditions were noted that required follow up. A 6-month follow-up visit was scheduled to evaluate cholesterol action and lifestyle behaviors for all subjects, regardless of their treatment qualification status.

A randomly selected subset of subjects for whom the physician determined that Pravachol was not appropriate, was asked to return for liver function testing at Assessment 3/Week 8 in order to act as case controls to compare changes to those subjects on active treatment.

Assessment 3

For OTC and Rx subjects, this visit documented the secondary objective: follow-up with the study physician 8 weeks after the initial consult. For those subjects who consulted the study physician, a laboratory test was performed to obtain the subject's lipid profile and to assess the subject's progress. In both OTC and Rx groups, if the subject did not meet his/her LDL-C goal in accordance with NCEP guidelines after 8 weeks of therapy with Pravachol 10 mg, his/her dose was titrated to 20 mg daily. OTC subjects were given a prescription and instructed to fill it at their local pharmacy. However, this did not preclude them from returning to the screening site to purchase additional Pravachol 10 mg, to continue on Pravachol 10 mg daily, or to double their dose of OTC medication. If the newly titrated OTC subject had prescription coverage, they were eligible to enroll into the "York Benefits" program. Rx subjects continued to fill prescriptions at their local pharmacy. The "York Benefits" program covered higher doses of Pravachol if a subject was titrated. Information regarding dosing compliance, adverse events, concomitant medications, and changes in dietary behavior assessed by MEDFICTS was collected. Subjects whose dose was titrated were asked to schedule a follow-up visit at Week 16. All other subjects were asked to schedule a Week 24-study closure visit.

Assessment 3B

For OTC and Rx subjects whose dose was titrated at Assessment 3, this visit documented the secondary objective: follow-up with a study physician after dose titration. For those subjects who consulted the study physician, the same assessments made at Assessment 3 were conducted during the Assessment 3B visit. Subjects who did not reach their LDL-C goal were titrated to 40 mg daily. All subjects were asked to schedule a 24-week study closure visit.

Assessment 4

This visit was the study closure visit. An attempt was made to contact all randomized subjects. Information regarding dosing compliance, lipid profile, adverse events, concomitant medications, changes in dietary behavior assessed by MEDFICTS and exercise and smoking behaviors was collected. Subjects who failed to keep the study closure visit were contacted by phone to collect information regarding cholesterol action and awareness, and dietary, exercise and smoking behaviors. If, during the telephone contact, it was discovered that an OTC subject had purchased, taken study medication, and not consulted a physician, the subject was asked to schedule a clinic visit with a study physician for follow-up. Those subjects who could not be reached by phone were sent a brief questionnaire to collect information about cholesterol action, awareness, diet, exercise and smoking behavior and study medication use for OTC subjects who purchased Pravachol 10 mg.

Comments
Currently approved Rx Pravachol label recommends testing serum cholesterol levels prior to initiation of the therapy and four weeks later, for efficacy monitoring. In addition, according to the label, liver function tests should be performed prior to and 12 weeks following initiation of therapy or elevation of dose. This study follows different assessment recommendations. Data has not been presented to support these changes. Those subjects, whose dose was titrated to a higher level, were used only to assess compliance with the follow-up visit, after 8 weeks of last dose titration. No further analysis was performed on this population.

Endpoints

Efficacy endpoint of this study was compliance with label instructions to consult the physician initially (OTC group only) and for follow-up (OTC and Rx group) after the purchase of the drug.

Statistical Issues

All statistical analyses were performed using SAS Version 6.12 on an open VMS operating system. All statistical hypothesis testing was carried out at the 2-sided $\propto = 0.050$ level. P-values ≤ 0.050 were considered statistically significant. No adjustments were made to account for multiplicity of testing.

Homogeneity at baseline was assessed by comparing the two randomized groups within each of the four analysis populations (Randomized, OTC Purchase, Consult, and Qualified) with respect to background and demographic variables. For continuous variables, comparisons were based on analysis of variance (ANOVA) adjusting for study center and randomization stratification factor (low vs. normal literacy). For categorical variables, the Cochran-Mentel-Haenszel summary chi-square test was used to assess baseline differences, controlling for randomization stratum and study center. The efficacy analysis consisted of calculation of the 95% confidence intervals.

Results

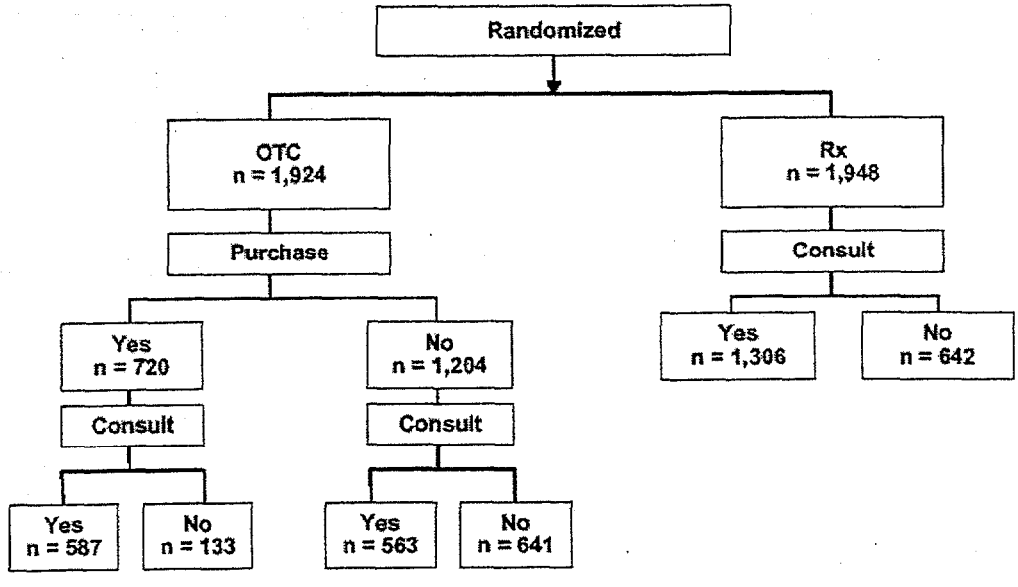
Population enrolled/analyzed

The analyses and summaries presented in the clinical report were based on the following data sets:

- Randomized Population - subjects who were randomized to either the OTC or Rx group at the screening site whether or not they took medication. This population was used to assess the baseline homogeneity of randomized groups with respect to demographic characteristics, as well as to compare OTC and Rx use with respect to compliance with lifestyle modifications.
- OTC Purchase Population - OTC subjects who purchased Pravachol 10 mg at any time during the study whether or not they took medication or qualified for treatment. This population served as the basis for the assessment of compliance to consult a physician within 2 months of product use.

- Consult Population - OTC or Rx subjects who consulted a physician (study or personal) during the study, whether or not they took medication or were qualified for treatment. This population was used to assess lipid profile, subsequent follow up with the physician, dose regimen compliance, and compliance with lifestyle modifications.
- Qualified Population - OTC and Rx subjects who consulted a physician (study or personal) during the study and qualified for Pravachol 10 mg use. This population was used to determine compliance to consult a physician for follow-up after the initial consult and compliance with the dosing regimen.
- Treated Population - OTC and Rx subjects who took any amount of study medication. This population was used to summarize adverse events and clinically significant laboratory changes.
- Qualified and Treated Population - OTC and Rx subjects who qualified for Pravachol 10 mg use and took any amount of study medication. This population was used to assess compliance with the dosing regimen.
- Dose Titrated Population - OTC and Rx subjects who qualified for Pravachol 10 mg, completed Assessment 3 and whose dose was titrated. This included OTC subjects whose dose was titrated to prescription Pravachol and Rx subjects whose dose was titrated to a higher dose. This population was used to assess compliance with the follow-up visit after a dose titration.

Figure 1. **Disposition of Randomized Population**



A total of 11,065 subjects responded to the advertisements by calling a centralized number. Operators staffing the call center informed subjects that they would have to visit the screening site to find out more information about the study, provided directions to the site and the hours of operation. Subsequently, 3,888 subjects were screened at the screening site. Approximately 80% of subjects learned of the study through advertisements and 20% were walk through. Although there is no correlation between those subjects who answered the advertisement through the call center (11,065) and those that were screened (3,888), the most common reasons for disinterest offered to the call center were: "needed more time to consider", "thought it was a

cholesterol screening program", and "the location was not convenient". Of the 3,888 subjects screened, 3,872 were randomized (1,924 OTC and 1,948 Rx). Disposition of randomized population is presented in Figure 1. One hundred and nineteen (3%) subjects were deemed ineligible to participate for the reasons listed below. Subjects may have had more than one reason for ineligibility.

- 1 (<1%) less than 18 years
- 1 (< 1%) breastfeeding
- 61 (2%) woman of childbearing potential
- 35 (1%) participated in a research study within the last 30 days
- 25 (<1%) did not have eligibility determined because the interview was discontinued

Comments

The purpose of the phone call center was to give information about the screening site and to direct interested subjects to the site. The protocol was amended about 3 months into the trial, and every subject had to answer the questions about their gender and child bearing potential prior to getting the information about the screening sites. All females were asked if they are one year post-menopausal or surgically sterile. Those who didn't meet the inclusion criteria were not given the information about screening sites. It is not clear how many of the total 11,065 who called, were women of child bearing age. No data were provided by the sponsor about the disposition of the subjects who called the phone call center. The sponsor states that only 2% (n=65) of participants were of child bearing age, however, that number comes from screened 3,888 subjects at the site. It is not known, how many would have come, if they were told on the phone, not to come. This might have been the most common reason for rejecting the participation in the study. No reasons for discontinuation of the interview were provided, by the sponsor, for the 25 ineligible subjects.

Table 3 summarizes the demographic characteristics of the randomized population. The age range was 18-88 years, 2,396 of 3,872 (62%) were male, 3,639 (94%) had at least a high school education, and 313 (8 %) read below a 9th grade reading level. Racial representation included 3,245 (84%) Caucasian, 300 (8 %) Black, 212 (5 %) Hispanic, 61 (2 %) Asian, and 45 (1 %) Native American. Although advertising was placed in media targeted at minority populations, representation of these groups in this study is somewhat lower than the national census where 13% and 11% are Black and Hispanic respectively. All geographic areas of the United states are equally represented: east 22%, midwest 24%, south 31%, west 23%. Demographically, both groups (Rx and OTC) were similar in terms of age, racial background, income, education, geographic region, except for the gender. There were more men in the OTC group vs. the Rx group 1,225 (64 %) vs. 1,171 (60 %), (p=0.02). There were also less women in the OTC group (n=697) vs. Rx group (n=777). Mean age for men was 53.6 years vs. 58.6 years for women. There was no significant difference between OTC and Rx groups regarding the age for different genders.

Table 3. Demographic Characteristics (Randomized Population)

	Statistics	OTC N = 1,924		Rx N = 1,948		Total N = 3,872		P-value
		n	%	n	%	n	%	
Age	N	1,922		1,943		3,865		0.691
	Mean	55.4		55.6		55.5		
	STD	12.1		11.7		11.9		
	Median	55		56		56		
	Min	18		19		18		
	Max	86		88		88		
Age Group	< 35	83	(4%)	76	(4%)	159	(4%)	0.952
	35 – 54	813	(42%)	827	(42%)	1,640	(42%)	
	55 – 74	915	(48%)	938	(48%)	1,853	(48%)	
	≥ 75	111	(6%)	102	(5%)	213	(6%)	
	Missing	2	(< 1%)	5	(< 1%)	7	(< 1%)	
Gender	Male	1,225	(64%)	1,171	(60%)	2,396	(62%)	0.020*
	Female	697	(36%)	777	(40%)	1,474	(38%)	
	Missing	2	(< 1%)	0	(0%)	2	(< 1%)	
Race	Asian	35	(2%)	26	(1%)	61	(2%)	0.692
	Black	148	(8%)	152	(8%)	300	(8%)	
	Caucasian	1,612	(84%)	1,633	(84%)	3,245	(84%)	
	Hispanic	103	(5%)	109	(6%)	212	(5%)	
	Native American	23	(1%)	22	(1%)	45	(1%)	
	Other	2	(< 1%)	5	(< 1%)	7	(< 1%)	
	Missing	1	(< 1%)	1	(< 1%)	2	(< 1%)	
Income	< $25,000	388	(20%)	433	(22%)	821	(21 %)	0.462
	$25,000 - $49,999	679	(35%)	658	(34%)	1,337	(35%)	
	$50,000 - $99,000	595	(31%)	576	(30%)	1,171	(30%)	
	≥ $100,000	188	(10%)	205	(11%)	393	(10%)	
	Missing	74	(4%)	76	(4%)	150	(4%)	
Education	No High School	24	(1%)	24	(1%)	48	(1%)	0.376
	Some High School	95	(5%)	88	(5%)	183	(5%)	
	High School Graduate	941	(49%)	937	(48%)	1,878	(49%)	
	College Graduate	863	(45%)	898	(46%)	1,761	(45%)	
	Missing	1	(< 1%)	1	(< 1%)	2	(< 1%)	
Literacy (REALM)	≤ 6th Grade	17	(< 1%)	22	(1%)	39	(1%)	0.253
	7th – 8th Grade	140	(7%)	134	(7%)	274	(7%)	
	≥ 9th Grade	1,753	(91%)	1,779	(91%)	3,532	(91%)	
	Missing	14	(<1%)	13	(<1%)	27	(<1%)	
CHD Risk Factor Profile	CHD	89	(5%)	104	(5%)	193	(5%)	0.508
	No CHD, ≥ 2 risks	606	(31%)	598	(31 %)	1,204	(31%)	
	No CHD, < 2 risks	1,229	(64%)	1,246	(64%)	2,475	(64%)	
Geographic Area	East	417	(22%)	424	(22%)	841	(22%)	0.997
	Midwest	463	(24%)	470	(24%)	933	(24%)	
	South	596	(31%)	606	(31%)	1202	(31%)	
	West	448	(23%)	448	(23 %)	896	(23%)	

Comments

There were no differences between the two groups (OTC vs. Rx) of randomized population except for the gender. Higher number of men enrolled in the OTC group may reflect the design of the study. In general, women are more aware of their health than men and one would expect more women to be enrolled. However, the inclusion and exclusion criteria may have influenced gender distribution among participants. It is not clear why the OTC group had more male than

the Rx group. This unequal distribution of gender between the groups could effect results of the trial. Subgroups of the lower literacy and racial minorities are underrepresented in this study. Subjects were randomized by their educational level. If different areas were targeted to ensure specific enrollment, and if the trial was continued for a longer period of time, it is possible that adequate representation of the lower literacy population could have been achieved.

A total of 2,466 (64%) subjects consulted a physician: 1,160 (60%) OTC and 1,306 (67%) Rx ($p < 0.001$). The differences in consultation rates between the OTC and Rx groups is most likely explained by OTC self-selection based on label information and warnings. Of the 1,924 OTC subjects randomized, 720 subjects purchased OTC Pravachol 10 mg. Although recruitment efforts were successful in randomizing subjects in minority groups (300 Blacks, 212 Hispanics, 113 Other), purchase rates were lower among minorities than Caucasians.

Subjects Prematurely Withdrawn from Study Medication (Treated Population)

Table 4 summarizes premature withdrawals from study medication according to reason. Of the 854 treated subjects, a total of 358 prematurely withdrew from the study (290 in the OTC group and 68 in the Rx group). The most frequent reason for withdrawal was "other" in 12% of subjects (18% OTC vs. 3% Rx). Examination of these 99 subject's verbatim responses revealed following:

- 58 subjects (51 OTC and 7 Rx) withdrew consent
- 24 OTC subjects consulted a physician who discontinued treatment
- 1 OTC subject discontinued for administrative reasons (e.g., insurance rejected reimbursement)
- 7 OTC subjects discontinued for other reasons
- 1 OTC subject discontinued for an unknown reason
- 6 subjects (4 OTC and 2 Rx) discontinued for protocol violations
- 2 subjects (1 OTC and 1 Rx) discontinued because of non-compliance

Since the only group with access to study medication prior to qualifying for treatment was the OTC group, the secondary most common reason for premature withdrawal, "discontinuation of treatment by a physician" (because the cholesterol level was at the NCEP defined goal), was seen only in that group. Other reasons in the OTC group for withdrawal were "subject required more aggressive therapy" and determining that Pravachol was "not appropriate for other reasons". Overall, 123 subjects in OTC group were withdrawn from the study by the physician.

There was no significant difference between the OTC vs. Rx in discontinuation due to adverse events (8% OTC vs. 5% Rx, $p=0.052$). The specific adverse events that lead subjects to discontinue are described in a safety section of the review.

Table 4. Subjects Prematurely Withdrawn From Study Medication

Reasons for Withdrawal	OTC (n=499)	Rx (n=355)	Total (n=854)
	N (%)	N (%)	N (%)
Other	89 (18)	10 (3)	99 (12)
Physician determined cholesterol levels normal	60 (12)	0 (0)	60 (7)
Adverse events	38 (8)	16 (5)	54 (6)
Subject withdrew without physician consultation	23 (5)	12 (3)	35 (4)
Physician determined more aggressive lipid lowering treatment necessary	21 (4)	0 (0)	21 (3)
Physician inappropriately qualified subject for treatment and then subsequently withdrew the subject	14 (3)	17 (5)	31 (4)
Lost to follow-up	14 (3)	8 (2)	22 (3)
Reason unknown	13 (3)	2 (1)	15 (2)
Physician determined Pravachol not appropriate other reasons	11 (2)	0 (0)	11 (1)
Reason Physician discontinued treatment unknown	7 (1)	3 (1)	10 (1)
Total	**290 (58)**	**68 (19)**	**358 (42)**

Comments

There is a significant difference of withdrawal rates between two groups ($p<0.00000$). More than a half of OTC treated population did not continue the treatment. The majority of withdrawals in OTC group (123 subjects or 25%) were done by a physician. This shows poor self-selection and inappropriateness of such a therapy for OTC population.

Health Care Status and Cholesterol Awareness

There was no difference between the OTC and Rx groups in each of these populations, so aggregate data is presented. Most subjects in the randomized population had access to health care and prescription medication coverage: 85% had a personal physician, 83% saw their physician regularly, 25% had seen a physician specifically about cholesterol and 72% had prescription medication coverage. Differences were noted in the health care status between men and women in the randomized population. More women than men had a doctor ($p=0.0001$) and saw their doctor at least once a year ($p=0.0001$). The Hispanic population had less access to health care: 73% had a doctor (vs. 86% Caucasian, $p=0.0001$) and 79% saw their doctor at least once a year (vs. 83% Caucasian, $p=0.027$). Subjects < 35 years utilized the health care system less frequently: 67% had a doctor and 64% saw their doctor regularly compared to subjects in the age range more likely to be interested in cholesterol lowering therapies: 81% and 78% of subjects 35-54 years, 89% and 87% of subjects 55-74 years and 95% and 96% of subjects ≥ 75 years respectively. In addition, subjects ≥ 75 years had less prescription coverage (56%) compared to subjects < 35 years (73%), 35-54 years (75%), 55-74 years (71%). The low literacy group used health care as the normal literacy group with the exception of prescription medicine coverage (62% low literacy vs. 73% normal literacy, $p=0.0001$). Cholesterol awareness data for the randomized population is presented in Table 5. Most of the subjects

(96%) were somewhat to extremely concerned about their cholesterol. Eighty-six percent of participants have been told that they have high cholesterol levels, and of those 74% learned about it from their physician. Seventy-four percent knew that a total cholesterol level < 200 mg/dl represented a healthy level. Knowledge about LDL cholesterol was very poor. Eighty percent of the randomized population did not know what a healthy LDL cholesterol level is.

Table 5. Baseline Cholesterol Awareness in Randomized Population

Characteristic	OTC (n=1,924)	Rx (n=1,948)	Total (n=3,872)
Degree of concern about cholesterol			
Extremely, very or somewhat	1,846 (96%)	1,875 (96%)	3,721 (96%)
Subject ever been told have high cholesterol	1,650 (86%)	1,666 (86%)	3,316 (86%)
Know what cholesterol level represents a healthy level:			
Total cholesterol: ≤ 200	1,424 (74%)	1,434 (74%)	2,858 (74%)
> 201	100 (5%)	82 (4%)	182 (5%)
Unknown	400 (21%)	432 (22%)	832 (21%)
LDL cholesterol: ≤100	132 (7%)	134 (7%)	266 (7%)
> 100	252 (12%)	244 (12%)	496 (12%)
Unknown	1,540 (80%)	1,570 (81%)	3,110 (80%)

There was a difference among the races (p=0.0001) with respect to the knowledge that a total cholesterol level < 200 mg/dl represents a healthy cholesterol level (Caucasian 76%, Black 56%, Hispanic 62%, Other 71%) as well as low vs. normal literacy (52% vs. 76%, p=0.0001). Differences were also seen in the age subgroup where knowledge of a healthy cholesterol level was lower in the < 35 years (57%) and ≥ 75 years (69%) compared to those 35-54 years (74%) and 55-74 (76%). There were no differences by gender with regard to cholesterol awareness.

Comments

The data from this study show that the majority of people who volunteered are concerned about their health and serum cholesterol level. However, their knowledge about specific laboratory values (LDL cholesterol) required for appropriate self diagnosis and treatment with cholesterol lowering agents is in general poor, and even worse in racial minorities and in the lower literacy population. Racial minorities, lower literacy group and extreme age categories represented a small fraction of total randomized population. Larger sample size might have given a more accurate representation of the general U.S. population. Of note, the sponsor tested participant's knowledge only about Total and LDL cholesterol. As mentioned earlier, NCEP guidelines list low HDL cholesterol as one of the risk factors for CHD and one possible determinant for drug therapy.

Cholesterol Lowering Action/ Summary of Baseline Concomitant Medications

In the randomized population, 364 (9%) out of 3,872 subjects were currently taking a prescription lowering medication while 687 (18 %) were currently using dietary supplements or OTC medications. No significant differences in previous or current cholesterol action were noted among the OTC and Rx groups and the consult population was similar to the randomized population. Detailed summaries of cholesterol lowering action can be found in Table 6.

Table 6. Cholesterol Lowering Action Currently Taking in Randomized, Consult, Qualified and OTC Purchase Populations

	Randomized Population (n=3,872)	Consult Population (n=2,466)	Qualified Population (n=720)	OTC Purchase Population (n=720)
No special diet	2,693 (70%)	1,703 (69%)	525 (73%)	489 (68%)
Dietary supplements or OTC drugs	887 (18%)	490 (20%)	157 (22%)	166 (23%)
Made dietary changes	1,616 (42%)	1,089 (44%)	304 (42%)	344 (48%)
Low fat/low cholesterol diet	994 (26%)	650 (26%)	168 (23%)	198 (28%)
Low calorie diet	143 (4%)	86 (3%)	22 (3%)	25 (3%)
Use of Rx drugs	364 (9%)	234 (9%)	8 (1%)	51 (7%)
Increase level of exercise	959 (25%)	654 (27%)	183 (25%)	210 (29%)
Postmenopausal women	1,206 (31%)	821 (33%)	200 (26%)	207 (29%)
Hormonal replacement therapy	629 (52%) out of 1,206	437 (53%) out of 821	109 (55%) out of 200	110 (53%) out of 207

Table 7 summarizes concomitant medication use (>2%) by drug classification for the randomized and treated populations. Consistent with the medical practices in a generally healthy population, the most commonly used classes of medications were vitamins, analgesics, and general nutrients. In addition, 629 (52%) out of 1,206 of post-menopausal women were currently taking hormone replacement therapy. As expected, cardiac medications (3%) and anti-diabetic medications (3%) were used less frequently. There were no differences between the OTC and Rx groups.

Comments

Cholesterol lowering practices such as increasing exercise or changing diet are well known and recognized among the practitioners to reduce the risk of CHD. In the study, there is a discrepancy in the participant's responses to the questions regarding their diet. When the subjects were asked if they are following any special diet, the majority answered "no" (70%); however, when asked if they made any changes in their diet (i.e., eating low fat/cholesterol foods) almost half of them said, "yes" (42%). Sponsor also made an attempt to analyze the subjects who are following American Heart Association (AHA) diet. Results of MEDFICTS questionnaire showed that 81% of randomized population are following AHA recommendations.

Table 7. Summary of Concomitant Medications (>2%) at Baseline by Class Randomized and Treated Populations

Drug Classification	Randomized N = 3872		Treated N = 854	
	n	%	n	%
Vitamins	1938	(50%)	476	(56%)
Analgesics	1081	(28%)	297	(35%)
General Nutrients	964	(25%)	256	(30%)
Lipid Reducing Agents	692	(18%)	102	(12%)
Estrogens	666	(17%)	149	(17%)
Antiinflammatory/Antirheumatic	630	(16%)	194	(23%)
Antacids	341	(9%)	99	(12%)
Antihistamines	278	(7%)	96	(11%)
Diuretics	277	(7%)	55	(6%)
Beta Blockers	275	(7%)	60	(7%)
Thyroid Therapy	260	(7%)	60	(7%)
Ace-Inhibitors	252	(7%)	61	(7%)
Laxatives	245	(6%)	66	(8%)
Psychoanaleptics	231	(6%)	68	(8%)
Calcium Channel Blockers	213	(6%)	35	(4%)
Antihypertensives	158	(4%)	37	(4%)
Psycholeptics	157	(4%)	30	(4%)
Antibacterials	132	(3%)	59	(7%)
Anti-Asthmatics	119	(3%)	28	(3%)
Progestogens	112	(3%)	22	(3%)
Antidepressants	105	(3%)	17	(2%)
Anti-Diabetics	103	(3%)	6	(< 1%)
Cardiac Therapy	102	(3%)	19	(2%)
Nasal Preparations	96	(2%)	36	(4%)
Corticosteriods	63	(2%)	22	(3%)
Urologicals	69	(2%)	22	(3%)

Coronary Heart Disease Risk Factor Profile

The CHD risk factor distribution of subjects in the different randomized population sets is presented in Table 8. The majority of subjects who responded to the advertisement were a lower risk population. The most frequently reported risk factors were age (n= 2,631; 68%), followed by family history of CHD (n=1,005; 26%) and hypertension (n=796; 21%); only 193 (5%) subjects had CHD and 138 (4%) had diabetes. In the consult population, there were more people in the Rx vs. OTC group with age as a risk (70% OTC vs. 73% Rx, p= 0.048).

The risk factor for low HDL-C was reported among those subjects who consulted a physician and had a lipid profile obtained.

Table 8. CHD Risk Factor Profile in Different Populations at Baseline

Characteristic	Randomized Population		Consult Population		Qualified Population Total	OTC Purchase Population
	OTC	Rx	OTC	Rx		
Total Number of Subjects	1,924	1,948	1,160	1,306	720	720
CHD	89 (5%)	104 (5%)	54 (5%)	65 (5%)	18 (3%)	29 (4%)
No CHD, ≥ 2 Risk Factors	606 (31%)	598 (31%)	362 (31%)	415 (32%)	242 (34%)	224 (31%)
No CHD, < 2 Risk Factors	1,229 (64%)	1,246 (64%)	744 (64%)	826 (63%)	460 (64%)	467 (65%)
History of diabetes	71 (4%)	67 (3%)	32 (3%)	37 (3%)	5 (<1%)	17 (2%)
CHD and Diabetes	9 (<1%)	17 (1%)	7 (<1%)	9 (<1%)	2 (<1%)	3 (<1%)
History of High Blood Pressure	410 (21%)	386 (20%)	237 (20%)	251 (19%)	117 (16%)	147 (20%)
Family History of Heart Disease	497 (26%)	508 (26%)	302 (26%)	363 (28%)	196 (27%)	180 (25%)
Current Smoker	186 (10%)	192 (10%)	97 (8%)	113 (9%)	41 (6%)	53 (7%)
Age (Male > 45, Female > 55)	1,286 (67%)	1,345 (69%)	810 (70%)	954 (73%)	542 (75%)	494 (69%)
Total number of Subjects in Consult Population	1,160	1,306	1,160	1,306	720	597
HDL < 35 mg/dl	129 (13%)	125 (11%)	129 (13%)	125 (11%)	63 (9%)	71 (13%)

Differences in prevalence of CHD risk factors observed among the demographic subgroups in the randomized population were similar to findings in general population described in other surveys. The percentage of current smokers was higher among Blacks than Caucasians (17% vs. 9% p=0.0002) and low vs. normal literacy (15% vs. 9%, p=0.004). Incidence of hypertension increased with age: 9% in subjects < 35 years, 14% in subjects 35-54 years, 26% in subjects 55-74 years, and 29% in subjects ≥ 75 years. The incidence of CHD also increased with age 3%, 3%, 6%, and 16% in these age groups respectively. Fewer women had a low HDL cholesterol as a risk factor than men (3% vs. 18%, p= 0.0001). This was also noted among Blacks vs. Caucasians (5% vs. 12% p=0.032).

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 presented in Table 9, shows that randomized population and consult population had the same profile. The CHD risk factor profile was also comparable between the OTC and Rx groups and among the subgroups for both the randomized and consult populations.

Table 9. CHD Risk Factor Profile at Baseline

	Randomized Population (% of Subjects)	Consult Population (% of Subjects)
CHD	5	5
No CHD, ≥ 2 Risk Factors	31	32
No CHD, < 2 Risk Factors	64	64

Lipid profile of tested at baseline randomized subjects presented in Table 10, shows that the majority of the studied population had elevated total and LDL cholesterol. However HDL cholesterol, one of the negative risk factors, levels were relatively high, with a mean of 50 mg/dl and median 48 mg/dl. Mean baseline LDL-C levels for the Qualified and Treated population were 162 (± 17) mg/dl and 163 (± 17) mg/dl for the OTC and Rx groups respectively.

Table 10. Lipid Profile at Baseline in Consult and Qualified and Treated Populations

Lipid	Qualified and Treated Population	Consult Population		
		OTC	Rx	Total
Total number of subjects	637	1,160	1,306	2,466
LDL-Cholesterol (mg/dl)				
N	605	850	1,102	1,952
Mean	162	147.3	149.1	148.3
S.D.	17	32.8	32.9	32.8
Median	163	146	148	147
Min.	97	45	11	11
Max	215	316	373	373
Total Cholesterol (mg/dl)				
N	607	889	1,170	2,059
Mean	245	233.9	236.7	235.5
S.D.	21	35.9	38.2	37.3
Median	245	231	234	233
Min.	155	127	112	112
Max	306	420	484	484
HDL-Cholesterol (mg/dl)				
N	607	888	1,169	2,057
Mean	50	50	50.7	50.4
S.D.	13	15	15	15
Median	49	48	48	48
Min.	23	19	15	15
Max	93	111	115	115
Triglycerides (mg/dl)				
N	607	889	1,170	2,059
Mean	162	189.6	189.2	189.4
S.D.	70	112.4	118.6	115.9
Median	146	163	157	159
Min.	43	28	42	28
Max	634	939	949	949

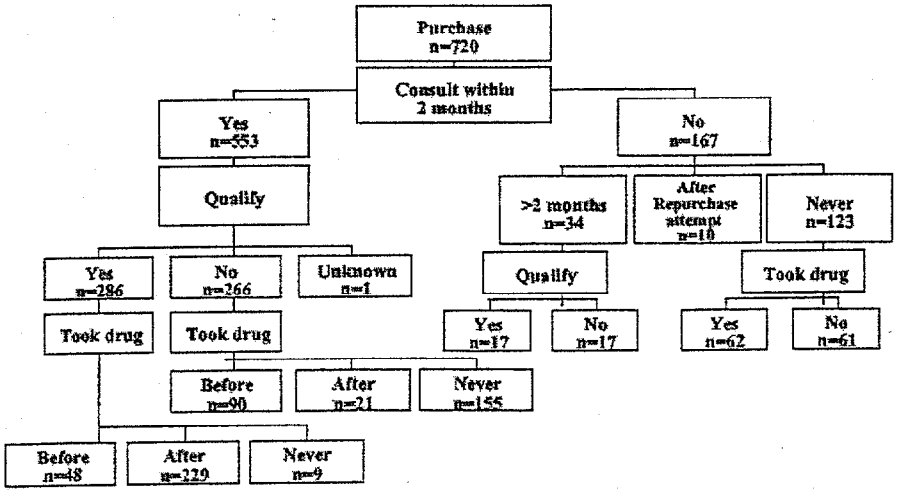
Comments

Analysis of the risk factors for CHD showed that the population enrolled in the study was fairly representative of general population. One factor, a negative one, that the sponsor failed to take into account is high HDL cholesterol level. NCEP guidelines clearly specify that HDL-C levels >60 mg/dl is a negative risk factor, which can negate one other risk factor. This factor may further reduce the risk factor profile of the analyzed population, as half of the studied population had HDL cholesterol levels above 48 mg/dl. Age of the participants may also have influenced these results. Qualified and treated population had more homogenous (less variation) laboratory values, higher overall total and LDL cholesterol levels than total consult population.

Efficacy Results

The primary efficacy end point of this study was to determine the proportion of OTC randomized subjects who, having purchased OTC Pravachol 10 mg, consult a physician within two months of using medication. The results of the behaviors of the OTC purchase population is shown in Figure 2. Of the 720 OTC subjects who purchased Pravachol 10 mg, 553 (77%) fulfilled the primary objective by consulting a physician within 2 months of product use. Of those who consulted physician within two months, 462 (64%) did that before ever taking the drug, 185 (26%) took at least one dose before seeing the doctor, and the behavior of the rest 73 (10%) subjects is unknown. An additional 34 subjects (5%) consulted after the predefined 2 month window of product use and were thus not included as meeting the primary objective; none of these subjects were prompted to consult following an attempt to repurchase additional medication. Sixty-one subjects (8%) never consulted a physician and did not take their medication. Seventy-two subjects (10%) took Pravachol 10 mg and never consulted a physician; included in this group are 10 subjects who had attempted to repurchase without physician consultation and were told they would have to consult in order to repurchase.

Figure 2. Behavior of OTC Purchase Population



There were some differences in demographic subgroups of analyzed population. Gender and literacy did not appear to have an impact on behavior to consult a physician. There were only 7 subjects who did not complete 9th grade education, of whom 5 consulted physician within 2 months giving a 71% efficacy rate. Analysis by REALM scores gave higher consult rate (74%) for lower literacy group (REALM <60) although the number of subjects remained small (n=47) in comparison to higher literacy group of 668 subjects. The sample size was small for racial minority groups, Blacks (n=39) and Hispanics (n=33) vs. Caucasians (n=626). Consult rates for these groups were 59%, 58% and 80% respectively. Subjects < 35 years also tended to consult a physician less frequently, although the sample size was small (n=21). Subjects who enrolled in the PRAVACARE Educational Program were more likely to consult a physician within 2 months than those subjects who did not enroll in the PRAVACARE Program (91% vs. 73%, p= 0.0001).

Of the 1,924 subjects randomized to the OTC group, 1,852 (96%) demonstrated behavior that presented no potential harm: 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, and 1,204 (63%) never purchased Pravachol 10 mg. Of the OTC subjects who purchased Pravachol 10 mg, consulted a physician within 2 months and did not qualify for treatment (n= 266), 58% (n=155) never took Pravachol 10 mg, 34% (n=90) stopped taking medication after being told they did not qualify. Of the 266 subjects who did not qualify for Pravachol therapy, 42% had a LDL-C > 130 mg/dl and 14% qualified for more aggressive prescription therapy. One subject's qualification for the therapy was not known. There were an additional 17 subjects who consulted a physician outside the 2 month visit and did not qualify because they required more aggressive prescription therapy. There was another group of 62 subjects who purchased the drug and took it , and never consulted a physician. Overall this gives a total of 169 subjects or 23% of OTC purchase population who present potential harm to themselves by taking the drug.

Total of 1,204 (63%) out of 1,924 subjects in OTC group did not purchase OTC medication. Forty-seven percent of non-purchasers consulted a physician and majority of those (501 out of 563) did not qualify for the therapy. Qualification of those who did not consult a physician is not known. A summary of the reasons OTC subjects did not purchase is presented in Table 11. The primary reason for non-purchase was the interest in consulting a physician first (47%) followed by cost (15%). Twenty-nine percent of the non-purchasers noted they were not appropriate OTC population, noted label warnings, or needed additional information prior to purchase.

Table 11. Reasons OTC Subjects Did Not Purchase Pravachol 10 mg

	N	%
Decided to consult physician	197	(47%)
Cost	63	(15%)
Did not know cholesterol level	39	(9%)
Need more information	37	(9%)
Cholesterol not between 200-240 mg/dl	14	(3%)
Cholesterol currently treated	14	(3%)
Noted labeled warnings/risk factor too high	13	(3%)
Not interested/other	13	(3%)
Concerned about side effects	10	(2%)
Wanted to try other methods first	7	(2%)
Unknown	9	(2%)

Comments

The fact that those subjects who were enrolled in educational program, did better than those who were not enrolled, show that more education is needed for the general population in their decision making process for hypercholesterolemia self-treatment. The overall efficacy analysis of OTC purchase population shows that almost a quarter (23%) of the subjects would take the drug inappropriately. Almost half of the non-purchase population (47%) would go to the physician before buying this product.

Secondary Variables

Behavior to Consult Physician for Follow-up After Initial Visit

Of the 720 subjects who were told by the physician that they qualified for Pravachol 10 mg there was no difference between OTC and Rx groups in following up with the physician: 85% (n=267 out of 315) and 83% (n=335 out of 405) respectively. Demographically, there were no significant differences in terms of age, gender, race, or literacy.

Behavior to Consult Physician Following Dose Titration

One hundred thirteen subjects (53 OTC, 60 Rx) had a dose titration at Assessment 3. This included OTC subjects whose dose was titrated to prescription Pravachol or Rx subjects who did not meet his/her LDL-C goal in accordance to NCEP guidelines after 8 weeks of therapy with Pravachol 10 mg. Their dose was titrated to 20 mg daily. They were asked to return for a second follow-up consultation with the physician at Week 16 (Assessment 3B). A total of 41 (77%) OTC and 52 (87%) Rx subjects complied (95% CI –23%, 4.9%). Because of the small number of the subjects in demographic subgroups, no conclusions can be made about these groups. If the subject's response to treatment with Pravachol 20 mg was not ideal at Week 16, the investigator could recommend an increase in dose of Pravachol to 40 mg per day. A total of 14 subjects in the OTC group and 21 subject in the Rx group received maximum dose of 40 mg per day during the study.

Tertiary Variables

MEDFICTS Dietary Modifications

Eighty-four percent of the subjects who qualified for Pravachol 10 mg were following an AHA Step I or II diet at study entry. The majority of the subjects in qualified population either maintained or improved their baseline dietary behavior.

Comments
Analysis of secondary and tertiary variables show expected results. Once the subject goes to the physician, he/she becomes Rx population in respect to follow-up compliance, whether he/she is part of the OTC or Rx group. Dietary modification behavior is very important when adding cholesterol lowering agent. Many participants of the study were enrolled in PRAVACARE education program. The number of the subjects evaluated at the end of this study is not large enough to predict what will happen when the drug will be available for majority of the OTC consumers.

Modification in Exercise and Smoking Behaviors

The OTC and Rx groups were comparable in their behavior with regard to exercise and smoking. During the length of the study, 13% OTC and 14% Rx of the qualified population had increases in their exercise patterns. Exercise levels were maintained in 62% OTC subjects and 63% Rx subjects. Twelve percent of both OTC and Rx subjects decreased their level of exercise over the same time period. Behaviors for the consult population were similar. A decrease in smoking behavior in the qualified population was reported for 2% of the OTC group and 1% of the Rx group. Smoking behaviors remained the same for 88% and 90% of OTC and Rx subjects respectively. Smoking behavior was unknown in approximately 10% of subjects.

Compliance issues/ Usage patterns

Compliance was measured by evaluating fasting lipid profiles at Week 8 and 24 and by pill count at each visit. Lipid profiles were analyzed at a central laboratory and transferred directly into the database. Subjects were instructed to return all used and unused medication at each visit. Study site personnel performed pill counts and results were recorded in the CRF. Because this was a naturalistic study, compliance data measured by pill count or self-report which was a less reliable measure of compliance than change in LDL-C, as subjects did not always bring medication with them when they consulted the physician since this is not typically done during a routine office visit. Overall compliance with Pravachol 10 mg as assessed by pill count or self-report, and defined by 80-120%, was seen in 54% OTC and 65% Rx groups (CI –19%, -3.7%).

Lipid Analyses

Baseline lipid profile parameters for the Consult population and Qualified and Treated population (took at least one dose) are discussed in CHD risk factor assessment section. For those subjects who qualified and took at least one dose of Pravachol 10 mg, statistically significant reductions from baseline 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 difference in the reduction seen between the OTC and Rx groups. The magnitude of the LDL-C reduction for the OTC and Rx groups is similar to what has been demonstrated in placebo-controlled dose response clinical trials. Importantly, 83% OTC and 77% Rx subjects achieved their NCEP defined LDL-C goal during the study. There were no significant differences among the gender or racial subgroups. A summary of the lipid results is presented in Table 12.

Table 12. Lipid Profile: Percent Change from Baseline Qualified and Treated Population (n=637)

	OTC	RX	95% CI
Total-C mg/dl	n=285	n=352	
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.

Comments

Analysis of compliance is not acceptable. The sponsor defines acceptable compliance as 80-120% of pills taken or self report. In the opinion of this reviewer, everyone who takes more medicine than they are supposed to take, is non-compliant. Compliance of more than 100% is also effecting over all decrease in serum cholesterol level. Participants of the study received additional information about cholesterol lowering strategies, such as diet, smoking cessation and exercise, which could also influence the results. There was no control group in the study. Therefore, efficacy in respect to lipid lowering action for Pravachol 10 mg is not reliable.

Extent of Exposure to Pravachol

Duration of treatment for those who took study medication is shown in Table 13. In the treated population the mean duration of treatment was significantly shorter ($p < 0.001$) for the OTC (109 ± 70 days) compared to the Rx group (153 ± 47 days). According to the sponsor, this difference can be explained by the 107 OTC subjects who took Pravachol prior to consulting but who appropriately discontinued treatment after consulting with the physician. When these subjects are excluded, the extent of exposure is 151 ± 54 days for the OTC group and 153 ± 46 days for the Rx group.

Table 13. Duration of Treatment Treated Population (n=854)

		OTC (n=499)		Rx (n=355)	
Overall Duration of Treatment	N	444		340	
	Mean	109.4		152.5	
	STD	69.5		46.6	
	Median	114		167	
	Range	1-257		1-265	
Duration of Treatment	Days	N	(%)	N	(%)
	0-7	22	(4%)	3	(<1%)
	8-14	27	(5%)	1	(<1%)
	15-21	17	(3%)	6	(2%)
	22-28	9	(2%)	1	(<1%)
	29-42	23	(5%)	9	(3%)
	43-63	78	(16%)	18	(5%)
	64-84	24	(5%)	4	(1%)
	85-112	22	(4%)	7	(2%)
	113-140	9	(2%)	21	(6%)
	141-168	93	(19%)	128	(36%)
	>168	120	(24%)	142	(40%)
	Missing	55	(11%)	15	(4%)

Comment
The extent of exposure to Pravachol 10 mg was significantly different in the two populations. This difference can be explained on the basis of high withdrawal rate in the OTC group.

Safety outcomes

Overall, Pravachol was well tolerated in this study population. A greater proportion of subjects in the Rx group experienced AEs compared to the OTC group (133 OTC [27%]) vs. (144 Rx (41%). A greater proportion of adverse events was 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 subjects. None of these adverse events were serious. Myalgia was reported in 7 (1%) of the OTC subjects and 4 (1%) of the Rx subjects; 5 subjects (4 OTC and 1 Rx) discontinued treatment because of myalgia. CPK levels were measured on 3 of the OTC and 1 of the Rx subjects. One subject with myalgia had an elevated CPK; all others were within the normal range and none required follow-up measurements. The one subject with myalgias and elevated CPK levels completed the study on therapy and the myalgias resolved prior to study completion. CPK levels were measured on an additional 26 subjects at the discretion of the investigator. Adverse events related to the hepatobiliary system occurred in 6 (1%) OTC subjects and 3 (< 1%) Rx subjects. These events included 7 transaminase abnormalities, 2 cholecystectomies, and 1 cholelithiasis. There were no adverse events of drug interactions reported.

A summary of the relationship of all reported adverse events to study medication is shown in Table 14. Events that occurred more than once during the study in the same subject were counted once using the episode with the closest relationship to study medication.

Table 14. Adverse Events Presented by Relationship to Study Medication Treated Population (n=854)

	OTC N = 499		Rx N = 355	
	n	(%)	N	(%)
Subjects with AEs	133	27	144	41
Related	45	9	42	12
Unrelated	84	17	101	28
Unassessable	4	<1	1	1

Considering only those AEs judged by the investigator as related to (certain, probable, possible) study medication (ADR), there were no differences noted between the OTC and Rx subjects. ADRs reported with an incidence of > 1% by body system are summarized in Table 15. ADRs were reported by 45 subjects (9%) in the OTC group and 42 subjects (12%) in the Rx group. ADRs related to the "gastrointestinal system" (10 [2%] OTC vs. 15 [4%] Rx) and musculoskeletal system" (15 [3%] OTC vs. 8 [2%] Rx) were the most common. 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 ADRs in the Rx group. Myalgias and muscle aches were the most frequently reported musculoskeletal system ADRs in both groups. The reported gastrointestinal system and musculoskeletal system ADRs all occurred at an incidence of 3%. ADRs related to the hepatobiliary system occurred in 4 (< 1%) OTC subjects and 3 (< 1%) Rx subjects. Among those subjects experiencing study-related adverse events, most were mild to moderate in nature with a similar distribution of AE severity between the OTC and Rx groups.

Table 15. Adverse Drug Related Events (>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%)

Deaths

No deaths were reported during the study.

Serious or Potentially Serious Adverse Events

A total of 19 subjects (11 OTC and 8 Rx) experienced one serious adverse event either during the study or within 1 month after cessation of treatment. An additional one subject (25-3345) reported a tumor of the right lung hilum 105 days after cessation of treatment. A subject listing of all serious or potentially serious events is presented in Table 16. None of these serious events were attributed to Pravachol.

Table 16. Serious or Potentially Serious Adverse Events Treated Population (n=854)

Tx Group Region# - Subject #	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

Subjects Prematurely Withdrawn for Adverse Events

Total of 55 subjects, 39 OTC and 16 Rx, withdrew treatment because of adverse events. Table 17 summarizes the reasons for discontinuation of study medication for adverse events. Myalgias and headaches, reported in 1% each of OTC and Rx subjects, were the events that most frequently led to study withdrawal.

Table 17. Reasons for Premature Withdrawals for Adverse Events Treated Population

Event	OTC (n=499)	Rx (n=355)	Total (n=854)
Total number	39 (8%)	16 (5%)	55 (6%)
Headache	3 (1%)	5 (1%)	8 (1%)
Myalgia	4 (1%)	1 (<1%)	5 (1%)
Muscle ache	1 (<1%)	1 (<1%)	2 (<1%)
Dysfunction, sexual	1 (<1%)	0 (<1%)	1 (<1%)
Dizziness	1 (<1%)	1 (<1%)	2 (<1%)
Heartburn	1 (<1%)	0 (<1%)	1 (<1%)
Dyspepsia	0 (<1%)	2 (<1%)	2 (<1%)
LFT abnormal	0 (<1%)	1 (<1%)	1 (<1%)
LFT increased	1 (<1%)	0 (<1%)	1 (<1%)
Weakness, unspecified	1 (<1%)	1 (<1%)	2 (<1%)
Abnormality, stool	1 (<1%)	1 (<1%)	1 (<1%)
Arrhythmia, sinus	1 (<1%)	1 (<1%)	1 (<1%)
Cramp, muscle	1 (<1%)	0 (<1%)	1 (<1%)
Disorder, mental	1 (<1%)	0 (<1%)	1 (<1%)
Disorientation/confusion	1 (<1%)	0 (<1%)	1 (<1%)
Flatulence	1 (<1%)	0 (<1%)	1 (<1%)
Herpes zoster	1 (<1%)	0 (<1%)	1 (<1%)
Impotence	1 (<1%)	0 (<1%)	1 (<1%)
Insomnia	1 (<1%)	0 (<1%)	1 (<1%)
Melena	1 (<1%)	0 (<1%)	1 (<1%)
Myocardial Infarction, acute	1 (<1%)	0 (<1%)	1 (<1%)
Nausea	1 (<1%)	0 (<1%)	1 (<1%)
Pain, unspecified	1 (<1%)	1 (<1%)	1 (<1%)
Pain, chest	1 (<1%)	0 (<1%)	1 (<1%)
Pain, joint	1 (<1%)	0 (<1%)	1 (<1%)
Pain, musculoskeletal	1 (<1%)	0 (<1%)	1 (<1%)
Reflux, esophageal	1 (<1%)	0 (<1%)	1 (<1%)
Spasm, bladder	1 (<1%)	0 (<1%)	1 (<1%)
Surgery, prostate	1 (<1%)	0 (<1%)	1 (<1%)
Weakness, muscle	1 (<1%)	0 (<1%)	1 (<1%)
Urinary Tract Infection	1 (<1%)	0 (<1%)	1 (<1%)
Anxiety	0 (<1%)	1 (<1%)	1 (<1%)
Neoplasm, malignant, prostate	0 (<1%)	1 (<1%)	1 (<1%)
Perforated peptic ulcer	1 (<1%)	0 (<1%)	1 (<1%)
Pain, abdomen	0 (<1%)	1 (<1%)	1 (<1%)
Rash	0 (<1%)	1 (<1%)	1 (<1%)
Side effect, unspecified	4 (<1%)	0 (<1%)	4 (1%)
Coronary Heart Disease	1 (<1%)	0 (<1%)	1 (<1%)
Elevated LFT	1 (<1%)	0 (<1%)	1 (<1%)

Adverse Events of Specific Interest

Drug Interactions

In this study, commonly used medications that are inhibitors of cytochrome P450 isozymes

such as cimetidine (n= 17), diltiazem (n=6), verapamil (n=12), erythromycin (n=3), clarithomycin (n=4), were evaluated, if used concomitantly with Pravachol 10 mg. Review of the CRFs for adverse events indicated no drug-drug interactions. In addition to review of use of concomitant medications metabolized by cytochrome P450 isozymes isoenzymes, the experience with co-administration with gemfibrozil and niacin was evaluated. There were 6 subjects (5 OTC and 1 Rx) who reported taking gemfibrozil and 61 subjects (38 OTC and 23 Rx) who took niacin concomitantly with Pravachol 10 mg. No drug interactions or adverse events of myopathy were reported.

Myopathy

There were no reports of myopathy defined as CPK levels > 10 times the upper limit of normal.

Adverse Events Related to Hepatobiliary System

The overall incidence of adverse events related to the hepatobiliary system in the treated (Rx and OTC) population was 9 (1% of the total adverse events reported). These included 7 (<1%) cases of transaminase abnormalities which are described below, 2 (<1%) cholecystectomies, and 1 (<1%) case of cholelithiasis. Importantly, no serious adverse events or deaths were attributable to the hepatic system. There were no differences between the OTC and Rx groups. A total of 7 subjects had transaminase abnormalities. Two of these subjects discontinued study medication as recommended by the investigator without discussion with the sponsor and in violation of protocol guidelines. In neither case was the elevation deemed a serious reaction nor were there any other signs of liver injury. The remaining 5 subjects had transaminase abnormalities reported as adverse events and the investigator did not discontinue study medication. Summaries for these 5 subjects are described below.

Serum Transaminase Analyses

Marked Abnormalities

A marked abnormality was defined as a value > 3 times upper limit of normal (ULN), or, if pretreatment value was > 3 times ULN, then > 4 times was used. There were no subjects with marked abnormalities in AST or ALT.

Changes from Baseline for AST and ALT

AST and ALT values were categorized at baseline as normal, high (1-1.5 x ULN), and very high (≥ 1.5 x ULN). Subjects who had mild elevations at baseline did not have any evidence of more progressive abnormalities. One subject (10-3608) initiated Pravachol 10 mg as recommended by the study physician; however, treatment was discontinued by the physician at Week 8 because the baseline serum transaminase levels were elevated prior to initiation of Pravachol 10 mg. Baseline serum transaminase values were AST 38 IU/L and ALT 64 IU/L; Week 8 values included AST 32 IU/L and ALT 66 IU/L. Since the elevation in serum transaminase levels was a preexisting condition, the study physician did not report this as an AE. However, the reason the subject discontinued Pravachol 10 mg is reported as "elevated liver function." Despite this, the sponsor did not count his elevated liver function within the adverse event tables.

Ninety-seven percent of the 533 subjects had a normal AST value at baseline and 98% of these subjects' AST values remained within normal limits. There were 8 subjects (2%) where the AST values rose to 1.5 times the upper limit of normal and 3 that rose between 1.5 and 1.8 times and the upper limit of normal. Of these 8 subjects, AST values were repeated in 5 and showed AST levels returned to normal in 3 subjects. All of the subjects remained on Pravachol treatment. Among the 15 subjects (3%) who had a AST values of 1-1.5 times the upper limit of normal at baseline, 73% became normal by Week 8, 27% remained mildly elevated and none became elevated greater than 1.5 times the upper limit of normal.

Similar findings were seen with respect to ALT values. Five hundred and nine subjects (95%) had normal levels at baseline of which 488 (96%) remained normal, 17 (3%) were up to 1.5 times the upper limit of normal, and 4 (< 1%) were between 1.5 and 2.1 times the upper limit of normal at Week 8. Among the 21 subjects with high ALT levels at baseline, 10 (48%) became normal, 9 (43%) remained high, and 2 (10%) were between 1.5 and 3 times the upper limit of normal. There were 2 (< 1%) subjects with very high ALT levels at baseline of whom 1 subject normalized and 1 subject remained at the same, at Week 8. Repeat ALT values were not performed for one subject.

There was no statistical difference in the absolute change from baseline in AST or ALT for either the OTC and Rx subjects who qualified and took Pravachol 10 mg.

There were two subjects withdrawn due to elevated liver function tests which were mild and resolved after the drug was discontinued. In neither case was the elevation deemed a serious reaction nor were there any other signs of liver injury. A short narrative description of these cases is presented below.

Subject 15-3037 (OTC group) a 39 year old white male who consulted the study physician before taking Pravachol 10 mg, with no history of hepatitis or alcohol abuse was recommended to discontinued Pravachol 10 mg because of elevated transaminase values. The subject was not taking any other concomitant medications. Baseline transaminase values were ALT 22 IU/L and AST 20 IU/L. Results of follow up transaminase values obtained 78 days after starting Pravachol 10 mg were ALT 54 IU/L and AST 34 IU/L. The investigator reported elevated transaminase values as an adverse event attributed to study drug. Pravachol 10 mg was discontinued 95 days after starting therapy without discussion with the Sponsor in violation of protocol guidelines. Repeat transaminase values reported 33 days after Pravachol 10 mg was discontinued were ALT 30 IU/L and AST 23 IU/L.

Subject 25-4028 (Rx group) a 60 year old white female with no history of hepatitis or alcohol abuse who consulted the study physician before taking Pravachol 10 mg was recommended to discontinue Pravachol 10 mg because of elevated transaminase values. Concomitant medications included Premarin 0.5 mg daily. Baseline liver function was ALT 25 IU/L and AST 22 IU/L. Follow up transaminase values, 57 days after starting Pravachol 10 mg was ALT 79 IU/L and AST 61 IU/L. The investigator reported elevated transaminase values as an adverse event and attributed the event to study medication. Pravachol 10 mg was discontinued 60 days after starting therapy without discussion with the Sponsor in violation of protocol guidelines. Repeat transaminase values obtained a month later were: ALT 26 IU/L and AST 23 IU/L.

Comments

The extent of exposure to Pravachol 10 mg during this study was relatively short and results may not reflect all of the safety issues. ADRs reported in this study showed an overall safe profile for Pravachol 10 mg. Most adverse events reported were non-serious and reversible in nature. There was no significant difference between the OTC vs. Rx groups in withdrawals due to adverse events (p=0.052). No significant drug interactions were noted in this study.

Summary of the PREDICT study:

- *This was an actual use trial to test consumer behavior in an OTC setting where Pravachol 10 mg was available for purchase and use: The design of this actual use study allowed enrollment of a relatively young population. It was biased in respect to enrollment, because some of the child bearing women interested in participation were excluded by the call center. Representation of a different geographic areas of the U.S. population was achieved. However, subgroups of racial minorities and lower literacy population are underrepresented in the study.*

- *The label used in the study was not identical to currently proposed OTC label for Pravachol 10 mg tablets. In addition, the label was not the only factor in the decision making process to purchase the product. Data gathered from the study showed that an educational program increases consumers' comprehension and decision making of self-treatment of hypercholesterolemia.*

- *Primary efficacy endpoint, to consult a physician within 2 months of purchase of Pravachol 10 mg, was achieved in 77% of OTC purchase population. One quarter of the OTC purchase population did not qualify for Pravachol 10 mg therapy as determined by a physician.*

- *Analysis of the health care status and cholesterol awareness showed that the majority of the enrolled population are concerned about their cholesterol and general health. However, their knowledge about specific serum cholesterol values is poor, especially in the racial minorities and in the lower literacy subgroups.*

- *The withdrawal rate among OTC purchase group was significantly higher than in the Rx group.*

- *Efficacy of Pravachol 10 mg tablets in respect to cholesterol lowering action is not reliable in this study for the following reasons: there was no placebo control group, compliance was not strictly monitored, and participants of the study received additional information about alternative cholesterol lowering strategies.*

- *Safety data gathered from this study showed an overall safe profile for Pravachol 10 mg tablets.*

- *Relatively short duration of the study and high withdrawal rate seen in this trial does not predict long term behavior, efficacy, and unexpected safety issues in the OTC population.*

2. OPTIONS 800-03-97

Protocol Issues

Primary Objectives

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

Secondary Objectives

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

Tertiary Objectives

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

Design

OPTIONS was a multicenter, pharmacy-based, open-label, actual use study designed to assess consumer behavior, compliance and safety among HMO subjects in a naturalistic setting.

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) and also collect reliable data by maximizing access to subjects' primary care physician and medical records.

The study was conducted at 20 U.S. pharmacies which served as the study sites. Of these, 14 were HMO staff model pharmacies in 5 states (TX, FL, OK, TN, VA), and 6 were retail type pharmacies in one state (DE). In addition, sites were selected to increase the likelihood of enrolling low literacy and minority subjects. The principal investigator at each site was a Registered Pharmacist employed by the pharmacy. No physicians were present at the enrollment sites. However, each study site 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. The staff model HMO is characterized as a health plan that owns its own clinics and employs salaried physicians and other health professionals who provide care exclusively to the plan's enrollees. The Independent Practice Association (IPA) model HMO subjects could enroll through one of the 6 retail pharmacies selected to participate in the study. The physicians of these subjects were in private practice and had managed care contracts with the selected HMO.

Study duration was 3 months. Subject recruitment occurred via mailers sent to a random sample of HMO members (without knowledge of medical history, cholesterol levels, or demographic profile), walk–through traffic in the participating pharmacies, and in some cities, radio and newspaper advertising.

For the staff model HMOs (14 sites), mailings were sent to a random sample of HMO members listed in the staff model pharmacy database. A total of 77,322 customers received the study brochure at least once. For the seven smaller sites, each with less than 4,500 members, the mailer was sent on 2 separate occasions to all HMO members listed in the pharmacy database. For the seven larger sites, the mailer was sent either to 4 of every 5 members, sequentially omitting every fifth name, or to 2 of every 3 members, sequentially omitting every third name. In the IPA model HMO (6 sites), approximately 84,000 HMO members (out of a total of approximately 210,000) were mailed the study brochure at least once in 3 rounds of mailings. The first mailing consisted of approximately 14,000 mailers sent to members from the medical groups with the greatest number of managed care members. The second mailing was sent to all 35,000 managed care members in the zip codes surrounding the 6 pharmacy study sites of whom 9,000 were from the first mailing. Because enrollment was less than expected, a third round of mailings which was expanded to include approximately 44,000 additional HMO members as well as the members from the second. Approximately 70,000 mailers were sent in this third and final round.

Comments
No detailed information was provided on the background of the study investigators. Three study sites were rejected from the participation for the following reasons: one site in the IPA model was terminated due to lack of enrollment, and one of each in staff model withdrew from participation prior to initiation and terminated due to failure to provide regulatory documentation. Study population does not represent overall U.S. consumers for the following reasons: 1) study sites were restricted to certain geographical area; 2) all participants had medical insurance and prescription drug coverage.

Advertisement material has been reviewed and it was found to be adequate. Total of 161,322 subjects were targeted for enrollment. Low interest in enrolling into the study could be partially explained by the content of recruitment advertisement. It stated that only subjects with total cholesterol level of 200-240 mg/dl can participate in the study.

Assessment 1
All subjects who responded to the recruitment materials and presented to the participating pharmacies were considered potential study subjects and were directed to trained interviewers (not the pharmacist). Prior to the interview, the subject was asked to provide evidence of HMO

membership. Once membership had been verified, the subject was asked to review and sign a brief consent form granting permission for an interview, at which point the subject was enrolled in the study.

The enrolled subjects were then shown a prototypical advertisement/concept, the OTC product package, apprised of the purchase price, and were asked about their interest in purchasing Pravachol 10 mg. Subjects were not required to purchase Pravachol 10 mg in order to participate in the study. The interviewer, who was not medically trained, then administered a questionnaire to collect information about demographics, literacy level, cardiovascular risk factors, health care status, cholesterol awareness, and cholesterol lowering actions. Literacy level was assessed by administering the REALM test.

Comments
The package label for Pravachol that was used in this study is worth some comments. The label used in this trial was different from currently proposed OTC Pravachol 10 mg label. It is not clear what treatment recommendations were used in this study. The criteria for the treatment on the label specifies only total serum cholesterol level (200-240 mg/dl), and the age by gender (≥35 years for men, ≥55 years for women). No LDL or HDL cholesterol levels were considered as criteria for initiation of therapy. This contradicts NCEP guidelines for the treatment of hypercholesterolemia.

Subjects who satisfied the inclusion/exclusion criteria and had an interest in purchasing Pravachol 10 mg were then asked to sign a second consent form and provide written permission for access to their medical records in order to verify their medical history. Subjects who were not interested in purchasing Pravachol 10 mg were only asked to provide written release for access to their medical records.

Once a subject was enrolled in the study, no further contact was initiated by the interviewers, the pharmacist (Principal investigator), or the sub-investigator during the 12 week study period. The pharmacist could counsel the subject on Pravachol 10 mg, but only at the request of the subject. Study personnel did not instruct subjects to contact their primary health care provider. The decision to contact a physician was to be made solely by the subject. During the course of the study, the subjects' medical records were reviewed weekly and the primary care physician provided an independent documentation of cardiovascular risk factors and relevant medical history, documented any contact with the subject since enrollment and, provided a recommendation as to the appropriateness of Pravachol 10 mg.

At the initial purchase, subjects who had not yet contacted their health care provider were allowed to buy a 1 month supply of study medication; subjects who already contacted their health care provider were allowed to buy up to a 3 month supply of medication either in one purchase or over time. For subsequent purchases, the IRB required that subjects not be permitted to buy additional medication after the initial 2 month purchase unless the subject consulted a physician; women of childbearing potential were not allowed to purchase more than a 1 month supply without consulting with their health care provider.

All subjects who purchased medication received Pravachol at a dose of 10 mg. Subjects had the option of purchasing 1) a Pravachol 10 mg starter kit which contained: 4 blister cards, each containing 7 tablets, a package insert, a PRAVACARE educational booklet, a business reply card for enrollment in the PRAVACARE Newsletter Program, and a rebate coupon for subsequent purchases or 2) Pravachol 10 mg Maintenance kit containing medication and a package insert only. Although subjects were reimbursed at the end of the study, they were not informed of this prior to week 12, nor was it stated in the informed consent.

Subjects could enroll into the PRAVACARE educational program. This program provided subjects with the PRAVACARE booklet which discussed high cholesterol and its consequences, the importance of diet, exercise and leading a healthy lifestyle; two newsletters; and two reminder postcards that reinforced key label communication messages.

Assessment 2 was performed for all enrolled subjects regardless of whether they had purchased Pravachol 10 mg 12 ± 4 weeks after the initial visit or product purchase date (whichever occurred later). Subjects were interviewed by telephone in order to collect information on behavior to contact their primary care provider, cholesterol awareness, medication compliance and safety. Subjects 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 subject enrolled in the study.

The sample size of 800 subjects was chosen on the basis of projections about the primary endpoint, the proportion of purchasers consulting their health care provider within 2 months of using Pravachol 10 mg. Assuming that 50% of the enrolled subjects would purchase Pravachol 10 mg, and 75% (n=300) of those purchasing medication complete the follow-up (Week 12) assessment, the margin of error about an estimate of compliance with respect to the primary endpoint of 85% will be 4.0% with an initial population of 400. If compliance is as low as 50%, a margin of error of 5.7% will be realized.

Following criteria were used for study population:
Inclusion Criteria

- ≥18 years
- Member of a participating HMO for at least 6 months

Exclusion Criteria

- Participation in a research study within the last 30 days
- Current pregnancy or lactation

Comments
The study design does not follow the recommendations of the currently approved Rx Pravachol label. Testing serum total, LDL and HDL cholesterol level as well as liver function tests before starting the therapy are prerequisites for Rx therapy. There is no provision for follow-up of cholesterol level or LFT's. To ensure safe and effective use of Pravachol, these laboratory values should be monitored, unless there are additional data to support not needing this information or a different follow-up schedule. Inclusion criteria defined as subjects 18 years or older, allowed to enroll relatively young population.

Endpoints

The primary endpoint for this study was to assess the proportion of subjects purchasing Pravachol 10 mg who consulted a health care provider within 2 months of product use as well as those who did not take Pravachol 10 mg subsequent to the consultation if therapy was not recommended.

Statistical Methods

All statistical analyses were performed using SAS Version 6.12 on an open VMS operating system. Descriptive summary statistics (mean, standard deviation, proportion) was used for all demographic variables.

Results

Population enrolled/analyzed

- Enrolled Population – All subjects who completed the Assessment 1 questionnaire. This population was used to describe the study population with respect to the purchase decision, behavior to consult a health care provider, and risk factor profile.

- Purchase Population – All subjects who purchased Pravachol 10 mg at any time during the study. This population served as the basis for the assessment of compliance to consult a health care provider within 2 months of product use, not to take Pravachol 10 mg subsequent to being told by the health care provider that it was not appropriate, and to consult a health care provider within 2 months of product use and/or self-select appropriately in accordance with the product label.

- Consult Population - All subjects who consulted a health care provider at any time regarding the appropriateness of using Pravachol 10 mg. This population was used to describe the demographic and baseline characteristics of subjects who chose to consult their health care provider.

- Treated Population - All subjects who took at least one dose of Pravachol 10 mg. This population was used to summarize adverse events.

Out of 161,322 targeted subjects, 2,207 subjects responded to the study recruitment materials and were screened for inclusion. One thousand four hundred and twenty-five subjects (65%) chose not to enroll: 594 (42%) were "Just curious", 252 (18%) cited "Time", and 246 (17%) gave "Other" as the reason for not enrolling. There was a difference between two different pharmacy models. A greater number of the subjects chose not to enroll in IPA model [273 out of 360 respondents (76%)] than in HMO model [1,152 out of 1,847 respondents (62%)].

Of the 782 subjects who enrolled, 355 (45%) responded to the mailer, 414 (53%) were walk-through, 12 (2%) responded to the newspaper or radio advertising or by word of mouth, and for 1 (<1%) subject the reason was unknown. Seven hundred and eighty two subjects (35%) enrolled in the study of whom 404 (52%) purchased at least one box of Pravachol 10 mg.

The majority of subjects were recruited through the HMO staff model pharmacies. 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 subjects who enrolled at the retail pharmacies [53 out of 87 (61%)] compared to the HMO staff model [351 out of 695 (51%)] pharmacies went on to purchase, although the final number of participants was small (53 vs. 351).

Table 2 summarizes demographic characteristics of the enrolled and purchase populations. For the enrolled population, mean age was 51±9.5 years for men and 50.7±10.4 years for, 46% of subjects were male, 93% had at least a high school education, and 12% read below a 9th grade level (assessed by the REALM test). Racial representation included, 68% Caucasian, 21% Black, 5% Hispanic, 3% Asian, and 1% Native American. Equal number of men and women purchased the drug.

Some differences were noted in demographic characteristics for subjects recruited at staff model study sites vs. the IPA model study sites. In general, subjects recruited from the staff model study sites were younger, less educated and had lower household incomes. There were no significant differences in literacy levels. In addition, a greater percentage of women (55% vs. 49%) and Blacks (23% vs. 9%) were recruited at the HMO study sites compared to the IPA model study sites.

Differences were noted across demographic subpopulations in the enrolled population. Although recruitment efforts were successful in enrolling minority subjects, purchase rates were lower among minorities. Some of the differences in purchase rates in the studied subpopulations are presented in Table 1.

Table 1. Purchase Rate in Different Demographic Subpopulations

		Purchase rate N (%)‡
Racial subgroups:	Caucasians (n=533)	296 (56%)
	Blacks (n=166)	70 (42%)
	Hispanics (n=36)	17 (47%)
	Other (n=36)	21 (58%)
Age subgroups:	<35 years (n=43)	14 (33%)
	35-54 years (n=451)	15 (52%)
	55-74 years (n=274)	153 (56%)
	>75 years (n=9)	4 (44%)
Gender:	Males (n=356)	200 (56%)
	Females (n=423)	204 (48%)
Literacy:	Low (n=95)	48 (51%)
	Normal (n=662)	352 (53%)
Income:	< 25,000 (n=94)	44 (47%)
	25-49,999 (n=266)	137 (52%)
	50-99,999 (n=300)	158 (53%)
	>100,000 (n=90)	60 (67%)

‡ *Percentages are based on the number of subjects in that subgroup*

Table 2. Demographic Characteristics of Enrolled Population

	Statistics	Enrolled Population N=782		Purchase Population N=404	
Age	N	777		404	
	Mean ± SD	51±10		51±10	
	Median	51		51	
	Min	18		18	
	Max	80		80	
		n	(%)	n	(%)
Age Group	<35	43	(5%)	14	(3%)
	35 – 54	451	(58%)	233	(58%)
	55 – 74	274	(35%)	153	(38%)
	≥ 75	9	(1%)	4	(<1%)
	Unknown	5	(<1%)	0	(0%)
Gender	Female	423	(54%)	204	(50%)
	Male	356	(46%)	200	(50%)
	Missing	3	(<1%)	0	(0%)
Race	Asian	21	(3%)	11	(3%)
	Black	166	(21%)	70	(17%)
	Hispanic	36	(5%)	17	(4%)
	Native American	10	(1%)	7	(2%)
	Caucasian	533	(68%)	296	(73%)
	Other	5	(<1%)	3	(<1%)
	Unknown	11	(1%)	0	(0%)
Education	No High School	10	(1%)	5	(1%)
	Some High School	30	(4%)	14	(3%)
	High School Grad.	429	(55%)	219	(54%)
	College Graduate	297	(38%)	166	(41%)
	Unknown	16	(2%)	0	(0%)
Literacy (REALM)	< 6th grade	17	(2%)	7	(2%)
	7th – 8th grade	78	(10%)	41	(10%)
	≥ 9th grade	662	(85%)	352	(87%)
	Unknown	25	(3%)	4	(<1%)
Income	< $25,000	94	(12%)	44	(11%)
	$25,000 - $49,999	266	(34%)	137	(34%)
	$50,000 - $99,000	300	(38%)	159	(39%)
	≥ $100,000	90	(12%)	60	(15%)
	Unknown	32	(4%)	4	(<1%)

Comments

The population enrolled in this study is not representative of the overall U.S. population. Differences in demographics between staff and IPA model sites were observed. IPA model study sites were located in one state (DE), and HMO model study sites were spread among 5 southern states (TX,FL,OK,TN,VA). The lower purchase rate in an younger population is expected especially when the label states that this product is indicated for men above the age of

35 and women above the age of 55 years. One would also suspect enrolled women be older than the men; however, there is no gender age difference seen in this study. Lower enrollment was observed in this study in the IPA model sites than in the HMO model. Subgroups of racial minorities, lower literacy, and lower income groups tend to have higher enrollment in HMO type of settings than in IPA. The population demographics may be skewed because of the lower overall enrollment in the IPA setting.

Health Care Status and Cholesterol Awareness

Health care status and cholesterol awareness for the enrolled and the purchase populations are summarized in Table 3. The results were similar in the enrolled and the purchase populations. Nearly all subjects saw a physician at least yearly, about one-third had seen their physician specifically for elevated cholesterol, and approximately 20% had known of their elevated cholesterol levels for at least 5 years.

Table 3. Summary of Baseline Health Care Status and Cholesterol Awareness

		Enrolled (N=782)	Purchase (N=404)
		N (%)	N (%)
See a doctor once a year		753 (96%)	393 (97%)
Have seen a doctor specifically about cholesterol		244 (31%)	128 (32%)
Ever been told of high cholesterol		657 (84%)	363 (90%)
When first diagnosed with high cholesterol	0-6 mo ago	129 (20%)	80 (22%)
	6-12 mo ago	78 (12%)	46 (13%)
	1-3 yrs ago	198 (30%)	113 (31%)
	3-5 yrs ago	98 (15%)	53 (15%)
	>5 yrs ago	150 (23%)	70 (19%)
	Unknown	4 (<1%)	1 (<1%)

Differences were noted in health care status and cholesterol awareness for subjects recruited at the staff model study sites vs. the IPA model study sites:

	HMO	IPA
• See a doctor once a year	97%	90%
• Had been told they had high cholesterol	85%	72%
• Had seen a doctor specifically about cholesterol	33%	20%
• First told of high cholesterol within the last 3 years	62%	54%

Differences were noted across the age subpopulations in the enrolled population:

	< 35yrs	35-54yrs	55-74yrs	≥ 75yrs
Had been told they had high cholesterol	70%	82%	90%	89%
Had seen a physician specifically about their cholesterol	35%	29%	34%	22%

Forty percent of subjects with lower literacy levels had seen a physician specifically about their cholesterol compared to 31% of subjects who read at or above a 9th grade level. There were no differences by gender or race with regard to healthcare status and cholesterol awareness.

Cholesterol Lowering Action

Table 4 summarizes the cholesterol lowering methods reported as "ever used" for the enrolled and the purchase populations. Twice as many subjects reported having "ever used" a dietary supplement or OTC medication [377 (48%)] compared to a prescription lipid lowering drug [161 (21%)]. The most common supplements used by subjects in each population were antioxidants, garlic, and fiber products. The purchase population was similar to the enrolled population.

Table 4. Cholesterol Lowering Actions Ever Used (Enrolled and Purchase Population)

	Enrolled (N=782)		Purchase (N=404)	
	N	(%)	N	(%)
Prescription Medication	161	(21%)	66	(16%)
Dietary Supplement/OTC Medications	377	(48%)	210	(52%)
Modify Diet	456	(58%)	242	(60%)
Lose Weight	225	(29%)	120	(30%)
Increase Level of Exercise	307	(39%)	166	(41%)

Minor differences were noted across study site type. The number of subjects recruited from the staff model study sites [149 (21%)] who had been treated previously with prescription medication was greater than subjects recruited from the IPA study sites [12 (14%)]. However, a greater percentage of subjects recruited from the IPA study sites had modified their diet (66% vs. 57%), lost weight (40% vs. 27%) and increased exercise levels (45% vs. 39%, respectively). There was no difference in the percentage who had used dietary supplement/OTC medications.

Across subpopulations, differences were noted for age and literacy.

- The number of subjects who had modified their diets or used prescription medication increased with age: 47% and 12% in subjects < 35 years, 58% and 14% in subjects 35-54 years, 61% and 32% in subjects 55-74 years and 67% and 56% in subjects ≥ 75 years.
- A greater number of subjects reading at or above the 9th grade literacy levels compared to low literacy subjects (60% vs. 51%) had modified their diets, used dietary supplements/OTC medications (50% vs. 42%) and increased their level of exercise (41% vs. 32%) compared to those with lower literacy levels.
- Subjects with lower literacy levels had previously used prescription medication more often (25% vs. 20%) than those subjects reading at or above the 9th grade level.

Table 5 presents the cholesterol lowering therapies that were being used at study entry. In the enrolled population, 16% were taking a prescription lipid lowering medication and 26% were currently using dietary supplements or OTC medications. Similar findings were seen in the purchase population.

Table 5. Cholesterol Lowering Therapies Currently Being Used (Enrolled and Purchase Population)

Action	Enrolled (N=782)		Purchase (N=404)	
	N	(%)	N	(%)
Dietary Supplements/OTC Medications	204	(26%)	99	(24%)
General Nutrition	140	(18%)	68	(17%)
Vitamins	140	(18%)	70	(17%)
Laxatives (fiber)	79	(10%)	35	(9%)
Diet Drug for Obesity	1	(<1%)	0	(0%)
Prescription Lipid Lowering Drugs	125	(16%)	48	(12%)
Other Prescription Drugs	3	(<1%)	3	(<1%)
Unknown	1	(<1%)	0	(0%)

Comments

Results of this data analysis are expected to be not applicable to a general U.S. population for the reasons mentioned earlier. Differences in health care status and cholesterol awareness in the two study models can be explained by the fact, that people in HMO type of care tend to use health care more, since the consumers are not charged for the actual visits. This makes a difference in selecting the cholesterol lowering action one takes first: changing a diet, losing weight and increasing an exercise level, or going to the doctor for prescription. Literacy subgroup analysis also reflects the prevalence for the enrollment in the two different health care settings.

Coronary Heart Disease Risk Factor Profile

The distribution of CHD risk factors were assessed by the physicians. The most frequently reported 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 subjects, respectively. Similarly, the most frequently reported risk factors seen in the purchase population were age (54%), hypertension (35%), and family history (29%). Differences in prevalence of CHD risk factors were noted across study site type. Subjects recruited at the staff model study sites compared to IPA model subjects had a greater incidence of diabetes (13% vs. 6%), hypertension (40% vs. 33%), and smoking (13% vs. 1%), whereas subjects recruited at the IPA model sites had a greater incidence of age as a risk factor (69% vs. 48%).

Differences in prevalence of CHD risk factors were observed among the demographic subpopulations in the enrolled population is presented in Table 6. The incidence of CHD, diabetes, and hypertension increased with age. The incidence of CHD was greater in Caucasians vs. Blacks. However, Blacks had a greater incidence of hypertension, diabetes and smoking (15% vs. 11%) when compared to Caucasians. Men had a greater incidence of CHD vs. women whereas more women had diabetes and hypertension. The percentage of diabetes and hypertension was higher among low literacy individuals than subjects of normal literacy.

Table 6. CHD Risk Factor Profile in the Demographic Subpopulations (Enrolled Population)

Subpopulation	CHD (% of subjects)*	Diabetes (%)	Hypertension (%)
< 35 yrs	3	3	23
35-54 yrs	2	10	32
55-74 yrs	13	19	52
>75 yrs	25	0	50
Caucasians	7	10	36
Blacks	3	20	51
Males	10	10	36
Females	3	14	42
Low literacy	4	18	51
Normal literacy	6	12	37

** Percentages are based on the number of subjects in that subgroup.*

The physician's independent assessment was carried out without knowledge of the subjects' self-reported assessment of risk factors. Overall, the concordance between subject and physician assessment of risk factors was very good. Subjects tended to overstate the presence of CHD, which was primarily due to subjects reporting the presence of angina more frequently than the physician (this discrepancy could be explained by subjects reporting angina for chest pain that had been diagnosed by their physician as "non-cardiac" in nature). 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 as assessed by the physician are shown in Table 7 for the enrolled and purchase populations. The CHD risk factor profile was comparable among both populations, and demonstrated that lower to moderate risk individuals were interested in the product.

Table 7. CHD Risk Factor Profile at Baseline

	Enrolled Population (% of subjects)	Purchase Population (% of subjects)
CHD	6	5
No CHD, ≥2 Risk Factors	35	35
No CHD, <2 Risk Factors	58	60

Mean Baseline Lipid Profile

The most recent laboratory results prior to study enrollment were used to describe baseline lipid profiles for the various subject populations. Lipid parameters for the Enrolled and Purchase populations for whom data was available are presented in Table 8. The findings in both populations are comparable with regard to mean lipid levels.

Table 8. Mean Baseline Lipid Profile (Enrolled and Purchase Populations)

	Enrolled (n=782)	Purchase (n=404)
Total Cholesterol mg/dl Mean ± SD Range Median	n = 579 234 ± 50 106 – 1033 233	n = 323 239 ± 56 115 – 1033 235
LDL-Cholesterol mg/dl Mean ± SD Range Median.	n = 445 148 ± 33 33 – 248 149	n = 246 150 ± 30 48 – 231 151
HDL-Cholesterol mg/dl Mean ± SD Range Median	n = 466 51 ± 17 20 –184 48	n = 260 51 ± 17 20 – 184 48
Triglycerides mg/dl Mean ± SD Range Median	n = 520 195 ± 353 10 – 7836 156	N = 291 215 ± 463 10 –7836 159

Table 9 summarizes concomitant medication use by drug classification for the enrolled and purchase populations. As expected in a target population of generally healthy, prevention-oriented individuals, the most commonly used medications were vitamins and estrogens in the enrolled population. Approximately 50% of women were taking hormone replacement therapy. Anti-diabetic (8%) and cardiac (3%) medications were used less frequently in the enrolled population. These results were not significantly different from the purchase population.

Table 9. Summary of Concomitant Medications (> 2%) at Baseline by Class (Enrolled and Purchase Population)

Drug Classification	Enrolled Population N = 782		Purchase Population N = 404	
	n	(%)	n	(%)
Vitamins	288	(37%)	154	(38%)
Estrogens	180	(23%)	105	(26%)
Antihistamines	96	(12%)	60	(15%)
Analgesics	95	(12%)	59	(15%)
Antinflammatory/Antirheumatic	95	(12%)	48	(12%)
ACE-inhibitors	85	(11%)	34	(8%)
Calcium channel blockers	85	(11%)	39	(10%)
Diuretics	79	(10%)	30	(7%)
General Nutrients	78	(10%)	39	(10%)
Antacids	70	(9%)	41	(10%)
Beta Blockers	70	(9%)	34	(8%)
Anti-diabetics	62	(8%)	24	(6%)
Thyroid therapy	58	(7%)	27	(7%)
Psychoanaleptics	54	(7%)	28	(7%)
Antidepressants	48	(6%)	23	(6%)
Anti-asthmatics	44	(6%)	26	(6%)
Antihypertensives	42	(5%)	21	(5%)
Antibacterials	37	(5%)	23	(6%)
Psycholeptics	37	(5%)	16	(4%)
Corticosteroids	26	(3%)	16	(4%)
Progestogens	26	(3%)	15	(4%)
Nasal preparations	22	(3%)	19	(5%)
Cardiac Therapy	20	(3%)	7	(2%)
Muscle Relaxants	19	(2%)	13	(3%)
Antiepileptics	16	(2%)	6	(1%)
Antispasmodics	15	(2%)	8	(2%)
Urologicals	14	(2%)	10	(2%)
Antithrombotics	13	(2%)	3	(<1%)
Renin-angiotensin system agents	12	(2%)	7	(2%)

Comments

The predetermined NCEP factors for classification of CHD risk are high total and LDL cholesterol levels. Even though laboratory tests were not required according to the protocol, the tested subjects lipid profile, seem to indicate a wide range of total and LDL cholesterol. Median total cholesterol level of 235 mg/dl in the purchase population suggests that

considerable number of subjects did not qualify for the therapy as specified on the label (total cholesterol level of 200-240 mg/dl). HDL cholesterol level was also relatively high (mean=51). Subjects enrolled in this study tended to overstate the presence of CHD as a risk factor. The enrolled and purchase populations were similar in terms of use of concomitant medications.

Subjects Prematurely Withdrawn from Study Medication

Table 10 summarizes reasons for premature withdrawal from the study medication. Of the 321 treated subjects, a total of 165 (51%) prematurely withdrew from the study. The most frequent reason for withdrawal was "Other", which occurred in 102 (32%) of the subjects that took Pravachol 10 mg. Examination of these subjects' verbatim responses revealed that 68 subjects discontinued because of non-compliance (e.g. too busy, forgot to take, pharmacy hours inconvenient, etc), 14 subjects stated that they wanted to talk with their physician or were awaiting physician approval, 4 subjects were denied repurchase due to failure to consult a physician, 8 discontinued for other reasons and 8 discontinued for unknown reasons. Twenty subjects (6%) discontinued treatment due to adverse events. The specific adverse events that lead subjects to discontinue are described in a safety section of the review.

Table 10. Reasons for Premature Withdrawal (Treated Population)

Reasons for Withdrawal	N=321	
Total	N (165)	51 (%)
Other	102	32
Adverse events	22	7
Health care provider did not recommend treatment	20	6
Unknown	11	3
Intercurrent illness	7	2
Treatment failure	2	<1
Lost to follow-up	1	<1

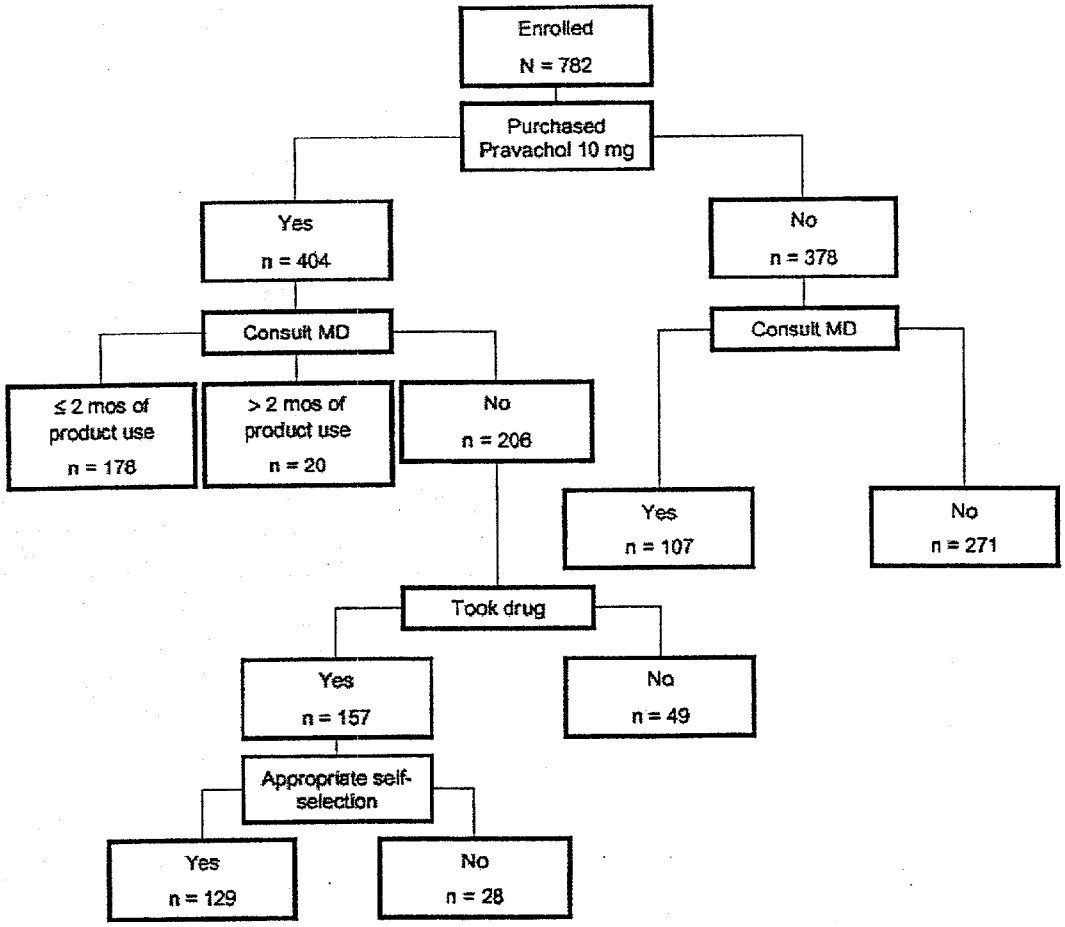
Comment

High rate of withdrawal again, shows poor compliance and need for health care provider intervention.

Efficacy Results

According to the sponsor, of the 782 subjects who enrolled into the study and who had the opportunity to purchase Pravachol 10 mg, 754 (96%) demonstrated appropriate behavior: 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 on the label; 49 (6%) did not consult, but did not take the medication; and 28 (7%) took the product, did not consult a health care provider and did not appropriately self-select. The results of the behavior of the enrolled population shown in Figure 1.

Figure 1. Summary of Behaviors



The majority of the subjects who took Pravachol 10 mg and did not consult a physician (75%) had spoken to their physician about their cholesterol within the 6 months prior to entering the study. There were several instances where the subject's physician initiated a contact. In 1 case, the physician advised a potential subject not to purchase the medication; this subject is included in the enrolled population but not the purchase population. There were 2 cases where the physician initiated contact with a subject and recommended treatment with Pravachol 10 mg. Both of these subjects took medication, self-selected appropriately and were included in the No Consult population. In an additional case, 1 subject returned to the study site to report an adverse event to the enrollment desk, at which time the physician intervened and instructed the subject to discontinue the use of Pravachol 10 mg. This subject was included in the consult population.

Three hundred and seventy-eight subjects did not purchase Pravachol 10 mg. Table 11 summarizes the reasons subjects elected not to purchase Pravachol 10 mg. The numbers cannot be added since a subject may have given more than one reason for not purchasing the product. Twenty-eight percent (n = 107) of subjects gave no reason for not purchasing. The rest, 271 subjects, gave 318 reasons for non-purchasing Pravachol. The primary reason for non-purchase

was interest in consulting a physician first (44%). Contraindications or other label warnings were the reasons given for non-purchase by 20% of subjects. In addition, there were 61 subjects (16%) who cited "Other" reasons for not purchasing, of which the most frequent included: 13 subjects "Did not have money with them"; 5 were "Concerned about side effects"; 5 felt their "Cholesterol was too low"; 4 were "Concerned about label warnings"; and 4 "Wanted more information". Three percent cited cost as the reason not to purchase.

Table 11. Reasons Subjects Did Not Purchase Pravachol 10 mg

Reason	N	(%)
Wanted to consult MD	167	(44%)
No reason given	107	(28%)
Other	61	(16%)
Male <35 years old, female <55 years old	24	(6%)
Already being treated	20	(5%)
Did not know cholesterol level	16	(4%)
Noted label warning/risk factors too high	14	(4%)
Cost	10	(3%)
Cholesterol level not between 200-240 mg/dl	5	(1%)
Wanted to consult a pharmacist	1	(<1%)

Behavior of the Purchase Population

Overall, 93% of the subjects in the purchase population exhibited behavior that presented no potential harm. Of the 404 subjects 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. An additional 20 subjects (5%) consulted after the pre-defined 2 month window of product use and were thus not included as meeting the primary objective. None of these subjects were prompted to consult following an attempt to repurchase additional medication. Of the 206 subjects who did not consult a health care provider, 49 subjects (12%) did not use any of the medication, 129 (32%) subjects took Pravachol 10 mg but appropriately self-selected according to pre-specified criteria defined in the protocol. Twenty-eight subjects (7%) who took medication did not consult and did not appropriately self-select. Although there were differences noted in baseline characteristics, there was no significant difference observed between behavior of the purchase population based on study site type. Overall, 92% and 97% of subjects at the staff model and IPA model sites, respectively, exhibited behavior that presented no harm. One hundred fifty (43%) subjects at the staff model sites fulfilled the primary objective by consulting their health care provider within 2 months of product use compared to 28 (53%) subjects at the IPA model sites (p-value = 0.168). An additional 19 (9%) subjects at the staff model sites versus 1 (4%) subject at the IPA model sites consulted after the pre-defined 2 month window (p-value = 0.365).

The data used for the primary analyses represents the more conservative physician – verified consultation with the subject. However, since this study was conducted in a "naturalistic" setting, using the subject's own (non-research) primary care physician, patient charts may not have been current. An analysis, based on the subjects' self-reported physician contact showed that 53% who took Pravachol 10 mg contacted their physician within 2 months of product use and an additional 5% outside the 2 month window. Of the subjects who did not contact a

physician, 10% did not take the medication, 26% took Pravachol 10 mg but appropriately self-selected according to the pre-specified criteria in the protocol, and 5% subjects took medication and did not appropriately self-select.

Inappropriate Self-Selection

Twenty-eight subjects did not appropriately self-select based on the pre-defined criteria: 4 had CHD, 14 had diabetes mellitus, 3 had liver disease and, 10 were currently on prescription cholesterol lowering medications. There were 12 males and 16 females in this group. The group is too small to analyze demographic differences. Twenty-five subjects out of 28 (89%) discussed cholesterol with a physician within 6 months of starting study to compare to only 57% such a behavior in consult population. One subject reported estrogen as a lipid lowering medication. While this subject self-selected appropriately according to the pre-specified criteria, she is counted in the no consult/inappropriate self-selection category.

Comments
The primary efficacy endpoint, which was to determine the proportion of subjects who purchased Pravachol 10 mg and consulted a health care provider within two months, was met by 44%. Data from this study also show that the subject's self-reported physician contact rate is higher (53%) than the physician's report. Overall this reflects poor compliance in respect to follow up.

The second primary efficacy endpoint for this study was to determine the proportion of subjects who, having purchased Pravachol 10 mg, do not take it subsequent to contacting their health care provider and being told that therapy is not recommended. The information gathered from the study is biased. All subjects had health insurance and personal health care provider. There were 5 cases in the study in which the contacts with the subjects were physician initiated.

No analysis of data were provided by the sponsor about the behavior of the population who purchased the drug and consulted a physician. The data, which were submitted, did not allow for a separate analysis of this population. However, of the total 782 enrolled subjects, a health care provider did not recommend Pravachol 10 mg to 291 (37%) subjects, of whom 95 (33%) purchased the drug.

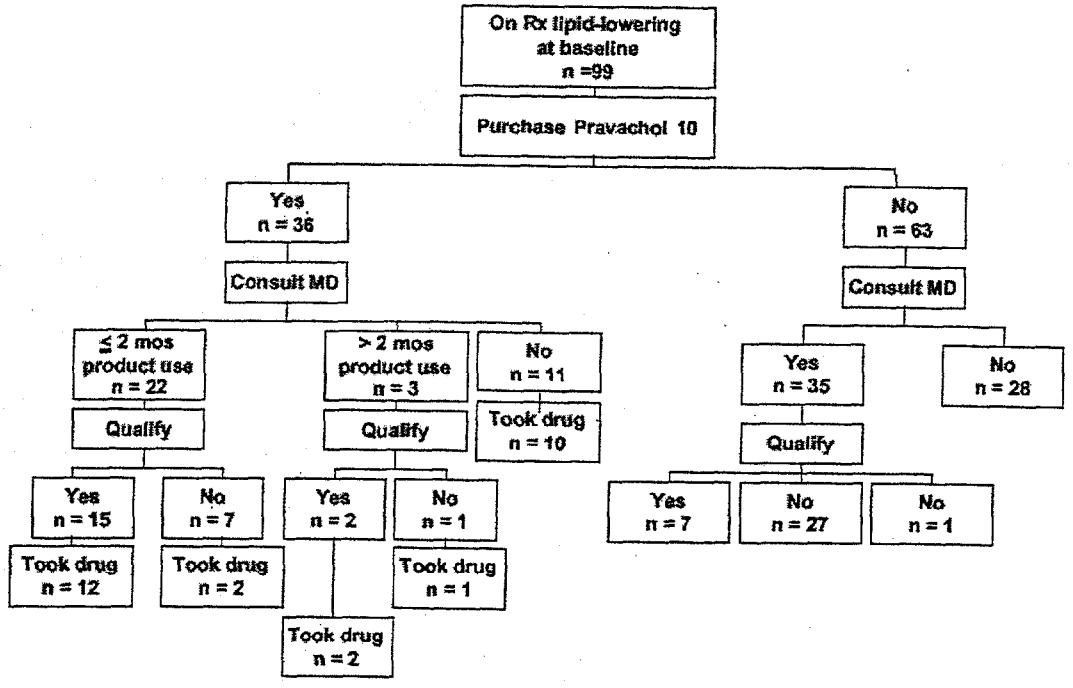
The main conclusion that the sponsor makes is that the majority of subjects enrolled in the study did not harm themselves by purchasing or not purchasing the medication. The main issue for actual use trial like this is to determine if the targeted populations can identify themselves and be able to use the product safely and effectively. Pravachol label used in this study clearly states that this drug is indicated for men above 35 years of age and women above 55 years of age with total cholesterol level 200-240 mg/dl. Four hundred and twenty three women were enrolled in the study, and 204 of them purchased the drug. One hundred twenty three (59.8 %) of those who purchased Pravachol, did not meet the age requirements. Only 4% (7 out of 200) of men below 35 years of age purchased the drug. Laboratory testing was not a requirement for the study. The qualification criteria that the sponsor is using for the treatment is not in compliance with the label, and therefore the analysis of appropriate self-selection Pravachol 10 mg is not acceptable.

As a tertiary objective, the sponsor tried to analyze in detail, the behavior of the subjects who did not purchase the drug. This analysis does not give any additional information for safe and effective use of Pravachol 10 mg by the OTC consumers. Forty four percent of the subjects in this group stated that they would like to consult a physician prior to purchase of Pravachol. Only one third of those who did not purchase Pravachol 10 mg consulted their physician.

Populations of special interest

A consideration in an Rx-to-OTC switch of a cholesterol lowering medication is the potential for a consumer to shift from a prescription lipid lowering medication to an OTC product. A total of 99 subjects were taking prescription lipid-lowering medications at baseline, thus putting them at risk for potentially shifting to less efficacious therapy. The behavior of these subjects is shown in Figure 2. Of the 99 enrolled subjects in this population, 60 (61%) consulted a health care provider.

Figure 2. Summary of Behavior of All Subjects on Lipid Lowering Medication at Baseline



Thirty-six subjects (36%) purchased Pravachol 10 mg. Sixty percent (n = 22) of the purchasers consulted a physician within 2 months of product use (an additional 3 subjects consulted after the pre-defined 2 month window). One subject (3%) never consulted a physician but did not take Pravachol 10 mg. Twenty-seven subjects took Pravachol 10 mg; 14 of these consulted the physician who recommended OTC therapy. Three subjects took Pravachol 10 mg although the physician indicated it was not appropriate; however, 1 of these subjects began prescription Pravachol 40 mg after taking the OTC product for 1 month. Ten subjects took Pravachol 10 mg

and never consulted. Their baseline lipid lowering medications and behavior are summarized in Table 12. Of these 10 subjects, one took 2 OTC tablets daily to achieve the prescription dose, 1 substituted OTC Pravachol 10 mg for prescription Pravachol (10 mg), and 1 took OTC Pravachol 10 mg for 2 months instead of cholestyramine, but then began prescription Pravachol. Thus, 11 subjects (11% of the total number of subjects on prescription lipid lowering therapy at baseline) shifted from prescription therapy to OTC. Three subjects attempted to repurchase OTC Pravachol 10 mg without consulting a health care provider.

Table 12. Summary of Behaviors for Subjects on Lipid Lowering Medication at Baseline (Who Took Pravachol 10 mg)

	Site/Subject	Baseline Prescription Medication	Study Behavior
Took/No Consult	0001/0001	Pravachol 20 mg	Took 1 month of Pravachol 10 mg; 2 tablets daily (Rx dose)
	0003/0003	Pravachol 10 mg	Took 2 months of Pravachol 10 mg
	0007/0031	Simvastatin (dose unknown)	Unknown if subject took Pravachol 10 mg
	0008/0015	Cholestryramine (dose unknown)	Subject discontinued cholestyramine to take Pravachol 10 mg. After 2 months of taking Pravachol 10 mg the subject began a prescription dose of Pravachol.
	0008/0040	Cholestyramine (dose unknown)	Subject took 1 month of Pravachol 10 mg.
	0014/0012	Pravachol (dose unknown)	Subject took 2 months of Pravachol 10 mg in place of prescription Pravachol.
	0017/0006	Simvastatin (dose unknown)	Subject stopped simvastatin at the time of the first use of Pravachol 10 mg.
	0018/0005	Simvastatin (dose unknown)	Subject took 2 months of Pravachol 10 mg.
	0019/0005	Gemfibrozil/atorvastatin (doses unknown)	Unknown if subject took Pravachol 10 mg.
	0022/0009	Fluvastatin (dose unknown)	Subject took Pravachol 10 mg for approximately 2 weeks and stopped for an unknown reason.
Took/Consulted within 2 months/ Did not qualify	0013/0048	Simvastatin (20 mg)	Subject took 1 month of Pravachol 10 mg
	0019/0028	Pravastatin (dose unknown)	Pravastatin prescription dose increased to 40 mg after 1 month of Pravachol 10 mg
Took/Consulted after 2 months/Did not qualify	0012/0022	Atorvastatin (dose unknown)	Subject took 1 month of Pravachol 10 mg

Comments

Subjects taking prescription lipid lowering agents comprised 13% of total enrolled population. Even though the majority (87%) of them showed appropriate behavior, there is still a risk of inappropriate use and the possibility that the population may substitute their prescribed therapy with readily available OTC product.

Safety outcomes

Duration of exposure for subjects who took Pravachol 10 mg is shown in Table 13. Nearly half of the subjects who took Pravachol 10 mg continued on treatment for more than 2 months.

Table 13. Duration of Treatment (Treatment Population)

Overall duration of Treatment (Days)	N=321
Mean	51 ± 29
Median	55
Range	1 – 147
Days	n (%)
1 – 7	22 (7%)
8 – 14	19 (6%)
15 – 21	9 (3%)
22 – 28	22 (7%)
29 – 42	73 (23%)
43 – 56	20 (6%)
>56	156 (49%)

Adverse Events

A summary of all reported adverse events by body system is presented in Table 14 for the Treated population (N = 321). Overall, 80 (25%) subjects reported treatment emergent adverse events. The most frequently reported adverse events involved the gastrointestinal system (7%) or were dermatologic in nature (7%). Myalgia was reported in 2 (<1%) subjects and was determined to be unrelated to study medication in both cases. Three subjects with a history of liver disease took Pravachol 10 mg and did not consult a health care provider. One subject experienced the following adverse events: leg cramps, respiratory congestion, and a laceration to the left arm. Each of the events were considered unrelated to medication and mild in severity.

Table 14. 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%)

A summary of investigator-assessed AEs and their relationship to study medication for all adverse events is shown in Table 15. Events that occurred more than once in the same subject during the study were counted only once using the episode with the strongest relationship to study medication.

Table 15. Adverse Events Presented by Relationship to Study Medication (Treated Population)

	N=321	
	N	(%)
Subjects with Aes	80	(25%)
Related	13	(4%)
Unrelated	63	(20%)
Unassessable	4	(1%)

Adverse events judged related to study medication were reported by 13 subjects (4%). Nausea and dizziness were the most frequent AEs [each in 3 subjects (<1%)] judged related to study medication. Eleven of these events were mild in severity, 1 moderate and 1 severe. One episode of nausea was considered moderate in severity and one episode of "cramp abdomen" was considered severe.

Deaths
No deaths were reported during the study.

A total of four subjects experienced serious or potentially serious adverse events either during the study or within 30 days of treatment cessation. None of these events were considered related to study medication. List of the events is presented in Table 16.

Table 16. Serious or Potentially Serious Adverse Events (Treated Population)

Site/Subject #	Age	Gender	Treatment Duration (Days)	Relationship	Serious Event
0007/0022	54	M	50	Unrelated	Pancreatitis
0017/0017	64	M	84	Unrelated	Squamous cell cancer
0019/0028	43	M	9	Unrelated	Pericardial cyst
0019/0091	60	M	24	Unrelated	Gastroesophageal reflux disease

Subjects Prematurely Withdrawn for Adverse Events

Twenty subjects (6%) out of total 321 treated discontinued treatment due to adverse events. Table 17 summarizes the reasons for discontinuation of study medication for adverse events. Nausea and dizziness were the events that most frequently led to study withdrawal. Five subjects had more than one adverse event which caused them to withdraw from the study.

Table 17. Reasons for Premature Withdrawals for Adverse Events (Treated Population) N=20

Event	N (%)
Nausea	4 (1%)
Dizziness	3 (1%)
Rash	2 (< 1%)
Cramp abdomen	2 (< 1%)
Diarrhea 2 (< 1%)	2 (< 1%)
Tachycardia	1 (< 1%)
Pain back 1 (< 1%)	1 (< 1%)
Anxiety 1 (< 1%)	1 (< 1%)
Insomnia 1 (< 1%)	1 (< 1%)
Fatigue 1 (< 1%)	1 (< 1%)
Edema 1 (< 1%)	1 (< 1%)
Abnormality kidney 1 (< 1%)	1 (< 1%)
Abnormality abdomen 1 (< 1%)	1 (< 1%)
Hypothyroidism 1 (< 1%)	1 (< 1%)
Flushing 1 (< 1%)	1 (< 1%)
Dyspepsia 1 (< 1%)	1 (< 1%)
Urticaria 1 (< 1%)	1 (< 1%)
Total	25 (8%)

Laboratory Data

Laboratory tests were not required for this study. However, after further review, one subject was found to have an increase of alkaline phosphatase that was mild in severity and unrelated to Pravachol 10 mg, and one subject reported an episode of hypoglycemia that was considered moderate in severity and unrelated to Pravachol 10 mg. Neither subject discontinued treatment due to the adverse event.

Comments

The incidence of AE's in this trial is low. The population of subjects taking the drug in this study was not large. Compliance was not monitored, and the length of treatment was short. Most of the adverse events were mild in severity.

Summary of the OPTIONS study:

- *Design of this actual use trial does not reflect natural OTC environment. Subjects enrolled in the study had their personal physicians, and were monitored for their actions.*

- *The population enrolled into the study is not representative of the overall U.S. population. Study sites were restricted to the certain geographic areas and the two different HMO type of settings.*

- *The label used in this study had certain criteria (serum cholesterol, age, gender) for qualification for the treatment. Because of the inclusion criteria, subjects enrolled into the study were relatively young. These variables were not accounted in the analysis of consumer behavior. Assessment of the appropriateness of the therapy did not follow current medical practice, or NCEP guidelines either.*

- *Primary efficacy endpoint, to consult a physician within 2 months of purchase of Pravachol 10 mg, was achieved in 44% of the subjects.*

- *Analysis of the health care status and cholesterol awareness showed that majority of the studied population are concerned about their cholesterol and general health. However, data from this study also showed consumers' low interest in Pravachol 10 mg therapy. Out of total 161,322 targeted subjects, 2,207 responded to the study recruitment materials and only 65% of those, chose to enroll.*

- *High withdrawal rate (51%), as noted in the PREDICT study, was observed in this study as well.*

- *Although laboratory tests were not required for this study, almost half of the subjects who purchased the drug, and whose lipid profile was available, did not meet the label indications (total cholesterol 200-240 mg/dl). The health care provider did not recommend Pravachol 10 mg tablets to 37% of the enrolled subjects.*

- *Duration of exposure for subjects, who took Pravachol 10 mg in the study, was relatively short. Only 156 (49%) of the treatment population continued therapy for 56 days or more. No new safety concerns were observed in the treated population during the study.*

Overall Benefit/Risk Assessment for OTC approvability and use

Several criteria determines whether a drug product is both safe and effective and appropriate for OTC status for particular indication at given dosage:

1) *The drug should have acceptable safety profile.*
   In this case as demonstrated in controlled and uncontrolled trials Pravachol is relatively safe. Safety and efficacy of Pravachol tablets for the treatment of hypercholesterolemia has been well established by clinical trials supporting its approval as prescription product. No new signals have appeared in the course of post-marketing surveillance attributable to either labeled use or misuse of prescription product. Post-marketing surveillance has limitations related to the nature of the reporting system. Reporting is voluntary and may be variable and incomplete; the population at risk is poorly defined; and our ability to infer causality or quantitative risk is quite limited. However, use in a large uncontrolled population as OTC drug may bring up more and unexpected adverse drug events in the future. The issue of Pregnancy Category X drug being OTC will have to be discussed further with pharmtox reviewers and Advisory Committee members. The behavior of women of childbearing age was not addressed in these two actual use trials.

2) *It should have low misuse and abuse potential, and be free of important food, drug, or disease interactions. These issues will be addressed by the Division of Endocrine-Metabolic drugs.*

3) *Consumer can self-diagnose, self-recognize and self-treat the condition.*
This is a major concern because hypercholesterolemia is not readily recognizable and is not symptomatic condition. It needs laboratory test to make a diagnosis. In addition, there are specific NCEP criteria defining the risk for CHD according to certain cholesterol levels for appropriate selection of treatment options. Assignment of patients to certain treatment categories is usually done on the basis of the average two cholesterol determinations to account for biological variations. Those issues as well as the length and the goal of the therapy were not addressed in these two actual use trials.

4) *Can be adequately labeled.*
The two actual use trials covered by this review showed poor consumer understanding of serum cholesterol levels required for appropriate self selection of the product. Pravachol package labels, used in the two actual use trials and the label comprehension study, were different from the currently proposed label for OTC Pravachol 10 mg tablets. Labeling will have to be discussed further regarding indications, population, dose, and duration of use.

These issues, as well as the risk-benefit assessment of Pravachol 10 mg tablets as an OTC product for treatment of hypercholesterolemia, warrant further discussion with members of the Nonprescription and Metabolic Endocrine Drug Advisory Committees.

Unless above mentioned issues are clarified, in the opinion of OTC reviewing medical officer, the data of the two actual use trials do not support approval of the NDA for Pravachol 10 mg tablets to be marketed as over-the-counter drug product in the U.S. market.

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CC:

NDA 21-198 (Archival)
HFD-510/Division Files
HFD-510/Orloff
HFD-510/Simoneau

HFD-560/Ganley
HFD-560/Katz
HFD-560/Shetty
HFD-560/Cook
HFD-560/Yuan
HFD-560/Lipnicki/ Mokhtari

HFD-42/Lechter