CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-898/S032

MEDICAL REVIEW(S)

Joint Clinical and Statistical Review

NDA #: 19-898/ Supplement 032

Drug: PRAVACHOL (pravastatin sodium) tablets

Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute

Indication: Secondary prevention based on The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study

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INTRODUCTION

The curvilinear relationship between low-density lipoprotein cholesterol (LDL-C) and total cholesterol (total-C) levels and the risk for atherosclerotic cardiovascular disease is well-established. In the past decade, clinical trials involving statins have provided evidence that total-C and LDL-C reduction in at-risk individuals resulted in reductions in fatal and nonfatal ischemic events without the offsetting increase in noncardiovascular deaths observed in some non-statin trials. This benefit has been documented in both primary and secondary prevention populations and across a broad range of cholesterols. More recent trials have targeted populations with cholesterol levels in the lower end of this spectrum but still within the range where a significant percentage of coronary events occur.

In particular, the Cholesterol and Recurrent Events (CARE) Trial demonstrated that further lowering of average cholesterol levels (mean LDL-C of 139 mg/dL) in a population with a recent myocardial infarction (MI) led to reductions in the risk of future ischemic events (composite endpoint of non-fatal MIs and fatal coronary events). In patients without clinical evidence of cardiovascular disease and who were at increased risk for disease, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) demonstrated that reduction of average to moderately elevated cholesterol levels (mean LDL-C of 150 mg/dL) decreased the risk of experiencing an initial ischemic event (composite endpoint of nonfatal MIs, fatal coronary events, and new onset angina). Unlike the Scandinavian Simvastatin Survival Study (4S) which enrolled patients with established CAD and markedly elevated serum cholesterol and thus had a relatively high rate of CHD death, neither of these trials was designed to detect a significant effect on CHD deaths or all-cause mortality. Table 1 summarizes four statin trials with clinical outcome data.

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

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

It is recognized that as an individual's risk for disease decreases the absolute benefits of treatment also decrease and may be offset by the risk of drug therapy. The need to address the benefits of treating patients with established CHD and lower cholesterols is essential since the risk for recurrent events is lower in this population as demonstrated

by a placebo event rate of 8.5% in 4S versus 5.7% in CARE for CHD mortality and 11.5% versus 9.4% for overall mortality.[1]

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial was a secondary prevention trial designed to determine if cholesterol reduction with pravachol in patients with average cholesterols would result in a reduction in CHD mortality. Established heart disease was defined by a history of recent myocardial infarction or hospitalization for unstable angina.

REVIEW OF LIPID TRIAL

STUDY DESIGN

Objectives

LIPID was a multicenter, double-blind, parallel-group, randomized, placebo-controlled clinical trial designed to determine if treatment with pravastatin in patients with a history of myocardial infarction or unstable angina and a total-C level within the range of 155-271 mg/dL would reduce the incidence of CHD mortality.

Secondary objectives included determining the effect of treatment with pravastatin on:

- the incidence of total mortality
- the incidence of nonfatal MI and fatal CHD (classified as CHD events)
- the incidence of total stroke and non-hemorrhagic stroke
- the incidence of cardiovascular mortality
- the incidence of myocardial revascularization procedures
- total-C, LDL-C, HDL-C, TGs, apo A1 and apo B
- the relationship of lipid fractions and changes in them to CHD mortality and other endpoints (events reduction analyses)
- total days of hospitalization

Eligibility Criteria

Inclusion criteria:

- men and women (non-lactating and postmenopausal or surgically sterile) ages 31 through 75 years
- patients who have experienced an acute MI or unstable angina pectoris (UAP) requiring hospitalization 3 months to 3 years prior to screening
- plasma TC 155-271 mg/dL after dietary counseling (this lab was obtained at week –4 during an 8 week dietary placebo run-in phase)
- demonstrated compliance in taking placebo (≥ 80%) during placebo run-in phase

Exclusion criteria include (but not limited to) the following:

- any cardiac surgery, angioplasty, major surgery, or major illness within the past 3 months (included acute MI or admission for UAP)
- NYHA Class III or IV CHF
- left ventricular EF ≤ 25%
- history of cerebrovascular disease (including stroke or TIA) within past 3 months
- renal or hepatic disease defined as serum creatinine ≥ 160 umol/L, serum albumin < 3.0 g/dL, bilirubin > 30 umol/L, serum ALT or AST > 1.5x the upper limit of normal (ULN)

- uncontrolled endocrine disease, chronic pancreatitis, dysproteinemia, porphyria, or SLE
- treatment with other lipid-lowering agents, cyclosporin, or other investigational drugs
- fasting TG levels ≥ 443 mg/dL

Screening and Randomization

Eighty-seven study centers throughout Australia and New Zealand screened men and women ages 31 through 75 years to assess eligibility. If the locally determined TC was > 271 mg/dL, the patient met all other eligibility criteria, and the patient consented to study participation, he/she would enter an 8-week dietary placebo run-in phase. Fasting lipid profiles were obtained at 4 weeks (week –4) for eligibility determination and at 8 weeks (week 0/randomization) for baseline values.

Patients were randomized by a central randomization system in a 1:1 ratio to pravastatin 40 mg or matching placebo tablets. Randomization was stratified by qualifying event (MI or UAP) within each study center using a randomized block design with a block size of 10. Patients with both qualifying events were stratified as MI.

Medication Dosing and Titration

Study medication was to continue for at least 5 years unless the study was stopped early or treatment was discontinued by the patient or investigator. All patients were started on either 2 tablets of pravastatin 20 mg or matching placebo administered at bedtime. The dose of study medication was adjusted if the subject's total-C fell below 116 mg/dL or if the subject developed a drug-related adverse reaction. If the total-C exceeded 309 mg/dL at a single visit or 290 mg/dL at two successive visits further dietary control was implemented. If additional lipid-altering drugs were required investigators were encouraged to prescribe cholestyramine although other agents were allowed and these subjects were not excluded from outcome analyses.

Study Visits and Laboratory Assessments After Randomization

Study visits were scheduled at 6 month intervals after randomization for the assessment of drug compliance, adverse events, and efficacy endpoints. Dietary recommendations were reinforced throughout the study duration and physical exams were performed annually.

Fasting blood for lipid parameters was collected locally and plasma was submitted to a designated central lipid laboratory. Total-C was determined 6 months after randomization and annually thereafter. HDL-C, TGs, and apolipoprotein B and A1 levels were measured at Year 1, 3, 5 and at study close (Table 2). LDL-C was calculated using the Friedewald formula at Year 1, 3, 5, and at study close if TGs were < 443 mg/dL. For samples with TGs > 443 mg/dL the LDL-C was not considered for analysis. All safety labs were determined at local labs using the following timetable:

Table 2. Timetable of Laboratory Assessment

Laboratory Assessment	Interval of Assessment
serum ALT/AST	every 3 mos during year 1, every 6 mos thereafter
serum CPK	every 12 mos
serum creatinine, bilirubin, alkaline phosphatase, hematologic profile	year 1, 5, and at close of study
fasting glucose	close of study
urinalysis	year 5 and at close of study

Protocol Amendments

The original study protocol was implemented on December 15, 1989. A total of 5 revisions to this protocol were made; 4 amendments took place after the first patient was enrolled. The majority of revisions were minor including guidelines for safety assessments, study medication discontinuation, ophthalmologic evaluations, and administrative changes. Three secondary endpoint measures were added to the protocol in December 1996 prior to unblinding of data. These included:

- incidence of total stroke and non-hemorrhagic strokes
- incidence of cardiovascular mortality
- incidence of revascularization procedures (CABG and coronary angioplasty)

In addition, the secondary endpoint, nonfatal and fatal MIs, was revised to be a combined incidence of nonfatal MIs and fatal CHD events.

Monitoring Committees and Endpoints Adjudication

The ***Management Committee*** was responsible for the design and conduct of the study and interacted with the ***Safety and Data Monitoring Committee (SDMC)*** which reviewed blinded study reports for serious adverse events (SAEs). The SDMC did not consist of any members affiliated with the Sponsor or the study centers. If total mortality or SAEs in the two treatment groups deviated from the null hypothesis by more than 3 standard deviations then the SDMC would recommend early study termination to the Management Committee.

The accurate designation of endpoint events was determined by the ***Outcome Assessment Committee*** (OAC) and the ***Stroke Assessment Committee*** (SAC) in a blinded fashion. The OAC was comprised of 3 cardiologists who reviewed data on all suspected MIs and all deaths. The SAC was comprised of 2 members from the Management Committee and a review panel consisting of 3 practicing neurologists. This committee reviewed each suspected stroke case to verify its occurrence and further classify the event as ischemic, cerebral/cerebellar hemorrhage, subarachnoid hemorrhage, or unknown type. All endpoint events were pre-defined and algorithms were established for their accurate adjudication.

The primary endpoint of CHD mortality consisted of the following: fatal MI; sudden cardiac death; death after possible MI; death secondary to heart failure; and death after coronary revascularization. Deaths occurring more than one hour after a cardiac resuscitation were also considered as primary endpoint events.

The secondary endpoint measure, all-cause mortality, was further categorized as coronary, cardiac but non-coronary, vascular but non-cardiac, cancer, trauma, suicide, or other.

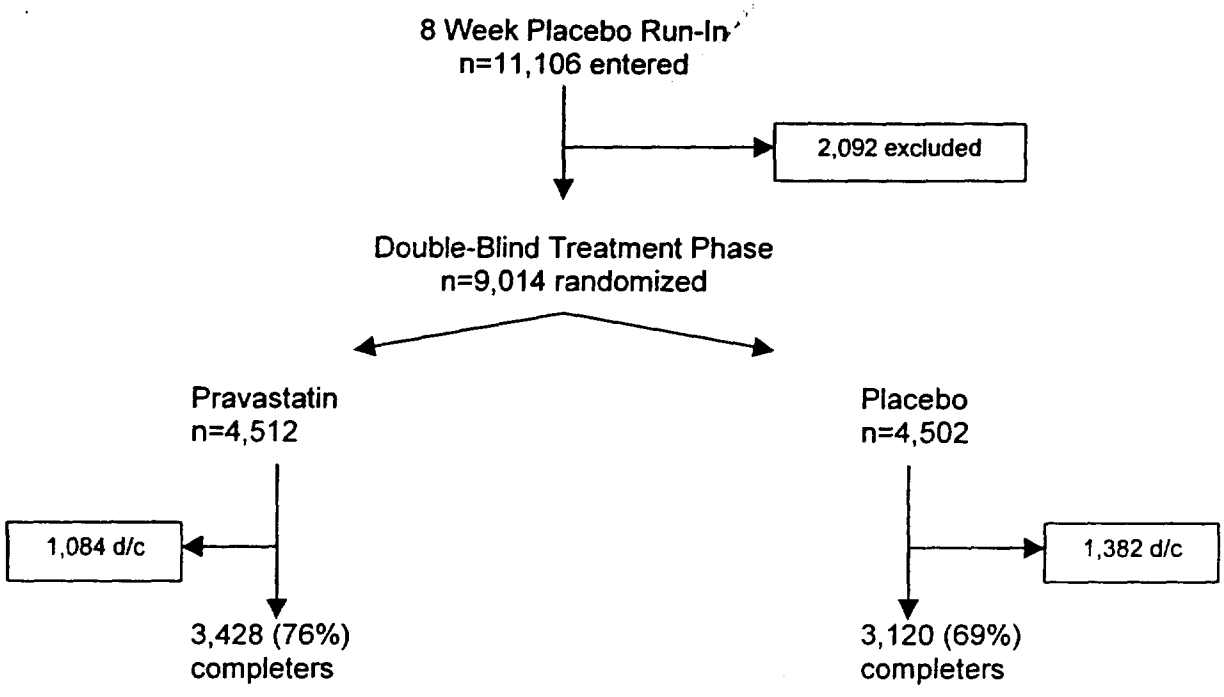
RESULTS OF LIPID

Patient Disposition

Eleven thousand one hundred and six subjects (11,106) were entered into the 8-week, single-blind, placebo run-in period (Figure 1). Of those, 2,092 were excluded from randomization for the following reasons: lipid profile not within designated range (8.3%); ischemic event within 3 months (1.4%); surgery/major illness within 3 months (0.9%); using prohibited medication (0.4%); abnormal LFTs (1.0%); laboratory abnormalities (0.8%); and discontinuations (6.8%). Nine thousand fourteen (9,014) subjects were

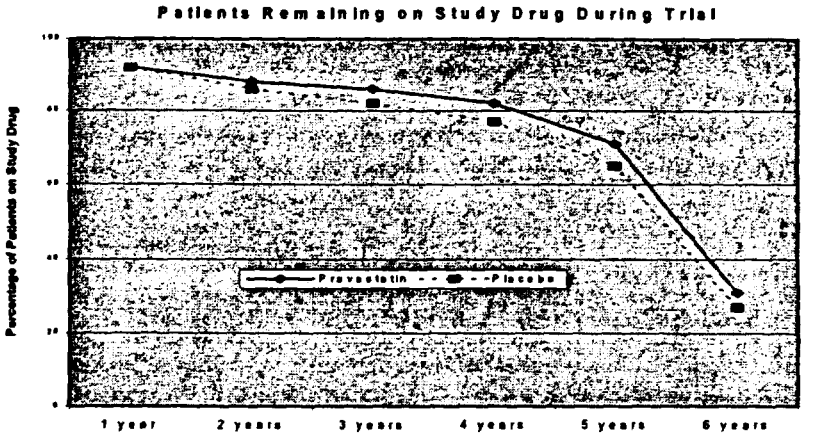
randomized to treatment with pravastatin 40 mg daily (4,512) or placebo (4,502) from June 12, 1990 through December 1, 1992. The final patient visit was on October 7, 1997.

Figure 1. Patient Disposition in LIPID Trial



Approximately 76% of patients in the pravastatin group and 69% in the placebo group completed the trial. One thousand eighty-four (1,084; 24%) patients exposed to pravastatin discontinued treatment permanently versus 1,382 (30.7%) patients in the placebo group. Discontinuations due to death from any cause and interruptions in therapy were not considered in these figures. The rate of discontinuation was similar between the 2 groups (see Figure 2). These patients continued to have all protocol-specified visits and procedures for ascertainment of events related to safety and efficacy. The mean duration of follow-up was 5.7 years in the pravastatin group and 5.6 years in the placebo group. Vital status was known for all but one study subject at the end of study.

Figure 2. Percent of Patients on Study by Year



Reasons for study drug discontinuations were collected on the case report forms under the following categories: suspected adverse drug reaction; abnormal ALT or CK; hospital admission; patient's decision; or other. These are broad classifications which may not adequately reflect the actual reason for study drug cessation. For example, the category 'patient's decision' may encompass a variety of reasons from patient relocation to treatment failure. Table 3 summarizes the reasons for permanent discontinuations as provided by the sponsor. Many patients were assigned to more than one category hence, the number of reasons for discontinuation exceeds the number of patients with permanent discontinuation.

Table 3. Reasons for Permanent Discontinuation of Study Medication*

	Pravastatin (n=4,512)	Placebo (n=4,502)
Patients Discontinuing Permanently	1,084	1,382
Reason for Discontinuation+		
Suspected Adverse Drug Reaction	110	99
Abnormal ALT/CK	54	40
Hospital Admission	249	336
Patient decision	654	813
Other	323	529

*Reason for discontinuation was not ascertained in 5 patients
+due to patients being assigned to more than one reason this number exceeds the actual number of patients discontinuing medication

In order to better define the reasons for permanent study discontinuation we assigned priorities to the reasons for discontinuation in the following manner: suspected ADRs > abnormal ALT/CK > hospital admission > patient decision > other. This approach allowed for patients to be counted only once and proportion of randomized subjects discontinuing for each reason could thus be calculated (Table 4). The most common reason documented for study discontinuation was patient decision (pravastatin, 11.1%; placebo, 13.9%). In previously reviewed statin trials, categories such as 'patient's decision' and 'other' have accounted for 5% or less of the cohort terminating study.

Table 4. Modified Reasons for Permanent Discontinuation of Study Medication

	Pravastatin (n=4,512)	Placebo (n=4,502)
Patients Discontinuing Permanently	1,084	1,382
Reason for Discontinuation		
Suspected Adverse Drug Reaction	111 (2.5%)	99 (2.2%)
Abnormal ALT/CK	31 (0.7%)	22 (0.5%)
Hospital Admission	238 (5.3%)	324 (7.2%)
Patient decision	501 (11.1%)	628 (13.9%)
Other	200 (4.4%)	307 (6.8%)
Unknown	3 (<0.1%)	2 (<0.1%)

Source: NDA 19-898/S032 CD submitted by sponsor containing raw data on study discontinuation (not archived)

A significantly greater number of patients in the placebo (986; 22%) versus pravastatin group (237; 5.3%) began open-label therapy with more placebo-assigned patients dropping in at < 1 year (placebo 68; 1.5% vs. pravastatin 4; 0.1%). Since efficacy endpoints were still being ascertained in discontinued patients, this difference could potentially diminish any beneficial effects attributed to pravastatin.

Baseline Demographics and Patient Characteristics

The two treatment groups were well-balanced with respect to baseline demographics and characteristics (Table 5). Two-thirds of the cohort had established CAD based on having experienced an MI within the previous 3-36 month period prior to screening. Male subjects (83.2%) accounted for the majority of the study population. The mean age was 60.8 years with approximately 39% of the cohort ≥ 65 years of age. For unknown reasons, information regarding ethnicity was not collected on the case report forms (CRFs) nor the menopausal status of female subjects recorded.

Table 5. Baseline Demographics and Patient Characteristics

Characteristic	Pravastatin (n=4,512)	Placebo (n=4,502)	Cohort (n=9,014)
Male	3756 (83.2%)	3742 (83.1%)	7498 (83.2%)
Female	756 (16.8%)	760 (16.9%)	1516 (16.8%)
Mean Age (years)	60.7	60.9	60.8
SD	8.5	8.4	8.4
Range	31-75	32-75	31-75
Qualifying Event			
MI	2879 (63.8%)	2875 (63.9%)	5754 (63.8%)
UA	1633 (36.2%)	1627 (36.1%)	3260 (36.2%)
Smoker			
Yes	914 (20.3%)	911 (20.2%)	1825 (20.2%)
No	3598 (79.7%)	3591 (79.8%)	7189 (79.8%)
Hypertension			
Yes	1867 (41.4%)	1891 (42.0%)	3758 (41.7%)
No	2644 (58.6%)	2609 (58.0%)	5253 (58.3%)

Characteristic	Pravastatin (n=4,512)	Placebo (n=4,502)	Cohort (n=9,014)
Unknown	1 (0%)	2 (0%)	3 (0%)
Diabetes			
Yes	396 (8.8%)	386 (8.6%)	782 (8.7%)
No	4116 (91.2%)	4116 (91.4%)	8232 (91.3%)
History of Stroke			
Yes	171 (3.8%)	198 (4.4%)	369 (4.1%)
No	4341 (96.2%)	4303 (95.6%)	8644 (95.9%)
Unknown	0 (0%)	1 (0%)	1 (0%)
Baseline TC (mg/dL)			
mean	218.8	218.6	218.7
SD	32.1	31.1	31.6
range			
Baseline HDL-C (mg/dL)			
mean	36.8	37.1	37.0
SD	9.0	9.2	9.1
range			
Baseline LDL-C (mg/dL)			
mean	149.7	150.3	150.0
SD	28.7	28.6	28.7
range			
Baseline TGs (mg/dL)			
mean	162.6	157.4	160.0
SD	91.2	79.0	85.4
range			

Patient Compliance

Patient compliance was determined by pill counts and defined as taking study medication ≥ 75% of the time. Compliance was similar in both groups with only 127 (2.8%) patients randomized to pravastatin versus 118 (2.6%) patients in the placebo group considered non-compliant. These patients were considered in the efficacy assessments unless otherwise noted.

Concomitant Medications

There were no significant differences in use of concomitant medications at baseline between treatment groups (Table 6). A significant percentage of patients reported aspirin use at baseline (82.4%).

Table 6. Concomitant Medication Use at Baseline

Medication	Pravastatin (n=4,512)	Placebo (n=4,502)	Cohort (n=9, 014)
ASA	3730 (82.7%)	3698 (82.1%)	7428 (82.4%)
Ca++ blockers	1543 (34.2%)	1576 (35.0%)	3119 (34.6%)
Beta-blockers	2083 (46.2%)	2150 (47.8%)	4233 (47.0%)
ACE-inhibitors	720 (16.0%)	713 (15.8%)	1433 (15.9%)
Nitrates	1346 (29.8%)	1331 (29.6%)	2677 (29.7%)
Antihypertensives	3376 (74.8%)	3446 (76.5%)	6822 (75.7%)
Insulin	58 (1.3%)	47 (1.0%)	105 (1.2%)
Oral hypoglycemics	193 (4.3%)	217 (4.8%)	410 (4.5%)
Estrogenic treatments	57 (1.3%)	56 (1.2%)	113 (1.3%)

Statistical Methods

The protocol-defined analysis was a time-to-event intent-to-treat (ITT) analysis using a Cox proportional hazards model. The following potential covariates were named in the

protocol: age, gender, smoking, other diseases, level of entry lipids, MI/unstable angina (stratifier) and time from MI/angina attack to enrollment. The main analyses performed by the sponsor and FDA include MI/unstable angina as a stratifier. Additional analyses including site in the model produced essentially the same results as presented in this review.

All available study endpoints from randomization up to and including the last scheduled visit date from all randomized subjects regardless of their compliance with study medication, discontinuation from study medication, or initiation of open-label lipid-lowering therapy were included in the analyses.

Subgroup analyses were performed by the FDA to examine the consistency of effect across important subgroups (qualifying event (MI or UAP); age (≥ 65, < 65); gender; history of hypertension; history of diabetes mellitus; and smoking). Subgroups were chosen so that comparisons to other databases (such as CARE, WOSCOPS etc.) could be made.

The event rates reported in the tables in this review are simply crude event rates (number of events observed divided by the total number of patients at risk). These rates were chosen to be consistent with rates presented in related reviews (4S, WOSCOPS and CARE) and in labeling for other statins.

Three interim analyses were planned after all patients had completed a minimum of 2, 3, and 4 years. The nominal significance level was set at .003 for each interim analysis. No significance level was named for the final analysis. Given that the observed p-value for the primary endpoint is less than .001, the impact of the interim analyses would be negligible.

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Efficacy Results

Primary Efficacy

The primary efficacy measure was total CHD mortality. There were a total of 660 CHD deaths in the LIPID trial with 287 (6.3%) occurring in the pravastatin group and 373 (8.3%) in the placebo group. More than half of the CHD deaths were classified as sudden cardiac death (393/660; 59.5%) Table 7.

Table 7. Differences in CHD Mortality in LIPID Trial Between Pravastatin and Placebo Groups

Cause-Specific Mortality	Pravastatin n=4,512	Placebo n=4,502	Cohort n=9,014
Fatal MI	34 (0.7%)	74 (1.6%)	108
Sudden Cardiac Death	182 (4%)	211 (4.7%)	393
Death in Hospital w/ Possible MI	19 (0.4%)	15 (0.3%)	34
Heart Failure due to CHD	36 (0.8%)	46 (1%)	82
Certified Coronary Death	2 (<0.1%)	5 (0.1%)	7
Death after Coronary Revascularization Procedure	10 (0.2%)	12 (0.3%)	22
Resuscitated Cardiac Death	4 (<0.1%)	10 (0.2%)	14
Total	**287 (6.3%)**	**373 (8.3%)**	**660 (7.3%)**

Source: NDA19-898/S032 endpt9.xpt, endpt1.xpt, vol. 5 table S6.2.1A

Pravastatin significantly reduced the risk of experiencing a fatal coronary event by 24% ($p<0.0004$, Figure 3 and Table 8).

Figure 3. Survival Curves for Total CHD Mortality

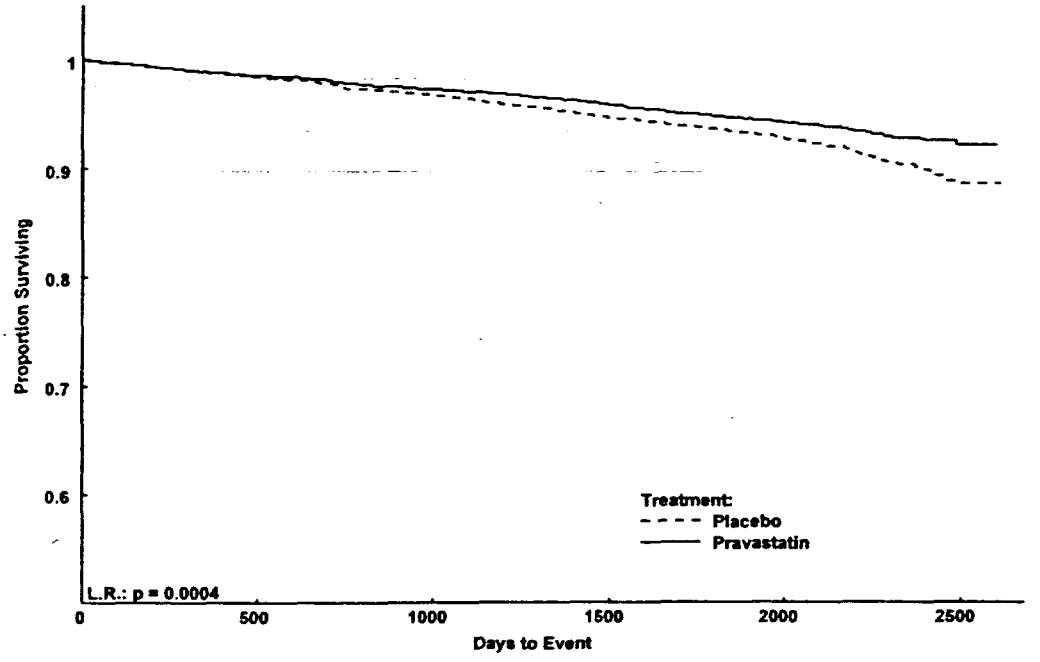
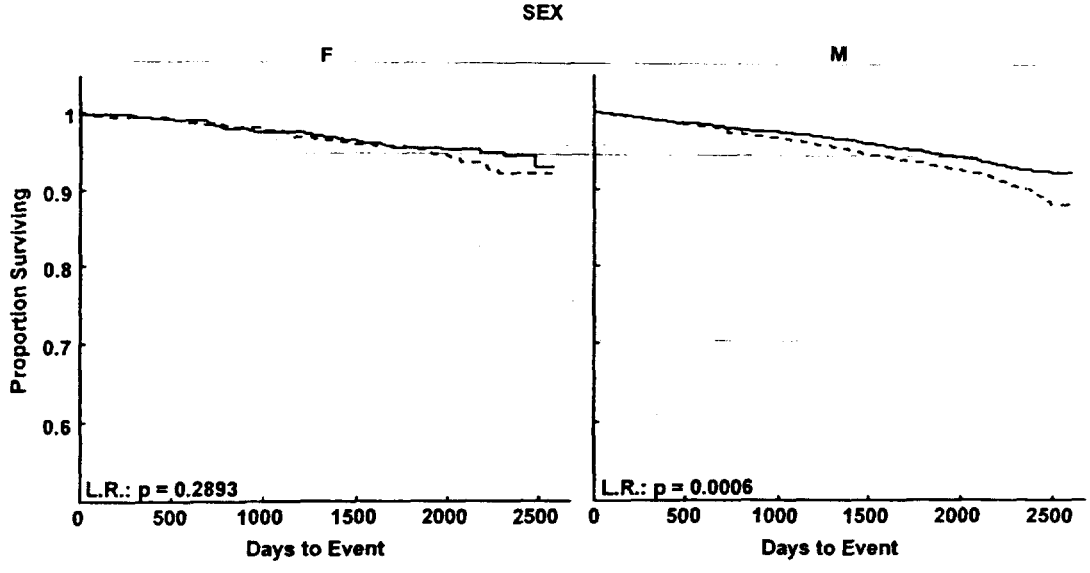


Table 8. Primary Efficacy Results for Total CHD Mortality

	# of Events/Total # of Patients (percent)		Relative Risk	95% CI	P-value
	Pravastatin	Placebo			
All Patients	287/4512 (6.4%)	373/4502 (8.3%)	0.76	0.65, 0.88	.0004
Strata					
MI	206/2879 (7.2%)	265/2875 (9.2%)	0.77	0.64, 0.92	.004
UAP	81/1633 (5.0%)	108/1627 (6.6%)	0.74	0.55, 0.98	.04
Gender					
Male	248/3756 (6.6%)	323/3742 (8.6%)	0.75	0.63, 0.88	.0006
Female	39/756 (5.2%)	50/760 (6.6%)	0.82	0.54, 1.25	.35
Age					
<65	127/2771 (4.6%)	162/2729 (5.9%)	0.76	0.61, 0.96	.02
≥65	160/1741 (9.2%)	211/1773 (11.9%)	0.76	0.62, 0.94	.009
Median Baseline LDL					
<149.6	147/2264 (6.5%)	178/2239 (8.0%)	0.81	0.65, 1.00	.052
≥149.6	140/2248 (6.2%)	195/2262 (8.6%)	0.71	0.57, 0.89	.002
Smoker					
Yes	59/914 (6.5%)	73/911 (8.0%)	0.79	0.56, 1.12	.18
No	228/3598 (6.3%)	300/3591 (8.4%)	0.75	0.63, 0.89	.001
History of Hypertension					
Yes	130/1867 (7.0%)	167/1891 (8.8%)	0.78	0.62, 0.98	.03
No	157/2644 (5.9%)	205/2609 (7.9%)	0.75	0.61, 0.92	.006
History of Diabetes					
Yes	52/396 (13.1%)	47/386 (12.2%)	1.07	0.72, 1.59	.73
No	235/4116 (5.7%)	326/4116 (7.9%)	0.71	0.60, 0.84	.0001

More than 70% of the CHD deaths in both treatment groups occurred in those subjects who had established heart disease as defined by a recent myocardial infarction and approximately 86% of these events occurred in males. In the subgroups comprised of women (Figure 4), diabetics and smokers, the risk reductions for CHD mortality did not achieve statistical significance.

Figure 4. Survival curves for Total CHD Mortality for females and males



Secondary Efficacy

Total Mortality

A total of 1,131 patients died during the study with 498 (11.0%) occurring in the pravastatin group versus 633 (14.1%) in the placebo group (Table 9). CHD deaths, the primary efficacy endpoint, accounted for the majority of deaths (660/1131; 58.4%) followed by cancer (269/1131; 23.8%). There were no categories in which the incidence of death was greater in the pravastatin group compared with the placebo group.

Table 9. Total Mortality in the LIPID Trial

Cause Specific Mortality	Pravastatin n=4,512	Placebo n=4,502	Cohort n=9,014
Coronary	287	373	660
Cardiac (non-coronary)	2	4	6
Vascular (non-cardiac)	42	56	98
Cancer	128	141	269
Trauma	5	5	10
Suicide	1	6	7
Other	33	48	81
Total	**498 (11.0%)**	**633 (14.1%)**	**1,131 (12.5%)**

Treatment with pravastatin resulted in a relative risk reduction of 23% ($p<0.0001$) for all-cause mortality (Table 10). Again, this risk reduction was not significant for women, smokers, or diabetics. Among women, the risk of dying during this trial was similar in both treatment groups (RR 0.99).

Table 10. Secondary Endpoint Results
Total Mortality

	# of Events/Total # of Patients (percent)		Relative Risk	95% CI	P-value
	Pravastatin	Placebo			
All Patients	498/4512 (11%)	633/4502 (14.1%)	0.78	0.69, 0.87	.0001
Strata					
MI	340/2879 (11.8%)	422/2875 (14.7%)	0.79	0.69, 0.92	.002
UAP	158/1633 (9.7%)	211/1627 (13%)	0.74	0.61, 0.91	.004
Gender					
Male	424/3756 (11.3%)	555/3742 (14.8%)	0.75	0.66, 0.85	.0001
Female	74/756 (9.8%)	78/760 (10.3%)	0.99	0.72, 1.36	.96
Age					
<65	210/2771 (7.6%)	208/2729 (9.8%)	0.76	0.64, 0.91	.003
≥65	288/1741 (16.5%)	365/1773 (20.6%)	0.79	0.68, 0.93	.003
Median Baseline LDL					
<149.6	259/2264 (11.4%)	308/2239 (13.8%)	0.83	0.70, 0.97	.02
≥149.6	239/2248 (10.6%)	325/2262 (14.4%)	0.73	0.62, 0.86	.0002
Smoker					
Yes	102/914 (11.2%)	127/911 (13.9%)	0.79	0.61, 1.02	.07
No	396/3598 (11.0%)	506/3591 (14.1%)	0.77	0.68, 0.88	.0001
History of Hypertension					
Yes	207/1867 (11.1%)	277/1891 (14.7%)	0.75	0.62, 0.90	.002
No	291/2644 (11.0%)	355/2609 (13.6%)	0.80	0.69, 0.94	.005
History of Diabetes					
Yes	79/396 (20.0%)	89/386 (23.1%)	0.86	0.63, 1.16	.31
No	419/4116 (10.2%)	544/4116 (13.2%)	0.76	0.67, 0.86	.0001

CHD Events (CHD Mortality or non-fatal MI)
This efficacy measure consisted of events classified as CHD mortality (primary endpoint) or non-fatal MI. There were 557 (12.3%) CHD events in the pravastatin group versus 715 (15.9%) events in the placebo group (Table 11). In this population of patients with established heart disease, more than half of recurrent CHD events were due to a nonfatal MI (719/1,272; 56.5%).

Table 11. Initial CHD Events (CHD deaths or Nonfatal MI) in the LIPID trial

CHD Event	Pravastatin (n=4,512)	Placebo (n=4,502)	Cohort (n=9,014)
CHD mortality	247	306	553
Nonfatal MI	310	409	719
Total	**557 (12.3%)**	**715 (15.9%)**	**1272 (14.1%)**

The risk reduction for pravastatin patients was the same as observed for the primary efficacy endpoint, 24% ($p<0.0001$, Table 12). Treatment with pravastatin resulted in significant reductions in risk of experiencing a CHD event across the different subgroups evaluated except women, smokers, and diabetics.

Table 12. Secondary Endpoint Results
CHD Mortality or Non-fatal MI

	# of Events/Total # of Patients (percent)		Relative Risk	95% CI	P-value
	Pravastatin	Placebo			
All Patients	557/4512 (12.3%)	715/4502 (15.9%)	0.76	0.68, 0.85	.0001
Strata					
MI	398/2879 (13.8%)	499/2875 (17.4%)	0.78	0.68, 0.89	.0002
UAP	159/1633 (9.7%)	216/1627 (13.3%)	0.71	0.58, 0.88	.001
Gender					
Male	467/3756 (12.4%)	611/3742 (16.3%)	0.74	0.66, 0.83	.0001
Female	90/756 (11.9%)	104/760 (13.7%)	0.89	0.67, 1.18	.42
Age					
<65	287/2771 (10.4%)	366/2729 (13.4%)	0.76	0.65, 0.88	.0004
≥65	270/1741 (15.5%)	349/1773 (19.7%)	0.77	0.66, 0.90	.001
Median Baseline LDL					
<149.6	279/2264 (12.3%)	324/2239 (14.5%)	0.84	0.71, 0.98	.03
≥149.6	278/2248 (12.4%)	391/2262 (17.3%)	0.69	0.60, 0.81	.0001
Smoker					
Yes	128/914 (14%)	153/911 (16.8%)	0.82	0.65, 1.04	.10
No	429/3598 (11.9%)	562/3591 (15.7%)	0.74	0.66, 0.84	.0001
History of Hypertension					
Yes	266/1867 (14.3%)	314/1891 (16.6%)	0.85	0.72, 1.00	.05
No	291/2644 (11.0%)	400/2609 (15.3%)	0.70	0.60, 0.81	.0001
History of Diabetes					
Yes	76/396 (19.2%)	88/386 (22.8%)	0.81	0.59, 1.10	.17
No	481/4116 (11.7%)	627/4116 (15.2%)	0.75	0.67, 0.85	.0001

All-Cause Strokes

The category, all-cause strokes, consisted of ischemic strokes, cerebral/cerebellar hemorrhages, subarachnoid hemorrhages, and strokes of unknown etiology. There were 419 events classified as strokes with the most common type of stroke being ischemic (74% of all stroke events). A total of 169 (3.7%) patients treated with pravastatin experienced a stroke compared to 204 (4.5%) patients in the placebo group. Treatment with pravastatin resulted in a 19% risk reduction in experiencing a stroke (p=0.05, Table 13).

Table 13. Secondary Endpoint Results
All Cause Stroke

	# of Events/Total # of Patients (percent)		Relative Risk	95% CI	P-value
	Pravastatin	Placebo			
All Patients	169/4512 (3.8%)	204/4502 (4.5%)	0.81	0.66, 1.0	.05
Strata					
MI	98/2879 (3.4%)	120/2875 (4.2%)	0.80	0.61, 1.05	.11
UAP	71/1633 (4.4%)	84/1627 (5.2%)	0.83	0.61, 1.14	.25
Gender					
Male	136/3756 (3.6%)	177/3742 (4.7%)	0.75	0.60, 0.94	.01
Female	33/756 (4.4%)	27/760 (3.6%)	1.28	0.77, 2.14	.34
Age					
<65	65/2771 (2.4%)	85/2729 (3.1%)	0.74	0.54, 1.03	.07
≥65	104/1741 (6.0%)	119/1773 (6.7%)	0.88	0.68, 1.15	.35
Median Baseline LDL					
<149.6	81/2264 (3.6%)	112/2239 (5.0%)	0.71	0.54, 0.95	.02
≥149.6	88/2248 (3.9%)	92/2262 (4.1%)	0.93	0.70, 1.25	.64
Smoker					
Yes	32/914 (3.5%)	42/911 (4.6%)	0.74	0.47, 1.17	.20
No	137/3598 (3.8%)	162/3591 (4.5%)	0.83	0.66, 1.05	.11
History of Hypertension					
Yes	100/1867 (5.4%)	107/1891 (5.7%)	0.92	0.70, 1.21	.57
No	69/2644 (2.6%)	96/2609 (3.7%)	0.70	0.52, 0.96	.03
History of Diabetes					
Yes	31/396 (7.8%)	40/386 (10.4%)	0.72	0.45, 1.16	.18
No	138/4116 (3.4%)	164/4116 (4.0%)	0.83	0.66, 1.04	.11

Non-Hemorrhagic Strokes

This category assessed the effect of pravastatin treatment on the risk of experiencing an ischemic stroke classified as: lacunar; cardioembolic; larger artery; cerebral; and small vessel infarcts. A total of 154 (3.4%) patients in the pravastatin group versus 196 (4.4%) patients in the placebo group experienced an ischemic stroke resulting in a 23% risk reduction (p=0.02) with pravastatin therapy (Table 14).

Table 14. Secondary Endpoint Results
Non-Hemorrhagic Stroke

	# of Events/Total # of Patients (percent)		Relative Risk	95% CI	P-value
	Pravastatin	Placebo			
All Patients	154/4512 (3.4%)	196/4502 (4.4%)	0.77	0.62, 0.95	.02
Strata					
MI	92/2879 (3.2%)	116/2875 (4.0%)	0.78	0.59, 1.02	.07
UAP	62/1633 (3.8%)	80/1627 (4.9%)	0.76	0.55, 1.06	.10
Gender					
Male	124/3756 (3.3%)	169/3742 (4.5%)	0.72	0.57, 0.90	.005
Female	30/756 (4.0%)	27/760 (3.6%)	1.17	0.70, 1.97	.56
Age					
<65	55/2771 (2.0%)	79/2729 (2.9%)	0.68	0.48, 0.95	.03
≥65	99/1741 (5.7%)	117/1773 (6.6%)	0.85	0.65, 1.11	.24
Median Baseline LDL					
<149.6	77/2264 (3.4%)	106/2239 (4.7%)	0.72	0.53, 0.96	.03
≥149.6	77/2248 (3.4%)	90/2262 (4.0%)	0.83	0.61, 1.13	.24
Smoker					
Yes	25/914 (2.7%)	41/911 (4.5%)	0.59	0.36, 0.97	.04
No	129/3598 (3.6%)	155/3591 (4.3%)	0.82	0.65, 1.04	.09
History of Hypertension					
Yes	92/1867 (4.9%)	103/1891 (5.5%)	0.88	0.67, 1.17	.38
No	62/2644 (2.3%)	93/2609 (3.6%)	0.65	0.47, 0.90	.009
History of Diabetes					
Yes	29/396 (7.3%)	37/386 (9.6%)	0.74	0.45, 1.20	.22
No	125/4116 (3.0%)	159/4116 (3.9%)	0.78	0.61, 0.98	.03

Treatment with pravastatin resulted in an overall risk reduction for all-cause strokes and non-hemorrhagic strokes but these reductions were modest compared to the primary endpoint and other secondary cardiovascular endpoints. For females, the relative risks for both stroke categories were greater than 1 suggesting increased risk in the pravastatin group; however, the non-significant p-values and the confidence intervals indicate that results favorable to pravastatin are also plausible.

Cardiovascular Mortality

Cardiovascular mortality was comprised of deaths classified as coronary, cardiac but non-coronary, and vascular but non-cardiac. There were 331 (7.3%) patients in the pravastatin group and 433 (9.6%) patients in the placebo group who died of a cardiovascular event. Treatment with pravastatin resulted in a 25% risk reduction in CV mortality ($p<0.0001$, Table 15). The subgroup results are consistent with the results for the other cardiovascular endpoints.

Table 15. Secondary Endpoint Results
Cardiovascular Mortality

	# of Events/Total # of Patients (percent)		Relative Risk	95% CI	P-value
	Pravastatin	Placebo			
All Patients	331/4512 (7.3%)	433/4502 (9.6%)	0.75	0.65, 0.87	.0001
Strata					
MI	233/2879 (8.1%)	301/2875 (10.5%)	0.76	0.64, 0.91	.002
UAP	98/1633 (6.0%)	132/1627 (8.1%)	0.73	0.56, 0.95	.02
Gender					
Male	284/3756 (7.6%)	376/3742 (10.1%)	0.74	0.63, 0.86	.0001
Female	47/756 (6.2%)	57/760 (7.5%)	0.87	0.59, 1.27	.46
Age					
<65	143/2771 (5.2%)	179/2729 (6.6%)	0.78	0.62, 0.97	.02
≥65	188/1741 (10.8%)	254/1773 (14.3%)	0.74	0.62, 0.90	.002
Median Baseline LDL					
<149.6	168/2264 (7.4%)	214/2239 (9.6%)	0.77	0.63, 0.94	.01
≥149.6	163/2248 (7.3%)	219/2262 (9.7%)	0.74	0.61, 1.13	.24
Smoker					
Yes	68/914 (7.4%)	82/911 (9.0%)	0.81	0.59, 1.12	.21
No	263/3598 (7.3%)	351/3591 (9.8%)	0.74	0.63, 0.87	.0002
History of Hypertension					
Yes	155/1867 (8.3%)	196/1891 (10.4%)	0.79	0.64, 0.98	.03
No	176/2644 (6.7%)	236/2609 (9.1%)	0.73	0.60, 0.88	.001
History of Diabetes					
Yes	56/396 (14.1%)	59/386 (15.3%)	0.92	0.64, 1.33	.66
No	275/4116 (6.7%)	374/4116 (9.1%)	0.73	0.62, 0.85	.0001

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Myocardial Revascularizations

A total of 1,290 coronary revascularization procedures (CABG and PTCAs) were performed during the treatment period with 584 (12.9%) and 706 (15.7%) occurring in the pravastatin and placebo groups, respectively. The majority of the procedures were CABG's in both groups (Table 16).

Table 16. Initial Revascularization Procedures Performed During LIPID Trial

Revascularization	Pravastatin (n=4,512)	Placebo (n=4,502)	Cohort (n=9, 014)
PTCA	195	241	436
CABGs	389	465	854
Total	**584 (12.9%)**	**706 (15.7%)**	**1290 (14.3%)**

Source: NDA 19-898/S-032 endpt6.xpt

Treatment with pravastatin resulted in an overall 20% risk reduction of undergoing a revascularization procedure in this trial (p<.0001, Table 16). Interestingly, this is the endpoint where borderline significant or significant results in favor of pravastatin were observed for females, smokers and diabetics.

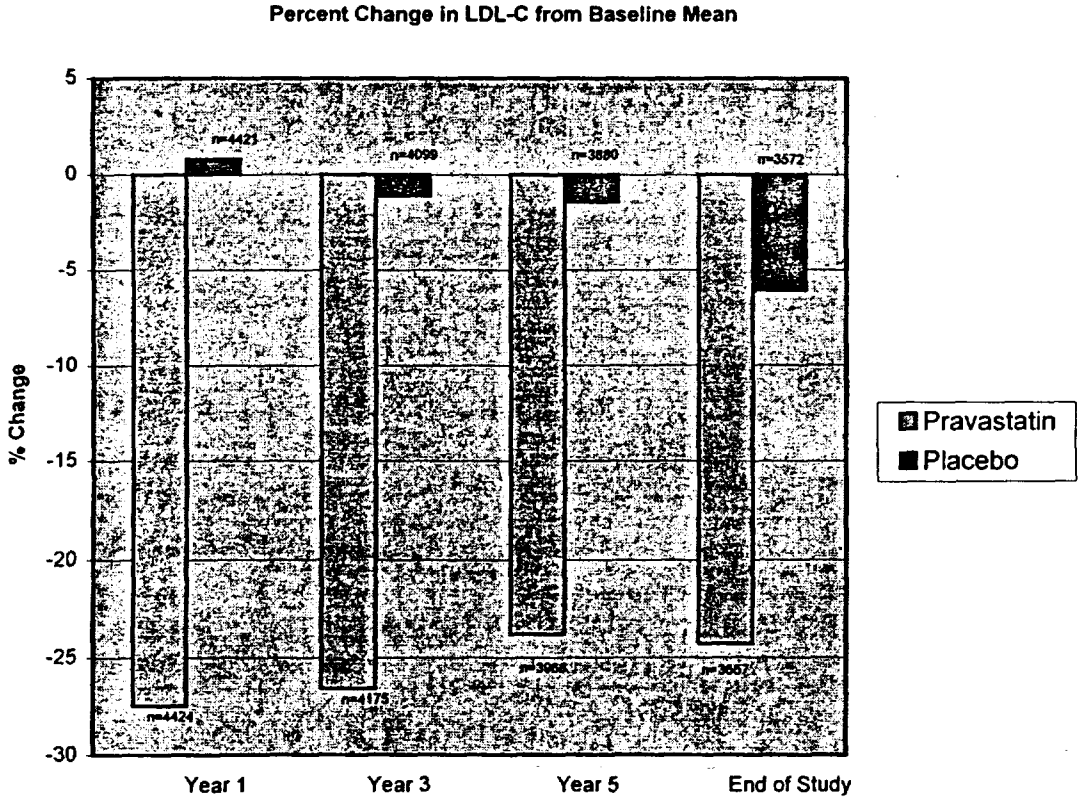
Table 17. Revascularization Procedures

	# of Events/Total # of Patients (percent)		Relative Risk	95% CI	P-value
	Pravastatin	Placebo			
All Patients	584/4512 (12.9%)	706/4502 (15.7%)	0.81	0.72, 0.90	.0001
Strata					
MI	361/2879 (12.5%)	442/2875 (15.4%)	0.80	0.70, 0.92	.002
UAP	223/1633 (13.7%)	264/1627 (16.2%)	0.82	0.68, 0.98	.03
Gender					
Male	507/3756 (13.5%)	603/3742 (16.1%)	0.82	0.73, 0.92	.0008
Female	77/756 (10.2%)	103/760 (13.6%)	0.75	0.56, 1.01	.06
Age					
<65	392/2771 (14.2%)	443/2729 (16.2%)	0.85	0.75, 0.98	.02
≥65	192/1741 (11.0%)	236/1773 (14.8%)	0.72	0.60, 0.87	.0006
Median Baseline LDL					
<149.6	288/2264 (12.7%)	322/911 (14.4%)	0.88	0.75, 1.03	.10
≥149.6	296/2248 (13.2%)	384/3591 (17.0%)	0.74	0.64, 0.86	.0001
Smoker					
Yes	110/914 12.0%)	133/911 (14.6%)	0.80	0.62, 1.03	.09
No	474/3598 (13.2%)	573/3591 (16.0%)	0.81	0.72, 0.91	.0006
History of Hypertension					
Yes	279/1867 (14.9%)	313/1891 (16.6%)	0.88	0.75, 1.03	.11
No	305/2644 (11.5%)	393/2609 (15.1%)	0.75	0.65, 0.87	.0002
History of Diabetes					
Yes	53/396 (13.4%)	79/386 (20.5%)	0.61	0.43, 0.87	.006
No	531/4116 (12.9%)	627/4116 (15.2%)	0.83	0.74, 0.93	.002

Changes in Lipid Profile

After one year of treatment the pravastatin group had a mean reduction in total-C of 19.7%, LDL-C 27.5%, TG 5.7%, and apoB 21.2%. Mean increases in HDL-C and apoA1 for the pravastatin group were 4.6% and 6.6%, respectively. These changes were persistent throughout the 5 years duration of drug exposure as depicted in Figure 5 for LDL-C. In contrast, the placebo treated patients demonstrated small changes in their lipid values that were not clinically meaningful.

Figure 5. LDL-C Percent change from baseline by year and treatment group



Relationship of Lipid Profile Changes to Cardiac Events (Event Reduction Analysis)

Relationship of Lipid Profile Changes to Cardiac Events (Event Reduction Analysis)
The effect of LDL-C lowering and its relationship to experiencing CHD events were evaluated using the first occurrence of one of the following endpoints: CHD mortality;

nonfatal MI; CABG; or PTCA. These endpoints were considered relevant consequences of CHD.

To assess the action of pravastatin on reducing CHD events an analysis was performed in a cohort of patients who would represent on-treatment effects of pravastatin. Patients were excluded from this analysis for the following reasons:

- non-compliant with study medications (<75% by pill counts during treatment exposure)
- missing valid baseline or on treatment LDL-C measurements
- TG > 443 mg/dL since LDL-C levels were calculated using the Friedewald formula
- experienced a cardiac event or discontinued study medication less than one year after randomization

Based on these criteria, there were 3,854 pravastatin-treated subjects (about 84% of the sample size) included in the event reduction analysis. An event reduction analysis was also performed in the intent-to-treat (ITT) cohort and any differences between the randomized subjects and the eligible cohort were evaluated.

The sponsor's analysis of the pravastatin patients was composed of the following steps:

1. Compute average on-treatment LDL. LDL measurements taken up to 6 months after drug discontinuation, at time of cardiac event, one day after switching to alternate lipid treatment, dates of death or last visit, whichever occurred first.
2. Compute deciles or quintiles based on average on-treatment LDL.
3. Using a Cox model including baseline prognostic variables for age, gender, and history of smoking, hypertension and diabetes, compare the lowest decile or quintile (the reference group) to each of the other deciles or quintiles.
4. Calculate relative risk and 95% CI for each pairwise comparison.

The results for deciles are shown in Table 18 below. There are approximately 385 subjects in each decile. The confidence intervals indicate considerable variability in the relative risk estimates; no significant differences between the reference group and the 9 higher deciles were observed (p-value for the highest decile is greater than .05).

Table 18. ERA Results
Pravastatin patients' average LDL grouped by deciles

LDL range	# of events	Relative Risk	95% CI
21-78 (reference)	68	1.0	
79-88	67	1.0	0.7, 1.3
88-95	57	0.8	0.6, 1.2
95-101	53	0.8	0.6, 1.2
101-107	45	0.7	0.5, 1.0
107-112	62	1.0	0.7, 1.4
112-119	64	1.0	0.7. 1.4
119-127	52	0.8	0.6, 1.2
127-139	67	1.1	0.8, 1.6
139-233	76	1.4	1.0, 2.0

The results for quintiles are shown in Table 19 below. There are about 770 patients in each quintile. The sponsor reports a significant difference between the highest quintile and the reference group in the study report (p=.05). It is interesting to note that there are more events observed in the reference group than in the next 3 quintiles. In addition, the reduction in LDL was highest in the reference group (36% change from baseline compared to 14% in the highest quintile).

Table 19. ERA results
Pravastatin patients' average LDL grouped by quintiles

LDL range	# of Events	Relative Risk	95% CI
21-88 (reference)	135	1.0	
88-101	110	0.8	0.7, 1.1
101-112	107	0.8	0.7, 1.1
112-127	116	0.9	0.7, 1.2
127-233	143	1.3	1.0, 1.6

The Event Reduction Analysis was a post hoc analysis. It was not described in the LIPID protocol. As such, the methodology is exploratory and henceforth changes in the methods (such as, the number of groupings and the definition of the reference group) will yield different results. Also the logic of the methodology is not evident, particularly given that the number of events in the reference group is greater than in the all but the highest group. Might this suggest that low LDL values increase risk?

The results of the sponsor's analyses failed to demonstrate a relationship between level of LDL and cardiac events, however, this failure to show a relationship does not mean that a relationship does not exist. The sponsor's conclusion that values of LDL lower than 127 do not further reduce risk is neither supported nor refuted by the data. Examination of the confidence intervals for the relative risks makes this quite evident.

Given that LDL changes are stable after one year of therapy, an analysis comparing placebo and pravastatin after one year of therapy grouping on LDL levels would be preferable to the analysis performed by the sponsor. The results of such an analysis were presented by FDA in their review of the AFCAPS/TexCAPS study and also in a published paper (Pedersen et al, Circulation 1998;97:1453-1460); both analyses showed a small but continuous gradient over the observed range of LDL values.

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Hospitalizations

In the study protocol, total days of hospitalization was named as a secondary endpoint; a statistical analysis plan to assess this variable was not presented in the protocol. The sponsor analyzed all-cause hospitalizations in two ways; a t-test to compare total days of hospitalization per 100 person years of follow-up and a multiplicative model to compare frequency and duration of hospitalizations. The results for total days of hospitalization per 100 person years show a significant treatment effect (Table 20).

Table 20. Sponsor's Results for Days of Hospitalization

	Pravastatin (n=4,512)	Placebo (n=4,502)	p-value
Means Days/100 person years FU (95% confidence interval)	296 (277,315)	349 (328, 370)	.001
Mean Days in Hospital	16.8	19.6	

The multiplicative model revealed a significant risk reduction of 9.6% (95% CI of 4.8%, 14.2%, p<.001).

Data regarding reason for hospitalization and events occurring during hospitalization were collected for each hospitalization. Events leading to hospitalization were not differentiated from events occurring during hospitalization but were categorized on the CRFs under vascular (Y/N), surgery/procedures (Y/N), and other events (Y/N). Within each category a subject could only be classified as 'yes' or 'no' but the categories were not mutually exclusive of each other. As a result, a subject could have a non-vascular admission but undergo a surgical procedure during hospitalization that was further defined as a CABG, PTCA, or other. After evaluation of several patient line listings wherein a CABG or PTCA was listed as a nonvascular admission, it was discovered that this occurred when the surgical procedure was not accompanied by another vascular event at the time of admission. Even though we consider this a misclassification which raises concerns regarding validity of the data, we did not redefine vascular hospitalizations to include these procedures in our analyses. To avoid introducing bias due to post-hoc selection and because of difficulties identifying actual reasons for admissions, we chose to use the definition of vascular admission as provided on the CRFs.

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The table below shows the events that occurred at the time of admission leading to hospitalization or during hospitalization. Multiple events could be recorded for each admission therefore the total number of events is greater than the total number of admissions.

Table 21. Admissions by events at the time of or during hospitalization*

	Pravastatin (n=4,512)	Placebo (n=4,502)
Total # of Admissions	11,743	12,819
Vascular Admissions	4,668	5,461
MI	427	581
UAP	1930	2363
CHF	687	765
CVA	177	205
Pulmonary emboli	57	60
other coronary event	398	477
other cardiac event	810	920
other vascular event	670	785
Non-vascular Admissions	7,074	7,357
Surgery		
CABG	196	225
Angioplasty	77	81
Carotid endarterectomies	5	9
Other surgeries	4564	4653
Other Non-vascular events	4035	4220
Cancer	1010	1031
Liver disease	28	31
Myositis	5	4
Trauma	221	211
Other non-vascular events	3006	3258

*One patient in each treatment group had an admission classified as unknown with respect to vascular or nonvascular cause

We examined the CABG and PTCA hospital data (Table) further primarily as an internal check for the revascularization endpoint. These data include all revascularization events not just first events. It is interesting to note that the treatment differences for revascularizations accompanied by a vascular event (i.e. counted with the vascular events) are larger than the differences seen for non-vascular event; this is consistent with the vascular event rates being treatment related.

Table CABG and PTCA Hospitlaizations

	Pravastatin (n=4,512)	Placebo (n=4,502)
CABG		
Total	423	524
Counted as vascular	227	299
Counted as non-vascular	196	225
PTCA		
Total	248	336
Counted as vascular	171	255
Counted as non-vascular	77	81

To compare the admissions, FDA compared the number of admissions per patient and also the number of patients with at least one admission for all-cause admissions and then by vascular/non-vascular. The focus here is on admissions, not duration of

hospitalization because duration may be dependent upon factors not related to baseline treatment.

The results in Table 23 clearly show that the all-cause differences in number of admissions and number of patients with admissions are due to the differences seen for vascular hospitalizations. Note that the magnitude of these differences is small.

Table 23. Hospitalizations

	Pravastatin	Placebo	p-value
All Cause Hospitalization			
# of Admissions/patient			
Mean (SD)	2.6 (3.3)	2.8 (3.4)	.0002
Median	2	2	
# Pts w/ at least one admission	3313/4512 (73%)	3411/4502 (76%)	.01
Vascular Hospitalization			
# of Admissions/patient			
Mean (SD)	1.0 (1.8)	1.2 (2.0)	.0001
Median	0	0	
# Pts w/ at least one admission	2004/4512 (44%)	2199/4502 (49%)	.001
Non-vascular Hospitalization			
# of Admissions/patient			
Mean (SD)	1.6 (2.3)	1.6 (2.4)	.50
Median	1	1	
# Pts w/ at least one admission	2716/4512 (60%)	2721/4502 (60%)	.81

Since all the endpoints in LIPID are assessed as time to first event, it seemed reasonable to assess the hospitalization data in this way also. The difference for vascular hospitalizations is statistically significant ($p<.0001$, Figure 6) but small in magnitude. There is clearly not a difference between the treatment groups for non-vascular hospitalizations ($p>.70$, Figure 7).

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Figure 6. Time to first vascular-related hospitalization

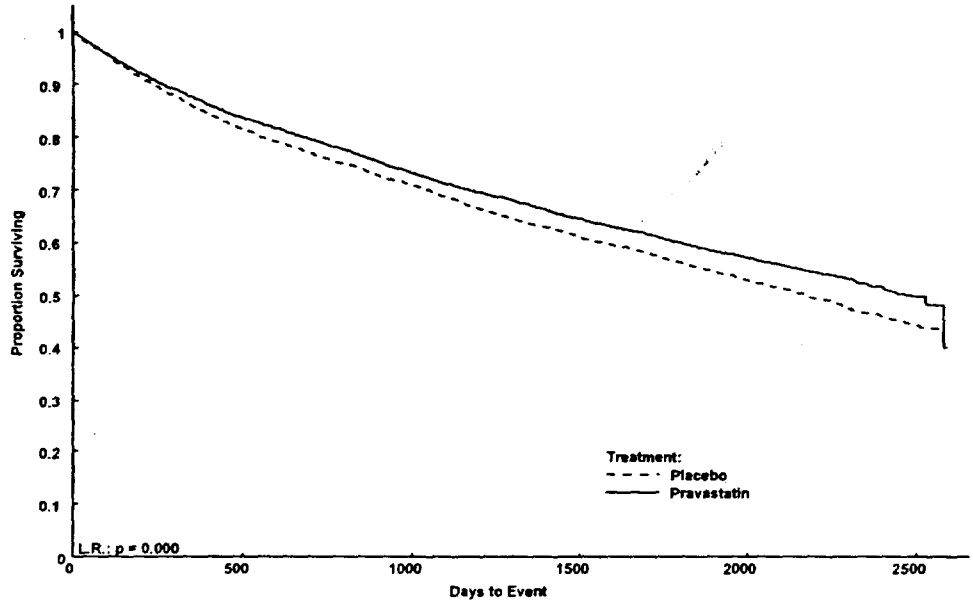
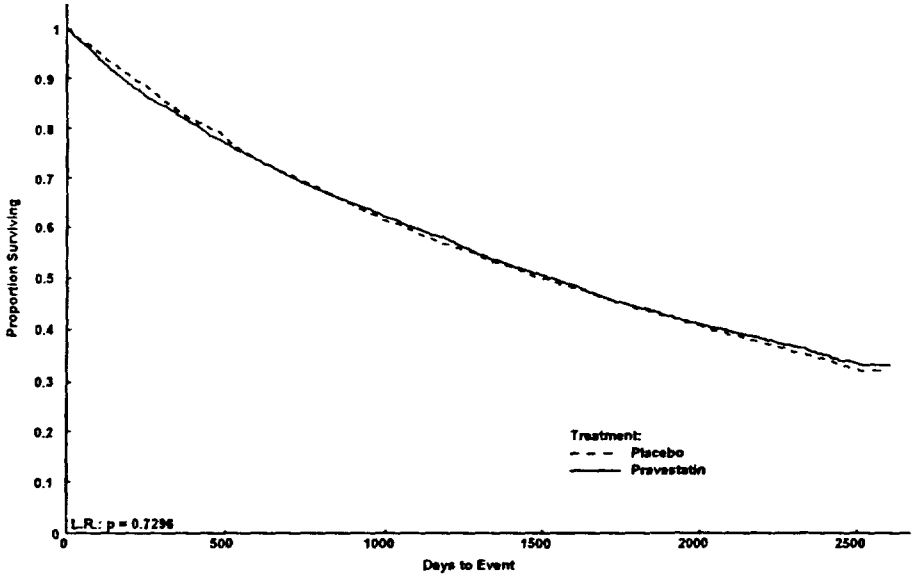


Figure 7. Time to first non-vascular hospitalization



LIPID has demonstrated a significant reduction in conventional cardiovascular endpoints. In accordance with these results, vascular hospitalizations are reduced. Our analyses have shown that the reduction in hospitalizations is a direct consequence of a reduction in cardiovascular events and provides no additional clinical evidence of efficacy . These analyses do not support the sponsor's proposed indication for reduction in days of hospitalization.

Conclusions from the Secondary Efficacy Endpoint Results
Treatment with pravastatin resulted in reductions in risk of experiencing a clinical event associated with atherosclerosis. The secondary endpoints, total days of hospitalization and event reduction analysis, were not measures of disease outcome and hence, were not considered valid measures of clinical efficacy.

Review of the data on total hospital admissions in the LIPID trial revealed an overall reduction in all-cause hospitalizations due to a significant reduction in hospitalizations due to vascular events. This finding merely supports the primary endpoint and those secondary endpoints that measure the effects on the natural history of atherosclerosis. A reduction in hospitalization due to atherosclerotic events is an expected finding and provides no additional information regarding clinical benefit but is at best a potential measure of cost-effectiveness.

Safety Results
Only serious adverse events (SAE) and non-serious suspected adverse drug reactions (ADR) were recorded in the case report forms (CRFs). Adverse events reported were obtained from only randomized patients who consumed at least one dose of study medication and whose event occurred up to 30 days after discontinuation date, last scheduled visit, or date of death. Since all endpoint events related to the cardiovascular system were also reported as an SAE it was not an unexpected finding that the majority of reports were for this body system. There were a total of 34,972 adverse events reported in 2,382 (52.8%) patients treated with pravastatin versus 2,383 (52.9%) in the placebo group. Table 24 summarizes AEs reported by body systems.

Table 24. Adverse Events Reported by Body System in the LIPID Trial

Body System	Pravastatin (n=4,512)		Placebo (n=4,502)	
	Number of Events Reported	Number of Subjects (%)*	Number of Events Reported	Number of Subjects (%)*
Cardiac	4415	1303 (28.9%)	5459	1461 (32.5%)
Complications of Medical Care	150	127 (2.8%)	176	152 (3.4%)
Dermatologic	688	377 (8.4%)	665	346 (7.7%)
Endocrine, metabolic	170	126 (2.8%)	256	137 (3%)
Gastro-intestinal	2512	811 (18%)	2735	853 (18.9%)
Hematologic	151	92 (2%)	228	124 (2.8%)
Hepatic, biliary	377	169 (3.7%)	502	185 (4.1%)
Infections	114	102 (2.3%)	136	124 (2.8%)
Malignancy	1044	438 (9.7%)	1048	432 (9.6%)
Musculo-skeletal	1194	494 (10.9%)	1168	483 (10.7%)
Nervous System	512	300 (6.6%)	556	303 (6.7%)
Other Reasons for Hospital Admission	225	131 (2.9%)	205	124 (2.8%)
Renal, GU	1821	593 (13.1%)	1612	563 (12.5%)
Respiratory	1222	588 (13%)	1240	564 (12.5%)
Special Senses	664	233 (5.2%)	694	246 (5.5%)
Trauma	209	172 (3.8%)	214	169 (3.8%)
Vascular (non-cardiac)	1171	506 (11.2%)	1438	579 (12.9%)
Unknown	0	0	1	1 (0.02%)
Total	16,639	6,562	18,333	6,363

Source: NDA 19-898/S032 eventa.xpt and eventb.xpt
*A patient was counted only once per body system but may be counted more than once in different body systems

For those body systems in which the incidence was higher in the pravastatin group (dermatologic, musculoskeletal, renal-GU, and respiratory) the individual line listing of AE was reviewed and no significant differences were noted between treatment groups.

Serious Adverse Events or Adverse Drug Reactions Resulting in Study Drug Discontinuation

Four hundred and eighty-three (483; 10.7%) patients randomized to pravastatin versus 574 (12.7%) patients treated with placebo discontinued study drug permanently due to an SAE or ADR. There was no body system or category for which there was a significantly greater incidence of discontinuation occurring in the pravastatin group compared to placebo.

Deaths

Total mortality was a secondary measure of efficacy and discussed in detail under the *Efficacy Results* section. Similar to the CARE and 4S trial, there were no excess deaths due to noncardiovascular causes in the treatment group [pravastatin (167; 3.7%) versus placebo group (200; 4.4%)]. Overall, noncardiovascular deaths accounted for only 32.4% of all deaths.

Abnormalities of Liver Function Tests

Clinically significant elevations of hepatic transaminases have been defined as consecutive elevations of > 3x ULN for ALT or AST values. In the pravastatin treatment group there were 27 (0.6%) patients with > 3x ULN ALT values. Fourteen of these were > 5x ULN on more than one occasion. In the placebo treatment group there were 11 (0.2%) patients with > 3x ULN ALT values and 2 of these were > 5x ULN on more than one occasion. None of these cases resulted in significant hepatic injury, jaundice, or death.

Abnormalities of Creatine Phosphokinase (CPK)

The incidences of marked abnormalities in CPKs were similar between the 2 treatment groups [pravastatin (n=110) 2.4% vs. placebo (n=103) 2.3%)]. The mean CPK value was 497 in the pravastatin group and 1,178 in the placebo group. This discrepancy was primarily due to one placebo patient experiencing rhabdomyolysis with a peak CPK level of 43,000. The suspect medication in this case was concomitant use of bezafibrate during study period. The median CPK values for both groups were comparable (311 vs. 335). There were no cases of rhabomyolysis reported in the pravastatin group and the incidence of myositis/myalgias was similar between the two treatment groups (0.2% vs. 0.2%).

Cancers

There were 625 (13.9%) patients in the pravastatin group versus 617 (13.7%) patients in the placebo group with reported SAEs of cancers. The most commonly reported cancer types were of the prostate (pravastatin 2.5% vs. placebo 2.6%) and skin (pravastatin 2.5% vs. placebo 2.2%). One hundred twenty-eight (128; 11.3%) patients treated with pravastatin versus 141 (12.5%) in the placebo group died of cancer.

In the CARE study there was an unexpected finding of excess breast cancer cases reported in women randomized to treatment with pravastatin (12; 4.2%) in contrast to the placebo group (1; 0.3%). During the supplemental NDA review of the CARE study the LIPID trial was completed and this data base was queried for the incidence of breast cancer. There were approximately 2.5 times more women randomized in the LIPID trial

compared to the CARE study and the median duration of follow-up was longer (5.9 vs. 4.9 years). There were similar numbers of new breast cancer cases reported in women for both treatment groups in LIPID (pravastatin; 10 vs. placebo; 9). There were 9 (1.2%) cases of malignant breast cancer reported in the pravastatin group versus 8 (1.1%) in the placebo group. One case of carcinoma in situ was reported in a pravastatin treated patient. These findings from the LIPID study and other documents reviewed in the CARE study (NDA 19-898/supplement 018) suppor that the imbalance in breast cancer observed in CARE was a chance finding.

Conclusions of Safety Review
There are no adverse events reported in the LIPID trial that are not already reflected in the current label.

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REVIEW OF FINANCIAL DISCLOSURE FORMS
None of the clinical investigators involved in the LIPID trial were reported to have financial interest in the outcome of this study.

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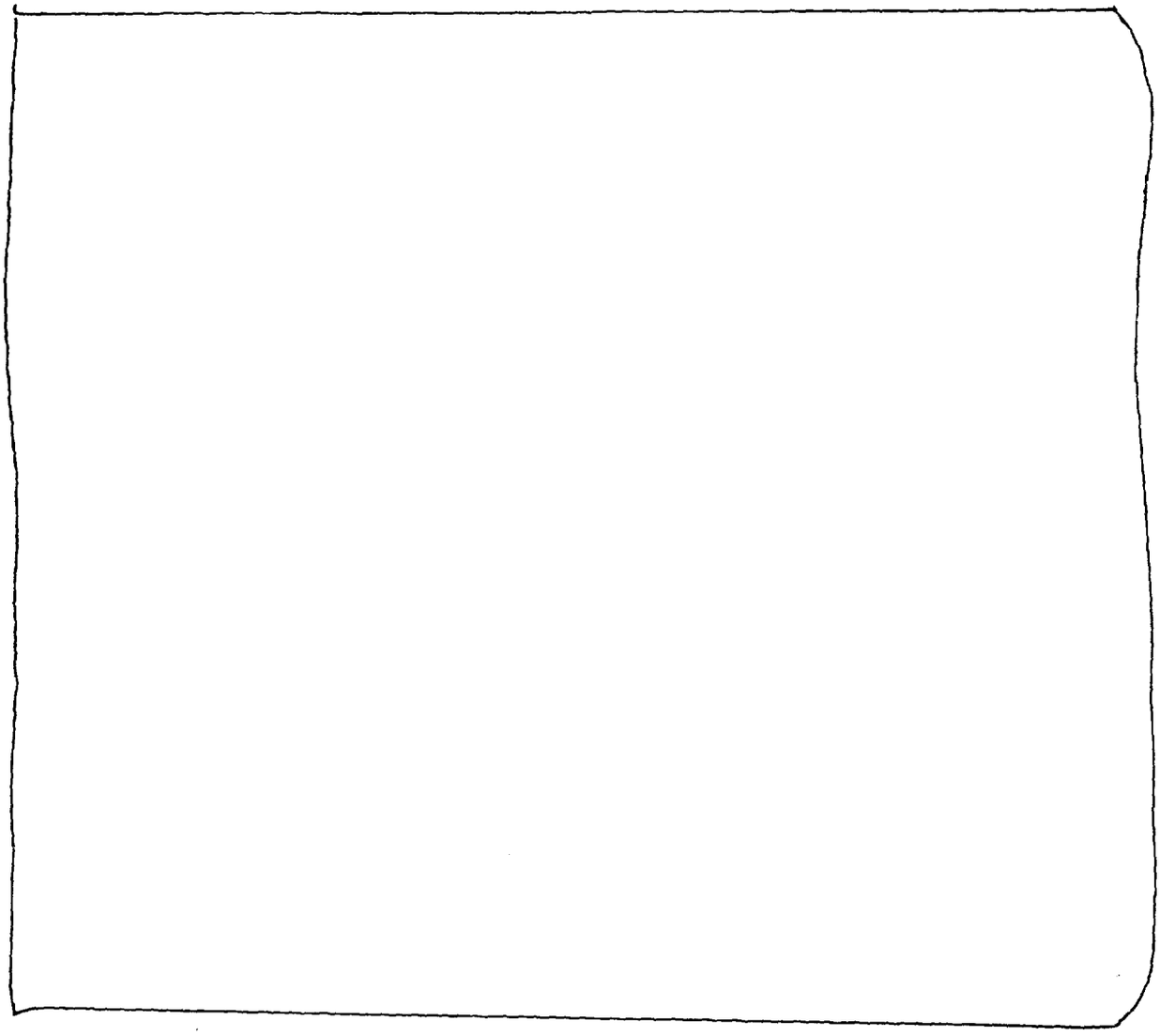
LABELING

SPONSOR'S PROPOSED LABELING

The major changes to the label are located in the *Clinical Pharmacology* and *Indications and Usage* sections. The sponsor also proposes to condense the safety findings from their three large, placebo-controlled trials as a single statement under the *Adverse Reactions* section.



CONCLUSIONS

The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial was a multicenter secondary prevention trial which enrolled men and women with a previous history of myocardial infarction or documented unstable angina as evidence of their heart disease. During the average follow-up of 5.6 years, patients randomized to treatment with pravastatin 40 mg daily, had a significant reduction in risk of experiencing a death due to coronary heart disease (primary endpoint) and other secondary endpoint measures associated with atherosclerosis. Although it is reasonable to conclude that the results of this study and numerous other lipid-lowering trials have successfully established the clinical benefit of cholesterol lowering in the primary and secondary prevention population, the question of whether this benefit is demonstrated in all subgroups of the cohort treated remains. In particular, women and diabetics continue to have insignificant risk reductions in many endpoints assessed (see Reviewers' Comments on Labeling).

The adverse experiences reported in this trial were similar to previously reported pravastatin trials. The rate of AEs reported in the LIPID trial was similar between pravastatin and placebo. The incidence of breast cancer cases reported during this trial

was similar between the 2 treatment groups and further provides reassurance that the slight increase of cases noted in the CARE trial was not related to drug treatment.

RECOMMENDATION

This application should be approved pending the appropriate labeling changes.

APPEARS THIS WAY ON ORIGINAL

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/S/ 2-1-00

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Joy D. Mele, M.S.
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Concur:
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HFD-510/MParks, DOrloff, JJenkins, MSimoneau
HFD-715/Biometrics Division 2 File, Chron, JMele, TSahlroot

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APPEARS THIS WAY
ON ORIGINAL

NDA 19-898
Pravachol (pravastatin sodium) tablets
Bristol-Myers Squibb
Indication: Secondary prevention of CHD based on the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study
Date of submission: April 28, 1999
Date of review: February 1, 2000

Medical Team Leader comments on sNDA

Background

The LIPID study was a large-scale, double-blind, randomized, placebo-controlled trial conducted in Australia to test the hypothesis that treatment with pravastatin 40 mg daily would reduce, relative to placebo, the risk of coronary and cardiovascular events in men and women, aged 31-75, with a history of MI or unstable angina and relatively low LDL-C levels. The primary endpoint for this trial was CHD mortality. Patients with TC between 155 and 271 mg/dL and TG < 443 mg/dL on diet were enrolled between 3 and 36 months after their qualifying event. Average duration of follow up was 5.6 years. The protocol specified a number of secondary endpoints including total mortality, various composite endpoints as measures of cardiovascular disease outcomes, stroke, and revascularization procedures. Finally, the sponsor defined an endpoint of total days of hospitalization. In addition, though not prespecified, the sponsor undertook a so-called event-reduction analysis to examine the relationship between on-treatment LDL-C levels and risk for events in the pravastatin group.

This is the largest statin trial to date, with 9014 patients in the total cohort (~4500 in each treatment group). Approximately 75% of pravastatin patients and 70% of placebo patients completed the trial. This is consistent with the other large statin trials. Vital and clinical status was ascertained for all but one patient at trial closure. At baseline, the treatment groups were well matched for gender, age, cardiovascular risk factors, and lipids. The trial population was 83% male and contained 20% smokers and 9% diabetics. Mean baseline TC, LDL-C, HDL-C, and TG were 218, 150, 37, and 160 mg/dL, respectively. 75% of patients were treated with antihypertensives at baseline and 82% were taking ASA. 47% were on beta-blockers and 35% on calcium channel blockers.

Results and comments

The mean percent change in LDL-C for the pravastatin group at the end of 1 year was 27.5%. By the end of the study, the mean percent reduction was approximately 24% in the pravastatin group and 6% in the placebo group. This is presumably related to use of lipid altering drugs in the placebo group which did increase over the course of the study.

The trial succeeded on the primary endpoint and was terminated early based on the results of an interim analysis. The CHD mortality rate in the placebo group was 8.3% and 6.3% in the pravastatin group (RR .76, p=0.0004). Approximately 90% of the mortal CHD events across the total cohort were fatal MI, sudden cardiac death, and death due to infarct-related CHF. Approximately half of the fatal events were coded as sudden cardiac death. Consistent trends were observed for the primary endpoint across subgroups based

upon gender, age greater or less than 65, qualifying event, and presence or absence of CHD risk factors. Despite a placebo event rate in the diabetic subgroup of 12%, there was no observed reduction associated with pravastatin therapy. This is of note since previous statin trials, particularly 4S, have shown effects in the diabetic subgroups as great or greater than those for the total cohort, though labeling to this effect has not been approved based upon relatively small sample sizes, the non-representative nature of the enrolled diabetics with regard to the general population of Type II diabetics, and with the knowledge that prospective trials of lipid altering in diabetics are ongoing.

LIPID also achieved a significant reduction in total mortality driven by the robust reduction in coronary and cardiovascular mortality, these latter categories accounting for two-thirds of the deaths in this trial. This is a finding in very close keeping with the results of 4S, a secondary prevention trial of simvastatin in coronary patients with mean LDL-C of approximately 200 mg/dL also powered for total mortality. As in that trial and in WOSCOPS, CARE, and AFCAPS/TexCAPS, the statin-associated reduction in cardiovascular mortality in LIPID was in no way offset by a countervailing increase in non-cardiovascular deaths that might have been attributed to active treatment.

Consistent with the other statin secondary prevention trials, LIPID also found significant pravastatin-associated reductions in the composite of CHD death or non-fatal MI, in all-cause and non-hemorrhagic stroke, in total cardiovascular mortality, and in myocardial revascularization procedures. Two-thirds of these procedures were CABGs across both treatment groups.

Regarding the effect of pravastatin treatment on risk of hospitalization, the FDA reviewers conducted an analysis using a time-to-first-event approach. This analysis showed a significant reduction in risk for hospitalization due to vascular causes (49% placebo, 44% pravastatin, p=0.001). There was no difference in the incidence of non-vascular admissions across treatment groups. The sponsor has proposed including data on number of days of hospitalization per 100 person years of follow up. The sponsor's analysis of this endpoint shows an approximate 15% statistically significant reduction associated with pravastatin therapy. In addition, the sponsor proposes an indication "to reduce total hospitalization."

Irrespective of the particular analysis or the specific wording in labeling, such information is not appropriate for inclusion in the pravastatin package insert. It constitutes, at best, health economic information and not information addressing clinical benefit to be expected with use of pravastatin. I am well aware of the use of the endpoint of hospitalization or cause-specific hospitalization in the assessment of efficacy in trials of therapies for CHF. In understanding the impact of therapies on the natural history of CHF and in order to assess any countervailing adverse effects of such interventions, it is necessary and therefore reasonable to examine data on cause-specific and total hospitalizations. CHF is not a medical condition for which assessment of disease course is always possible using so-called "hard" clinical endpoints. Benefits in CHF treatment may accrue as improved exercise tolerance, improved sense of well-being, reduction in episodes of PND or nocturia, or improvement in orthopnea. Instruments for assessment

of these markers of disease course are far from perfect. Other surrogates are also examined, including heart rate, heart size, ejection fraction, and pulmonary capillary wedge pressure, though these have not been relied upon as definitive evidence of benefit. Short of emergent hospitalization (perhaps a more direct surrogate for acute severe decompensation) or cardiac death, valid measures of clinical benefit are not readily available in the characterization of disease course in patients with CHF. Furthermore, the analysis of rate of hospitalization provides for internal validation of trial outcomes with regard to the more indirect surrogates listed above.

By contrast, the effects of therapeutic interventions on the course of atherosclerotic disease are assessed using hard clinical endpoints, in effect direct, clinically relevant measures of disease outcome: fatal and non-fatal MI, sudden death, stroke, and revascularization procedures. Such was the case for LIPID, a trial in which clinical endpoint events were strictly defined in the protocol and carefully adjudicated by an endpoints committee, and in which vital and clinical status was known for all but a single trial participant at trial closure. The robust primary and non-primary clinical endpoint results of this trial support changes in labeling to reflect the expected benefits of pravastatin therapy in the reduction of risk for cardiovascular events in patients with moderate elevations in LDL-C and a history of symptomatic coronary atherosclerosis. The endpoint outcome of the study with regard to hospitalization, while perhaps not in doubt, is simply a reflection of the benefits of pravastatin therapy on direct measures of disease course. As such, it adds no additional useful clinical information to our understanding the effects of pravastatin therapy in this population. Pravastatin is recommended to reduce the risk of MI, sudden death, stroke, etc. but not directly to prevent hospitalization. If the patients on pravastatin are having fewer acute coronary and cardiovascular events, as these events dominate the population's clinical course for the duration of the trial, it follows, of course, that rate of hospitalization will also decrease. But, this information is not essential to an enumeration of the clinical benefit of this intervention. Again, this is in contrast to the case of CHF, where direct, clinically relevant measures of disease course are much less readily available and where hospitalization is accepted as a valid surrogate for what is assumed to be a serious decompensation in clinical and functional cardiovascular status. To re-emphasize, no such surrogate has been accepted as valid for atherosclerotic disease nor is necessary in order to assess benefit or risk of a particular therapeutic intervention.

The Event Reduction Analysis (ERA) conducted by the sponsor and proposed for inclusion in labeling is a post-hoc, exploratory, hypothesis-generating data analysis intended to examine the relationship between on-treatment LDL-C levels and risk for cardiac events (a composite) in the 84% of pravastatin-treated LIPID participants meeting criteria for inclusion. A similar analysis was conducted using data from CARE (also proposed for inclusion in labeling). It is notable that related post-hoc analyses from WOSCOPS and CARE were published several years ago and have been held forward by BMS as evidence that LDL-C reduction beyond 25 or 30% from baseline gives no additional benefit in terms of cardiovascular disease event reduction (see references). The LIPID trial was neither designed nor adequately powered to examine event rates in subgroups based on percent LDL-C reduction from baseline (or on-treatment LDL-C).

Specifically, the proposed labeling contains a figure depicting, as a function of on-treatment LDL-C (by quintiles of the pravastatin group), risk ratios for CHD events (normalized to the rate in the quintile with the lowest on-treatment LDL-C concentrations). For the purposes of this analysis, a composite endpoint based on the first occurrence of CHD death, non-fatal MI, CABG, or PTCA was employed. The point estimates for the risk ratios suggest that the risk of events rises only for the quintile with the highest on-treatment LDL-C levels, perhaps indicating that LDL-C lowering beyond 25% from baseline reaps no additional benefits. However, the 95% confidence limits for these estimates all overlap to a greater or lesser extent. This finding simply highlights the fact that there are insufficient numbers of patients in these quintiles to draw any definitive conclusions about the relationship between LDL-C level on treatment and CHD risk.

On the basis of the sponsor's analysis, it is not possible to exclude an effect of degree of LDL-C reduction from baseline on outcomes. It is interesting that a published analysis of the 4S trial of simvastatin showed a strong correlation between on-treatment LDL-C levels, as well as change from baseline in LDL-C, and reduction relative to placebo in major coronary events (see references). Furthermore, as stated earlier, LIPID was designed as a trial to compare the effects of pravastatin and placebo on outcomes. Patients all received the same dose, 40 mg, of pravastatin. This was not a trial in which patients were randomized to different LDL goals with the intent of comparing, between groups, cardiovascular event rates. Such a trial is ongoing with another statin, the results of which will shed further light on the issue of any additional benefits associated with incremental cholesterol lowering.

In conclusion, the results from LIPID with regard to rates of hospitalization and the impact of degree of LDL-C lowering on risk of events should not be included in labeling.

Recommendation
This supplement should be approved contingent on agreement on final labeling.

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ODE II/CDER/FDA

/S/
2-1-00

Recommendation code: AP

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2/1/00

CC:
NDA 19-898 Arch
HFD-510
HFD-510: Parks/Mele

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